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# The prediction of the analgesic placebo effect is moderated by direction of attention: Results from fibromyalgia and healthy controls

Mariana Agostinho [a,b,c], Galia Emergui [a,d], Rita Canaipa [b,c,#], Roi Treister [a,*,#]

[a] The Cheryl Spencer Department of Nursing, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel
[b] Universidade Católica Portuguesa, CIIS, Center for Interdisciplinary Research in Health, Portugal
[c] Universidade Católica Portuguesa, Faculty of Health Sciences and Nursing, Lisbon, Portugal
[d] Sagol Department of Neurobiology, University of Haifa, Israel

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ABSTRACT

Despite extensive research, reliable predictors of the placebo response remain elusive. The within-subject variability (WSV) of pain reports has emerged as a potential predictor, with multiple studies confirming its predictive value. But the results have been mixed. We recently showed that direction of attention moderates WSV's role in predicting the placebo response in patients with chronic back pain. This observational study aims to further examine the relationship between direction of attention, WSV, and the placebo effect in fibromyalgia patients (FM) and healthy controls. Participants completed a demographic questionnaire, clinical pain diaries (for FM), and the revised Self-Consciousness Scale (SCS-R). Afterward, participants underwent two experimental procedures: (1) the Focused Analgesia Selection Test (FAST), assessing experimental WSV of pain reports, and (2) an experimental placebo paradigm. Moderation and regression analyses examined the role of the SCS-R subscales in moderating the prediction of the placebo effect by the WSV of pain reports. Sixty-nine participants (healthy: 37, FM: 32) completed the protocol. Groups did not differ in SCS-R subscales, WSV, or placebo effect magnitude ($p \geq 0.281$). At low levels of private self-consciousness ($p=0.013$) and social anxiety ($p=0.017$) among FM, clinical WSV played a significant role in predicting the placebo effect. Public self-consciousness for FM showed a similar trend toward significance. These findings underscore attention as a relevant moderator of the placebo effect, emphasizing the need for improved measurement tools to predict the placebo effect.
*Perspective:* We highlight the role of direction of attention in the prediction of the placebo effect. Our current findings validate our previous recent results from a cohort of chronic back pain patients, implying that direction of attention should be used in future attempts to improve the prediction of the placebo effect.

## Introduction

The prediction of the placebo response is the focus of a very long investigation. As early research by Beecher and others[1–3] and more recent studies[4–8] have shown, the ability to predict the analgesic placebo response has long been considered a holy grail in clinical research.

The analgesic placebo response is defined as the measurable change in pain following the administration of an inert substance or treatment.[9] According to the classical theorem, the two key underlying mechanisms driving the placebo effect are conditioning[10–12] and the recipient's expectations of analgesia.[13–15]

Within-subject variability (WSV) of clinical daily pain reports has emerged as a significant predictor of the analgesic placebo response across various clinical pain conditions such as fibromyalgia (FM),[16] neuropathic pain,[17,18] and irritable bowel syndrome.[19] However, other studies examining peripheral neuropathic pain[20] and low back pain[21] found minimal to no association between clinical WSV of pain reports and the placebo response. The WSV in response to experimental pain as assessed via the Focused Analgesia Selection Test (FAST) was also found to predict the placebo response in diabetic neuropathy[22] and knee osteoarthritis[23] and showed a trend toward significant prediction in chronic back pain.[24]

The Bayesian theorem (i.e., predictive coding) has appeared as a promising model for understanding the relationship between the WSV of

* Correspondence to: Faculty of Social Welfare and Health Sciences, University of Haifa, Abba Khoushy Ave 199, Haifa, Israel.
*E-mail address:* rtreister@univ.haifa.ac.il (R. Treister).
# equal contribution

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pain reports and the placebo response. According to this model, pain perception (posterior) is generated by integrating noxious sensory signals (the likelihood function, in Bayesian terminology) with knowledge based on prior experience (priors). The final subjective percept (posterior function) will be closer to the factor that is characterized with larger confidence (i.e., certainty/precision). As hypothesized by Kuperman et al.,[25] WSV derived from either clinical or experimental pain might be regarded as a proxy measure for the certainty of the likelihood function. In light of this hypothesis, lower WSV represents greater confidence in the likelihood function, resulting in a lower effect of priors and hence a lower placebo effect. Computational experiments led by Anchisi and Zanon[26] and by Hoskin and colleagues[27] demonstrated that the Bayesian model indeed explains changes in pain perception better than other models do.

Recently, we found that the prediction of the placebo response by the WSV is moderated by two subscales of the revised Self-Consciousness Scale (SCS-R)[28]: public self-consciousness and social anxiety. Specifically, the prediction was significant only at low or moderate values of these two types of direction of attention. Pagnini et al.[29] proposed a framework explaining how different types of attention may differently influence how sensory input is processed and modified, and may thus affect the placebo effect. As such, mindful attention toward nociceptive signals will increase the certainty of the likelihood and will result in a lower placebo effect, assuming the priors remain constant.

This study aimed to assess whether our previous results with chronic back pain could be replicated in healthy volunteers and patients with FM undergoing an experimental placebo paradigm. In light of findings by Shani et al.,[24] we hypothesized that WSV's prediction of the placebo effect will be significant when participants had low levels of both public self-consciousness and social anxiety.

## Methods

The current report is the second publication from a study in which conditioning, expectations, and the placebo effects were assessed in FM and healthy controls. In the first report, conditioning, expectations, the placebo effects and the associations between those factors were compared between the groups.[30] In contrast, the current report focuses on the potential relationships between WSV and all of the above in both groups.

### *Participants*

Healthy female volunteers were recruited through the Haifa University's Participation Pool (Sona Systems, https://www.sona-systems.com/) and via posts on university boards, social media, and flyers. Inclusion criteria included: (1) age ≥18; (2) basic proficiency in Hebrew, Arabic, or English. Exclusion criteria included: (1) any persistent or chronic pain condition; (2) psychiatric, cognitive, or neurological disorders; (3) history of substance abuse/dependence; (4) regular medication intake (except oral contraceptives); (5) pregnancy or breastfeeding. Participants were also requested to refrain from taking analgesic medication within 48 h before the laboratory visit.

