Research Paper

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Learned expectations and uncertainty facilitate pain during classical conditioning

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Abstract

Pain spontaneously activates adaptive and dynamic learning processes affecting the anticipation of, and the responses to, future pain. Computational models of associative learning effectively capture the production and ongoing changes in conditioned anticipatory responses (eg, skin conductance response), but the impact of this dynamic process on unconditional pain responses remains poorly understood. Here, we investigated the dynamic modulation of pain and the nociceptive flexion reflex by fear learning in healthy human adult participants undergoing a classical conditioning procedure involving an acquisition, reversal and extinction phase. Conditioned visual stimuli (CS+) coterminated with a noxious transcutaneous stimulation applied to the sural nerve on 50% of trials (unconditioned stimuli). Expected pain probabilities and cue associability were estimated using computational modeling by fitting a hybrid learning model to skin conductance response elicited by the CS+. Multilevel linear regression analyses confirmed that trial-by-trial changes in expected pain and associability positively predict ongoing fluctuations in pain outcomes. Mediation analysis further demonstrated that both expected probability and associability affect pain perception through a direct effect and an indirect effect mediated by descending modulatory mechanisms affecting spinal nociceptive activity. Moderation analyses further showed that hyperalgesic effects of associability were larger in individuals reporting more harm vigilance and less emotional detachment. Higher harm vigilance was also associated with a stronger mediation of hyperalgesic effects by spinal processes. These results demonstrate how dynamic changes in pain can be explained by associative learning theory and that resilient attitudes towards fear/pain can attenuate the adverse impact of adaptive aversive learning processes on pain.

Keywords: Fear conditioning, Reinforcement learning models, Pain, Nociceptive flexion reflex, Nociception, Expectations, Uncertainty

1. Introduction

Pain has an important teaching function: past pain episodes shape our current reactions to pain, which in turn influences our future responses to painful events. The influence of learning on pain perception may be particularly important when individuals are subjected to successive episodes of acute pain, as observed in many chronic pain syndromes.[6,10,15] Unfortunately, we still know very little of the dynamic influence that learning continuously exerts on pain perception during repeated exposure to painful stimuli.

Previous studies using conditioned cues to manipulate expectations about pain[20,25] have shown that pain perception generally increases following cues that predict the occurrence of noxious stimuli or signal more intense stimulation (ie, "conditioned hyperalgesia"). However, these studies examined averaged pain responses after an initial conditioning phase during which participants are assumed to have acquired stable cue-pain associations, thereby treating learning as a static process. Here, by contrast, we opted to examine the dynamic influence of learning over pain as associations are formed and updated at every trial. More specifically, we used computational methods to extract trial-by-trial values of latent variables reflecting core associative learning processes. We predicted that these latent learning variables would explain trial-by-trial fluctuations in pain ratings and spinal nociceptive flexion reflexes (NFRs) induced by noxious electrical stimulations during classical conditioning.

In their simplest form, computational models posit that associative learning is driven entirely by prediction errors, ie, the difference between expected and experienced outcomes. In typical conditioning paradigms, expectations about outcomes, or the valuation processes underlying the assessment of upcoming reward/punishment magnitude and probability,[23] can be inferred from indirect measures (eg, anticipatory skin conductance responses [SCRs]). By fitting the model to the data, the values of the latent variable (eg, expectations) that best predict the indirect indexes of learning (eg, anticipatory SCRs), can be estimated for each trial. However, in many conditions, simple models based solely on prediction errors provide an incomplete account of associative learning. Recent studies have shown that hybrid models comprising an associability term provide a better account of anticipatory SCRs[24] and self-reported pain expectations[9] than standard learning models relying only on prediction

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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errors/expectations. Hybrid models posit that the rate at which expectations are updated after outcomes (ie, the "learning rate") varies as a function of each trial's informational value. This additional variable, called "associability," increases when predictions are unreliable (ie, there is more to learn when outcomes are difficult to predict), and has been suggested to involve increased attentional demands associated with uncertainty about the outcomes.[23] Recent brain imaging studies have shown that these 2 fundamental learning variables—associability and expectations—are associated with activity in different brain networks, confirming that they may reflect at least partly distinct neural processes.[9,24] Here, we predicted that the dynamic influence of associability and expectations would provide a more comprehensive account of ongoing effects of aversive learning on pain responses.

In this study, participants underwent a classical delay-conditioning task during which one of the 2 predictive cues (CS+) was associated with a 50% probability of being followed by a painful electric shock (unconditioned stimulus [US]). Anticipatory SCRs to the predictive cues were used to extract trial-by-trial estimates of associability and expected shock probability (henceforth referred to as EShock). Because associability normally decreases as participants gradually learn the fixed probability of pain during acquisition, cue-outcome associations were reversed during the experiment to transiently decouple pain predictions and associability. Moreover, to examine how learning exerts its effects at various levels of nociceptive processing, we recorded spinal NFRs in addition to pain ratings in response to the painful electric shocks.[28–30] We then examined the relationship between learning variables derived from SCRs to predictive cues, and pain ratings and NFRs in response to subsequent electric shocks. Finally, we explored the influence of several relevant personality traits on the relationship between learning variables and pain responses to identify individual factors affecting the magnitude of conditioned hyperalgesia.

2. Methods

2.1. Participants

The sample consisted of 47 healthy young adults between 19 and 32 years of age (25 male, 22 female) recruited from advertisements in local University settings (Université de Montréal as well as McGill and Concordia Universities). Ethical approval for the study was obtained by the ethics research committee of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM).

Potential participants were considered eligible to take part in the study on meeting the following criteria: no pregnancy, no psychological/psychiatric condition (such as major depressive disorder and substance abuse), no medication intake (except for oral contraceptives), no pain-related diseases (such as chronic pain or neuropathic pain), and no regular use of anti-inflammatory or analgesic medications. Potential participants were invited to visit the Laboratory of the Neuropsychophysiology of Pain (UdeM, Canada) for a screening and familiarization session to assess their pain thresholds and physiological signals (skin conductance and NFR) and for a second visit to complete the experimental paradigm. Nine participants were not retained after the familiarization session for one of the following reasons: extreme pain thresholds, excessive use of alcohol, drugs, or analgesic medication, discomfort with the nature of the noxious stimuli (electrical stimulations), or absent/unstable skin conductance or NFRs to the painful stimuli. Fifty participants participated in the experimental session, but 3 subjects were excluded from data analysis because of poor electrodermal signal or very inconsistent NFRs. Finally, computational learning model fits were extremely deviant for 2 participants (with predicted SCR values below or over 10 SDs from the mean), yielding a remaining total of 47 participants included in the analyses.

