Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness

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Pain reduction and enhancement can be produced by means of conditioning procedures, yet the role of awareness during the acquisition stage of classical conditioning is unknown. We used psychophysical measures to establish whether conditioned analgesic and hyperalgesic responses could be acquired by unseen (subliminally presented) stimuli. A 2 × 2 factorial design, including subliminal/supraliminal exposures of conditioning stimuli (CS) during acquisition/extinction, was used. Results showed significant analgesic and hyperalgesic responses ($P < 0.001$), and responses were independent of CS awareness, as subliminal/supraliminal cues during acquisition/extinction led to comparable outcomes. The effect was significantly larger for hyperalgesic than analgesic responses ($P < 0.001$). Results demonstrate that conscious awareness of the CS is not required during either acquisition or extinction of conditioned analgesia or hyperalgesia. Our results support the notion that nonconscious stimuli have a pervasive effect on human brain function and behavior and may affect learning of complex cognitive processes such as psychologically mediated analgesic and hyperalgesic responses.

classical conditioning | awareness | consciousness | placebo | nocebo

It has been well established that pain can be altered by associative learning procedures (1–3). In the present study, we sought to establish whether conditioned analgesic and hyperalgesic responses could be acquired by unseen (subliminally presented) stimuli.

The human brain can process sensory stimuli outside of conscious awareness (4), but it is not clear to what extent learning can take place when we are not aware of the associations being made. On one hand, associative learning with subliminally presented stimuli has been demonstrated [e.g., by Degonda and colleagues (5)]; on the other hand, a sizeable literature indicates that pain conditioning is mediated by conscious expectations (6–10). Studies of fear learning in humans suggest that emotional contingencies can be acquired nonconsciously, as demonstrated by conditioned changes in autonomic and motor responses (11–14). In addition to evidence for conditioning of low-level physiological responses, a recent literature challenges the idea that nonconscious processing stops at an early perceptual level (4), suggesting that higher-order cognitive representations, such as meaning and goal pursuits, can be acquired nonconsciously (15). Moreover, findings from neuroimaging studies show that nonconscious stimuli have extensive representations in the human brain, activating a large number of cortical areas (16–18) at frequency bands previously seen as markers of conscious awareness (19). Taken together, these results suggest that nonconscious stimuli have a pervasive effect on human brain function and behavior and may affect learning of complex cognitive processes such as psychologically mediated pain responses.

In a previous study, we found that consciously conditioned analgesic and hyperalgesic pain responses could be activated by means of nonconscious cues (20), yet it is not clear to what extent learning of conditioned pain responses can take place nonconsciously. Here, we studied the relationship between consciousness and associative learning in a pain perception context. Healthy participants were randomly assigned to one of four experimental groups, including an acquisition phase and a test phase, using either subliminal or supraliminal conditioned stimuli (CS), respectively (Fig. 1). Each participant was conditioned by pairing high- and low-intensity thermal pain stimuli with two different visual cues, hereafter called High CS and Low CS. During the test phase, a previously unconditioned visual cue was introduced, hereafter called the Control cue.

Results

The random assignment of participants to the four experimental groups led to comparable group characteristics regarding age, sex, and pain sensitivity (Table 1). During the conditioning phase, participants across all groups rated high pain temperatures as mean = 53 (SD = 18) on a numeric response scale (NRS) ranging from 0 (no pain) to 100 (worst imaginable pain), and low pain temperatures were rated as mean = 15 (SD = 13) NRS. Pain ratings during the test phase are displayed in Fig. 2*A*. These data were analyzed using a 3 × 2 × 2 mixed-model ANOVA. Cue type (High CS/Low CS/Control) was the within-subject factor; acquisition type and activation type (subliminal/supraliminal) were between-subject factors. The ANOVA revealed a significant effect of cue type on pain ratings during the test phase [$F(2, 86) = 29.53$; $P < 0.001$; $\text{eta}^2 = 0.41$] (Fig. 2). All pairwise comparisons (Bonferroni corrected) between the High CS, Low CS, and Control cues were significant ($P < 0.001$), indicating effects on pain ratings in both directions (i.e., analgesia and hyperalgesia) (Table 2). Pain ratings were independent of cue exposure type, as the main effect for the factors acquisition type (subliminal/supraliminal) and activation type (subliminal/supraliminal) were nonsignificant, and none of the interactions approached significance.