Female FM patients were recruited via advertisements on notice boards at the University of Haifa campus and posts on relevant social media forums. Additionally, FM-related associations shared the study advertisement through dedicated informative channels with their members. The study focused on females due to the larger prevalence of FM in women and the predominance of research conducted in female FM populations ensuring comparability with existing literature. Inclusion criteria included: (1) age ranging from 18 to 70; (2) basic proficiency in Hebrew, Arabic, or English; (3) formal diagnosis of FM in physician-generated medical records (American College of Rheumatology criteria);[31,32] (4) daily pain intensity ≥4/10 in the previous week. Exclusion criteria included: (1) clinically unstable cardiovascular, cerebrovascular, renal, respiratory, hepatic, or other progressive physical disease (e.g., diabetes or multiple sclerosis); (2) pregnancy or breastfeeding; (3) history of substance abuse/dependence except for prescribed cannabis. Participants were instructed to continue routine analgesic treatment as prescribed and to refrain from over-the-counter analgesics (as SOS analgesics) before the laboratory visit.

Power analyses using the G*Power Software (Faul 2009; version 3.1.9.6)[33] were conducted to ensure sufficient statistical power for detecting correlations between the WSV of pain reports and experimental placebo paradigm outcomes. Based on effect size of 0.4, alpha of 0.05 and power of 0.8 the needed number of participants was 34 in each group, 68 in total. To verify that this N would be sufficiently powered to also detect the moderating role of the SCS-R subscales and to assess the increment of explained variance due to the interaction between independent and moderator predictors, we ran an additional power analysis. This analysis was based on a multiple regression and an $R^2$ increase for a statistical power of 0.8 and a medium effect size of 0.35 (based on calculation from Shani et al.),[24] with an alpha set at 0.05. This power analysis revealed that N=31 in each group would provide sufficient power.

### *Tools and procedures*

#### *Assessment of demographic and medical information*

Sociodemographic and general medical information was collected from both groups. FM participants were also asked to report clinical characteristics such as the time elapsed since pain diagnosis, comorbidities, therapies previously utilized and to complete the Fibromyalgia Impact Questionnaire Revised (FIQR) to characterize illness burden and quality of life.[34] One week before the laboratory visit, FM participants were also prompted to report their average daily pain intensity once a day on a computerized visual analog scale, from 0 ("no pain") to 100 ("worst pain imaginable") (Qualtrics XM, Provo, UT, USA). Mean pain and within-subject standard deviation (i.e., clinical WSV) were calculated.

#### *Assessment of WSV of pain reports in response to experimental pain*

The FAST is an experimental paradigm that assesses the WSV of pain intensity reports in response to a random sequence of noxious heat stimuli applied through a TSA2 thermode (30 $mm^2$ × 30 $mm^2$, Medoc TSA II −2001 device, Ramat Yishai, Israel).

Participants were first familiarized with the task requirements, and the investigator then verified that the participants understood the task. The participants were instructed to focus on their sensations and to rate their pain after each stimulus.

The thermode was placed onto the ventral surface of each participant's dominant forearm. Throughout the testing phase, each of the 7 stimulus intensities was presented 7 times in a blinded random order, for a total of 49 stimuli per participant. For the healthy group, the FAST stimulus intensities ranged from 44°C to 50°C, as done previously.[35-38] Because of heightened sensitivity inherent in the FM condition[39] and based on the increased sensitivity observed in the FAST procedure in a previous study with FM population,[40] the intensities in the FAST paradigm for the FM participants were slightly adjusted to range from 43°C to 49°C (a reduction of one degree Celsius, for each stimulus). All other aspects of the FAST protocol were kept identical. The experimental protocol began with a baseline temperature of 32°C, ramping up to one of the defined temperatures for 3 s, followed by a return to baseline, for a total of 8 s (including the ramp-up, the defined temperature stimulus, and the cooldown, with slightly different ramp-up and cooldown rates to create a total fixed stimulus duration of 8 s). To mitigate excessive peripheral sensitivity or habituation, the thermode location was slightly adjusted (about 2–3 centimeters) every 10 stimuli. After each stimulus, the participant verbally reported their pain intensity on a 0–100 numerical rating scale ranging from 0 ("no pain") to 100 ("worst pain imaginable").

Three main FAST outcomes were calculated and represent different

aspects of the experimental WSV: (1) The Pearson coefficient of determination ($R^2$) was based on a power regression function of concordance between pain intensity ratings and stimulation temperature, indicating the proportion of variability. A higher $R^2$ reflects lower WSV. (2) Intraclass correlation (ICC) was computed from a 2-way mixed model for the 7 presentations of each of the 7 intensity levels. A higher ICC signifies lower WSV. (3) The coefficient of variation (CoV) was calculated as the ratio of the standard deviation to the mean for the reports in response to each stimulus intensity and then averaged across intensities. A higher CoV indicates greater variability in pain reporting. Importantly, we hypothesized that the WSV as assessed during the FAST procedure is a proxy measure of the certainty of the likelihood function.[25] However, this would be true only as long as the prior function is constant. While the FAST procedure is done in controlled environment, we have no reason to assume that there are changes in the priors during the procedure, but this could not be verified, hence the WSV should only be regarded as a proxy measure which might not purely reflect the certainty of the likelihood.