2.2. Stimuli

Visual stimuli were presented on a computer screen monitor with E-Prime2 Professional (Psychology Software Tools, Sharpsburg, PA). The CSs (cue1 and cue2) consisted in coloured fractal images (circles filled with computerized random colors and shape patterns) presented for 2 seconds on a black background. The USs coterminated with CS presentation, and consisted of a 30 ms transcutaneous electrical stimulation (trains of 10 1-millisecond pulses at 333 Hz) delivered with an isolated DS7A constant current stimulator (Digitimer Ltd, Welwyn Garden City, United Kingdom) triggered by a train generator (Grass Medical Instruments, Quincy, MA) and controlled by a computer running E-Prime2 Professional. Stimulation electrodes were positioned on degreased skin on the retromalleolar path of the right sural nerve. Nociceptive flexion reflex thresholds were assessed based on the NFR staircase thresholding method previously described.[3] The value corresponding to 135% of the threshold intensity was calculated to be administered as the US intensity in the fear-conditioning paradigm.

2.3. Measures and dependent variables

Physiological measures were recorded using BIOPAC Systems Inc. and AcqKnowledge data acquisition software (version 4.2).

2.3.1. Subjective pain ratings

A visual analog scale (VAS) was used to indicate the pain level elicited by each electrical stimulation (0: no pain to 100: extremely painful). The VAS consisted in a graduated horizontal bar shown on the computer screen with a cursor moved using a computer keyboard response pad. Subjective pain ratings were normalized across trials for each participant before data analysis.

2.3.2. Electromyographic recording

Electromyography was recorded using 2 pregelled electrodes on degreased (and shaved if necessary) skin at the level of the right biceps femoris. A ground electrode was placed on the right tibial bone. The electromyographic signal was amplified 1000 times, and sampled at 1000 Hz and band-passed filtered (100-500 Hz). The electromyographic signal was transformed online using the root mean square (RMS) transform (computed over 20 consecutive samples). Finally, the RMS was integrated offline over 90 to 180 milliseconds postshock onset and was defined as the raw NFR scores. Raw NFR scores were then normalized into z-scores across all trials of the conditioning task for each participant.

2.3.3. Electrodermal recording

Electrodermal activity was recorded using 2 electrodes placed on the palmar surface of the left hand. The signal was amplified (5 μs/volt) and bandpass filtered (1-5 Hz). The signal was temporally smoothed offline at 500 milliseconds. Using SCRalyze,[4] the SCR was assessed to CS− and CS+ unpaired. Skin conductance responses were determined using a general-linear model–based approach, by convolving a standard canonical SCR basis

function to event onsets. This function was then regressed onto the acquired data, and beta values estimating the goodness of fit of the model onto the data were computed. To obtain an SCR estimate for each CS trial, one model per trial was conducted, a procedure shown to be effective in estimating trial-by-trial responses in time series data.[26] For each model, a regressor was entered with the event onset for the trial of interest, and another regressor with all other CSs onsets was included. Shock onsets and pain rating periods were also entered as regressors of noninterest to account for residual variance in the data. Thus, these analyses yielded an estimate of SCR amplitude for each trial (henceforth referred to simply as "SCR" for the sake of conciseness).

2.4. Testing procedure

For their initial screening session, participants provided informed consent and were asked a series of questions concerning demographic variables. They were then prepared for electrophysiological recordings after which they were submitted to the NFR thresholding procedure. Finally, they were given a battery of self-report questionnaires to fill out. Trait anxiety was assessed using the State-Trait Anxiety Inventory (STAI).[33] Dispositional mindfulness was assessed using the Five Factor Mindfulness Questionnaire[5] because of its inverse relationship with pain catastrophizing,[32] and because of the role of mindfulness meditation in attenuating pain perception and developing resilience in the management of chronic pain.[17,21,38] This 39-item questionnaire is composed of 5 subscales assessing different dimensions of dispositional mindfulness: "Observe" (ability to observe inner experiences), "Describe" (ability to describe inner experiences), "Aware" (acting with awareness), "Non-judgment" of and "Non-reactivity" to experiences. Dispositional mindfulness was also assessed using the 15-item Mindful Attention Awareness Scale "designed to assess a core characteristic of dispositional mindfulness, namely, open or receptive awareness of and attention to what is taking place in the present."[11] In addition, the Pain Catastrophizing Scale[34] was administered, which is a 13-item questionnaire assessing the degree to which individuals catastrophize about their pain with 3 subscales: pain magnification, pain rumination, and helplessness towards pain. Depressive symptoms were assessed using the Beck Depression Inventory,[8] and punishment sensitivity was assessed using the Behavioral Inhibition/Activation Scale.[12] Finally, the Temperament and Character Inventory (TCI)[1] was administered to assess several different personality facets, and our focus was on its following subscales because of their relevance to fear/pain processing and trait mindfulness: harm avoidance (sum of scores on the subscales of "Anticipatory worry & Pessimism vs Uninhibited optimism," "Fear of Uncertainty," "Shyness with strangers," and "Fatigability & asthenia"), self-transcendence (sum of scores on "Self-forgetful vs Self-Conscious Experience," "Transpersonal Identification vs Self-Differentiation," and "Spiritual Acceptance vs Rational Materialism"), and self-directedness (sum of scores on "Responsibility vs blaming," "Purposefulness vs lack of goal-direction," "Resourcefulness," "Self-acceptance vs Self-striving," and "Enlightened Second Nature").

Participants were invited to return a few days later for a second visit to complete the experiment. After being prepped for electrophysiological recordings, the procedure for NFR thresholding was conducted to determine the intensity of electrocutaneous stimulation administered during the task. Before the start of the task, 2 trials of each CS (without any shocks) were presented, and a "baseline" block of 10 stimulations at the individually determined intensity. Participants then underwent the fear-conditioning paradigm (**Fig. 1**), which was adapted from previous work[31] and included phases of acquisition (Blocks 1 and 2), reversal (Blocks 1 and 2, in which stimuli assigned as CS+ /CS− in the acquisition phase were reversed), and extinction (presentation of CSs alone). In the acquisition and reversal blocks, one image was paired and coterminated with the shock at a contingency rate of 50% (CS+), and the other was never paired with the shock (CS−). Each US was followed with an interval (jittered between 4 and 8 seconds; to allow the recording of a SCR to the US) and the VAS. The intertrial intervals consisted of a white cross centered on a black background (duration jittered between 9, 10, 11, and 12 seconds).