A paired samples *t* test across all experimental groups showed that the hyperalgesic effect was significantly larger than the analgesic effect [$t(46) = 4.8$; $P < 0.001$, two-tailed], indicating that our experimental design had a greater effect on the expectancy of aversive events.

Significance

It is unclear to what extent new learning can take place outside of conscious awareness. In the present study, we used psychophysical measures and classical conditioning to establish whether psychologically mediated analgesic and hyperalgesic responses could be acquired by unseen (subliminally presented) stimuli. Our study demonstrates that analgesia and hyperalgesia can be learned without conscious awareness, suggesting that higher-order cognitive processes may be affected by implicit learning mechanisms.

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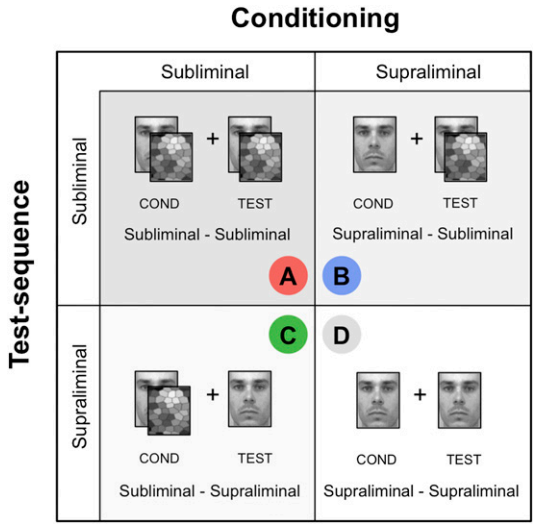

Fig. 1. Stimulus parameters and experimental design. The conditioning procedure (COND) included images of two male faces (conditional cues) presented on a computer screen. Human faces used with permission from KDEF. Each face cue was consistently paired with either a high or low heat pain stimulus on the volar forearm. After conditioning, a test sequence was performed (TEST) in which the High cue, the Low cue, and a neutral Control cue were paired with identical moderate heat stimuli. Subliminal images were shown by means of masked faces, and supraliminal images were shown unmasked. Faces were exposed for 12 ms during masked trials (followed by an 84-ms mask) and for 100 ms during unmasked trials. Participants were randomly assigned to one of four combinations of subliminal/supraliminal conditioning and subliminal/supraliminal test sequence.

The difference between ratings of High Pain and Low Pain temperatures during conditioning was correlated significantly with the difference in analgesic and hyperalgesic responses during the test phase ($r = 0.4$; $P = 0.011$), indicating that the perception of the unconditioned response affected the conditioned responses.

There were no significant correlations between participants' self-reported level of neuroticism and analgesic ($r = 0.18$; $P = 0.243$, two-tailed) or hyperalgesic ($r = -0.16$; $P = 0.283$, two-tailed) responses.

Discussion

We demonstrate that nonconscious associative learning can produce conditioned analgesic and hyperalgesic pain responses. Our experiment included both subliminal (unseen) and supraliminal (seen) conditioned stimuli and found no significant difference in outcomes between the two. In a previous study (20), we provided evidence for nonconscious activation of analgesic and hyperalgesic responses established with supraliminal stimuli during an earlier conditioning phase. Thus, we extend our previous findings by demonstrating that new learning of conditioned pain responses can occur even when the conditioned stimulus is presented subliminally during the acquisition phase.

Our demonstration of nonconscious conditioning of pain is in line with the behavioral responses of patients with blindsight and in some patients with amnesia or prosopagnosia (21). In both cases, patients may deny awareness of presented stimuli, yet the response to the stimuli clearly reveals effects on behavior. Because the brain is hierarchically organized, and information may reach the brain at different levels (22), it is likely that learning can take place at any level of perceptual information processing. In our experiment, the subliminal stimuli were unrecognized by the participants, yet they were presented long enough for the brain to pick up the contingencies and create predictive knowledge and drive pain modulation (23). In a previous study, we used neuroimaging to study the neural correlates of nonconscious activation of analgesic and hyperalgesic responses (24) and found higher involvement of subcortical brain areas during nonconscious versus conscious trials, suggesting a hierarchical activation of neural pathways for nonconscious and conscious conditioned responses. The present data conceptually extend our previous study by concluding that new associations can be acquired at a very basic level of information processing, where brief exposures of visual cues can form significant analgesic and hyperalgesic responses. In contrast to studies of subliminal fear conditioning in humans, with demonstrated effects on autonomic and motor responses (11–14), our study suggests that low levels of the brain's hierarchical organization are susceptible for learning that affects higher-order cognitive processes (as our primary outcome measured subjective pain reports). Theories of placebo analgesia have posited that placebo responses are the result of top-down expectations and predictions of pain (relief), integrated with bottom-up sensory signals at multiple levels of the neural hierarchy (23, 25, 26). Here we demonstrate, for the first time to our knowledge, not only that the reflection of top-down predictions is manifested at lower levels of the neural axis but also that new associative learning of pain responses can take place in the absence of conscious awareness.