*Placebo paradigm*

The placebo paradigm used was established by Colloca et al.[41] At first, healthy participants underwent individual calibration according to a series of delivered noxious stimuli of various intensities ranging from 43°C to 50°C administered by the TSA2 thermode (described in the previous section) attached to the non-dominant forearm. Each stimulus ramped up to the target temperature, remaining at that temperature for 3 s, and then returned to baseline (32°C), with a total duration of 8 s per stimulus. After each stimulus, the participants verbally reported their pain intensity on a 0–100 numerical rating scale ranging from 0 ("no pain") to 100 ("worst pain imaginable"). The goal was to individually calibrate stimulus intensities that would induce high (80/100), medium (50/100), and low (20/100) pain reports and choose these stimuli for the steps described below. If participants' ratings did not match the values above, the closest available rating (e.g., 30/100 for 43°C) was chosen and the stimulus temperature was adjusted up or down by 0.5°C (e.g., 42.5°C). To individualize the stimuli intensities for FM participants, in an attempt to minimize participants discomfort, we used the pain reports from the last block of stimuli during the FAST (which always preceded the placebo paradigm, see Study design section), based on the same algorithm as described above.

After calibration, a transcranial direct current stimulation (tDCS) device (Soterix Medical, Woodbridge, New Jersey, USA) connected to 2 sham electrodes, was attached next to the thermode and was introduced deceptively as an analgesic device that could reduce pain intensity once active. The aim was to induce anticipation or experience of treatment benefit, but the electrodes were in fact never active. Participants were falsely informed that when a green cue would show up on the screen, the "analgesic device" was activated, as opposed to the red cue, which signaled that the device was not activated.

The paradigm began with a conditioning phase, consisting of 24 cues displayed on a screen (red and green squares and a central fixation cross) prompting participants for a heat stimulus. Unbeknownst to the participants, 12 visual cues in red were paired with stimuli previously calibrated to elicit high pain (80/100), and the 12 green visual cues paired with stimuli calibrated to induce low pain (20/100). These cues were split into two blocks of 12 trials each, with a 3-minute rest between blocks. In the placebo phase, participants were presented with 12 visual cues (6 red and 6 green), each paired with the medium stimulus intensity individually calibrated to induce medium pain (50/100). Participants were blinded to stimulus intensities. In response to each stimulus, participants were instructed to report their pain intensity using a computerized visual analog scale ranging from 0 ("no pain") to 100 ("worst pain imaginable"). Participants' expectations were also measured at 3 time points: baseline (baseline expectations, E1), after conditioning (reinforced expectations, E2), and after the placebo phases (after-treatment expectations, E3) on a computerized visual analog scale, ranging from 0 to 100 in response to the question "On a scale of 0–100, how much do you believe that the electrodes will decrease [for E1] or decreased [for E2 and E3] your pain?". Participants provided their responses by sliding a cursor along the scales using a computer mouse.

The main outcomes include: (1) expectations at E1–E3, (2) conditioning strength, and (3) the placebo effect. Conditioning strength and the placebo effect were calculated as the difference between the average pain intensities reported for stimuli paired with a red cue and those paired with a green cue in the conditioning and the placebo phases, respectively.

*Revised self-consciousness scale*

The SCS-R measures three dimensions of self-consciousness: private self-consciousness, public self-consciousness, and social anxiety. Private self-consciousness reflects the tendency to focus inwardly on one's thoughts and feelings, while public self-consciousness pertains to the tendency to focus outwardly, reflecting an individual's self-perception as a social object, complemented by the social anxiety subscale that captures the level of discomfort a person experiences in social situations. This 22-item questionnaire is divided into subscales, with each item rated on a Likert scale ranging from 0 ("not like me at all") to 3 ("very much like me"). The score for each dimension is calculated individually by summing the responses to the relevant items belonging to each subscale: 9 items for private self-consciousness (items 1, 4, 6, 8, 12, 14, 17, 19, and 21); 7 items for public self-consciousness (items 2, 5, 10, 13, 16, 18, and 20); and 6 items for social anxiety (items 3, 7, 9, 11, 15, and 22). Test-retest reliability demonstrated reasonable stability over time.[28]

*Study design*

The study received approval by the University of Haifa Ethics Committee (approval number 186/22) with participants recruitment and enrollment occurring between February 2023 and July 2024. The research involved deception since participants were falsely told that the aim was to investigate a new analgesic device. Eligible participants signed informed consent, completed study questionnaires online, including (for FM participants) daily pain reports the week before the laboratory visit. All participants were invited to the laboratory to perform the FAST followed by the experimental placebo paradigm (with a 10-minute break between the two tasks). At the end, participants were debriefed about the deception and the real aims of the study, compensated for their participation (200 NIS), and offered the opportunity to retract their data if they wished. None of the participants asked to retract their data.

*Statistical analysis*

Statistical analyses were performed with IBM SPSS Statistics software (version 27) and R studio for visualization purposes (R studio version 1.1.463; R version 3.5.3). Descriptive statistics are presented as mean (SD) for all variables of interest. Variable normality was assessed with Shapiro-Wilk tests followed by kurtosis and skewness inspection. To explore group differences in sociodemographic variables and the SCS-R, both Student's t-tests and Mann-Whitney were utilized. Sociodemographic characteristics significantly different between groups were included as covariates in subsequent analyses.

To explore whether participants in both groups could distinguish different stimulus intensities in the FAST paradigm, we employed the Friedman test followed by the Wilcoxon signed-rank test. Afterward, to detect between-group differences in the main outcomes of the FAST, we conducted 3 univariate analyses of covariance (ANCOVAs). Each FAST main outcome was inserted into a separate model as a dependent variable with group as between-subjects factor, and covariates identified. Additionally, a correlational analysis was conducted to test associations between experimental and clinical WSV outcomes. Between-group

differences in expectations, conditioning, and placebo effect were explored with repeated-measures ANCOVAs followed by post-hoc comparisons with Bonferroni correction for multiple comparisons. To examine between-group differences across SCS-R subscales, we conducted three separate univariate ANCOVAs each including a SCS-R subscale as dependent variable, group as the between-subjects factor and relevant covariates.

