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Expectations, conditioning, and the placebo effect do not differ between fibromyalgia patients and healthy controls but might be differently associated

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ABSTRACT

Introduction: Individuals with chronic pain such as fibromyalgia (FM) are often experiencing disappointing outcomes from clinical therapies, which theoretically should condition them to experience low placebo analgesia. However, no consistent differences in the placebo effect were found between healthy controls (HC) and chronic pain patients. This study examined the expectations, conditioning, and placebo effect in HC and FM, and the relationships between these factors in both groups.

Methods: Female HC and FM patients were recruited, provided demographic and clinical information and underwent the experimental placebo paradigm. This paradigm has the advantage of measuring expectations (baseline, reinforced, and after placebo), conditioning, and placebo effect. Mixed factorial ANCOVAs, correlational analysis, stepwise and moderation regression analysis were employed.

Results: Thirty-seven HC and 32 FM patients participated. Three Mixed factorial ANCOVAs showed no main effects of group or interactions for expectations ($p = .692$), conditioning ($p = .357$), or placebo effect ($p = .819$). Reinforced expectations predicted the conditioning strength ($r = .48$, $p = .008$) and placebo effect ($r = .44$, $p = .014$) in HC but not in FM participants. In FM, duration of pain predicted the reinforced expectations ($r = -.38$, $p = .035$) and moderated the prediction of the placebo effect by the conditioning strength (b = .04, $p = .011$).

Conclusion: While the classical placebo theorem is supported in healthy controls, with conditioning influencing expectations, which in turn predict the placebo effect, these associations are not observed in fibromyalgia, where prior clinical experience plays a more significant role. These findings underscore the impact of previous negative clinical experiences on the placebo effect and, possibly, on responses to effective treatments.

1. Introduction

Despite ongoing research, the etiology of nociplastic pain in fibromyalgia (FM), affecting approximately 5 % of women worldwide, remains unclear [1,2]. The proposed pathophysiology combines top-down and bottom-up mechanisms, including central and peripheral sensitization [3,4]. A better understanding of factors influencing pain perception in FM may lead to new treatment approaches.

One such factor of growing interest is the placebo effect. A placebo is a substance or an intervention that, without inherent medical effects, can nonetheless provide relief [5]. A placebo response is the reduction in symptoms after placebo administration (or manipulation). The placebo response is attributed to two driving forces: the placebo effect, which is the reduction in symptoms due to conditioning (i.e., past experience), and/or expectations of pain relief, and the non-specific factors, such as natural course of the disease, regression to the mean and methodological biases [6–11].

Colloca and Benedetti [12] introduced an experimental placebo

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paradigm using repeated conditioning steps combined with verbal suggestions aimed to induce expectations of pain relief. This method allows separate assessments of expectations (before and after conditioning, and after placebo), conditioning, and the analgesic placebo effect. In a series of studies [12–15], Colloca and colleagues demonstrated that the placebo effect is a learning phenomenon, influenced by the number of conditioning trials [14], which models prior clinical experience. They demonstrated that in healthy controls (HC), the conditioning strength modulated the placebo effect [12], that the magnitude of the placebo effect was larger after conditioning than after verbal suggestion [13,14], and that conditioning, but not verbal suggestion alone, induced neural changes and subjective pain reduction [16]. Furthermore, Colloca et al. [15] found that patients with Temporomandibular joint Disorder (TMD) reported higher reinforced expectations than healthy, but those did not account for the placebo effects. Instead, conditioning strength mediated placebo effects in both patients and HC. This aligns with findings from previous experimental settings in which prior therapeutic experiences had an impact on later treatment outcomes, generalizing across time and different treatment modalities [17,18] independently of explicit expectations.

In addition to findings based on experimental tasks, clinical evidence demonstrates that past treatment experiences are associated with treatment expectations of pain relief from current interventions [19–21]. Indirect evidence for the relevance of prior clinical experience to the placebo response could also be found in multiple studies consistently reporting the negative correlation between illness duration, as one facet of prior clinical experience, and the placebo response [22–30]. Patients with long-term chronic pain are more likely to have had more negative clinical experiences, which may lessen their expectations of pain relief from future interventions, and hence may diminish their placebo effect.

Despite the possible prior negative clinical experience of chronic pain patients, comparable placebo effects were demonstrated in HC and patients with chronic pain such as FM [31], TMD [32,33], osteoarthritis [31], irritable bowel syndrome [34], episodic migraine [35], and atopic dermatitis [36]. These findings are further supported by a meta-analysis by Forsberg et al. [37].