The inclusion of a control cue in the present study allows for the interpretation of increased pain (compared with control) in response to hyperalgesic cues and decreased pain (compared with control) in response to analgesic cues. Studies of conditioned pain responses usually report the difference in ratings between high cues and low cues, only offering an indication of a relative change in pain perception without directionality. Here, we were able to address within-subject differences between conditioned analgesia and conditioned hyperalgesia.

In recent years, conditioned analgesic and hyperalgesic responses in humans have been studied largely within the context of placebo and nocebo effects, including creams, pills, and

Table 1. Participant characteristics

Variable	Group A	Group B	Group C	Group D
Age	25.1 (5.2)	25.9 (4.7)	29.5 (10.1)	25.0 (5.2)
Male/female ratio, M/F%	39/61	36/64	58/42	27/73
High pain temperature (calibrated), °C	47.5 (1.1)	47.1 (1.5)	47.1 (1.4)	47.5 (1.6)
Low pain temperature (fixed), °C	44.5 (1.1)	44.1 (1.5)	44.1 (1.4)	44.5 (1.6)
Moderate pain temperature (fixed), °C	46.0 (1.1)	45.6 (1.5)	45.6 (1.4)	46.0 (1.6)
Pain rating, high temperature (NRS)	51.7 (20)	51.4 (16.5)	53.8 (17)	55.9 (19)
Pain rating, low temperature (NRS)	11.6 (9.5)	18.8 (18)	18.3 (12.2)	14.2 (13)

Calibrated high pain temperatures represent the temperature at which each participant rated pain around 60 on a 0–100 pain NRS. Low pain temperatures were set as 3 °C below the calibrated high pain temperature (fixed), and moderate pain was set as the temperature right in between high and low pain (fixed). Pain ratings (0–100 NRS) are from the conditioning phase, when tailored high and low temperatures were used. Values represent group means and SDs.