Moderation analysis (Model 1, PROCESS version 4.2 for SPSS) followed by Johnson-Neyman post hoc tests were employed to explore the role of the SCS-R subscales as moderators. Each WSV outcome (clinical WSV, FAST $R^2$, FAST ICC, and FAST CoV) was tested as a predictor of the placebo effect, with the SCS-R subscales acting as moderators. This analysis was performed separately for each group. Between-group differences were further tested using a 3-way interaction and reported in the Supplementary materials.

Additionally, separate linear regression analyses were conducted to explore WSV outcomes as predictors of expectations and the placebo effect for each group. In each model, clinical WSV, FAST $R^2$, FAST ICC, and FAST CoV were set as independent variables/predictors, and expectations (E1-E3) and the placebo effect as the dependent variables. As an exploratory analysis, we also conducted a moderation analysis to explore between-group differences in the relationship between the different WSV outcomes and expectation ratings (E1, E2, E3), while controlling for covariates. Each WSV outcome was introduced as a predictor of the expectations (dependent variables) with group as a moderator.

All analyses were conducted with a significance level set at $p<0.05$.

## Results

Details about participants' flow throughout the study are depicted in the Consolidated Standards of Reporting Trials diagram (Figure 1). Thirty-seven healthy females (Figure 1a) and 32 female FM participants (Figure 1b) completed the study protocol.

### *Participants' demographic characteristics*

Table 1 presents age, BMI, education, and working status for both groups. The FM group was significantly older ($Z=-5.918$, $p<0.001$) and had a larger BMI ($t(61)=-2.072$, $p=0.042$) than the healthy participants. Given these differences, age and BMI were used as covariates in further analyses.

**Table 1**
Demographic and clinical characteristics.

| Characteristics | Healthy | | FM | | p |
|---|---|---|---|---|---|
| | Mean (SD) | Median | Mean (SD) | Median | |
| **Age** | 24.00 (6.75) | 22.00 | 42.28 (14.29) | 41.50 | <0.001 |
| **BMI** | 23.66 (5.09) | 21.85 | 26.44 (5.57) | 26.57 | 0.042 |
| **Education** | 13.43 (1.57) | 13.00 | 14.50 (2.75) | 14.50 | 0.058 |
| **Working status** | **N (%)** | | **N (%)** | | **p** |
| Yes | 19 (51.4%) | | 20 (62.5%) | | 0.352 |
| No | 18 (48.6%) | | 12 (37.5%) | | |
| **FM clinical characteristics** | **Mean (SD)** | | **Median** | **Min – Max** | |
| **Mean pain** | 71.78 (15.62) | | 66.00 | 48 – 100 | |
| **Clinical WSV** | 9.88 (4.65) | | 10.26 | 1.51 – 18.46 | |
| **Years since diagnosis** | 5.84 (5.01) | | 4.50 | 1 – 20 | |
| **FIQR** | | | | | |
| Function | 17.82 (6.86) | | 18.00 | 2.33 – 29.00 | |
| Impact | 13.72 (5.19) | | 14.50 | 2.00 – 20.00 | |
| Symptoms | 31.69 (8.39) | | 32.50 | 10.50 – 47.50 | |
| Total | 63.23 (18.15) | | 68.92 | 21.17 – 93.00 | |

BMI, body mass index; FIQR, Fibromyalgia Impact Questionnaire Revised; FM, fibromyalgia; WSV, within-subject variability.

### *Clinical characteristics of Fibromyalgia patients*

Fibromyalgia participants reported a mean pain of 71.78 (15.62) with within-subject standard deviation (clinical WSV) of 9.88 (4.65) for the week before the laboratory visit (Table 1). Additional clinical characteristics are summarized in the Supplementary materials (Table S1).

### *WSV of pain reports in response to experimental pain using the FAST*

Healthy volunteers' median pain intensity ranged from 15.71 (20.21) for the lowest stimulus intensity (44 °C) to 85.71 (25.78) for the highest (50 °C). In the FM group, median pain intensities ranged from 13.86 (22.00) for the lowest stimulus intensity (43 °C) to 90.21 (12.18) for the highest (49 °C) (Figure 2a and Table S2). To evaluate differences in median pain intensity reports across stimulus intensities, Friedman tests followed by post hoc Wilcoxon signed-rank tests were conducted independently for both groups. Significant differences across stimulus

