

Reduced selective learning in fibromyalgia patients versus healthy controls

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Abstract

Impaired selective fear learning has been advanced as a core mechanism involved in excessive spreading of protective responses such as pain-related fear and avoidance leading to disability in chronic pain conditions. Using the litmus test for selective learning effects, the blocking procedure, we tested the hypothesis that fibromyalgia patients show less selective threat learning than healthy controls. We introduce a novel selective learning task based around a clinical diary scenario. On a trial-by-trial basis, participants rated whether they expected certain situations (A, B, Z, X) in the diary of a fictive fibromyalgia patient would trigger pain in that patient. The procedure did not involve any experimental pain induction, since the verbal outcomes “pain” or “no pain” were used. During the elemental acquisition phase, one situation was followed by “pain” (A+, e.g. “Kim slept badly, and reports pain”), whereas another situation was followed by “no pain” (Z-, e.g. “Kim was stressed, and reports no pain”). During the compound acquisition phase, another situation (X), referred to as the blocked stimulus, was presented in compound with a previously pain-eliciting situation and also paired with “pain” (AX+, e.g., Kim slept badly” and “Kim has vacuumed”, and reports pain). Simultaneously, a novel situation was introduced and also followed by “pain” (B+). Within-group comparisons showed blocking (i.e., significant difference between B and X) in the healthy controls, but not in the fibromyalgia patients. This study is the first in directly assessing differences in selective learning between fibromyalgia patients and healthy controls using a blocking procedure.

Introduction

Pain serves a vital alarm function: the accurate prediction of when and where in the body pain occurs promotes survival, as it drives appropriate action in protecting against bodily threat[39]. Pavlovian conditioning is the critical mechanism underlying the prediction of the occurrence of potentially harmful stimuli in the environment[28-30]. More specifically, when a stimulus (conditioned stimulus; CS) has previously been paired with pain (unconditioned stimulus; US), this stimulus in itself may eventually elicit fear and prompt avoidance behavior (conditioned response; CR)[27]. Because multiple external, internal and proprioceptive indicators may co-occur with a pain episode, identifying discriminate predictors of pain among all these stimuli is challenging. Failure to pinpoint actual predictors of pain can lead to the spreading of fear to other stimuli that co-occurred with the pain episode, resulting in persistent anxiety and avoidance behavior[6; 14; 26; 37]. For example, if someone experiences a shooting pain when getting out of bed, this person may not only attribute the pain to the specific stretching movement actually causing the pain, but also to having slept badly or even to the strenuous exercise the day before.

One possible mechanism explaining the maladaptive spreading of protective responses is impaired selective threat learning. Accumulating evidence shows that individuals suffering from chronic pain display impaired differential learning and excessive generalization in differential conditioning paradigms and generalization protocols[15; 23-25], both suggesting a lack of selectivity. The most clear-cut way to investigate selective learning effects in the laboratory, however, is the *blocking procedure*[7; 17]. In a blocking procedure, one event (A+) is paired with pain (US) in a first stage. Another event (X), referred to as the *blocked stimulus*, presented in compound with the original pain-eliciting event is also paired with pain in a second stage (AX+). During the crucial test of X alone, fear responding is typically weak or *blocked*, despite the previous pairing with the pain. However, individual differences in the magnitude of the blocking effect exist. For example, Boddez et al.[3] demonstrated that high trait anxiety scores in a subclinical sample were associated with elevated US-expectancy for the blocked stimulus (X), indicating impaired selectivity in the learning of associations between events.

Because it is commonly acknowledged that the conditions for causal learning (i.e. relationship between two *neutral events*) are very similar to those underlying Pavlovian conditioning (with a *biologically*

relevant US)[2; 9; 33], we developed a pain-relevant selective learning task, using a clinical diary scenario. Participants rated on a trial-by-trial basis whether they expected that certain situations in the diary of a fictive fibromyalgia patient would trigger pain in that patient. They received feedback in the format of the verbal outcome “pain” or “no pain”. Assessing pain expectancy judgments to these scenarios enabled us to evaluate selective learning without experimentally inducing pain or worsening patients’ symptoms. Based on previous research showing excessive generalization in people with chronic pain, suggesting a lack of selective learning, we hypothesized that fibromyalgia patients would show less blocking than healthy controls.

Materials and Methods

Participants

A convenience sample of 27 patients with fibromyalgia (26 females, mean \pm SD age = 46 \pm 9 years), and 27 age-matched healthy, pain-free controls (mean \pm SD age = 48 \pm 9 years) participated in the study. 5-year ranges were used to match healthy controls (HC) to patients[24]. Patients with FM had a doctor-based diagnosis of fibromyalgia satisfying the American College of Rheumatology (ACR) new diagnostic criteria for fibromyalgia[43] and experienced substantial reductions in daily life functioning caused by this condition. The inclusion criterion for the HC group was to not have fibromyalgia. FM patients and healthy controls were excluded when they were diagnosed with dyslexia, other pain conditions and any conditions that might influence cognitive or verbal abilities (i.e., stroke, brain injury). Additionally, HC were excluded from participation if they had (ever) been diagnosed with a psychiatric disorder including clinical depression and panic/anxiety disorder. Because of the high comorbidity between FM and mood and anxiety disorders[18; 35; 42] this extra criterion did not apply to the FM group. The study protocol was approved by the Social and Societal Ethics Committee of KU Leuven (registration number: G-2015 03 197). Fibromyalgia patients were recruited through patient organizations and from pain clinics in the Limburg region (Belgium), and healthy controls were recruited through local advertisement. All participants provided written informed consent. Table 1 shows detailed demographic information and clinical characteristics of FM patients and HC.