Given the prior negative experience of FM and other chronic pain patients, one would expect a stronger placebo effect in HC than in clinical groups, but based on the literature, this does not seem to be the case. To shed more light on this matter, we applied the experimental placebo paradigm in both HC and FM patients to compare both groups' expectations of pain relief, conditioning, and placebo effect and to examine how these factors interacted with each other.

2. Methods

2.1. Participants

Healthy female volunteers and female FM patients were recruited through various channels, including advertisements on notice boards at the University of Haifa campus, the university pool of participants, relevant social media forums, and FM association websites. Prior to enrollment, at first contact via phone or mail, potential participants confirmed that they met all inclusion and exclusion criteria. The inclusion/exclusion criteria were further verified through self-report in the sociodemographic questionnaire after signing informed consent during the laboratory visit. Detailed information about inclusion and exclusion criteria for each group are found in the Supplementary materials.

2.2. Tools and procedures

2.2.1. Study design

The study received approval by the University of Haifa Ethics Committee (186/22). The research included deception: participants were falsely told that the study aimed to investigate the effects of a new analgesic device. Eligible participants were invited to sign informed consent and to complete the study questionnaires including demographic and medical information via an online link. During the visit, all participants underwent the experimental placebo paradigm (Fig. 1). At the end of the session, participants were debriefed about the true purpose of the experiment and were offered to retract their data, but none requested a retraction. Lastly, participants were rewarded for their participation (200 NIS).

2.2.2. Assessment of demographic and medical information

Socio-demographic characteristics were collected for both groups. In addition, FM participants were asked to report relevant clinical characteristics such as other medical conditions, medication, and therapies utilized. During the week preceding laboratory visits, FM participants recorded average daily pain intensity using an online computerized visual analog scale (VAS) (0 = "no pain" to 100="worst pain imaginable"; Qualtrics XM). In addition, number of years since pain began (duration of pain) served as a proxy measure of "prior clinical experience." To evaluate quality of life and daily functioning, FM participants completed the Fibromyalgia Impact Questionnaire Revised (FIQR) [38].

2.2.3. Experimental placebo paradigm

The experimental placebo paradigm was done as in Colloca et al., 2020 [15]. We attached a TSA2 thermode (30 mm × 30 mm, Medoc TSA-2001 device, Ramat Ishai, Israel) to the participant's dominant ventral forearm to individually calibrate pain ratings for high (80/100), medium (50/100), and low (20/100) pain intensities, using a series of randomly delivered noxious stimuli of various intensities.

After calibration, in addition to placing the thermode on the forearm (this time, on the non-dominant forearm), we connected two sham electrodes to a transcranial cranial Direct Current Stimulation (tDCS) device (Soterix Medical, Woodbridge, New Jersey, USA) placed near the thermode. Participants were deceptively informed that these electrodes would reduce their pain intensity when active. The statement was designed to induce anticipation for pain relief (electrodes were in fact a sham prop and were not active).

The experimental placebo paradigm had two parts (Fig. 1). In the *conditioning phase*, 24 visual cues (squares with a fixation cross in the middle) were displayed on a screen: 12 red cues paired with high-intensity noxious heat stimuli (80/100) and 12 green cues paired with low-intensity noxious heat stimuli (20/100). This phase was divided into two blocks (12 stimuli each), with 3-min breaks between blocks. Participants were falsely informed that a green square cue indicated that the "analgesic device" was working (i.e., reduced the pain) and that the red square cues indicated the device was not working. In the *placebo phase*, participants were presented with 12 visual cues (6 red and 6 green), each paired with the medium noxious heat stimulus (50/100), individually calibrated. Participants were blinded to stimuli intensities. Further details on the thermode calibration for the experimental placebo paradigm are found in Supplementary materials.

Across the procedure, participants were requested to report their pain intensity after every heat stimulus, on a computerized VAS of 0–100 (0 = "no pain"; 100 = "the worst imaginable pain").

Participants' expectations of pain relief were recorded at baseline (baseline expectations, E1), after the conditioning phase (reinforced expectations, E2), and after the placebo phase (after-treatment expectations, E3) on a computerized VAS of 0–100, in response to the question: "On a scale of 0-100, how much do you believe that the electrodes will decrease [E1] or decreased [E2, E3] your pain?"

