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Conscious Awareness Differentially Shapes Analgesic and Hyperalgesic Pain Responses

Cuizhen Liu
National University of Singapore

Min Pu and Weicheng Lian
South China Normal University

Li Hu
Chinese Academy of Sciences

Dean Mobbs
California Institute of Technology

Rongjun Yu
National University of Singapore

A large proportion of human cognitive processes may operate outside of conscious awareness. Subliminally presented visual stimuli that are not consciously perceived have a pervasive effect on behavioral and autonomic responses. Recent studies have claimed that placebo/nocebo effects, which are previously thought to require conscious expectancies, can be elicited to comparable levels regardless of whether the stimuli were consciously perceived or not. We systematically explored the role of consciousness in conditioned analgesic and hyperalgesic pain responses using both classical delay conditioning procedure and trace conditioning procedure. In 2 experiments (total $N = 247$), we found that analgesic and hyperalgesic responses were differentially dependent on the conscious awareness of the relevant stimuli. Specifically, the analgesic response was only significant when stimuli were supraliminal in both conditioning/acquisition phase and test/activation phases. While the hyperalgesic responses were acquired and activated irrespective of stimulus exposure (supraliminal/subliminal), the magnitude of this response was larger when stimuli were supraliminal in the test stage. Our results indicate that analgesic responses require both conscious conditioning and conscious activation, challenging the view that classical conditioning of analgesic pain responses operates without conscious awareness. Hyperalgesic responses are generally not dependent on the consciousness of stimuli, suggesting the presence of a valence-specific rapid regulatory mechanism to enable adaptive responses in threatening circumstances. Our study demonstrates a nascent role of consciousness in the learning of complex cognitive processes.

Keywords: conditioning, awareness, analgesic placebo, hyperalgesic nocebo

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Pain is a dynamic experience induced by both sensory stimulation and psychological modulation (Auvray, Myin, & Spence, 2010). The sensations of pain are substantially modulated by cognitive and affective processes (Bushnell, Čeko, & Low, 2013; Wiech, Ploner, & Tracey, 2008). Numerous studies have demonstrated the cognitive modulation of pain, including belief (Wiech, Farias et al., 2008), learning (Ploghaus et al., 2000), expectancy (Freeman et al., 2015), emotion (Wiech & Tracey, 2009), and attention (Bantick et al., 2002).

A powerful example of how pain is affected by subjective belief and experience is analgesia or hyperalgesia (Wiech, Ploner, et al., 2008). In clinical contexts, a placebo that has no intended therapeutic function could lead to pain relief if subjects believe that the treatment is effective in reducing pain (Gupta & Verma, 2013).

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Cuizhen Liu, Department of Psychology, National University of Singapore; Min Pu and Weicheng Lian, School of Psychology and Center for Studies of Psychological Application, South China Normal University; Li Hu, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences; Dean Mobbs, Division of Humanities and Social Sciences, Computation and Neural Systems Program, California Institute of Technology; Rongjun Yu, Department of Psychology, National University of Singapore.

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Correspondence concerning this article should be addressed to Rongjun Yu, Department of Psychology, National University of Singapore, 9 Arts Link, Singapore 117570. E-mail: psyyr@nus.edu.sg

Conversely, a nocebo hyperalgesia response can be elicited if subjects anticipate an increase of pain after treatment (Häuser, Hansen, & Enck, 2012). Such placebo and nocebo effects can also occur without explicit expectancy or conscious awareness. For example, a simple conditioning procedure can elicit increased or decreased pain report without the involvement of any expectancy (K. B. Jensen et al., 2012; K. B. Jensen, Kaptchuk et al., 2015; K. B. Jensen, Kirsch, Odmalm, Kaptchuk, & Ingvar, 2015). Because of the considerable effects placebo and nocebo can have in clinical practice and research, a large body of research has investigated the mechanisms in which placebo/nocebo effects are based. Specifically, there is a lively debate about factors that shape placebo effects and the form of learning that mediates the placebo effect.

Debate Between Expectancy and Conditioning: The Role of Consciousness in Shaping Placebo Analgesia and Nocebo Hyperalgesia

Expectancy and conditioning are known to play important roles in analgesic and hyperalgesic pain perception (Kirsch et al., 2014; Stewart-Williams & Podd, 2004). The critical role of expectancy in eliciting placebo analgesia and nocebo hyperalgesia has been highlighted in pain modulation. Neuroimaging studies show that anticipation of either decreased or increased pain response are related to decreased or increased brain activity in pain-matrix brain regions such as the thalamus, insula, and anterior cingulate cortex (ACC), demonstrating an expectation-triggered alteration of sensory pain transmission (Tracey, 2010; Wager et al., 2004). Moreover, the reported magnitude of alteration of pain is associated with prefrontal cortex (PFC) activity during anticipation of pain alteration, confirming that top-down cognitive evaluation from the PFC is needed to generate and maintain expectations that contribute to the modulation of pain (Koyama, McHaffie, Laurienti, & Coghill, 2005; Wager et al., 2004).