--Insert Table 1 about here--

Stimulus material

Informed by multidisciplinary discussions and reviewing the literature on illness beliefs in fibromyalgia, we selected six situations that patients viewed as plausible triggers of (increased) pain episodes. Four of these situations captured in one single sentence served as the cues or conditioned stimuli (CS) during at least one of the experimental phases. These sentences were formulated in the third person with a fictive fibromyalgia patient, Kim (a gender-neutral name in Dutch) as the subject. The following sentences were used: “*Kim was stressed*” [emotional distress], “*Kim has vacuumed*” [activity-based trigger], “*Kim slept badly*” [physical trigger], and “*The weather was bad today*” [environmental trigger]. These sentences correspond to stimuli A, B, X and Z in the experimental design. Two additional situations were used during the practice phase: stimuli C and D. The following sentences were used: “*Kim had a marital dispute*” [social trigger], and “*Kim has walked the dog*” [activity-based trigger]. Which stimulus served as A, B, X and Z in the experimental phases or C and D in the practice phase was counterbalanced across participants.

The CSs were presented on a white computer background screen in font type Arial, black font color, and size 20.5. The outcome or unconditioned stimulus (US) was the text “PAIN” or “NO PAIN” presented in the same font type, color and size. All stimuli were presented in a blue frame including the rating scale with anchors 0 = “certainly no pain” and 10 = “certainly pain” at the bottom of the screen (see Figure 1).

--Insert Figure 1 about here--

*Outcome measures**Pain expectancy judgments.*

During the selective learning task, participants indicated their trial-by-trial pain expectancy on a continuous rating scale with anchors 0 = “certainly no pain” and 10 = “certainly pain” presented at the bottom of the screen. During the pre-rating phase, participants rated whether they expected that the specific situations (CSs) would trigger pain in themselves (i.e., assessing a priori beliefs), whereas during the

remainder of the experiment pain expectancy judgments pertained to Kim, a fictive fibromyalgia patient (i.e. assessing learning effects).

Post-experimental questionnaires.

In order to thoroughly characterize both groups and describe possible psychological differences between them, all participants filled out a series of questionnaires after completing the experimental task. (1) Pain severity was measured with the Chronic Pain Grade Scale (CPGS)[40], which assesses pain intensity and interference because of pain in daily life. Six out of seven items measure pain intensity on a 10-point scale ranging from 0 “no pain” to 10 “pain as bad as it could be”. In the seventh item, respondents are asked to estimate the number of days in the past six months on which pain significantly hindered their daily activities. Combining the pain intensity score and the disability score leads to the classification into one of four grades of chronic pain: Grade I, representing low pain intensity and low disability; Grade II, representing high pain intensity but low disability; Grade III, representing high disability that is moderately limiting; and Grade IV, representing high disability that is severely limiting. (2) Pain cognitions were measured with the Pain Cognition List (PCL)[36]. The PCL consists of five subscales: Limitations Catastrophizing, Internal control, Trust, and Optimism. (3) Fear of movement was measured with the Tampa Scale of Kinesiophobia (TSK)[31], which consists of 17 items evaluating fear of movement and fear of (re)injury. (4) Pain disability was measured with the Fibromyalgia Impact Questionnaire (FIQ)[4], which assesses functional status of fibromyalgia patients. The total score ranges from 0-100, with 0 indicating no functional interference at all and 100 severe impact of fibromyalgia on daily functioning. (5) Positive and negative affectivity were measured with the trait version of the Positive and Negative Affect Schedule (PANAS)[11; 41]. Participants indicate to what extent they experience ten negative and ten positive emotions *in their normal daily life*. (6) Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS)[34; 44]. (7) Fear of pain was measured with the Fear of Pain Questionnaire (FPQ)[22; 32], which assesses pain-related fear and anxiety (8) Attentional control and attentional shifting were measured with the Attentional Control Scale (ACS)[8].

Protocol

The selective learning task was programmed in JavaScript, and presented in HTML and CSS supported by a standard web browser. The post-experimental questionnaires were completed using a web survey tool (<https://www.limesurvey.org>). The experiment lasted approximately 15 minutes and the completion of the post-experimental questionnaires lasted approximately 10 minutes. Participants were allowed to take a break between both parts of the experiment. Data collection took place online; participants completed the task at home on their own computer. During a screening interview and verbal explanation of the study background and aims via telephone, we emphasized the importance of completing the task alone without any help from others, and preferably in a quiet environment. All the participants confirmed that they understood the importance of a quiet and solitary data collection environment and agreed to make every effort to comply with this request. Next, participants received an e-mail with the written information recapturing the research aims, task requirement and estimated time to complete the online task. The e-mail also contained the informed consent form (which they could sign by replying to the e-mail with the statement “read and approved”) and two web links: one to start the experimental task and one to start the post-experimental survey.

Selective learning task

In a between-subjects scenario contingency learning task using a blocking procedure, both fibromyalgia patients (FM) and healthy controls (HC) were presented with consecutive pages taken from the diary (CSs) of Kim, a fictive fibromyalgia patient. They were instructed that it was their task to predict whether this fictive fibromyalgia patient would feel pain in the aftermath of the described diary situations. The pain expectancy rating scale was displayed on the screen together with each CS (see Figure 1). Using the mouse, participants could indicate their pain expectancy by moving a slider on the rating scale. The pain expectancy rating was registered when the participant clicked on the “confirm” button below the rating scale. They could only confirm their answer after the stimulus was presented for 500 ms. When the participant confirmed his/her pain expectancy judgment, the CS and the rating scale disappeared, and the outcome (“PAIN” or “NO PAIN”) was displayed on the screen for 2.5 s. A new trial commenced after an intertrial interval of 1.5 seconds during which the computer screen was blank. Blocking was primarily evaluated using

the pain expectancy judgment for each CS situation. The experiment consisted of five phases that will be described in more detail below: the pre-rating phase, the practice phase, the elemental acquisition phase, the compound acquisition phase and the test phase (see Table 2).