The main outcomes were (1) expectations at the three time points, (2) conditioning strength, and (3) placebo effect. The conditioning strength was calculated as the difference between pain reports in response to stimuli paired with the red cue and the green cue, averaged across the 12 pairs during the conditioning phase (total of 24 stimuli). The placebo effect was calculated similarly, as the difference between pain reports in response to stimuli paired with the red cue and the green

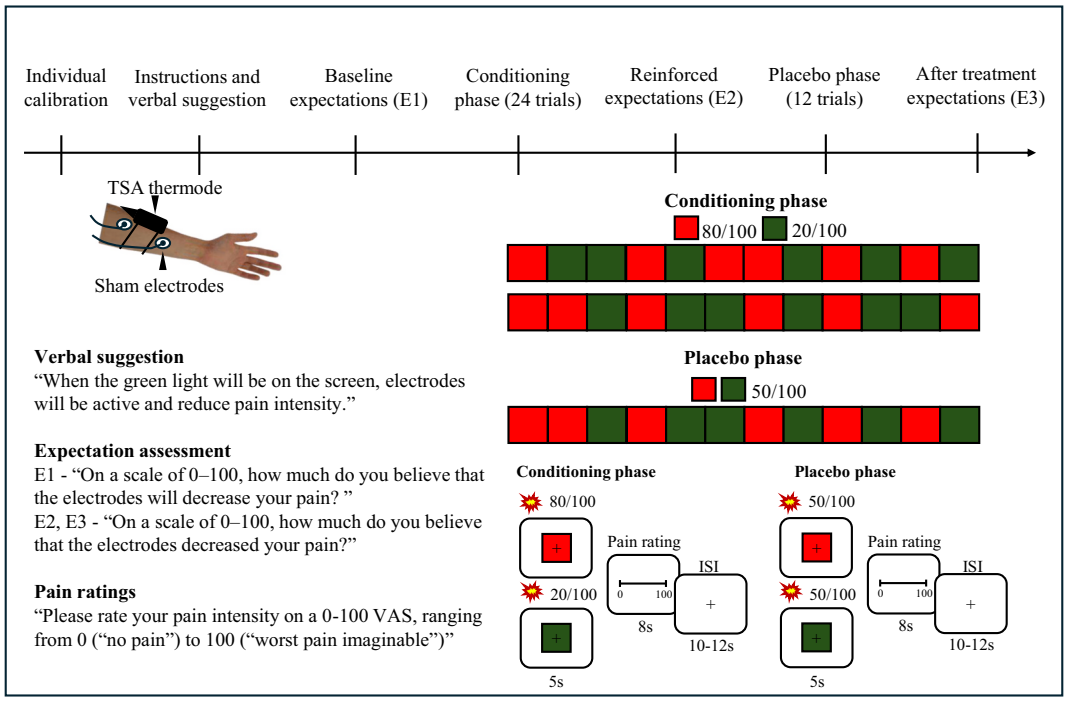

Fig. 1. Detailed description of the experimental placebo paradigm.

cue, averaged across the 6 pairs during the placebo phase.

2.3. Statistical analysis

Based on a power analysis, we aimed to recruit a total of 34 participants from each group. Detailed information about the power analysis is found in the Supplementary materials.

General statistical considerations and detailed description of each statistical test used are presented, by the order of presentation in the Results, in the Supplementary materials. In summary, to assess within and between groups differences in expectations, conditioning and the placebo effect, mixed factorial ANCOVAs were used, followed by pairwise post-hoc tests with Bonferroni correction for multiple comparisons. In addition, univariate ANCOVAs were used to explore group differences in the magnitude of the conditioning strength and the placebo effect, followed by pairwise post-hoc tests with Bonferroni correction. We additionally compared placebo effect sizes between groups with Cohen's d and a Fisher r-to-z transformation and classified participants using a permutation test with 1000 resamples [15]. Further, we employed partial correlations and two separate stepwise linear regressions to identify between group differences. Finally, correlational analyses followed by a moderation analysis with Johnson-Neyman post hoc tests were used to explore the role of the duration of pain at low (−1 SD), mean, and high (+1 SD) levels. Significance was set at $p < .05$.

3. Results

Information about enrolment could be found in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Supplementary Fig. S1). A total of 37 healthy female volunteers (panel A, left side) and 32 female patients with FM (panel B, right side) completed the study.