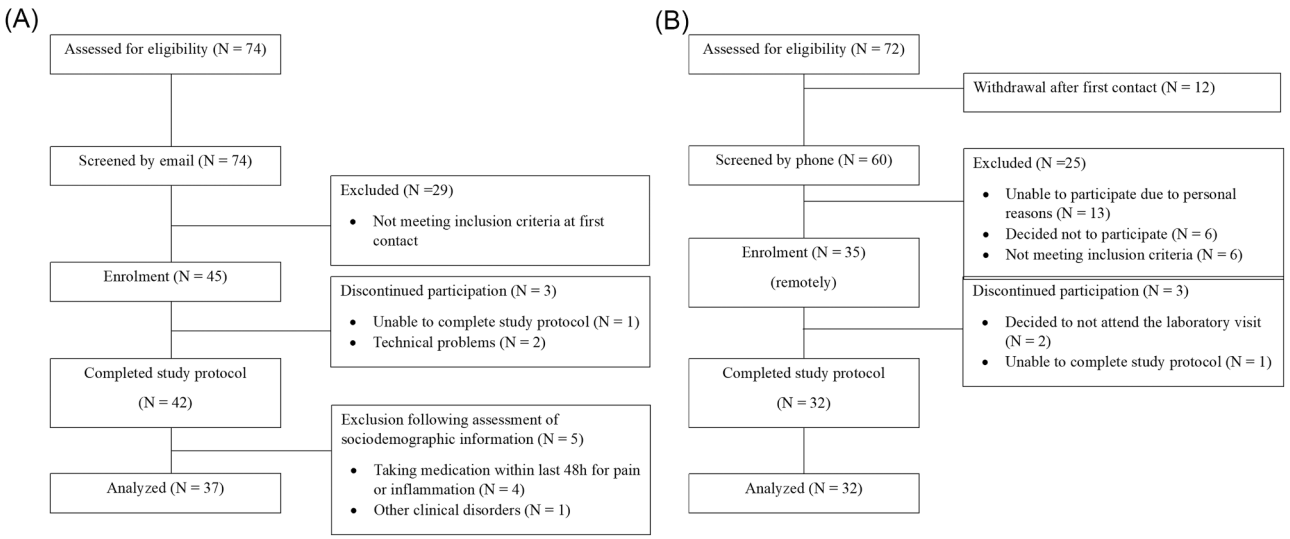


**Fig. 1.** Participant's flow diagram, including screening procedure (A: Healthy; B: FM patients).

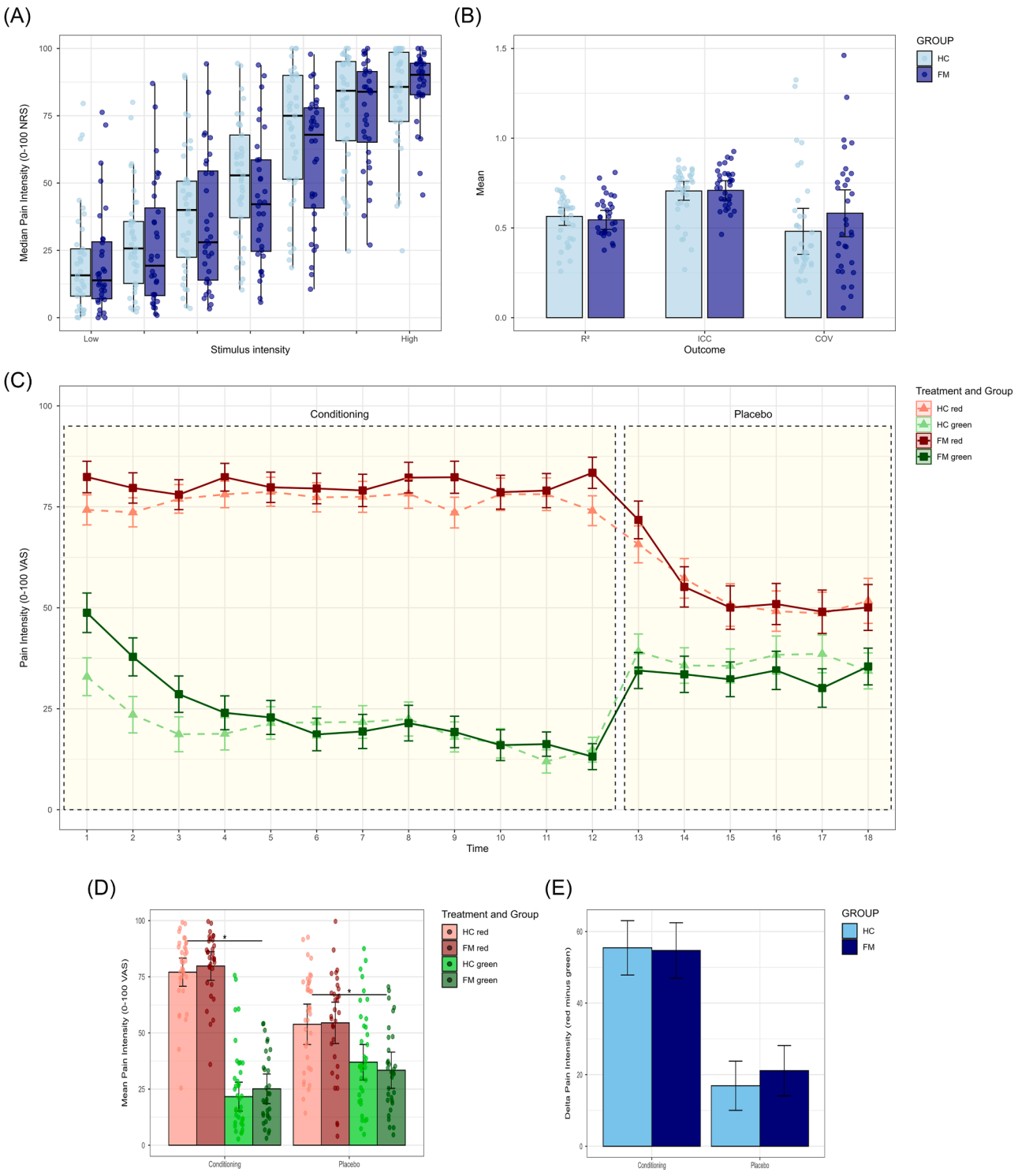


**Fig. 2.** Descriptive statistics and adjusted means of the Focused Analgesia Selection Test (FAST) outcomes and the experimental placebo effect. (a) Median pain intensity reports in response to different stimulus intensities in the FAST paradigm. Each box plot represents the interquartile range, from the lower to the upper quartile. The central line within the box denotes the median. *Light blue:* healthy controls (HC); *dark blue:* fibromyalgia (FM) patients. (b) The adjusted mean of the main outcomes of the FAST, with no significant differences between cohorts in any of the outcomes. (c) Trial-by-trial adjusted (covariates: age and BMI) mean pain ratings for red and green cues during conditioning (trials 1–12) and placebo phase (13–18) in each cohort. *Triangles:* ratings for red and green cues in HC; *squares:* ratings for red and green cues in FM. (d) Mean pain intensity in response to the stimuli paired with red and green cues in HC and FM. *Light green and light red:* HC; *darker green and darker red:* FM. (e) The difference between the reports in response to the stimuli paired with the red and green cues in the conditioning and the placebo phases in HC and FM. *Light blue:* HC; *darker blue:* FM.

intensities were found in both healthy (Friedman tests: $X^2(6)=203.208$, $p<0.001$) and FM (Friedman tests: $X^2(6)=175.937$, $p<0.001$) groups. Post hoc tests confirmed that the reported pain intensities were significantly different between all stimulus intensities (all p-values <0.001).