Acquisition and reversal blocks consisted of 40 trials (20 CS−, 10 CS+ unpaired, and 10 CS+ paired) and lasted 13 minutes each. Trials were presented in a pseudorandom order, with the constraint that there were no more than 2 consecutive presentations of the same trial type. Also, the first trial of each block always consisted of a paired CS+, and the second always consisted of a CS− to instantiate learning contingencies at the onset of the block. The assignment of the CS+ in the acquisition

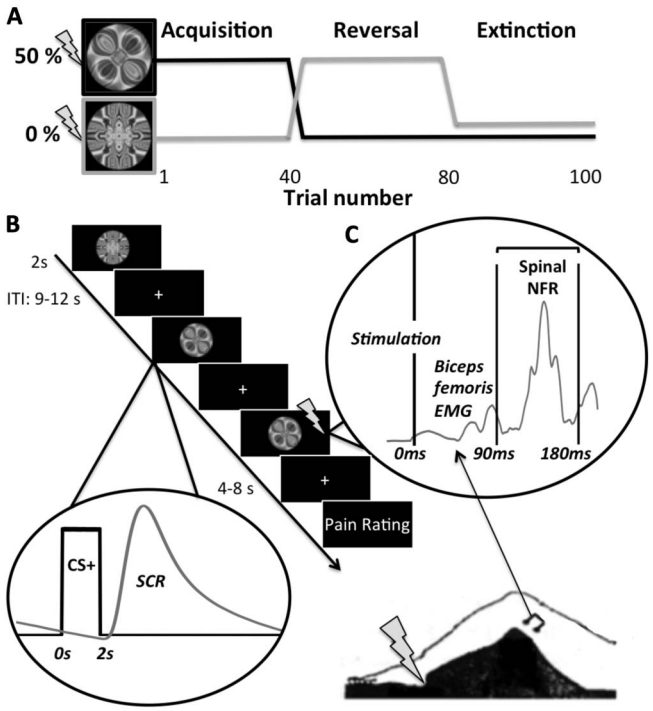

Figure 1. Experimental paradigm. (A) In the initial acquisition stage (trials 1-40), one cue was associated with a 50% chance of being followed by an electric shock (CS+), whereas the other cue was associated with a 0% chance of shock (CS−). In the reversal stage, the reinforcement contingencies between the 2 cues were reversed, such that the previous CS+ became the new CS− and the previous CS− became the new CS+. In the extinction phase, both cues were associated with a 0% chance of shock. (B) Example of each type of trial (CS−, CS+, and CS+ paired). Each trial began with the presentation of one of the 2 cues. On reinforced (CS+ paired) trials, the presentation of the cue coterminated with an electric shock (30 ms) to the right sural nerve and participants were asked to rate their pain after a jittered interval of 4-8 seconds. Then, after another jittered intertrial interval (ITI) of 9 to 12 seconds, the following cue was presented. During unreinforced (CS− or CS+ unpaired) trials, there were no pain ratings, and fear-conditioned responses to visual cues were assessed by examining skin conductance responses (SCRs; with a typical latency between 0.5 and 2 seconds) from electrodermal activity recordings. (C) Electromyographic activity was recorded using electrodes placed on the biceps femoris. The NFR was observable at a latency of 90 to 180 milliseconds poststimulation onset.

phase (stimulus A or B) was counter-balanced across subjects. The extinction block lasted 10 minutes and consisted of 40 trials of unreinforced CSs (20 trials for each image). The assignment of the CS+ in the acquisition phase (stimulus A or B) was counter-balanced across subjects. A final block of 10 stimulations without any CS was then administered to account for nonspecific changes in the NFR as a function of time.

At the end of the experiment, electrodes were removed and participants completed a postexperimental interview assessing their awareness of CS–US pairings adapted from previous studies.[7,22] They were then debriefed and remunerated 15 $/hour for their time.

2.5. Data analyses

2.5.1. Self-report questionnaire analyses

To reduce the number of individual trait dimensions, a principal component analysis using an oblique rotation method was conducted on the different self-report questionnaire data scales using SPSS Version 21.0. Data included in the analyses were BDI scores (square root transformed to correct for a positively skewed distribution), Mindful Awareness Attention Scale scores, Pain Catastrophizing Scale scores (sum of scores on the magnification, rumination, and helplessness towards pain), Behavioural Inhibition Scale (BIS) scores, scores on each Five-Factor Mindfulness Questionnaire subscale, trait anxiety scale scores, as well as the TCI subscales of harm avoidance, self-transcendence, and self-directedness.

The first 3 components extracted explaining a total of 62% of the variance in the data were retained to use as moderators of the fear-conditioning–induced modulation of pain. Factor loadings onto the questionnaire dimensions are illustrated in **Table 1**. The first factor loaded positively onto pain catastrophizing, trait anxiety, harm avoidance, punishment sensitivity (BIS), depressive symptoms, and negatively onto "Non-reactivity to inner experiences." This factor was labeled as "Harm vigilance," because it combines attributes specific to catastrophizing pain attitudes, avoidance behaviors, anxiety, and emotional volatility. The second factor loaded (positively onto FFMQ "Describing experiences," "Observing experiences," and self-transcendence. This factor was labeled as "Emotional Detachment," because it combined the dimensions of trait mindfulness oriented towards cultivating separation between the self and emotional experiences. The last factor loaded positively onto "Acting with Awareness," "Non-judgment of experiences," self-directedness, present-moment awareness, and negatively onto depressive symptoms. This factor was labeled as "Acceptance/positive affect," because it combined aspects related to trait mindfulness involved in emotional acceptance and living in the present moment, low negative affect, and tendencies to avoid harm.

Table 1

Individual trait dimensions and their loadings onto factors obtained from the principal component analysis.

	Principal component analysis factors		
	Harm vigilance	Emotional detachment	Acceptance/ positive affect
Individual Trait Dimensions			
Pain Catastrophizing (PCS)	0.64		
Describing Experience (FFMQ)		0.66	
Observing Experience (FFMQ)		0.77	
Acting with Awareness (FFMQ)			0.78
Non-judgmental (FFMQ)			0.68
Non-reactivity (FFMQ)	−0.64		
Trait Anxiety (STAI)	0.70		
Self-Transcendence (TCI)		0.73	
Self-Directedness (TCI)			0.68
Harm Avoidance (TCI)	0.90		
Present Moment Awareness (MAAS)			0.74
Depressive Symptoms (BDI)			−0.68
Punishment Sensitivity (BIS)	0.89		

BDI, Beck Depression Inventory; BIS, Behavioral Inhibition Scale; FFMQ, Five-Factor Mindfulness Questionnaire; MAAS, Mindful Awareness Attention Scale; PCS, Pain Catastrophizing Scale; TCI, Temperament and Character Inventory.