--Insert Table 2 about here--

Pre-rating phase. Before the onset of the experiment, we assessed participants' a priori beliefs as to whether CSs are considered plausible precursors of pain. Participants rated A, B, X and Z; these stimuli were now presented in the second person referring to themselves instead of the third person referring to the fictive fibromyalgia patient. The following sentences were presented one time each: "*You were stressed*", "*You had vacuumed*", "*You slept badly*", and "*The weather was bad today*". The presentation order of the stimuli was randomized across participants. Participants indicated their pain expectancy for each situation on a continuous rating scale with anchors 0 = "certainly no pain" and 10 = "certainly pain". No outcome was presented after these four pre-rating trials.

Practice phase. During this phase the participants practiced the use of the rating scale and how to interpret the outcomes. For this purpose, two other stimuli C and D were used: "*Kim had a marital dispute*" and "*Kim has walked the dog*". These stimuli did not appear in the remainder of the experiment. After participants gave their pain expectancy judgment for stimulus C, the outcome "PAIN" was presented for 2.5 s (exemplary of a CS+ trial). An orange frame with the clarifying text "*Kim reports that this activity led to pain*" accompanied the outcome. Then an intertrial interval of 1.5 s was inserted before the following stimulus was presented on the screen. After participants gave their pain expectancy judgment for stimulus D, the outcome "NO PAIN" was presented for 2.5 s (exemplary of a CS- trial). An orange frame with the clarifying text "*Kim reports that this activity led to no pain*" accompanied the outcome. The presentation order of the two practice trials was randomized and which of both stimuli served as the CS+ was counterbalanced across participants. Such clarifying messages were only presented during the practice phase to ensure that participants understood the meaning of the respective outcomes. After the practice phase and before the instructions of the elemental training phase were presented the screen cleared for 3 s.

Elemental acquisition phase. During this phase, differential conditioning was established using two stimuli (A and Z): A was consistently followed by the “PAIN” outcome (CS+) and Z was consistently followed by the “NO PAIN” outcome (CS-). As described earlier, in this contingency learning task each CS is presented as a transcript of the diary of Kim, a fictive fibromyalgia patient. Participants were explicitly informed that certain situations may occur several times in the diary. They were also told that, in order to keep track of the situation, each CS would be presented together with the word “Day” positioned on top of the screen, accompanied by a number starting at 1 and increasing each trial (e.g. Day1 for trial 1 etc.). This phase consisted of 12 trials: 6 A+ trials and 6 Z- trials, presented in a randomized order.

Compound acquisition phase. During this phase, a novel stimulus B was consistently followed by the “PAIN” outcome (CS+) and Z was still consistently followed by the “NO PAIN” outcome (CS-). In addition, the compound stimulus AX (i.e. A and X presented concurrently on the screen) was also consistently followed by the “PAIN” outcome (CS+). Because during the elemental phase, participants have learned that stimulus A suffices to predict the “PAIN” outcome, stimulus X is redundant and learning about this stimulus is expected to be blocked. Therefore X is referred to as the blocked stimulus. This phase consisted of 18 trials: 6 B+ trials, 6 Z- trials and 6 AX+ trials, presented in a randomized order.

Test phase. The crucial test comprised three trials: one single presentation of B, Z, and X, in a randomized order. These trials were not followed by the usual “PAIN” or “NO PAIN” outcomes, but instead participants received the message that “*The diary does not say whether Kim had pain or not*”. This method of unreinforced testing was used in order not to contaminate the subsequent test trials.

Results

We performed multiple repeated measures (RM) ANOVAs to evaluate potential differences in elemental acquisition, compound acquisition, and blocking between fibromyalgia patients and healthy controls. Our main dependent variables were pain expectancy judgments for stimuli B and X at test. The Greenhouse-Geisser procedure was used in case the sphericity assumption was violated (corrected p -values are reported with uncorrected degrees of freedom, together with ϵ). For X, the data distributions showed slight deviations from normality, but the ANOVA procedure has been shown robust to these violations – at least given a moderate sample size [12]. The data was further analyzed using planned comparisons testing

our clear-cut a priori hypotheses. The effect size η_p^2 is reported for all omnibus ANOVA effects. All statistical analyses were performed with Statistica 13.1 software (Tulsa, OK, USA).

Differences in a priori beliefs between patients and healthy controls

In order to evaluate potential pre-existing differences between the stimuli before the learning task, we conducted a RM ANOVA with Stimulus Type (A, B, X and Z) as a within-subjects variable and Group as a between-subjects variable on the pain expectancy judgments during the pre-rating phase. This analysis yielded a main effect of Group, $F(1, 52) = 345.85, p < .001, \eta_p^2 = .87$. The main effect of Stimulus Type and the interaction were not significant, both $F_s < 1$. These results elucidate a clear dissociation in a priori beliefs regarding the stimuli between the fibromyalgia patients and the healthy controls (see Figure 2). The fibromyalgia patients reported to expect experiencing pain themselves in all the situations that we used as stimuli in the selective learning task, whereas the healthy controls overall gave low pain expectancy ratings, indicating that they believed that these situations would not lead to pain for themselves.