3.1. Participants' demographic characteristics

Both groups' demographic characteristics are depicted in Supplementary materials Table S1. Both age and BMI were significantly higher for FM than for HC participants (age: Z = -5.92, $p < .001$; BMI: t(61) = −2.07, $p = .042$). The two groups' mean education level in years did not significantly differ. Given that age and BMI differ significantly between groups, those variables were used as covariates in all subsequent analyses.

3.2. Clinical characteristics of FM patients

Participants' mean pain during the week before the laboratory visit was 71.78 (SD = 15.62) on a 0–100 computerized VAS, mean duration of pain was 12.42 years (SD = 10.69, ranging from 0 to 40). Other clinical characteristics are summarized in Supplementary Table S2.

3.3. Experimental placebo paradigm

3.3.1. Expectations of pain relief

The mixed factorial ANCOVA estimates are shown in Fig. 2A and Table S3. After adjusting for age and BMI, the expectations of pain relief for HC were 50.94 (5.97) at baseline, 71.39 (5.52) after conditioning (reinforced expectations), and 55.18 (5.70) after the placebo phase. Expectations of pain relief for FM group were 55.76 (6.22) at baseline, 72.01 (5.75) after conditioning (reinforced expectations), and 42.18 (5.94) after the placebo phase. The mixed factorial ANCOVA was conducted to explore differences in expectations of pain relief across time and between groups revealed a significant main effect of time ($F(2,116) = 5.77$, $p = .004$, $\eta^2 = .09$). Pairwise post-hoc tests are detailed in the Supplementary document. No significant effects for group ($F(1,58) = .16$, $p = .692$) or interaction between time and group ($F(2,116) = 1.22$, $p = .299$) were found. The covariates age ($F(1,58) = 1.18$, $p = .283$) and BMI ($F(1,58) = .02$, $p = .900$) were not statistically significant, indicating that they did not account for a meaningful portion of variance in expectations.

3.3.2. Differences in conditioning across groups

The individually calibrated stimuli adjusted for the covariates elicited a mean pain intensity in the conditioning phase of 76.56 (3.31) for the red cues and 20.22 (3.15) for the green in HC and 80.55 (3.46) for the red cues and 23.85 (3.29) for the green in FM (Fig. 2B, Table S3). A mixed factorial ANCOVA with Greenhouse-Geisser correction showed a main effect of treatment ($F(1,52) = 24.78$, $p < .001$, $\eta^2 = .32$) and time