2.6. Computational modeling

Different computational learning models (Rescorla–Wagner and Pearce–Hall hybrid) were[23] fitted to trial-by-trial SCR data to unreinforced cues (CS− and CS+ unpaired), from which fear learning parameters to CS+ paired trials were estimated. The following models were tested: a Rescorla–Wagner model (RW model; driven by prediction errors), and a RW/Pearce-Hall hybrid model (RW/PH hybrid), in which the expected value or probability of shock at each trial is computed as a function of prediction errors AND in which the learning rate is dynamically modulated by associability at each trial. Finally, an intercue-dependent RW/PH hybrid model was conducted, which was a variant of the RW/PH hybrid model in which EShock and associability were updated for the cue presented at each trial, as well as for the unpresented cue. In this model, a cue-dependency term was added reflecting the fact that prediction error signals from the US may also allow learning about the cue to which participants had been previously exposed to, but which was not part of a current trial. For example, on the presentation of a cue paired with a US, an assumption could potentially be made that the other cue was not associated with the US.

2.6.1. Learning model selection

Model fit indices to SCR data were extracted for each subject: Aikake Information Criteria (AIC), and Bayesian Information Criteria (BIC). Nonparametric paired samples comparisons (Wilcoxon test) were conducted on AIC and BIC to compare model fit indices between the RW/PH hybrid, the intercue-dependent RW/PH hybrid, and the RW models. Model fits were superior for the intercue-dependent RW/PH hybrid model compared with the other 2 models ($Ps < 0.05$, AIC and BIC indices were smaller for the RW/PH hybrid model vs the RW model, and AIC/BIC indices were significantly or marginally significantly smaller for the intercue-dependent RW/PH hybrid

Table 2

Wilcoxon signed rank test statistics for comparison of computational model AIC/BIC fit indices.

	RW model		RW/Pearce-Hall (PH) hybrid	
	AIC	BIC	AIC	BIC
RW/Pearce-Hall (PH) Hybrid	Z = −4.61**	Z = −5.97**	—	—
Inter-cue dependent RW/PH Hybrid	Z = −2.30*	Z = −5.78**	Z = −1.76#	Z = −5.78**

Significant effects of predictors are indicated on the graph with asterisks. *$P < 0.05$, **$P < 0.001$, #$P = 0.079$.
PH, Pearce-Hall; RW, Rescorla-Wagner.

vs the RW/PH hybrid models, see **Table 2**). The fact that the RW/PH hybrid models had a superior fit to our data than the RW model indicates that learning was better modeled as a function of both associability and prediction error, and that learning was accelerated following enhanced prediction errors and decelerated following smaller errors. In addition, the superior fit to our data of an intercue-dependent RW/PH hybrid model compared with a RW/PH hybrid model indicates that learning about the cue that was *not* presented on a given trial occurred based on information obtained from the cue that *was* present on that trial.

2.6.2. Model descriptions

For the Rescorla–Wagner model (Equations 1, 2), expected shock probabilities (denoted as *V* in the following equations) on a given trial (*t*) were updated as a function of the prediction error (δ) obtained on the preceding trial. The prediction error—discrepancy between the actual outcome (λ) administered on a given trial and the expected outcome—was modulated by a constant learning rate (α). Pain administration was coded as 1 and absence of pain as 0.

$$V_{t+1} = V_t + \alpha \times \delta_t \quad (1)$$

$$\delta_t = \lambda_t - V_t \quad (2)$$

For the RW/PH hybrid model (Equations 3–5), expected shock probabilities were modeled in the same way as in the RW model, but the learning rates were dynamically modulated by an associability term (*a*). The associability term was updated as a function of the prediction error's absolute value (the surprising quality of the outcome, whether it be unexpected pain or unexpected pain omissions), and modulated by a constant term (**γ**).

$$V_{t+1} = V_t + a_t \times \alpha \times \delta_t \quad (3)$$

$$\delta_t = \lambda_t - V_t \quad (4)$$

$$a_{t+1} = \Upsilon \times |\delta t| + (1 - \Upsilon) \times a_t \quad (5)$$

More specifically, the RW/PH hybrid intercue-dependent model depicted the nature of our fear-conditioning paradigm involving 2 distinct CSs, ie, the CS+ paired with the US, whereas the other cue (CS−) predicted the absence of pain in a given learning phase. Thus, fear learning parameters were not necessarily updated independently from one another. In other words, the unpresented cue at each trial would be updated according to a prediction error computed by attributing the "opposite" outcome. Therefore, the RW/PH hybrid intercue-dependent model consisted of a variant of the RW/PH hybrid model by attributing specific parameters to the cue presented on each trial (*c_pres*) and the cue that was not presented on that trial (*c_unpres*).

$$Vc\_pres_{t+1} = Vc\_pres_t + ac\_pres_t \times \alpha c\_pres \times \delta c\_pres_t \quad (6)$$

$$\delta c\_pres_t = \lambda_t - Vc\_pres_t \quad (7)$$

$$ac\_pres_{t+1} = \Upsilon c\_pres \times |\delta c\_pres_t| + \left(1 - \Upsilon c\_pres\right) \times ac\_pres_t \quad (8)$$

In the same way, associability and expected pain on each trial were updated for the cue that had not been presented (*c_unpres*) by attributing it the opposite outcome, denoted by $|1-\lambda_t|$.

$$Vc\_unpres_{t+1} = Vc\_unpres_t + ac\_pres_t \times \alpha c\_unpres \times \delta c\_unpres_t \quad (9)$$

$$\delta c\_unpres_t = |1 - \lambda_t| - Vc\_unpres_t \quad (10)$$

$$ac\_unpres_{t+1} = \Upsilon c\_unpres \times |\delta c\_unpres_t| + (1 - \Upsilon c\_unpres) \times ac\_unpres_t \quad (11)$$

Following previous recommendations,[2] expected shock probabilities and associability values at each trial for each subject were computed from the model's fixed parameters averaged across subjects: αc_pres = 0.19, αc_unpres = 0.22, γc_pres = 0.21, γc_unpres = 0.33, X0 = 18.23, X1 = −13.21, X2 = −18.17, V0 = 0.35, a0 = 0.49.

Figure 2 shows skin conductance data to unreinforced cues (CS− and CS+ unpaired) averaged per learning phase (A) and trial-by-trial (B). **Figure 2B** also shows predicted SCR estimations to reinforced and unreinforced cues from the intercue-dependent RW/PH hybrid model. Expected shock probabilities (C) and associability (D) related to each cue are also shown in **Figure 2**.