Descriptive statistics of the main outcomes of the FAST for both groups are presented in Figure 2b. The three univariate ANCOVAs conducted to compare differences between groups on each outcome of the FAST while controlling for age and BMI showed no group differences on any of the FAST outcomes ($R^2$: $F(1,57)=0.201$, $p=0.655$; ICC: $F(1,59)=0.004$, $p=0.953$; CoV: $F(1,59)=0.962$, $p=0.331$). Age and BMI did not significantly influence the outcomes in any of these models (all p-values $\geq 0.57$).

In the FM group, the clinical WSV was found to positively correlate with the CoV ($r=0.404$, $p=0.022$, 95% CI [0.064, 0.660]).

*Experimental placebo paradigm group comparisons*

Detailed descriptions of the placebo paradigm results, both within and between groups, are summarized in Figures 2c-e and the Supplementary analyses (Table S3). There were no significant differences in the magnitude of expectations ($F(1,58)=0.158$, $p=0.692$), conditioning ($F(1,52)=0.863$, $p=0.357$), and the placebo effect ($F(1,59)=0.053$, $p=0.819$) between healthy and FM participants.

*SCS-R subscales do not differ between FM and healthy controls*

The adjusted means for the SCS-R subscales are presented in Table 2. Univariate ANCOVAs revealed no significant differences between groups in any of the SCS-R subscales (private: $F(1,59)=0.796$, $p=0.376$; public: $F(1,59)=1.185$, $p=0.281$; social anxiety: $F(1,59)=0.428$, $p=0.515$).

*SCS-R subscales moderate the relationship between the clinical WSV of pain intensity reports and the prediction of the placebo effect*

We used each subscale of the SCS-R as a moderator of the relationship between experimental and clinical WSV outcomes (SD, $R^2$, ICC, and CoV) and the placebo effect.

For the FM participants, the clinical WSV significantly interacted with the private subscale in predicting the placebo effect ($B=-0.310$, $SE=0.117$, $t=-2.646$, $p=0.0132$), with private self-consciousness explaining 24.5% ($R^2$) of the variance in the placebo effect and a change in the $R^2$ of 18.9%. The analysis of the simple slopes of the clinical WSV on the placebo effect was significant at low levels of private self-consciousness ($B=2.069$, $SE=0.896$, $t=2.310$, $p=0.028$) but not at average ($p=0.411$) or high levels ($p=0.240$). The Johnson-Neyman post hoc analysis revealed that the clinical WSV prediction of the placebo effect was significant when private self-consciousness was below 15.59, indicating a significant interaction for 18.75% of the FM participants (Figure 3a).

Similarly, the interaction between the clinical WSV and the social anxiety subscale was also significant ($B=-0.389$, $SE=0.154$, $t=-2.537$, $p=0.017$), indicating that the prediction of the placebo effect by the clinical WSV was moderated by social anxiety. The model explained 24.5% ($R^2$) of the variance in the placebo effect, and the change in $R^2$ was 17.3%. The simple slope of the clinical WSV on placebo effect was significant at low levels of social anxiety ($B=2.052$, $SE=0.829$, $t=2.476$, $p=0.020$) but not at average ($p=0.496$) or high levels ($p=0.198$). Johnson-Neyman post hoc revealed that the slope of the clinical WSV on placebo effect was significant for values below 6.56 of the social anxiety ratings, indicating a significant interaction in 25% of the FM participants (Figure 3b).

The moderation model using the clinical WSV interacting with the public self-consciousness subscale revealed a trend toward significance