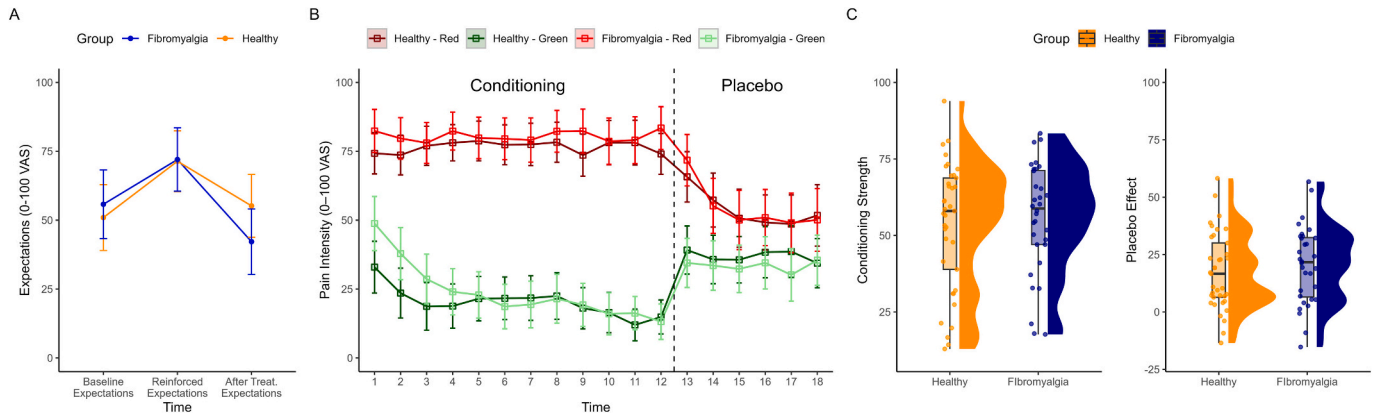

Fig. 2. Expectations of pain relief, pain ratings, conditioning strength and the placebo effect.
(A) Expectations of pain relief over time: mean of expectation ratings adjusted for age and BMI are depicted over time, separated by groups (blue: FM participants, orange: HC).
(B) Trial-by-trial ratings of pain: adjusted average (controlling for age and BMI) pain ratings for red and green cues during the conditioning (trials 1–12) and placebo phases (trials 13–18) separated by groups. Dark red: mean red trials pain ratings for healthy (HC); dark green: mean green trials pain ratings for HC; light red: mean red trials pain ratings for fibromyalgia (FM), light green: mean green trials pain ratings for FM. Error bars represent 95 % confidence interval.
(C) Raincloud plots depict the pain rating distributions for conditioning strength and placebo effect. Each point represents individual participant data for conditioning strength (red minus green during the conditioning phase) and placebo effect (red minus green during the placebo phase), with data points colour-coded by group (blue: FM participants, orange: HC). Median, interquartile range, and frequency distribution, with half-violin plots on the right to illustrate the distribution shape, are shown separately for conditioning strength and placebo effect across groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(F(5.47, 234.51) = 3.35, p = .005, η^2 = .06), but not a treatment*time interaction (F(11, 359.20) = 1.36, p = .221). The main effect of group was not found (F(1,52) = .86, p = .357), and covariates were not significant (lowest p-value = .173 for BMI). The differences in pain intensity ratings between the red cue and the green cue conditioning trials was further operationalized as the conditioning strength with adjusted means for covariates of 55.44 (3.87) for HC and 54.71 (3.95) for FM participants (Fig. 2C). No significant differences between groups were found in the magnitude of the conditioning strength (univariate ANCOVA, F(1,59) = .01, p = .906).

3.3.3. *Differences in placebo effects between groups*

During the placebo phase, the stimuli elicited an adjusted mean pain intensity of 53.87 (4.60) for the red cues and 36.97 (4.03) for the green in HC and 54.51 (4.69) for the red cues and 33.40 (4.12) for the green in FM (Fig. 2B, Table S3).

To further explore differences in pain intensity across time between groups, the mixed factorial ANCOVA with Greenhouse-Geisser correction showed a main effect of treatment (F(1,59) = 5.24, p = .026, η^2 = .08) and an interaction between treatment and time (F(3.94, 232.53) = 2.64, p = .035, η^2 = .04). No significant main effect of time (F(2.81,165.60) = .36, p = .771), or group was observed (F(1,59) = .05, p = .819). Neither age nor BMI showed significance (lowest p = .145 for BMI). Pairwise comparisons showed differences between treatment at all-time points, suggesting no extinction of the effect (treatment*time: all p-values<.001), for both groups (group*treatment*time: largest p-value = .040). Further details on confirmatory analyses regarding pain reports in the HC and FM groups can be found in Supplementary Materials.

In addition, a placebo effect calculation was based on the mean differences between the red and green cues. The mean HC placebo effect of 17.31 (16.59) (range: −13.50 to 58.19) and the mean FM placebo effect of 20.68 (17.09) (range: −15.26 to 56.76) highlighted the wide distribution of placebo effect in both groups (Fig. 2C).

According to a univariate ANCOVA, the adjusted mean placebo effect was 16.90 (3.51) for HC and 21.11 (3.58) for FM and showed no significant difference between groups (F(1,59) =.56, p = .457).

In addition, the placebo effect sizes did not differ between groups (HC: d = .81; FM: d = .99; Z = -.32, Fisher r-to-z transformation, p = .49), and a permutation test showed that 56.76 % of HC (21 of 37) and 56.25 % of FM (18 of 32) responded to placebo; the proportions were not significantly different (p = 1.00).

3.4. *Associations among expectations, conditioning and the placebo effect*

In HC, reinforced expectations were significantly correlated with the conditioning strength (r = .48, p = .008, 95 % CI [.21, .70]) and the placebo effect (r = .45, p = .014, 95 % CI [.13, .66]) (Fig. 3A and B). No such correlations were found for the FM participants (Fig. 3A and B). A moderate correlation was found between conditioning strength and placebo effect in HC, while a strong correlation was observed in FM patients (HC: r = .39, p = .035 95 % CI [.04, .63]; FM: r = .57, p = .001, 95 % CI [.35, .74]) (Fig. 3C).