3. Results

3.1. Effects of conditioning on anticipatory SCRs

To demonstrate the efficacy of our paradigm to elicit conditioned fear responses, we first examined anticipatory SCRs in response to the 2 predictive cues, averaged within the first (early) and second (late) halves of the acquisition, reversal and extinction phases of the experiment.[31] As expected, results of a 2 (cue 1, cue 2) × 6 (acquisition-early/late, reversal-early/late, extinction-early/late) analysis of variance revealed a significant Cue X Phase interaction ($F_{(1.47,71.86)} = 11.36$, $P < 0.0001$ with Greenhouse-Geisser Correction; **Fig. 2A**). Follow-up paired t-tests revealed that SCRs to the CS+ were higher than SCRs to CS− during conditioning (acquisition-early, $t_{(46)} = 3.15$, $P = 0.003$; acquisition-late, $t_{(46)} = 3.41$, $P = 0.001$; reversal-early, $t_{(46)} = 2.46$, $P = 0.018$; reversal-late, $t_{(46)} = 2.97$, $P = 0.005$). Moreover, conditioned SCRs decreased significantly at reversal and extinction when cues stopped to be paired with shocks (cue 1 acquisition-late vs reversal-early: $t_{(46)} = 3.07$, $P = 0.004$; cue 2 reversal-late vs extinction-early: $t_{(46)} = 3.55$, $P = 0.001$). Skin conductance responses were also significantly higher for cue 1 than cue 2 during early-extinction ($t_{(46)} = 3.42$, $P = 0.001$), suggesting that participants may have expected another reversal at the onset of the extinction phase.

The conventional demonstration of the conditioned fear-responses shown in **Figure 2A** was further expanded to a trial-by-trial analysis, allowing for the estimation of EShock and Associability, the 2 key parameters of the hybrid learning model. Estimates of each parameter were optimized using computational modeling. The global pattern of CS+/CS− discriminative learning was clearly captured by the model in the acquisition and reversal phases as shown by the time course of the predicted SCR (**Fig. 2B**). Learning parameters were then extracted from the optimized model for each trial and each subject according to the individual time series of CS+/CS− and US (see group averages in **Fig. 2C, D**). EShock and Associability for the reinforced trials (ie, paired CS+), reproduced in **Figure 3A**, provided learning-related predictors of responses to the noxious electrical stimulation.

3.2. Effects of conditioning on responses to electric shocks

The time course of mean shock-evoked pain and NFR responses displayed in **Figure 3B** did not reveal a global pattern of

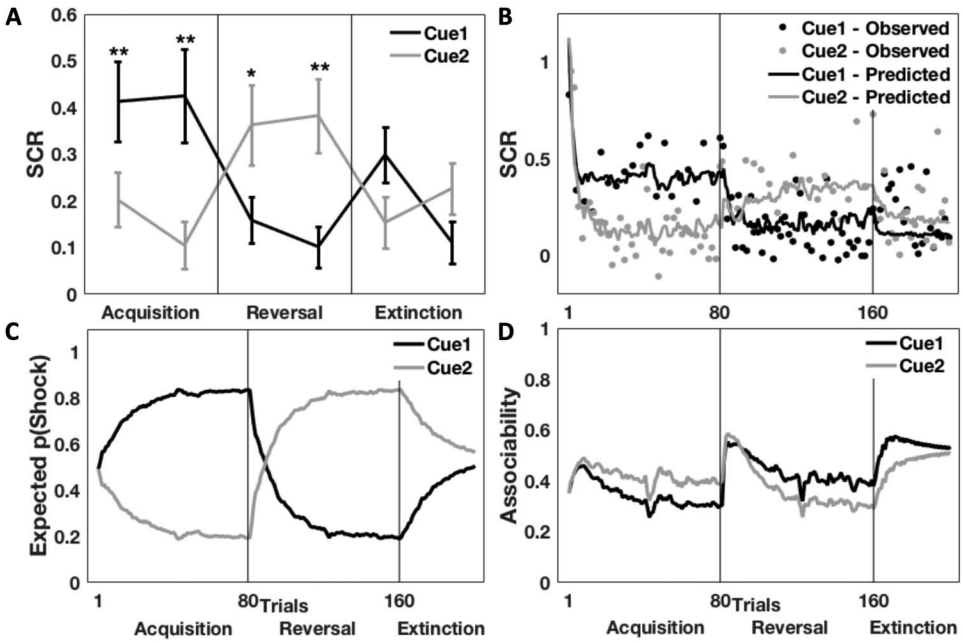

Figure 2. Anticipatory skin conductance responses (SCRs) and associability and expected probability of shock (expected *P* [shock]) estimates throughout the acquisition, reversal, and extinction phases of the experiment. (A) Anticipatory SCRs for all unreinforced (CS− and CS+ unpaired) trials of the experiment, averaged (± SEM) across the whole group for the early (first half) and late (second half) phases of acquisition, reversal, and extinction (*$P < 0.05$, **$P < 0.01$, paired *t*-tests). (B) SCRs predicted from the computational learning model (lines) and observed SCRs (dots). Note that while anticipatory SCRs cannot be measured for reinforced trials (CS+ paired) because of the temporal contiguity between the CS and the US, computational estimates can be derived from these trials, and used to predict pain responses (see Fig. 3C, D) (C, D) Trial-by-trial expected *P* (shock) (C) and associability (D) estimates, averaged over the whole group. CS, conditioned stimulus; US, unconditioned stimulus.

modulation across the early vs late parts of the acquisition and reversal phases using a conventional analysis based on trial and group averaging (analysis of variance, *P's* > 0.05). However, both responses seemed to be consistently lowest on the first trials of the acquisition and reversal phases, as compared to their immediate neighboring trials (first vs second acquisition trial: $F_{(1,46)} = 6.72$, $P = 0.013$; last acquisition trial vs first reversal trial: $F_{(1,46)} = 12.97$, $P = 0.001$; and first vs second reversal trial: $F_{(1,46)} = 18.74$, $P < 0.001$). Not surprisingly, computational modeling also indicates that these key learning trials show very large shifts in EShock probability and associability (**Fig. 3A**). Notably, these shifts are visible in the group averages because learning starts or contingencies change consistently in all subjects in those specific trials. This implies that trial and group averaging may mask dynamic effects and that the individual pattern of trial-by-trial fluctuations in pain responses may relate to immediate adjustments in the ongoing learning processes.