--Insert Figure 2 about here--

Selective learning task

To test for acquisition in the pain expectancy judgments, we conducted a 2 x 2 x 6 RM ANOVA including Group (HC/FM) as between-subjects variable and Trial (1-6) and Stimulus Type (A+/Z-) as within-subjects variables. The analysis yielded significant main effects of Stimulus Type, $F(1, 52) = 96.99, p < .001, \eta_p^2 = .65$, Trial, $F(5, 260) = 4.94, p < .001, \epsilon = .79, \eta_p^2 = .09$, and Group, $F(1, 52) = 44.92, p < .001, \eta_p^2 = .46$; the latter indicating that the FM group gave overall higher pain expectancy judgments than the HC group. As expected, the Stimulus Type x Trial interaction was significant, $F(5, 260) = 31.21, p < .001, \epsilon = .66, \eta_p^2 = .38$, showing that pain expectancy judgments evolved differently for A+ and Z- over time. This interaction was not modulated by Group, $F(5, 260) = 1.03, p = .40, \epsilon = .66$, suggesting that differential acquisition materialized to the same extent in both groups. Mean pain expectancy judgments for each stimulus type are displayed separately for the elemental and the compound phase in Figure 3A. Follow-up within-group planned contrasts confirmed that no pre-existing differences were present between A+ and Z- during the first trial of acquisition neither in the FM group nor in the HC group, both $F_s < 1$. However, at the

end of the elemental acquisition phase, pain expectancy judgments were higher for A+ compared with Z- both in the FM group, $F(1, 52) = 70.57, p < .001$, and the HC group, $F(1, 52) = 37.13, p < .001$.

--Insert Figure 3 about here--

A similar analysis, that is a 2 x 3 x 6 RM ANOVA including Group (HC/FM) as between-subjects variable and Trial (1-6) and Stimulus Type (B+/Z-/AX+) as within-subjects variables, was carried out to evaluate differential learning effects in pain expectancy judgments in the compound acquisition phase. The analysis showed significant main effects of Stimulus Type, $F(2, 104) = 117.85, p < .001, \epsilon = .77, \eta_p^2 = .69$, Trial, $F(5, 260) = 4.26, p < .01, \epsilon = .65, \eta_p^2 = .08$, and Group, $F(1, 52) = 41.86, p < .001, \eta_p^2 = .45$. Again, fibromyalgia patients gave overall higher pain expectancy ratings than the HC group irrespective of stimulus type (see Figure 3A). The Stimulus Type x Trial interaction was significant, $F(10, 520) = 4.39, p < .001, \epsilon = .55, \eta_p^2 = .08$, showing that pain expectancy judgments evolved differently for AX+, B+ and Z- over time. Group status did not modulate this interaction, $F < 1$. Follow-up within-group planned contrasts confirmed that at the end of the compound acquisition training, pain expectancy judgments were higher for AX+ and B+ compared with Z- in the FM group, $F(1, 52) = 71.48, p < .001$, as well as in the HC group, $F(1, 52) = 48.12, p < .001$.

To test our main hypothesis of selective learning, we performed a 2 x 3 RM ANOVA including Group (HC/FM) as between-subjects variable and Stimulus Type (B/Z/X) as within-subjects variables on the pain expectancy judgments in the test phase. This analysis revealed significant main effects for Group, $F(1, 52) = 37.65, p < .001, \eta_p^2 = .42$, and Stimulus Type, $F(2, 104) = 65.14, p < .001, \epsilon = .87, \eta_p^2 = .56$. The Stimulus Type x Group interaction was significant, $F(2, 104) = 4.10, p < .05, \epsilon = .87, \eta_p^2 = .07$. Follow-up within-group planned contrasts confirmed that pain expectancy judgments for B were higher than for X in the HC group, $F(1, 52) = 10.38, p < .01$, but not in the FM group, $F(1, 52) = 2.50, p = .12$ (see 3B). The between-group contrast comparing the difference between B and X between the FM group and the HC group, however, was not significant, $F(1, 52) = 1.35, p = .25$. Taken together, these results at least provide partial evidence for a blocking effect in the HC group, but not in the FM group.

Relationship between a priori beliefs and selective learning

In order to explore the relationship between a priori beliefs regarding the test stimulus (X) and the blocking effect, we calculated non-parametric Spearman rank correlation coefficients between the expectancy judgments for X during the pre-rating phase and the magnitude of the blocking effect (B-X at test) for both groups separately. A non-parametric correlational analysis was conducted because the pre-ratings of X were not normally distributed. The correlational analysis showed that pre-ratings of X and magnitude of the blocking effect (B-X at test) were not correlated in the FM group ($\rho_{(pre-rating\ X, B-X\ at\ test)} = -0.35, p = .08$) nor in the HC group ($\rho_{(pre-rating\ X, B-X\ at\ test)} = 0.21, p = .29$).

Post-experimental questionnaires

Two fibromyalgia patients failed to complete the questionnaires. The final sample size included for the analyses on the post-experimental questionnaires was 52. As expected, there were significant differences between FM patients and HC on most of the included questionnaires (see Table 3).

--Insert Table 3 about here--

Discussion

Increasing evidence suggests that chronic pain patients display impaired differential learning and excessive generalization in pain-relevant fear conditioning paradigms as well as in basic contingency learning tasks[15; 23-25]. These findings point towards a lack of selectivity. Yet, the litmus test for selective learning effects is the blocking procedure[7; 17]. This study is innovative in *directly* assessing differences in selective learning between FM patients and HCs using such a blocking procedure. We introduced a novel selective learning task based around a clinical diary scenario. Participants rated on a trial-by-trial basis whether they expected certain situations (CSs) in the diary of a fictive fibromyalgia patient would trigger pain (US) in that patient. The procedure did not involve any experimental pain induction, but the verbal outcomes “pain” or “no pain” followed the CS+ and CS- respectively. We hypothesized that FM patients would show less blocking than the HCs, indicated by a smaller difference in pain expectancy judgments between the blocked stimulus (X) and the CS+ (B).