To further explore differences driving the placebo effect, we conducted two separate stepwise linear regressions. For HC, the final model was significant (F(1,35) = 9.51, p = .004), suggesting that an interaction between the reinforced expectations and conditioning strength positively predicted the placebo effect (B = .003 SE = .001, t = 3.08, p = .004, 95 % CI [.001, .005]) and explaining 19.1 % (adjusted R^2 = .19, R^2 = .21) of its variance, corresponding to a medium to large effect size (f^2 = .26). In contrast, for the FM group, the most important predictor of the placebo effect was the conditioning strength (F(1,30) = 16.05, p < .001, B = .55, SE = .14, t = 4.01, p < .001, 95 % CI [.30, .87]), explaining 33 % (adjusted R^2 = .33, R^2 = .35) of the variance in the placebo effect corresponding to a large effect size (f^2 = .53). The results of similar regression analyses combined for the two groups can be found in the Supplementary analyses.

3.5. *Associations between placebo paradigm and duration of pain in FM and the role of duration of pain as a moderator of the prediction of the placebo effect*

In the FM group, reinforced expectations and duration of pain were negatively correlated (r = −.38, p = .035, 95 % CI [−.72, .04]) (Fig. 3D). Moreover, a moderation analysis revealed that the duration of pain moderated the relationship between conditioning and placebo effect (B = .04, SE = .02, t = 2.74, p = .011), explaining R^2 = 48.9 % of the variance in placebo effect (Fig. 3E). The simple slopes showed that this