Conditioning has been thought to represent an automatic associative mechanism in eliciting analgesic and hyperalgesic pain perception. In a typical classical conditioning procedure, a neutral stimulus (e.g., geometric shape; conditioned stimulus [CS]) is repeatedly paired with a potent stimulus (e.g., noxious heat; unconditioned stimulus [US]) that evokes a biologically meaningful response (e.g., painful experience; unconditioned response [UR]). After several times of association, the CS can, by itself, evoke a negative response (conditioned response [CR]). Even when there is no verbal information in a conditioning procedure, subjects may consciously learn the association between CS and US, and such awareness of the association may in turn strengthen the conditioned response (Kirsch et al., 2014). Findings from neuroimaging studies further support the involvement of top-down modulation of pain during conditioning, showing a general PFC signal change across differential CSs, which predicts subsequent sensory input-evoked pain networks (Büchel, Geuter, Sprenger, & Eippert, 2014; Lui et al., 2010).

In brief, classical conditioning and expectancy may work independently or interactively in pain modulation. Expectancy alone, mainly manipulated by verbal instruction, could lead to hyperalgesia and analgesia effect (Atlas & Wager, 2012). Conditioning combined with verbal information elicits stronger effects (Jepma & Wager, 2015; Reicherts, Gerdes, Pauli, & Wieser, 2016). Conditioning may be confounded with the expectancy effect as participants can predict future events after they learn the cue–outcome associations. Indeed, many studies have proved that the effect of conditioning on pain modulation is mediated by conscious expectancy (Benedetti et al., 2003; Kirsch et al., 2014; Peciña, Stohler, & Zubieta, 2014). A promising strategy to disentangle classical conditioning from expectancy is subliminal conditioning, in which CS is displayed for tens of millisecond and masked. In such subliminal conditioning, subjects are blind to the CS in the whole conditioning procedure, thus are unable to make explicit predictions about the incoming stimuli (K. B. Jensen et al., 2012; K. B. Jensen, Kaptchuk et al., 2015; K. B. Jensen, Kirsch et al., 2015).

Analgesic and hyperalgesic pain responses may differ according to our conscious awareness of the CS. Specifically, participants may be more sensitive to threat-related cues (e.g., high pain) compared to safety-related signals (e.g., low pain) because threat-related cues could be signals of harm even when they are unseen (Gross & Canteras, 2012; LeDoux, 2012; Maren, 2005). Subliminal fearful stimuli have been shown to elicit behavioral expression of fear and enhanced amygdala activity (Liddell et al., 2005; Raio, Carmel, Carrasco, & Phelps, 2012). Such an ability to unconsciously learn which stimuli are dangerous is vital for survival and adaptation to the complex environment. In contrast, analgesic responses may require individuals to be aware of the relationships among the stimuli. There is robust evidence showing that the magnitude of the placebo effect is mediated by self-reported consciousness (Colloca & Benedetti, 2009; Colloca & Miller, 2011). Although a few studies have also provided support for comparable analgesic and hyperalgesic responses in the absence of consciousness (K. B. Jensen et al., 2012; K. B. Jensen, Kirsch et al., 2015), closer inspection suggests that hyperalgesic responses may be more automatic and less dependent on consciousness than analgesic responses.

The Role of Consciousness Regarding Delay Conditioning and Trace Conditioning

Recent studies have demonstrated that analgesic and hyperalgesic pain responses can occur without conscious awareness in a delay conditioning paradigm in which the CS and US overlap (K. B. Jensen et al., 2012; K. B. Jensen, Kaptchuk et al., 2015; K. B. Jensen, Kirsch et al., 2015). Specifically, two face cues that were presented supraliminal or subliminally were consistently associated with a high or low heat stimulus respectively during the conditioning stage. Then the high cue, low cue, and a new cue were all paired with identical moderate heat stimuli during the test stage. Results showed significant analgesic and hyperalgesic responses in which subjects rated the low-cue associated heat stimuli as less painful and high-cue associated stimuli as more painful in comparison with the rating to new-cue associated stimuli, even though identical intensities of heat stimuli were delivered. Importantly, it was found that supraliminal and subliminal conditioning and test led to comparable effects, suggesting that consciousness is not required during either acquisition or activation of conditioned analgesic and hyperalgesic responses. A recent study using similar conditioning procedures further demonstrates nonconscious activation of previously explicitly conditioned placebo analgesia and nocebo hyperalgesia (Egorova, Park et al., 2015). Collectively,

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these findings suggest that placebo and nocebo effects can be learned or activated either consciously or unconsciously in a delay conditioning procedure.