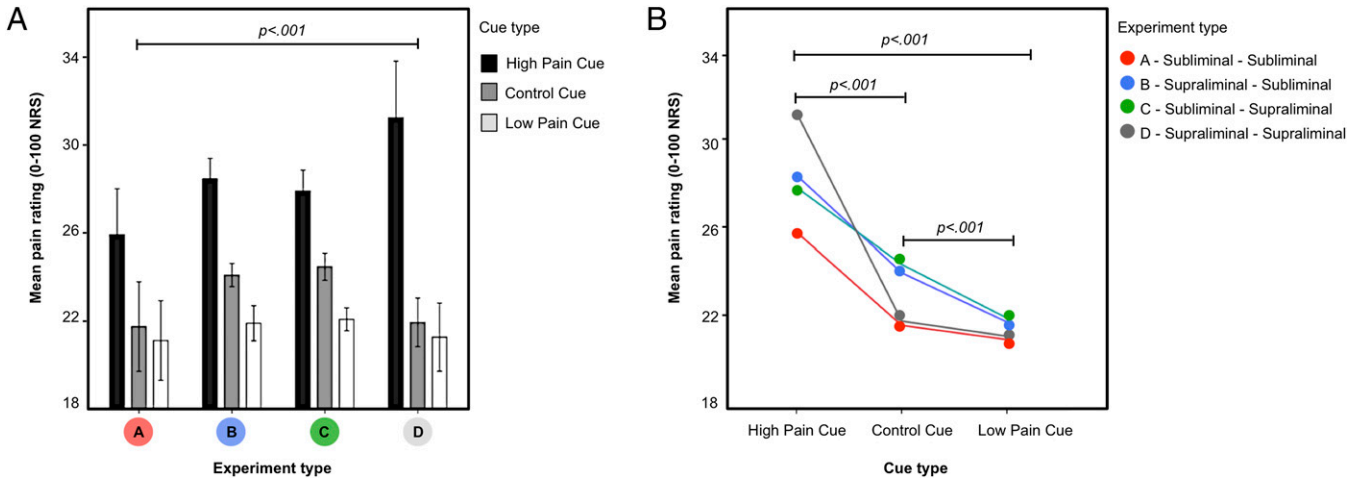

Fig. 2. Pain ratings during subliminal and supraliminal analgesia and hyperalgesia trials. Identical moderate temperatures were paired with a conditioned High Pain cue, Low Pain cue, or Control cue to test how predictive cues changed participants' pain perception. Participants rated pain intensity on a 0–100 NRS. (*Left*) Representation of pain ratings during the test sequence that followed the initial conditioning sequence. Bars represent the average pain rating in response to identical moderate temperatures. Error bars represent 2 intrasubject SEs. The *P* value ($P < 0.001$) reflects the main effect for cue type across all experimental groups. (*Right*) Illustration of the interaction of cue type (High, Low, Control) by experimental group (A, B, C, and D). *P* values reflect the pairwise comparisons between cue types across experimental groups (High–Control, Low–Control, High–Low).

infusions that constitute the placebos used as conditional stimuli. Although this study did not include placebos *stricto sensu*, we believe that our data map well onto that literature, as we used visual cues as conditional stimuli, standing in for placebos. Our data thus challenge the current notion that placebo and nocebo responses can be dichotomized and explained either as the result of an automatic nonconscious conditioning process or by the formation of conscious expectancies by, for example, verbal suggestions (10). Previous studies have reported that conditioning procedures for physiological functions that can be consciously perceived (e.g., pain reduction) are mediated by expectancy compared with responses that are not consciously perceptible (e.g., hormone release) (7, 10). How can we reconcile the apparent difference in outcomes between studies indicating that conditioned placebo and nocebo analgesia responses are mediated by expectancy and our data showing that conditioned analgesic and hyperalgesic responses can be acquired and activated with cues that are not consciously perceived (20, 24)? We believe that the answer may lie in differences between conditioning procedures. Typically, classical conditioning involves stimuli with discrete onsets that are repeatedly paired with the unconditioned stimulus, optimally with very short intervals between the onset of the CS and the onset of the unconditioned stimulus (27). This is the method used in our previous studies showing effects of nonconscious cues on placebo and nocebo responses (20, 24). In studies showing expectancy mediation of conditioned responses, the CS has been applied only once during the so-called conditioning procedure. In most of these studies, lowered levels of noxious stimulation are administered at a location on the body where a placebo cream (the CS) has been applied. It is possible that these single CS administration procedures do not qualify as classical conditioning. Instead, they may be thought of as conditioning-like, experiential expectancy manipulations, and their effects may depend on conscious perception of the CS during both acquisition and the test phase. Conversely, our data indicate that more typical classical conditioning procedures can produce analgesia and hyperalgesia even when the CS is presented outside of conscious awareness. Although cognitively mediated conditioning effects have been shown in animals (28, 29), it seems implausible that the conditioning effects observed in such simple organisms as sea slugs (Aplysia) (30) would involve conscious expectancies. Although cognitive mediation may be the norm in humans, it would not be surprising if vestiges of simpler nonconscious processes would also be operative under some conditions. It remains to be established whether the subliminally conditioned analgesic and hyperalgesic responses we have found are mediated by consciously accessible expectancies.

When comparing the magnitude of the analgesic and hyperalgesic effects, we found that the hyperalgesic response was significantly more pronounced than the analgesic response. During very rapid exposures, such as the masked visual cues in our experiment, it is possible that threat-related cues are more salient than safety-related signals, representing a valuable evolutionary adaptation to challenges in the environment. The literature on nonconscious processing of fear reveals robust autonomic and cerebral activations in response to subliminal exposures of feared stimuli (12, 14, 31, 32), supporting the idea that aversive cues are rapidly processed in neural circuits independent of conscious awareness.

Inspection of Fig. 2 suggests that the conditioned analgesic effect might have been greater in conditions in which one, but not both, of the CS were presented subliminally. However, the three-way interaction did not approach significance, and previous studies

Table 2. Pairwise comparisons of test sequence pain ratings with Bonferroni adjustments for multiple comparisons

Comparison	Mean difference (SD)	*t*	*P*	95% confidence interval	Cohen's d_z
High–Control	5.21 (7.42)	4.82	0.00003	2.65–7.96	0.70
Control–Low	1.53 (2.73)	3.84	0.0009	0.57–2.53	0.56
High–Low	6.75 (7.88)	5.87	0.000001	3.98–9.72	0.86

using similar methods have reported significant analgesic effects with supraliminal cues at both acquisition and testing (20, 24). Hence, this apparent dependence of the analgesic effect on mixing subliminal and supraliminal cues is likely not reliable.