The effects of EShock and associability on pain responses were examined using multilevel regression analyses in which fear learning parameters at each trial were entered at the first level and subjects at the second level. Specifically, we predicted self-reported pain and NFR scores at each trial from EShock and Associability to shock-predicting cue (CS+ paired) using multilevel regressions as implemented in Hierarchical Linear Modelling (HLM) software. Results are shown in **Table 3** and confirmed that both EShock (*Beta* = 0.68, $t = 4.16$, $SE = 0.16$, $R^2 = 0.28$, $P < 0.001$) and Associability (*Beta* = 1.18, $t = 4.23$, $SE = 0.28$, $R^2 = 0.29$, $P < 0.001$) positively predicted pain ratings and NFRs (*Beta* = 0.82, $t = 4.52$, $SE = 0.18$, $R^2 = 0.32$, $P < 0.001$; *Beta* = 1.60, $t = 4.75$, $SE = 0.34$, $R^2 = 0.34$, $P < 0.001$ for effects of EShock and Associability, respectively). As can be observed in **Figure 3**, the combined contribution of EShock and Associability derived from the learning model allows making a prediction that explains a significant amount of the trial-by-trial variance in pain and the NFR (**Fig. 3C, D**, respectively).

Moreover, although EShock was relatively low in the first few trials of the acquisition and reversal phases, associability rapidly peaked after the surprising first cue-shock pairings of both phases. The combined influence of EShock and associability therefore paints a very dynamic and complex portrait of learning effects on pain. Indeed, pain seems to be increased when shocks are either expected with a high probability or when uncertainty is high. In contrast, participants experienced less pain when they were most certain that they would not receive an electric shock; ie, at the first reinforced trials of the reversal phases (see dip at reversal in **Fig. 3B**). Average effects of expected *P* (shock) (A) and Associability (B) on pain ratings and NFRs are illustrated in **Figure 4**.

Learning processes affected both pain perception and the spinal nociceptive response and the possible relation between those modulatory effects was further assessed in multilevel mediation analyses. Given that the modulation of pain perception is often assumed to reflect at least in part the involvement of cerebrospinal mechanisms affecting spinal nociception,[36] we tested the hypothesis that pain modulation by learning variables (EShock or associability) was mediated by the corresponding changes in the NFR (implemented with custom code written in Matlab, http://wagerlab.colorado.edu/tools, see **Fig. 5**). Moreover, to account for the significant negative relationship between EShock and associability (*Beta* = −1.05, $SE = 0.02$, $t = -61.72$, $P < 0.001$), each variable was regressed onto the other and the residuals (ie, EShock controlling for associability and vice-versa) were entered as predictors in the 2 mediation models tested. Results showed that the NFR was a significant mediator of the

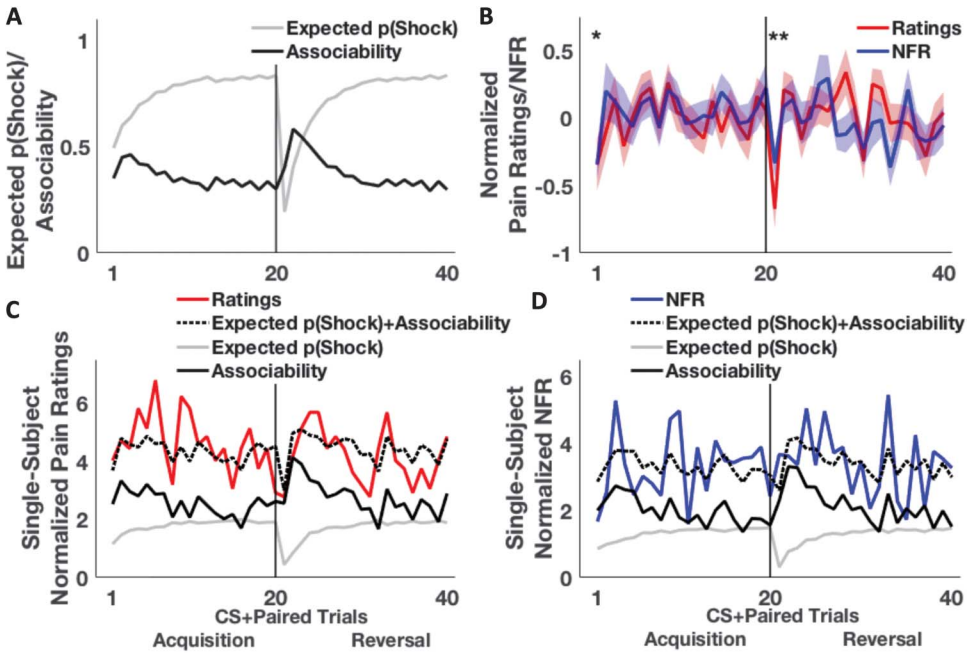

Figure 3. Relationship between expected shock probabilities (expected *P* [shock]), associability, pain ratings, and nociceptive flexion reflexes (NFRs) for reinforced (CS+ paired) trials. (A) Average associability and expected *P* (shock) estimates. (B) Average pain ratings and NFR amplitudes (lines), with shaded areas representing SEs of the mean. (C, D) Relationship between pain ratings, NFR amplitudes and associability/expected *P* (shock) estimates for 2 individual subjects. Trial-by-trial associability and expected *P* (shock) estimates were weighted by their regression coefficients to illustrate the multilevel regressions effects reported in Table 3. For parcimony, the intercepts of the regression models predicting pain ratings and NFRs from expected *P* (shock) and associability estimates (Table 3) were removed from observed pain ratings and NFRs. Pain responses were consistently lowest on the first trials of the acquisition and reversal phases, as compared to their immediate neighboring trials (first vs second acquisition trial; last acquisition trial vs first reversal trial; first reversal trial vs second reversal trial). ***$P < 0.001$, *$P < 0.05$. CS, conditioned stimulus.

effects of both learning variables on pain ratings ($c = 1.44$, $SE = 0.28$, $P < 0.001$, $ab = 0.11$, $SE = 0.04$, $P = 0.012$, for the effect of EShock on ratings and its mediation by NFRs; $c = 2.34$, $SE = 0.43$, $P < 0.001$, $ab = 0.28$, $SE = 0.08$, $P = 0.001$ for the effect of associability on ratings and its mediation by NFRs). However, the *c* path remained significant after accounting for the NFR mediation (*c′* in **Fig. 5**) indicating that effects of both learning processes on pain perception could be explained in part, but not entirely, by the descending modulation of spinal nociception.