First, during acquisition both groups successfully learned to differentiate between the CS+ (A and B) and the CS- (Z). That is, participants in both groups rated their pain expectancy for A+ higher than for than

Z- during the elemental acquisition phase; they also gave higher ratings for B+ and AX+ than Z- during the compound acquisition phase. There was no difference in differential learning between FM patients and HCs. This corroborates earlier findings by Meulders et al.[24; 25] demonstrating in a voluntary joystick movement paradigm, in which one movement (CS+) was consistently followed by a noxious electrocutaneous stimulus and another movement (CS-) was not, that FM patients acquired differential fear of movement-related pain to the same extent as the HC group, albeit slower. These findings however contradict those of Jenewein et al.[15] showing learning deficits in FM patients compared to patients with osteoarthritis and HC in a differential fear conditioning paradigm using geometrical figures as CSs and a painful heat stimulus as US. In their study, one CS+ was followed by a painful high-temperature stimulus in 50% of the trials, and by a non-painful low-temperature stimulus in the other 50% of the trials, whereas the CS- was always followed by the low-temperature stimulus. The partial reinforcement schedule and the relatively short acquisition phase compared to the studies of Meulders et al.[24; 25] may explain this discrepancy. In another study by Meulders et al.[23] contingency learning using hand pain scenarios was investigated in chronic hand pain patients. In this study, hand pictures in different postures were used as CSs, with the words “no pain” and “pain” as outcomes. Chronic hand pain patients showed slower and significantly less differential acquisition in pain expectancy judgments than the HC group. One possible explanation may be that there was a significant generalization component embedded in the acquisition training. That is, the CS+ was a picture of a hand that was always presented in the same posture, but could be presented in four different orientations. Consequently, participants needed to learn the predictive value of posture regardless of orientation and thus generalize pain expectancy across the different orientations. It is possible that chronic pain patients are slower in integrating this information and working out predictive schemes.

Second, we found at least partial support for our main hypothesis. In particular, the HC subjects, but not the FM patients, showed a significant difference in pain expectancy judgments in response to B and X at test. This lack of blocking in the FM patients corroborates our selective learning hypothesis. In contrast to our expectations, however, the crucial Group x Stimulus Type (B vs. X) interaction did not reach significance, which means that replication in a larger sample is warranted before this result can be endorsed. There are several plausible explanations for this non-significant interaction. A first explanation relates to the use of *maximal outcomes* during the elemental acquisition phase of this experiment. Beckers et al.[1]

demonstrated that blocking effects are stronger when submaximal outcomes are used. More specifically, when during the elemental training phase A+ is followed by a submaximal outcome (e.g. 5 on a 10-point scale) and AX+ during the compound training phase is also followed by this submaximal outcome, then it becomes quickly clear that X is redundant and has no causal relation to the outcome. In contrast, if outcome maximality (e.g. 10 on a 10-point scale) is used for both A+ and AX+, the role of X in causing the outcome remains ambiguous. That is, one cannot evaluate whether X has a causal relationship to the outcome or whether a ceiling effect is at play. In the current study, the outcomes “pain” and “no pain” were used, alluding to an “all or nothing” framing of the outcome, but pain expectancy judgments were given on a scale from 0-10 (0=certainly no pain; 10= certainly pain), which may have confused participants. Future research could apply submaximal outcomes during training to determine whether this generates stronger blocking effects, at least in the control group. An alternative explanation concerns the use of verbal labels “pain” and “no pain” as outcomes instead of actual painful stimulation. Increasing the motivational value and salience of the US by using a fear conditioning procedure, may increase the sensitivity to detect group differences. Boddez et al.[3] was able to reveal differences in selective learning between high and low trait anxious people using such a fear conditioning procedure. It needs to be highlighted however that the selective learning task, even without experimental pain induction, was able to differentiate between groups: FM patients gave overall higher pain expectancy judgments than the HC group (main effect of Group). This implies that the current task has at least some diagnostic validity and taps into an underlying mechanism that differentiates between diagnostic groups[38].

Some findings deserve further attention. First, as mentioned, FM patients gave overall higher pain expectancy judgments for both CS+ and CS- than HCs. The behavior expected based on the actual contingencies, however entails high pain expectancy ratings for the CS+ and low ratings for the CS-. From that point of view, it can be argued that the data pattern of the HC group is remarkable because they show relatively low ratings for the CS+. One possible explanation may be that they interpret the pain-scale in terms of the *amount* of pain they expect the patient to experience rather than *whether or not* the patient would feel pain. An alternative explanation may lie in the fact that a priori pain expectancy beliefs of the FM patients are higher for all CSs than for the HCs. It is plausible that although we explicitly instruct participants not to take their own experiences/expectations about pain into account during the task, that patients’ personal

history push the pain expectancy judgments to the higher end of the scale. FM patients indeed showed an *expectancy bias*. Yet, this expectancy bias for X (i.e. higher pre-ratings for X) was not associated with less blocking in FM patients, suggesting that both expectancy biases and impaired selective learning are unique characteristics for chronic pain pathology.

One particular strength of the experimental paradigm used in this study is that it allows us to tap into fundamental mechanisms underlying associative learning, and that it can easily be modified to test other pain populations. Since this experimental procedure is an adaptable and easily applicable method to identify selective learning deficits in different pain populations without the need of experimental pain induction, this method has the potential to boost knowledge progress in fundamental pain research.

Some limitations should be highlighted. First, our sample contained mostly female participants with fibromyalgia; therefore the generalization of these results to a male population or other pain conditions at this point is not justified. Nevertheless, we believe that the use of this sample is justifiable; several authors have recommended using female samples because of the higher prevalence of women among chronic pain conditions[13; 21]. Second, the groups also differed in medication use[5; 10], comorbidity with anxiety[3; 16; 19; 20] and depression, which may have impacted learning. These features may be viewed as confounding factors. However, it can be argued that these characteristics are intrinsically related to the clinical profile of chronic pain patients. In our total sample, correlations between the anxiety and depression scores and the blocking effect (B-X) were calculated and turned out to be weak and non-significant (see supplementary Table S.1). Therefore, it seems implausible that the observed differences in selective learning are merely due to differences in anxiety or depression. With regard to medication use, we previously argued that it is not likely that the use of medication in the patient group explains all the observed differences between patients and HC, since the different drugs that were used by our patient sample may have opposite effects [24; 25].