Previous studies suggest that high trait neuroticism is associated with the engagement of brain regions responsible for emotional and cognitive appraisal during anticipation of pain (33). The inclusion of a neuroticism scale (34) aimed to control for the possibility that pain responses would be biased by participants' level of trait neuroticism. We did not find any significant correlations between neuroticism and pain reports in this study. Previous studies suggest that pain unpleasantness measures, but not pain intensity, are influenced by neuroticism (35, 36). Hence, if we had asked for affective pain ratings (in addition to pain intensity ratings), we may have found a link between our results and trait neuroticism.

There was a significant correlation between the perceived difference between High and Low Pain stimuli during conditioning and the analgesic and hyperalgesic responses during the subsequent test sequence. This was reported in our previous study (20) and illustrates that the strength of the learning signal, represented by the reported pain difference between high and low temperatures, establishes the effects of conditioning, regardless of conscious awareness.

Our results demonstrate that conscious awareness of conditioned stimuli is not required during either acquisition or activation of conditioned analgesic and hyperalgesic responses, and that low levels of the brain's hierarchical organization are susceptible for learning that affects higher-order cognitive processes.

Online Methods

Participants. This experiment involved 49 healthy participants, randomly assigned into four experimental groups (Fig. 1): group A ($n = 13$, 8 women), group B ($n = 12$, 7 women), group C ($n = 12$, 5 women), and group D ($n = 12$, 8 women). All participants were generally healthy, with no chronic illnesses or psychiatric diagnoses. None of the participants reported receiving any medication apart from hormonal contraceptives. Two participants were excluded from the statistical analysis, as they did not keep their eyes open during the entire experiment because of sleepiness. Participants were recruited by posting flyers at different universities, libraries, and residential buildings and through an electronic bulletin board. A small monetary compensation was sent to participants via check after participation.

Material. The Pathway system from Medoc with a 3×3 cm advanced thermal stimulator (ATS) thermode was used to generate thermal pain stimuli. Each pain stimulus lasted for 4 s. Visual presentations were shown with an 85-Hz, 19.8-inch cathode ray tube monitor (Sony, model GDM-F520) with a resolution of $1{,}920 \times 1{,}440$. The masked stimulus presentations were synchronized with a refresh rate of 12 ms. The experiment was programed using Presentation 13.0 (Neurobehavioral Systems). The images used in this experiment were taken from The Karolinska Directed Emotional Faces set (37), which is a set of images developed for use in perception, attention, emotion, memory, and backward masking experiments. The set consists of 70 individuals (35 men and 35 women), mean age 25 y (range, 20–30 y), with seven different facial expressions per individual. This study included 12 male faces, and the images that were used represented men with neutral face expressions.

Procedure. Participants were selected by inclusion and exclusion criteria via email and then scheduled for an experiment. Participants were informed that the study would examine pain, learning, and cognitive functions, but the full purpose of the study was not revealed until after the experiment was over. The Local Ethics Committee in Stockholm approved the study before the experiments being carried out, and all participants gave their written informed consent before participating.

The experiment was conducted in a quiet room with a temperature of 21 °C. Participants were placed straight in front of the monitor, which was placed ∼70 cm from the subject's face. The thermode stimulator was placed on the subject's left volar forearm. High Pain temperatures were calibrated for each subject by ascending temperatures starting from 40 °C. High Pain was set at ∼60 of 100 on a 0–100 NRS, where 0 is no pain at all and 100 is highest imaginable pain. Low Pain was set to a fixed 3 °C below the calibrated High Pain temperature.

After calibrating the High Pain temperature, the experiment was carried out. The experiment first had a conditioning sequence and then a test sequence. The conditioning and the test sequence presented either unmasked (clearly visible) cues or masked (nonrecognizable) cues. The following instruction was given to participants in all four experiment groups: "You will be shown pictures on the screen. Each picture will be paired with a pain stimulus on your arm. Your task is to concentrate on the screen at all times, and after each pain stimulus I would like you to rate how painful you experienced the stimulus with the same 0–100 verbal scale that you used during the calibration." The conditioning sequence was divided into two blocks of ∼7 min each, with a break of around 1.5 min in between. During the break, the participant could rest and look away from the monitor. The conditioning sequence included 40 stimuli in total: 20 high-pain temperatures (paired with High Pain cues) and 20 low-pain temperatures (paired with Low Pain cues). Experiments containing masked cues had this additional instruction: "The pictures will be shown very quickly, so it will be hard to perceive them clearly. We programmed it like this on purpose, and your task is just to focus on the screen and rate the pain, even if you can't see the pictures properly."