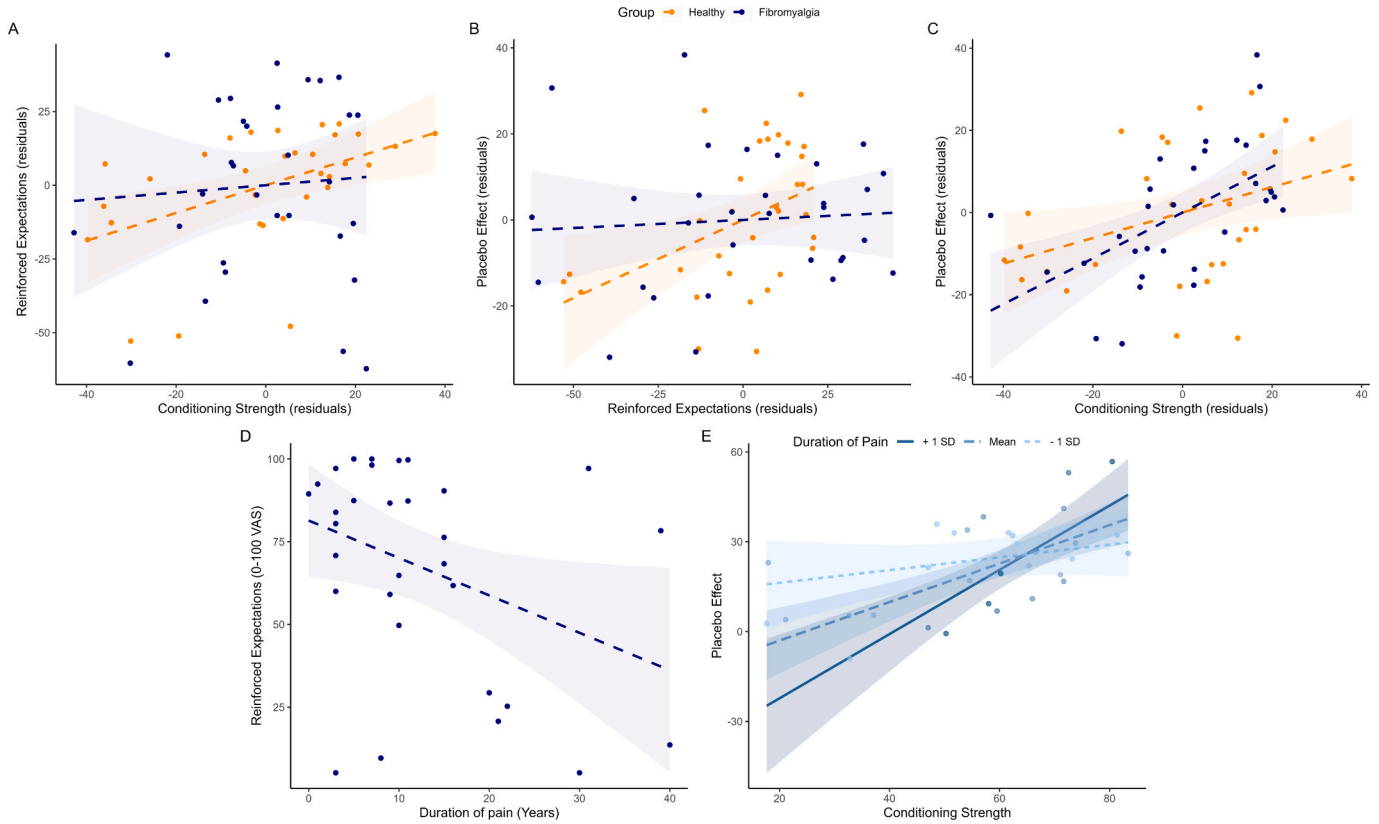

Fig. 3. Differences in associations among main outcomes of the experimental placebo paradigm across groups.
Panels A-C: Reinforced expectations were partially positively correlated with (A) conditioning strength and (B) placebo effect for HC but not for FM. (C) Conditioning strength and the placebo effect were partially positively correlated in both groups, though they were stronger in the FM (orange: HC, blue: FM). Panels D-E: Among the clinical factors examined, duration of pain (D) correlated negatively with reinforced expectations and (E) moderated the relationships between conditioning strength and placebo effect: The longer duration of pain strengthened the positive associations between conditioning strength and placebo effect (at mean and + 1 SD). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interaction, explaining an additional R^2 = 14.2 % of the variance in placebo effect, was significant at average duration of pain (B = .64, SE = .13, t = 4.95, 95 % CI [.38–.91], $p < .001$) and longer duration (B = 1.07, SE = .24, t = 4.56, 95 % CI [.59–1.55], p = .001) but not at shorter duration (p = .214), with a medium to large effect size (f^2 = .22). According to Johnson-Neyman post-hoc analysis, the interaction became significant when duration of pain exceeded 3.93 years, which included 74.19 % of the FM participants.

4. Discussion

The current study aimed for an in-depth investigation of the interactions between conditioning, expectations of pain relief and the placebo effect in HC and FM patients. The main findings are threefold. First, both HC and FM groups showed no differences in expectations of pain relief, conditioning, and placebo effect. Second, there were descriptive differences in the associations between these factors. Finally, duration of pain predicted the FM group's expectations and moderated the prediction of the placebo effect by the conditioning strength.

The first finding, the absence of between-group differences in expectations of pain relief, conditioning, and the placebo effect, corresponds with other studies that utilized experimental placebo paradigms (e.g., Lee et al. [34], Power et al. [31] Wang et al. [33,39]) found no differences between healthy and chronic pain patients. Further, a meta-analysis of 71 studies (55 with healthy volunteers and 16 with patients) found no differences in the magnitude of placebo effects of healthy individuals and chronic pain patients [37]. In contrast, Colloca et al. 2020 [15], using the same placebo paradigm with a very large cohort of TMD and healthy participants, did find differences in conditioning strength and expectations between TMD patients and healthy controls. It might be that with larger sample sizes, significant differences between the FM and HC group could have been detected.

The second finding highlights the descriptive differences between HC and FM groups in the associations between conditioning, expectations, and placebo effects. While, as expected, conditioning strength predicted the reinforced expectations, which in turn predicted the placebo effect in HC, no such associations existed in FM patients. A possible explanation relates to the third main finding of the current study: In FM patients, prior clinical experience predicted the reinforced expectations and moderated the prediction of the placebo effect by the conditioning strength. Years with pain could represent one facet of prior clinical experience: The longer the patients suffer from pain, the more they experience negative (or disappointing) treatment results, they generate lower conscious expectations for benefit which disposition them to demonstrate lower placebo effect.

Experimentally induced prior negative experience has been shown to prevent the formation of expectations for pain relief after conditioning [12]. Our results echo those findings, but in our case, it was the actual clinical prior experience (as assessed by the duration of pain) that dominated the expectations for pain relief and modulated the prediction of the placebo effect by the conditioning strength. This might be particularly relevant for FM patients, who have been shown to have difficulty in updating learned pain associations [40]. Hence, the lack of association between the conditioning strength and the reinforced expectations, and between the reinforced expectations and the placebo effect in FM patients could be attributed to the dominance of their prior clinical experiences over the effect of learning during the conditioning phase. This is in line with Peerdeman et al. [41], who propose that

verbal suggestion might be more efficient in healthy than in chronic pain patients, probably because of the prior negative clinical experience. Given that the placebo effect is an integral part of the response to any treatment, the time patients suffer from pain could lower their response to effective treatments as well.

Assessing prior clinical experiences can be challenging. Approaches include standardized interviews [42], open discussion/free recall [43], and expectation questionnaires assessing the number of past treatments and perceived benefits [20,39,43–48]. Specifically, in studies with FM patients, prior clinical experience was assessed through measures such as symptoms/illness duration [25,49] or medication history [49].