To conclude, this study provides direct, yet partial evidence for impaired selective learning in FM patients using a scenario contingency learning task. We believe that deficits in selective threat appraisal may contribute to the transition from regional musculoskeletal pain to widespread pain through the proliferation

of anxiety and expectancy biases. Future research should explore how these deficits can be targeted in cognitive-behavioral treatments.

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Figure captions

Figure 1. Schematic overview of the experimental task and trial timing during an exemplary A+ and Z- trial during the elemental acquisition phase.

Figure 2. Mean pain expectancy judgments for the unreinforced stimuli A, B, X, and Z during the pre-rating phase for the fibromyalgia patients and the healthy controls separately. Note – during this phase the stimuli were presented in the second person (referring to themselves) not in the third person (referring to a fictive fibromyalgia patient).

Figure 3. Mean pain expectancy judgments separately for the fibromyalgia patients and the healthy controls **A.** during the elemental and compound acquisition phases for stimuli A+, B+, AX+ and Z, and **B.** during the test phase for the unreinforced stimuli B, X, and Z. Note – ** = $p < .01$.

Figure 1

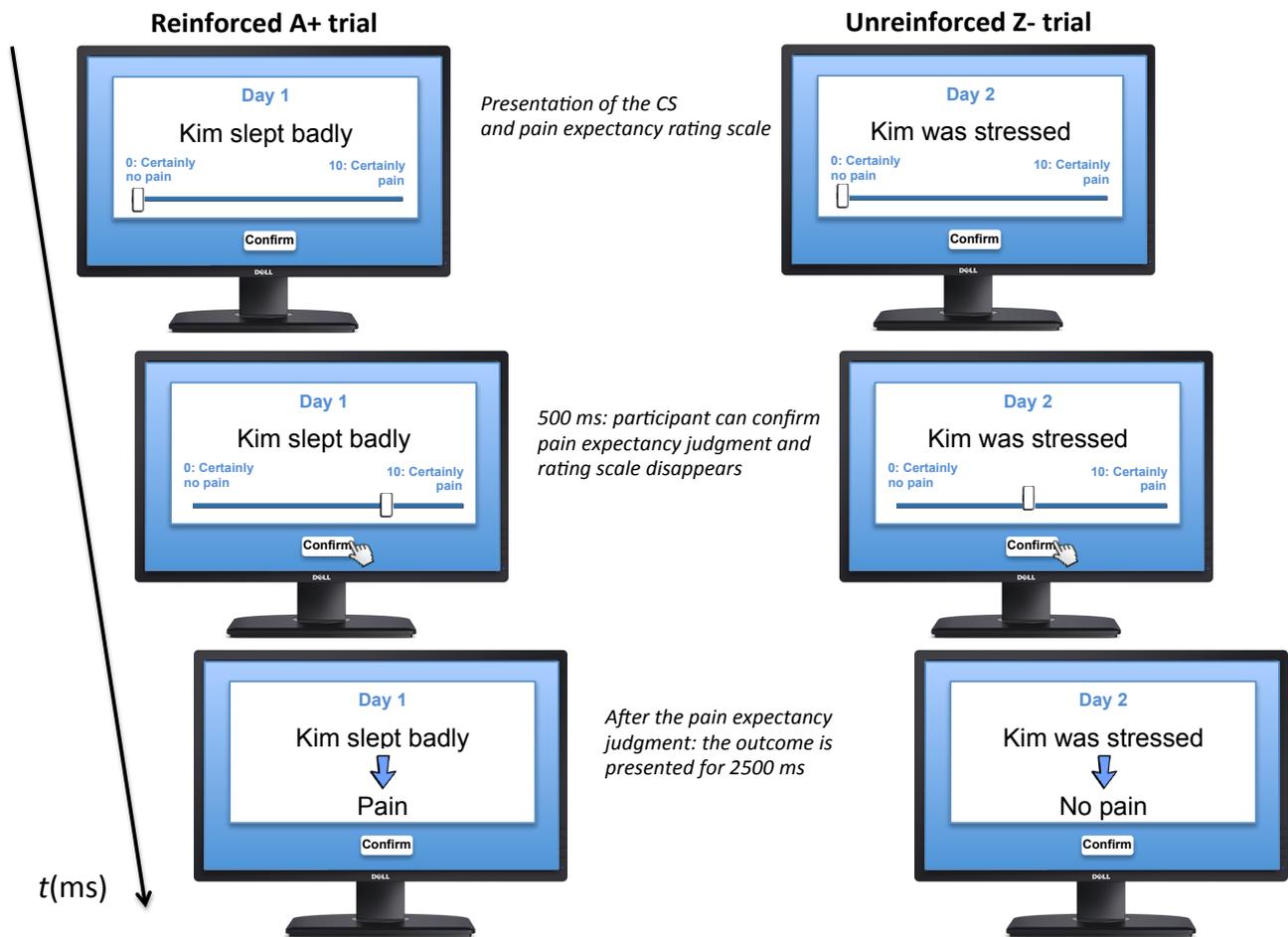


Figure 2