The test sequence followed immediately after the conditioning sequence and contained 60 stimuli: 20 High Pain cues, 20 Low Pain cues, and 20 previously unconditioned Control cues. Two initial cues in each sequence were paired with their original temperatures from the conditioning sequence to prevent extinction. The ratings from these real temperature trials were not included in the statistical analysis. All remaining cues were paired with identical moderate temperatures, determined as the temperature in between each participant's low and high pain temperatures; for example, if High Pain = 48 °C and Low Pain = 45 °C, then Moderate Pain = 46.5 °C. The test sequence was divided into three blocks of ∼7 min each with a 1.5-min break in between. In all four experimental groups, the two faces associated with high or low pain were counterbalanced to reduce the risk that a certain face would contribute to higher or lower pain ratings.

Visual cues during unmasked trials (supraliminal trials) had a duration of 100 ms; visual cues during masked trials (subliminal trials) had a duration of 12 ms (target image, one refresh cycle), followed by a mask for 84 ms (seven refresh cycles). The mask had the same size and color as the face images, but instead of facial features, the mask consisted of small squares put together to a random mosaic (Fig. 1). The same mask was used for all masked trials. The experimental leader was placed in a chair diagonally behind the subject to record participants' pain ratings and to monitor the participants' focus on the screen. The experimental leader repeated each verbal pain rating with a clear voice to ensure correct recordings of pain ratings by allowing the subject to correct the experimental leader if necessary.

To verify that the masked stimuli were truly nonrecognizable, all participants were asked to perform a face recognition test at the end of the experiment. The recognition test consisted of masked exposures of 24 face images: half of the faces were used earlier in the experiment, and half of them were novel faces. The participants were asked to say whether they had seen the face before by answering yes or no. The face images were exposed for 12 ms, and then a mask was exposed for 84 ms, the same parameters used for masked trials in the experiment. The participants were given the following instruction: "You will be shown some faces on the screen again. Some are new and some you have seen before. Your task is to decide whether or not you have seen the faces previously during the experiment. The faces will be shown very quickly, so you might not be able to tell if you have seen the face before or not. I want you to answer 'yes' or 'no,' and if you are unsure, you have to guess."

As in our previously published experiments (20, 24), the overall recognition rate of masked cues was 59%. The correlation between recognition accuracy and the difference in postconditioning pain ratings for High minus Low cues was not significant ($r = -0.06$; $P = 0.669$), indicating that the recognition rate did not explain any of the variance in the conditioning effects. One participant was statistically deemed an outlier, as this participant was correct on all 24 trials in the recognition test. Still, the exclusion of this participant from the overall analyses of study outcomes did not affect any of the results. When excluding all participants with a recognition rate >55%, resulting in a 48% recognition rate of masked stimuli, the conclusions from of the overall ANOVA and the pairwise comparisons are confirmed. The ANOVA revealed a significant effect of cue [$F(2, 28) = 10.91$; $P < 0.001$; $\text{eta}^2 = 0.44$]. All pairwise comparisons among the High, Low, and Control Cues were significant ($P < 0.05$). There were no significant main effects involving cue type (subliminal/supraliminal) during the acquisition or test phases, nor did any of the interactions approach significance. A d′ sensitivity analysis, which takes the "hit" versus "false alarm" rate into account when quantifying the

accuracy of participants' answers, indicated that participants performed at chance level [mean d′ = 0.04; $t(47) = 0.12$; $P = 0.846$, two tailed]. We thus conclude that the masked stimuli used in this experiment were truly nonrecognizable and that the degree of accurate recognition of masked stimuli did not explain any variance in conditioned pain ratings in our experiment.

To control for any variance in pain ratings based on participants' level of neuroticism, all participants were assessed for trait neuroticism, using the 12-item neuroticism scale from the Eysenck personality questionnaire (34). At the very end of the experiment, participants were asked to fill out this pen and paper questionnaire.

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