Our results are in line with Kosek et al. [25], who found a negative correlation between time of symptoms onset and placebo response, suggesting that the time of symptoms onset might be useful in capturing prior clinical experience. The importance of the length of time with pain as a facet of prior clinical experience is also highlighted by the extensive literature demonstrating consistent negative correlations between duration of pain and the clinical placebo response in Randomized Clinical Trials (RCTs) across various conditions, including FM [24,25], neuropathic pain [28,30], diabetes mellitus [26], chronic arthritic diseases [27], psychiatric disorders [29], depression [22], and attention deficit hyperactivity disorder [23].

Data on longitudinal preclinical and clinical studies suggests that chronic pain involves neuroplastic mesolimbic changes driven by negative clinical experience and associative learning [50–52]. According to this view, chronic pain is maintained by subconscious learning [53,54]. The more years with pain, the stronger these learning processes and the higher the risk that pain "gets stuck" [55]. Our results conform with this view, suggesting that in FM patients, implicit learning may have a stronger impact on placebo than conscious expectations have due to verbal suggestion. The results are also consistent with findings that in chronic pain patients, classical conditioning can, under certain circumstances, operate through unconscious learning to induce placebo effects without being mediated by conscious expectations [6,36,56]. The contribution of the prior clinical experience to the FM placebo effect could also explain the lack of differences in placebo between the two groups. In FM, perhaps, verbal suggestion is less effective [41], but conditioning is more effective, with the net effect of no differences between FM and HC in the magnitude of placebo effect.

Our findings do not fully coincide with Colloca et al. [15], who found that conditioning strength predicted reinforced expectations and directly mediated placebo effects in both patients and healthy controls. One possible explanation for these mixed results is the difference between the two studies' chronic pain populations. Colloca et al.'s large cohort of chronic TMD pain patients differs from FM patients, although both conditions are classified as nociplastic pain. The underlying learning mechanisms might differ for FM and TMD. Wang et al. [39] proposed that TMD patients exhibit placebo effects through conscious expectations formed during conditioning. In contrast, our study results suggest that the placebo effect in FM might be generated more through unconscious learning mechanisms (i.e., conditioning).

A few limitations deserve consideration. First, only female FM patients were included, because female FM patients far outnumber males. Second, the absence of a control group with only verbal suggestion (i.e. no conditioning) restricts the application of our findings to placebo effects induced by both conditioning and verbal suggestion. Third, in the placebo paradigm, conditioning strength was simulating prior clinical experiences [15]. This surely differs from actual prior clinical experience. In addition, our groups differed in age and BMI, hence those variables were controlled in all analyses. Our results should be interpreted with caution, given that both age and BMI could affect the results of quantitative sensory testing [57–60]. Worth mentioning is that age in the FM group did not significantly correlate with the duration of pain. Nonetheless, it would be of benefit to confirm our findings in future studies with a matched control group. Lastly, the lack of differences in the conditioning, expectations and the placebo effect could be attributed to the relatively low statistical power. Similarly, the low statistical power might also contribute to the lack of statistical differences in the moderation analyses. Larger studies are needed to confirm our results.

5. Conclusion

In summary, comparable placebo effects were observed in HC and FM, but with distinct underlying mechanisms. While in HC the classical placebo theorem is supported by the findings - conditioning predicts expectations, which predicts the placebo effect, in FM those associations are not seen, and are modulated by prior clinical experience. Those findings highlight the significant and potentially negative role of prior negative clinical experience in the placebo effect and, potentially, in response to effective treatments.

CRediT authorship contribution statement

Galia Emergui: Writing – original draft, Investigation, Formal analysis, Data curation. **Mariana Agostinho:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Rita Canaipa:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Roi Treister:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Statement of ethics

The current study received approval from the University of Haifa Ethics Committee University of Haifa scientific committee (approval number 186/22) and was conducted according to the ethical principles in the Declaration of Helsinki for medical research involving human participants. All participants signed informed consent before participating in the study. At the end of their participation, they were debriefed about the study's real purpose and given the opportunity to withdraw their data.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: (Roi Treister reports financial support was provided by Israel Science Foundation. Mariana Agostinho reports financial support was provided by Foundation for Science and Technology. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2025.112207.

Data availability statement

Data is available upon reasonable request from R.T.
This research was not preregistered in an independent registry.

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