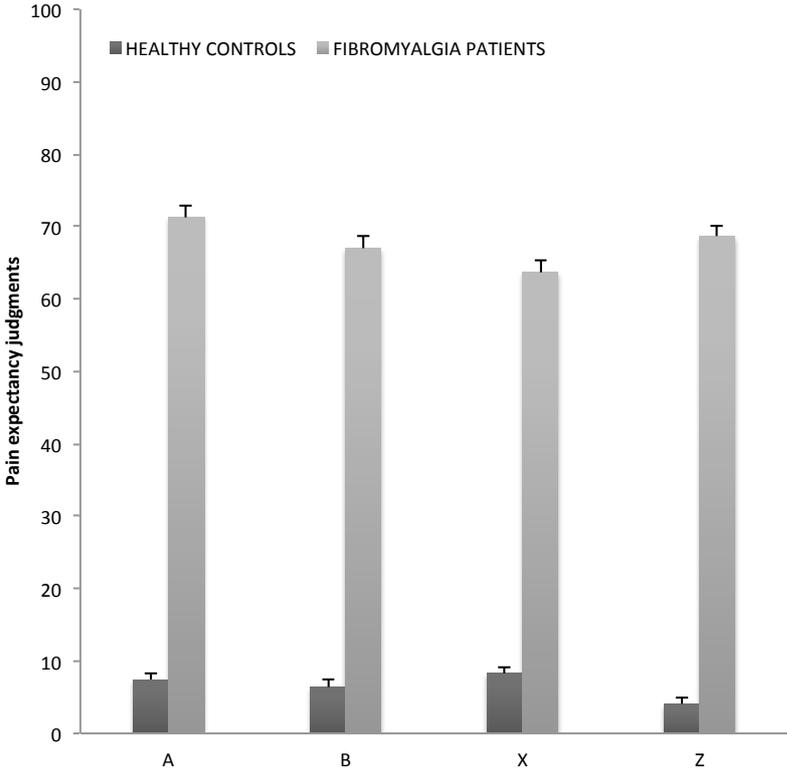
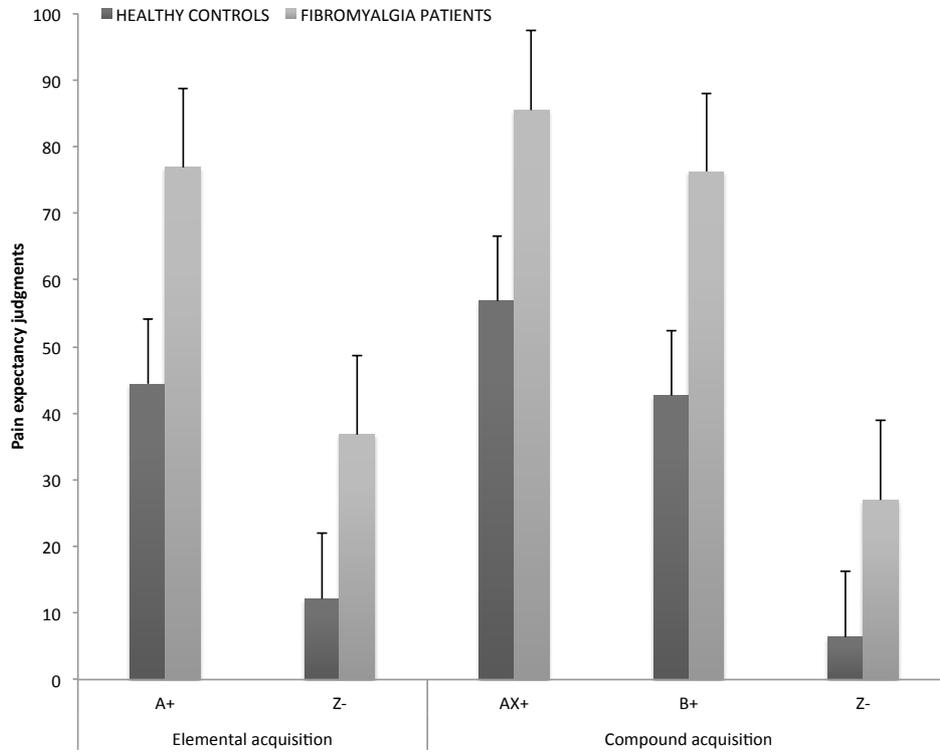


Figure 3

A. Elemental and compound acquisition phase



B. Test phase

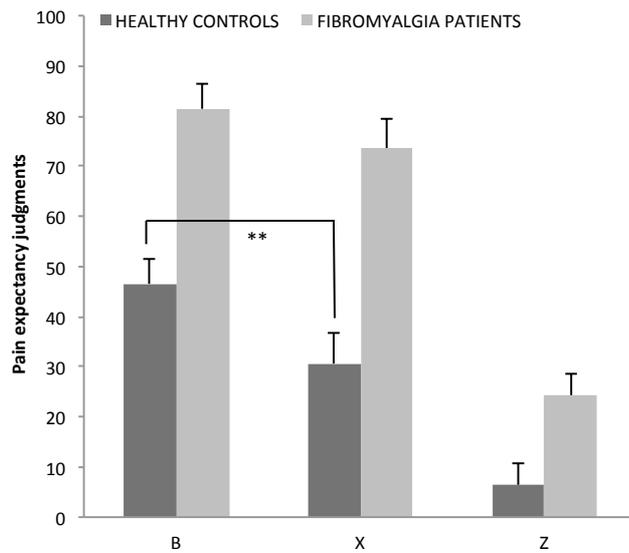


Table 1. *Demographic and clinical characteristics for the FM group and the HC group separately.*

	FM group	HCgroup
<i>Highest education level (FM: n=25; HC: n=27), %</i>		
Primary school	8	0
Vocational secondary education	28	0
Technical secondary education	28	15
General secondary education	8	11
Bachelor's degree	28	55
Master's degree	0	20
<i>Occupation (FM: n=25; HC: n=27), %</i>		
Working	16	92
Studying	4	4
Unemployed/invalidity/retired	80	4
<i>Type of medication (FM: n=26), %</i>		
Antidepressants	58	–
Benzodiazepines	31	–
Opioids	42	–
Paracetamol	50	
NSAID	27	–
Other	31	–
Pain treatment (yes–no) (FM: n=25; HC: n=27), %	92	4
Medication (yes–no) (FM: n=25; HC: n=27), %	96	18

Note – FM = fibromyalgia; HC = healthy control; NSAID = NonSteroidal AntiInflammatory Drugs; Other medication includes muscle relaxants, antipsychotics and beta-blockers. Assessment of the education level, occupation and pain treatment and medication (yes/no) was part of the web survey including the post-experimental questionnaires, two patients failed to fill out this survey. We failed to collect the medication use details from one patient; no such data was collected for the healthy controls.