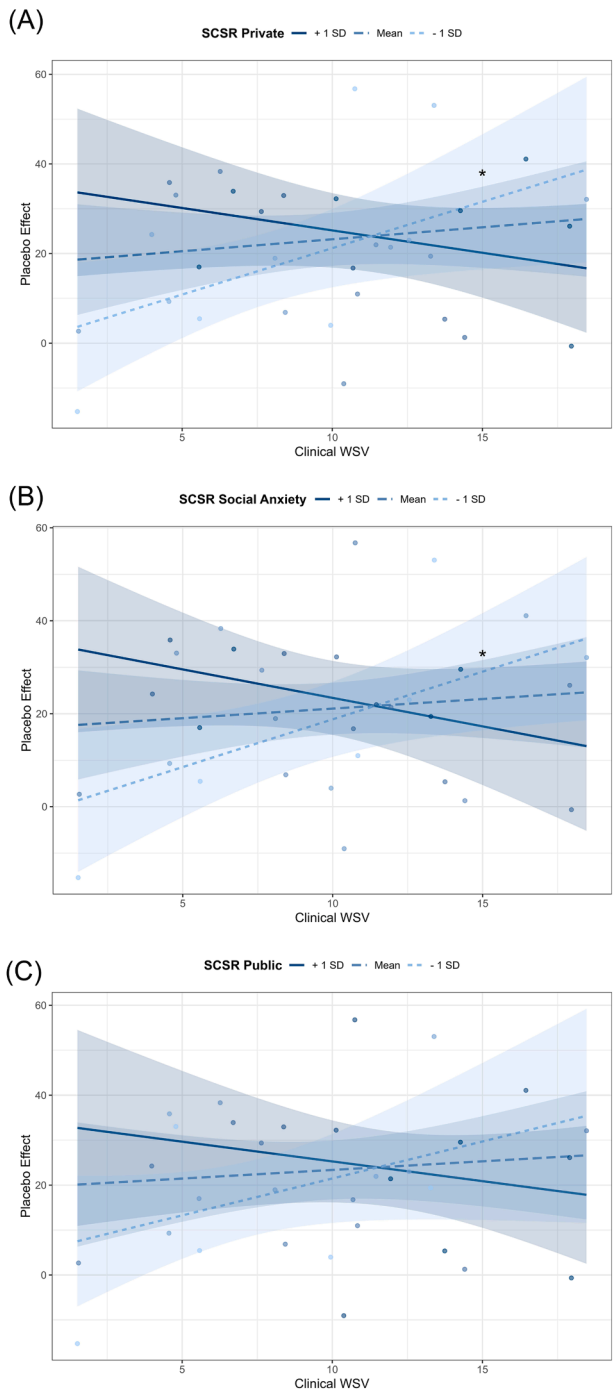


**Fig. 3.** Among FM participants the placebo response prediction by the clinical WSV is moderated by the SCS-R subscales. (a) Low levels of private self-consciousness moderate the prediction of the placebo by the clinical WSV. (b) Social anxiety at low levels also moderates the prediction of the placebo effect by the clinical WSV. (c) Public self-consciousness shows a trend toward significance in moderating this relationship. The low (dashed light blue) and high levels (full dark blue) of the moderators are based on ±1 standard deviation from the mean, (significance: *p-value<0.05).

**Table 2**
SCS-R adjusted means.

| | Healthy | | FM | | p |
|---|---|---|---|---|---|
| **SCS-R subscale** | **Adj. mean** | **SE** | **Adj. mean** | **SE** | |
| **Private** | 18.42 | 0.83 | 19.60 | 0.84 | 0.376 |
| **Public** | 13.53 | 0.73 | 14.81 | 0.74 | 0.281 |
| **Social anxiety** | 8.76 | 0.83 | 9.63 | 0.84 | 0.515 |

(p=0.062) for low levels of the moderator as well (p=0.105) (Figure 3c).

Among healthy controls, no moderation by the SCS-R subscales was found (all p-values ≥0.205 for the interactions).

Interestingly, the moderation analyses revealed that only the clinical WSV demonstrated predictive utility, while the experimental WSV did not (with any of the SCS-R subscales).

*WSV of pain reports alone did not predict the placebo effect in FM or healthy participants, but predicted reinforced expectations in FM*

Separate linear regressions showed that in the FM group, none of the 4 models, in which the WSV of pain report outcomes (clinical WSV, $R^2$, ICC, and CoV) were tested independently as predictors, predicted the placebo effect (all p-values ≥0.335). The same results were observed for the healthy group (all p-values ≥0.140). Additional results combining both groups in unified analyses could be found in the Supplementary materials.

As an exploratory analysis, we assessed if the WSV outcomes were associated with participants' expectations reported during the placebo task. In the FM group, reinforced expectations were significantly predicted by two FAST outcomes: the FAST $R^2$, ($F(1,28)=33.78$, $p<0.001$, explaining 55% ($R^2=0.55$)), with a negative association (B=−214.10, β=−0.739, SE=36.83, t=−5.81, 95%CI [−289.55, −138.64]) and by FAST ICC ($F(1,30)=6.79$, p=0.014); explaining 18% ($R^2=0.18$), (B=−129.40, β=−0.430, SE=49.64, t=−2.61, 95% CI [−230.77, −28.02]). No significant relationships were found between the FAST outcomes and expectations at baseline or after-treatment. In the HC, no such relationships were found. The Clinical WSV also did not predict expectations in FM (all p. values ≥ 0.364).

Further, we examined whether group moderated the relationship between the different WSV outcomes and expectation ratings (E1, E2, E3), while controlling for age and BMI. The relationship between FAST $R^2$ and reinforced expectations was moderated by group. The model was significant ($F(5, 55)=9.34$, $p<0.001$), and explained 41% of the variance in reinforced expectations. There was a significant interaction between FAST $R^2$ and group, (B=−205.43, SE=45.49, t=−4.52, $p<0.001$), indicating that the FAST $R^2$ predicted reinforced expectations differently for each group, with this interaction term accounting for 20% of the explained variance of the reinforced expectations. Simple slopes analysis revealed that in FM, the FAST $R^2$ was a significant negative predictor of reinforced expectations (B=−202.40, SE=35.93, t=−5.63, 95%CI [−274.42, −130.39]), but not in HC (p=0.917). Similarly, the group moderated the reinforced expectations by the FAST ICC ($F(5, 57)=4.23$, p=0.002) explaining 27.1% of the variance in reinforced expectations, with a significant interaction between FAST ICC and group (B=−153.44, SE=50.86, t=−3.02, p=0.003) explaining 11.6% of the variance. The simple slopes analysis identified that for FM, the FAST ICC predicted reinforced expectations (B=−131.70, SE=42.12, t=−3.13, p=0.003 95%CI [−216.04, −47.36]) but this was not found in healthy controls (p=0.479). Age and BMI did not significantly contribute to any of these models (all p. values ≥ 0.102).

## Discussion

This study investigated whether direction of attention would moderate the ability of WSV to predict the placebo effect. The main findings were that two of the SCS-R outcomes, private self-consciousness and social anxiety, significantly moderated the prediction of the placebo effect by the clinical WSV of pain reports. In addition, the third SCS-R outcome, public self-consciousness, showed a trend toward significant moderation.

In FM patients, all three SCS-R subscales were found to moderate the clinical WSV's ability to predict the placebo effect (with the exception of public self-consciousness, which was only marginally significant). For all three SCS-R subscales, the prediction of the placebo by the WSV was significant only at lower levels of self-consciousness or social anxiety.

Very similar results were recently seen in another study from our group.[24] In that study, the SCS-R public self-consciousness and social anxiety subscales moderated the WSV's prediction of the analgesic placebo response. Hence, direction of attention clearly plays a significant role in the prediction of the placebo effect.

However, few fundamental differences between the results of the two studies should be mentioned. Shani et al.[24] found that the *experimental* WSV predicted the *clinical* placebo response, whereas our current study found that the *clinical* WSV predicted the *experimental* placebo effect. Moreover, in Shani et al.,[24] public self-consciousness and social anxiety significantly moderated the prediction of the placebo response, whereas in the current study, private self-consciousness and social anxiety were the moderators.