Finally, to examine the influence of personality traits on learning-induced pain modulation, we first performed a PCA on scores of several psychological questionnaires (listed in **Table 1**). This allowed reducing the dimensionality of the data to 3 personality components: harm vigilance, emotional detachment, and acceptance (see Methods). These 3 variables were then tested as second-level moderators in our mediation models. Results showed that harm vigilance significantly increased 1—the effects of associability on NFRs (path *a*, **Fig. 5**), as well as 2—the NFR mediation between associability and pain ratings (path *ab*, **Fig. 5**), and 3—the NFR mediation between EShock and pain ratings (path *ab*, **Fig. 5**). Moreover, emotional detachment also decreased the strength of the relation between associability and NFRs (path *a*, **Fig. 5**). None of the personality components were significantly correlated with the fixed parameters of the learning model (all *P*s > 0.05) suggesting that the effects of personality factors on pain processing could not be explained simply by underlying interindividual differences in associative learning. This indicates that personality traits influence how learning affects pain processing.

Table 3

Multilevel regression analysis on pain ratings and NFR scores predicted by fear learning parameters.

	Beta	SE	*t*	R^2	*P*
Dependent variable: pain ratings to US					
LEVEL-1 predictors					
Intercept	−1.09	0.24	−4.66	—	<0.001***
Expected shock (US) probabilities	0.68	0.16	4.16	0.28	<0.001***
Associability	1.18	0.28	4.23	0.29	<0.001***
Dependent variable: NFR scores to US					
LEVEL-1 predictors					
Intercept	−1.19	0.21	−5.64	—	<0.001***
Expected shock (US) probabilities	0.82	0.18	4.52	0.32	<0.001***
Associability	1.60	0.34	4.75	0.34	<0.001***

Significant effects of predictors are indicated on the graph with asterisks (***$P < 0.001$).
NFR, nociceptive flexion reflex; US, unconditioned stimulus.

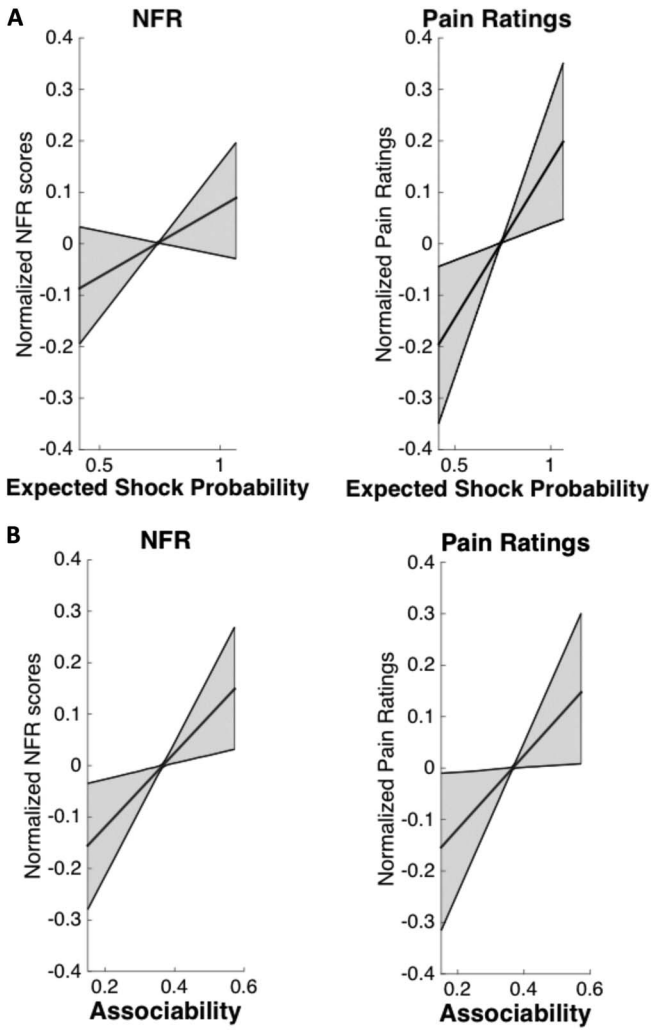

Figure 4. Average effect of expected probability of shock (expected *P* [shock]) (A) and Associability (B) on pain ratings and nociceptive flexion reflex (NFR) scores. The shaded gray area shows the 95% confidence interval for the regression slopes. Variability in the intercept values across participants has been removed for display purposes. ***$P < 0.001$, *$P < 0.05$.

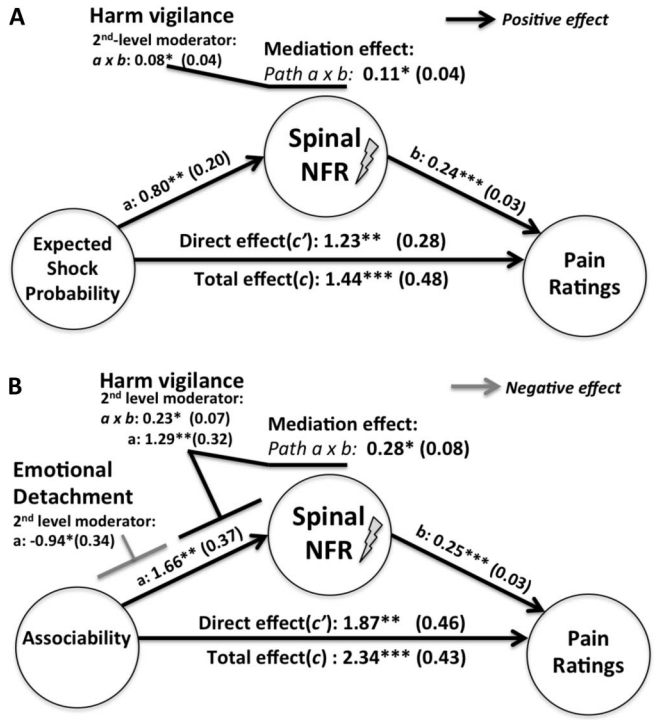

Figure 5. Multilevel mediation models of the effects of expected probability of shock (expected *P* [shock]) and associability on pain ratings. Path coefficients are shown for each path (*a*, *b*, *c*, and *c'*) and mediation effects ($a \times b$) with SEs in parentheses. (A) Nociceptive flexion reflex (NFR) scores partially mediated the effect of expected probability of shock (expected *P* [shock]) on pain ratings. Harm vigilance increased NFRs mediating effects (mediation term a × b). (B) NFRs partially mediated the effect of associability on pain ratings. Harm vigilance increased the effects of associability on NFRs (path *a*) and NFRs mediating effects (mediation term $a \times b$). Emotional detachment decreased the effects of associability on NFRs (path *a*). Average effect of expected *P* (shock)/Associability on pain ratings and NFRs are shown in Figure 4. ***$P < 0.001$, *$P < 0.05$.