Table 2. *Experimental design*

<i>Pre-rating phase</i>	<i>Practice phase</i>	<i>Elemental acquisition phase</i>	<i>Compound acquisition phase</i>	<i>Test phase</i>
A*	C+	6A+	6B+	X
B*	D-	6Z-	6AX+	B
X*			6 Z-	Z
Z*				

Note – During each phase stimuli were presented in a random order. The following sentences: *Kim was stressed*, *Kim has vacuumed*, *Kim slept badly*, and *The weather was bad today* were used as A, B, X and Z and counterbalanced across participants. “*” refers to the use of the second person as a reference instead of the third person (being Kim) during the pre-rating phase; no outcomes were presented during this phase. Two additional sentences were used during the practice phase: stimuli C and D (*Kim had a marital dispute* and *Kim has walked the dog*). “+” indicates that the “PAIN” outcome is presented after the stimulus; “-” indicates that the “NO PAIN” outcome is presented after the stimulus. During the test phase the usual outcomes are not presented but X, B and Z are followed by this statement *The diary does not say whether Kim had pain or not* (i.e. unreinforced test).

Table 3. *Questionnaire scores for the fibromyalgia (FM) group healthy control (HC) group separately.*

Total sample $N=52$	FM group ($n = 25$)		HC group ($n = 27$)		t	p -value
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>		
CPGS – pain intensity	68.80	9.71	23.83	17.75	-11.20	< .0001
CPGS – pain disability	69.07	12.93	13.33	18.77	-12.37	< .0001
CPGS – number of days disability	65.04	54.96	3.19	11.99	-5.71	< .0001
PCL – catastrophizing	52.00	14.80	27.96	8.84	-7.17	< .0001
PCL – limitation	27.64	5.08	16.89	4.49	-8.10	< .0001
PCL – optimism	21.96	5.28	28.89	4.08	5.32	< .0001
PCL – internal control	14.72	4.01	19.74	3.32	4.93	< .0001
PCL – trust	12.16	3.13	15.56	2.36	4.44	< .0001
TSK – total score	38.88	10.13	33.19	5.82	-2.51	< .05
FIQ – total score	70.69	9.48	23.51	10.71	-16.77	< .0001
PANAS – positive affect	29.40	7.81	39.81	5.07	5.75	< .0001
PANAS – negative affect	25.92	10.96	16.19	4.22	-4.29	< .0001
HADS – anxiety	10.36	5.48	4.63	3.36	4.58	< .0001
HADS – depression	9.04	4.27	2.30	2.33	7.14	< .0001
FPQ – medical pain	19.32	6.00	17.96	5.94	-0.82	= .417
FPQ – minor pain	17.16	6.85	14.44	3.48	-1.82	= .074

FPQ – severe pain	27.52	10.10	27.63	8.50	0.04	= .996
FPQ – total score	64.00	19.49	60.04	15.20	-0.82	=.416
ACS – total score	46.00	11.56	56.52	7.96	3.85	< .001

Note – Two patients failed to fill out the questionnaires. CPGS = Chronic Pain Grade Scale: pain intensity (item 1-3), pain disability (item 4-6) and days of disability (item 7). Based on the CPGS scales, 0% (0/25) of the fibromyalgia patients was classified as Grade I (low disability - low intensity), 4% (1/25) as Grade II (low disability - high intensity), 36% (9/25) as Grade III (high disability - moderately limiting) and 60% (15/25) as Grade IV (high disability - severely limiting); PCL = Pain Cognition List: subscales are calculated for catastrophizing, limitation, optimism, internal control and trust; TSK = total score of Tampa Scale of Kinesiophobia; FIQ = total score of Fibromyalgia Impact Questionnaire; PANAS = Positive and Negative Affect Schedule: subscales are calculated for positive affect and negative affect; HADS = Hospital Anxiety Depression Scale: subscales are calculated for anxiety and depression; FPQ = total score of Fear of Pain Questionnaire: subscales are calculated for medical pain, minor pain, and severe pain; ACS = total score of Attentional Control Scale.

Table S.1 *Spearman ρ correlation coefficients between the different psychological questionnaire scores and the blocking effect (B-X) across groups.*

Total sample $N=52$	ρ coefficient	p -value
CPGS – pain intensity	-0.08	.56
CPGS – pain disability	-0.09	.53
CPGS – number of days disability	-0.16	.26
PCL – catastrophizing	-0.13	.37
PCL – limitation	-0.19	.17
PCL – optimism	0.20	.15
PCL – internal control	0.24	.08
PCL – trust	0.07	.62
TSK – total score	-0.21	.13
FIQ – total score	-0.15	.29
PANAS – positive affect	0.19	.17
PANAS – negative affect	-0.22	.12
HADS – anxiety	-0.14	.31
HADS – depression	-0.20	.15
FPQ – medical pain	0.14	.33
FPQ – minor pain	-0.08	.58
FPQ – severe pain	-0.10	.48
FPQ – total score	0.00	.99
ACS – total score	0.07	.62

Note – CPGS = Chronic Pain Grade Scale: pain intensity (item 1-3), pain disability (item 4-6) and days of disability (item 7); PCL = Pain Cognition List: subscales are calculated for catastrophizing, limitation, optimism, internal control and trust; TSK = total score of Tampa Scale of Kinesiophobia; FIQ = total score of Fibromyalgia Impact Questionnaire; PANAS = Positive and Negative Affect Schedule: subscales are calculated for positive affect and negative affect; HADS = Hospital Anxiety Depression Scale: subscales are calculated for anxiety and depression; FPQ = total score of Fear of Pain Questionnaire: subscales are calculated for medical pain, minor pain, and severe pain; ACS = total score of Attentional Control Scale.