A few possible explanations for these inconsistent results merit considerations. First, the attention processes might differ between FM and chronic back patients.[42–49] Furthermore, the prediction of a clinical placebo response might differ from the prediction of experimental placebo effect.[50,51] Nonetheless, the fact that it is always lower levels of attention that significantly moderated the WSV's prediction of the placebo response suggests some consistent results across the studies.

In the early studies, Gibbons and colleagues[52,53] concluded that the placebo response might be lower when attention directed to the self is induced through mirror manipulation. Similarly, Benedetti and colleagues[54] demonstrated that the effectiveness of an anesthetic cream would be greater if the participants focused their attention on the treated body part. Conversely, Geers et al.[55] asked individuals to monitor changes in bodily sensations and found that their placebo responses were stronger when their symptom detection was biased by their certainty of receiving a drug. As these different findings show, the effects of attention on the placebo response might depend on the context.

Research investigating attention's role in the placebo effect in conditioning-based placebo paradigms is limited. As such, Johnston et al. [56] manipulated pain expectancy using auditory cues signaling high or low upcoming pain and independently manipulated attention using task incentives to direct attention either toward or away from the body. They found that high pain expectancy increased pain intensity through mechanisms independent of attention to the body. Similarly, Feldhaus et al. [57] employed conditioning procedures introducing placebo and nocebo ointments paired with noxious heat stimuli in addition to assessments of attentional processes, in a large group of healthy participants. Individuals with lower heat detection thresholds showed stronger nocebo effects, suggesting that heightened attentiveness to sensory input may amplify negative expectations. More generally, the role of attention in placebo and nocebo effects can be found in Barbiani et al.,.[58]

The SCS-R measures direction of attention in general and does not focus on specific sensory (or nociceptive) signals of attention. This broad scope could suggest another possible explanation for the differences between the current results and those of Shani et al.[24] In future studies, it might be useful to assess attention specifically toward nociceptive sensations rather than general attention. This could be tested through direct manipulations of somatic focus (body vs. environment), mental imagery techniques, attentional biases towards pain, or self-reported measures of general attention to nociceptive sensations (e.g., the Pain Vigilance and Awareness Questionnaire).[59–62] Integrating such approaches into placebo studies along with neurophysiological markers in studies comparing healthy individuals and chronic pain patients could deepen our understanding of how attention and expectations shape the placebo response.

In the current study, WSV alone, either clinical or experimental, did not significantly predict the placebo effect in either cohort. This finding reflects the mixed results in the literature. In some studies, WSV did not predict the placebo response[20]; in one study the WSV showed only minimal predictive value;[21] and in others, the WSV predicted the placebo response.[16–19,22,23,63–69] While all previous reports focused on the relations between WSV and the placebo response, this is the first report

that extends these associations to the placebo effect, suggesting that the relations between the WSV and the placebo response might be specifically with the placebo effect, rather than with the non-specific factors, which are part of the placebo response.

Both the current study's results and those of Shani et al.[24] represent a step toward improved prediction of the placebo response. We now understand that a single predictor by itself might not be reproducible but that using more than one predictor, as done in the moderation analyses, improves our ability to predict the placebo effect. Other statistical approaches aimed at predicting the placebo response by merging information from multiple characteristics should further improve the placebo prediction.

An interesting unexpected finding was the prediction of the reinforced expectations by the experimental WSV. According to the hypothesized model published in Kuperman et al.,[25] we regarded the WSV as a proxy measure of the certainty of the likelihood. In fact, in none of the previous studies expectations were measured. The current finding suggest that the theoretical model could be updated, as follows: (1) low WSV could imply that the certainty of the likelihood is high, hence participants are "tuned" to their ascending sensory signals, and are less affected by the priors. (2) large WSV could imply that the priors are very certain, hence the percept is less affected by the ascending sensory signals and rely more on the priors. The current study is the first in which expectations were measured alongside the WSV. Given that those associations were found only in FM, future research focused on the potential associations between WSV and both the placebo effect (or response) and participants' expectations for benefit is needed before updating the theoretical model.

Several limitations should be acknowledged. First, FM patients recruited from the general population may present different characteristics, burden of illness, and disability levels than presented by patients recruited from clinical settings. Second, because of the higher prevalence of FM among women, only female patients were included in this study. This reduces the external validity, and future research should include male FM patients to increase generalizability. Third, because the study did not correct for multiple comparisons and because the FM group was relatively small, the validity of our results awaits replication in a larger cohort. Forth, our decision to reduce stimulus intensity by 1 °C for FM participants in the FAST procedure may limit the comparability of results between groups. Nevertheless, this adjustment minimized group differences in pain scores, allowing a fair comparison of WSV. Fifth, the individual calibration for the experimental placebo paradigm was performed differently for both groups. However, the average pain intensities were as expected/planned (Figure 2d) (about 80/100 for the red cues and about 20/100 for the green cues), which confirmed that our calibration achieved its aim.

To conclude, our findings highlight the important moderating role of direction of attention in using the WSV to predict the placebo effect. Future studies should investigate the moderating role of attention in the prediction of the placebo response by other predictors. Improving the prediction of the placebo response could improve clinical care by promoting new strategies for personalized pain treatments and could increase the assay sensitivity of clinical trials by identifying and excluding participants who are expected to show very large placebo responses.

## Statement of Ethics

The current study received approval from the University of Haifa Ethics 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 prior to their participation in the study. At the end of their participation, participants were debriefed about the study's real purpose and given the opportunity to withdraw their data.

## CRediT authorship contribution statement

M.A. was responsible for data collection, processing, analysis, and manuscript writing. G.E. contributed to data collection and manuscript writing. R.C. supervised and contributed to the manuscript preparation, and R.T. oversaw all the studies' activities and the writing of the manuscript. All the co-authors reviewed the manuscript and approved its final version.

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## Declaration of Competing Interest

All authors declare no conflicts of interest.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2025.105512.

## Data Availability Statement

Data is available upon reasonable request to R.T.

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