The only personality trait that differed with respect to sex was harm vigilance, with males reporting less harm vigilance (M = −0.37, SD = 0.18) than females (M = 0.36, SD = 0.22). Females exhibited an enhanced mediation effect (albeit marginally significant) of the NFRs on the relationship between Associability and pain ratings (Beta = 0.31, STE = 0.16, z = 1.92, $P = 0.06$). No other sex differences were found to moderate any other path between fear learning parameters and NFRs/pain ratings.

4. Discussion

Pain plays an important role in teaching us about potential sources of harm in our environment. Pain-evoking stimuli further trigger associative learning mechanisms that constantly refine our predictions about what is most likely to cause us pain. Here, we used computational modeling to demonstrate that associative learning produces transient states of conditioned hyperalgesia that are paradoxically induced by both pain predictability and uncertainty. Indeed, the only moment when participants did not seem to suffer from hyperalgesic effects is when they were the most certain that they would not receive a painful electric shock. Effect sizes were large,[35] suggesting that the influence of learning on pain processing is considerable and may potentially have an important impact on pain perception in our day-to-day lives.

When only considering the averaged effects of trial number on pain processing, the hyperalgesic effects of conditioning could only be observed as the difference between the relatively low pain ratings and NFRs in response to the first shocks of the acquisition and reversal phases of the experiment, and the higher pain indexes observed throughout the rest of the experiment. However, results from computational modeling revealed that the apparent lack of learning effects after the first cue-pain pairings was in fact caused by opposing effects of expected pain (EShock)—which steadily rises as participants are exposed to repeated cue-pain associations—and associability—which tends to decrease as predictions become more accurate. Because these 2 parameters were estimated by fitting the learning models to anticipatory SCRs, and not to unconditioned responses to electric shocks, the opponency between EShock and associability effects cannot be because of over fitting of the learning model, and therefore likely reflects the workings of learning mechanisms that are affecting both anticipatory SCRs and pain responses to electric shocks. For the same reason, the strong and significant relationship between our computational estimates of associability/EShock and both measures of pain processing provide a convincing additional validation of the selected hybrid learning model.

According to reinforcement learning theories, EShock and associability reflect qualitatively different learning processes. Expected probability of shock simply refers here to the subjective probability of receiving an electric shock, and therefore broadly reflects the learning process that is generally implied in most fear-conditioning studies.[20] However, in contrast with more traditional analyses splitting acquisition and reversal phases in early and late phases (see **Fig. 2A**), EShock is estimated on a trial-by-trial basis. Thus, rather than considering the overall reinforcement rate (eg, 50%) across blocks of pseudorandom trials, modern implementations of learning models consider the effective and unique sequence of reinforcement experienced by the subject on a trial-by-trial basis. Computational modeling, therefore, provides EShock estimates that are better tailored to the unique sequence of reinforcement that is experienced by each subject.

In contrast with EShock, the associability term used in our learning model reflects the informational value of the outcome with respect to reinforcement contingencies. Associability is therefore expected to go down as predictions become more and more accurate (ie, reduced prediction error), and to rise when participants have recently been surprised by an unexpected outcome (ie, on trials that follow a large prediction error). Indeed, after having been surprised, attention towards the outcome of the following trial is increased because it may confirm or disconfirm a potential change in contingencies. Recent brain imaging studies have reported that different brain regions may encode EShock (ventral striatum) and associability (amygdala and basolateral amygdala)[9,24] during the presentation of the outcome during aversive conditioning. In addition, animal studies have shown the involvement of the central nucleus of the amygdala and its interplay with other brain systems (including striatal circuitry) in attentional changes related to associability.[16,18,19] Our data suggest that the output of these 2 systems may ultimately converge onto a single effector system responsible for allocating attentional resources to the processing of the US. The pain facilitating effects of associability found here are also in line with previous work[37] demonstrating that vicariously learned uncertainty (estimated using a Bayesian framework) about the intensity of impending pain had hyperalgesic effects.

In contexts in which cue-outcome probabilistic relationships are subject to frequent change, Bayesian modelling frameworks used to estimate different levels of uncertainty have explained amygdala activity[27] and autonomic arousal responses to US[14] during fear learning. Therefore, future work should extend our study in tasks in which cue/outcome associations are highly volatile, using Bayesian frameworks to estimate subjects' uncertainty with respect to outcomes and the stability of cue-outcome states, to model ensuing fluctuations in pain responses to the US.

Finally, this study demonstrated that learning effects on pain were partly mediated by spinal nociceptive processes, indicating that conditioned hyperalgesia at least partly relies on descending cerebrospinal modulatory pathways that gate the transmission of ascending nociceptive signals at the spinal level. Still, a significant part of learning effects on pain was not mediated by spinal nociceptive processes, and could therefore reflect higher-order (ie, supraspinal) processes affecting pain perception as a function of its predictability. Interestingly, interindividual differences in harm vigilance and emotional detachment specifically affected the portion of learning effects that was mediated by spinal nociceptive processes. Indeed, participants that were more harm vigilant and/or less emotionally detached displayed stronger spinal facilitation, which in turn contributed more to the hyperalgesic effects observed in pain perception. Thus, the parsing of learning effects into EShock/associability and spinally mediated/unmediated effects allowed us to reveal the precise mechanisms by which predisposing personality traits may influence conditioned hyperalgesia.

By contrast, the facilitatory effects of associability on pain responses was reduced in individuals with elevated dispositions to adopt detached and nonreactive attitudes towards their inner and emotional experiences. However, here the moderating effect was only found on the NFR, suggesting that in the context of learning, emotional detachment may reduce the reactivity to the noxious stimulus without having indirect consequences on pain perception. Previous studies have suggested that trait mindfulness is inversely related to pain catastrophizing in a chronic pain–patient sample and that it moderates the relationship between catastrophizing and reported pain intensity.[32] The present findings should motivate further investigation of the impact of emotional regulation training on aversive learning processes to unravel potential benefits in preventing learning-induced pain facilitation.[13]

In conclusion, this study demonstrates that pain perception is under the constant influence of learning processes that dynamically control the sensory gating of painful stimuli as a function of each individual's unique reinforcement history. This suggests that when an individual is submitted to repeated episodes of pain, a significant proportion of the pain perceived may become rapidly facilitated by learning and attentional factors. A better understanding of the psychological and neural mechanisms underlying learning effects on pain could therefore provide important insights into the sequence of psychological and neural events that lead to pain chronicity, and hopefully indicate novel ways of breaking the vicious circle by which expected and/or uncertain pain causes more pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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