Whether the unconscious placebo and nocebo effects observed in delay conditioning would generalize to trace conditioning is unclear. As the CS and US overlap in delay conditioning, previous studies have shown that awareness does not appear necessary in this process. In contrast, in trace conditioning, a temporal gap (i.e., the trace interval) separates CS termination and US onset. It has been argued that the trace interval increases the complexity of the conditioning task and requires an awareness of the CS–US relationship for CR acquisition. Indeed, evidence has shown that trace conditioning is dependent on awareness of CS–US contingency (Clark, Manns, & Squire, 2001, 2002; Clark & Squire, 1998; Knight, Nguyen, & Bandettini, 2006). For instance, trace conditioning with a 500 ms or 1,000 ms interval between the end of CS and the onset of US showed CR only in healthy participants who learned the CS–US associations (Clark & Squire, 1998). While evidence from neuroimaging studies indicates that trace conditioning resembles delay conditioning in that both depend on the cerebellum, trace conditioning is found to also dependent on the hippocampus, a region that is important in coding temporal information of CS–US (Cheng, Disterhoft, Power, Ellis, & Desmond, 2008; Knight, Cheng, Smith, Stein, & Helmstetter, 2004). These findings emphasize the importance of consciousness in trace conditioning. On the other hand, however, trace conditioning is also possible without consciousness. Studies with subliminal presentation of CS in trace conditioning have showed conditioned responses such as event-related potential activity (Wong, Bernat, Bunce, & Shevrin, 1997), skin conductance response (Katkin, Wiens, & Öhman, 2001), as well as rapid amygdala brain activation (Balderston, Schultz, Baillet, & Helmstetter, 2014), providing biological evidence that subliminal CS is represented in the brain. Therefore, it remains controversial whether awareness is necessary for trace conditioning.

Two recent studies have examined the role of consciousness in trace conditioning in the context of placebo and nocebo effects. Specifically, with supraliminal cues during the conditioning stage, and subliminal cues during the test stage, Egorova, Yu et al. (2015) did not observe any placebo or nocebo effect while Tu et al. (2019) only observed a nocebo effect. These studies suggest that, in trace conditioning, the placebo effect requires conscious activation whereas the role of consciousness in activating the nocebo effect remains elusive. It is worth noting that whether the nocebo effect could be learned with nonconscious cues has not been examined in trace conditioning.

The type of CS matters in conditioning procedures (Egorova, Park, & Kong, 2017). In K. B. Jensen et al.'s studies (K. B. Jensen et al., 2012; K. B. Jensen, Kaptchuk et al., 2015; K. B. Jensen, Kirsch et al., 2015), which show placebo and nocebo effects without consciousness, the authors used neutral faces as CS. Evidence has indicated that facial cues might be a special case, giving extremely salient and social characteristics of faces compared to neutral cues such as words or symbols (Axelrod, Bar, & Rees, 2015). Whether previous findings of placebo and nocebo effects using faces as CS would generalize to unprepared CS such as neutral visual cues in subliminal conditioning remains to be examined.

In the present study, first, we explored the effect of consciousness on analgesic and hyperalgesic pain responses in a delay conditioning procedure in Experiment 1. We used neutral visual cues rather than faces as CS (K. B. Jensen et al., 2012; K. B. Jensen, Kaptchuk et al., 2015; K. B. Jensen, Kirsch et al., 2015). The use of abstract visual cues rather than faces may exert a distinct influence on unconscious learning, given that faces are extremely salient compared to abstract visual cues. Conscious/unconscious processing was manipulated by supraliminal or subliminal presentation of CS. Remarkably, we directly compared the effect of consciousness on both analgesic and hyperalgesic responses at both the conditioning/acquisition stage and the test/activation stage in the same experiment.

In Experiment 2, we examined whether results observed in delay conditioning would generalize to trace conditioning. Given the heated debate on whether trace conditioning requires much more consciousness compared to delay conditioning, it is imperative to test whether the two forms of conditioning show distinct impacts in the context of pain modulation under different states of consciousness. Theoretically, if trace conditioning relies more on awareness of the contingency between the CS and US, subliminal trace conditioning procedures would produce smaller placebo/nocebo effects compared to delay conditioning. In contrast, if consciousness is not a necessity in trace conditioning, at least nocebo hyperalgesia would be subliminally conditioned. Both experiments were approved by the Institutional Review Board of the university and were carried out in accordance with the approved guidelines.

Experiment 1

In Experiment 1, we explored the role of consciousness in pain perception by adopting a delay conditioning procedure in which geometric cues (CS) overlapped with shock stimuli (US). A 2×2 factorial design with either supraliminal or subliminal exposure of CS during either conditioning (acquisition) or test phase was used. Such combination of supraliminal or subliminal exposure allowed us to examine whether conditioned analgesic and hyperalgesic responses could be acquired and then triggered without conscious awareness of CS.

Method

Participants. one hundred and twenty-nine healthy volunteers from the local community gave written informed consent to participate in the study. Participants who failed to distinguish between high pain versus low pain (high pain rating minus low pain rating smaller than 1 on a 9-point self-report Numeric Rating Scale in conditioning phase) were excluded from analysis. This resulted in the inclusion of 119 participants for statistical analysis (mean age $\pm$ *SD*: 19.98 $\pm$ 1.89). Sample size was determined prior to recruitment based on the magnitude of previously reported effect sizes and participant numbers in similar unconscious learning experiments.

Participants were randomly assigned to one of four experimental groups as follows (Figure 1): supraliminal conditioning/supraliminal test group (1a, $n = 29$); supraliminal conditioning/subliminal test group (1b, $n = 33$); subliminal conditioning/supraliminal test group (1c, $n = 29$); and subliminal conditioning/subliminal test group (1d, $n = 28$).

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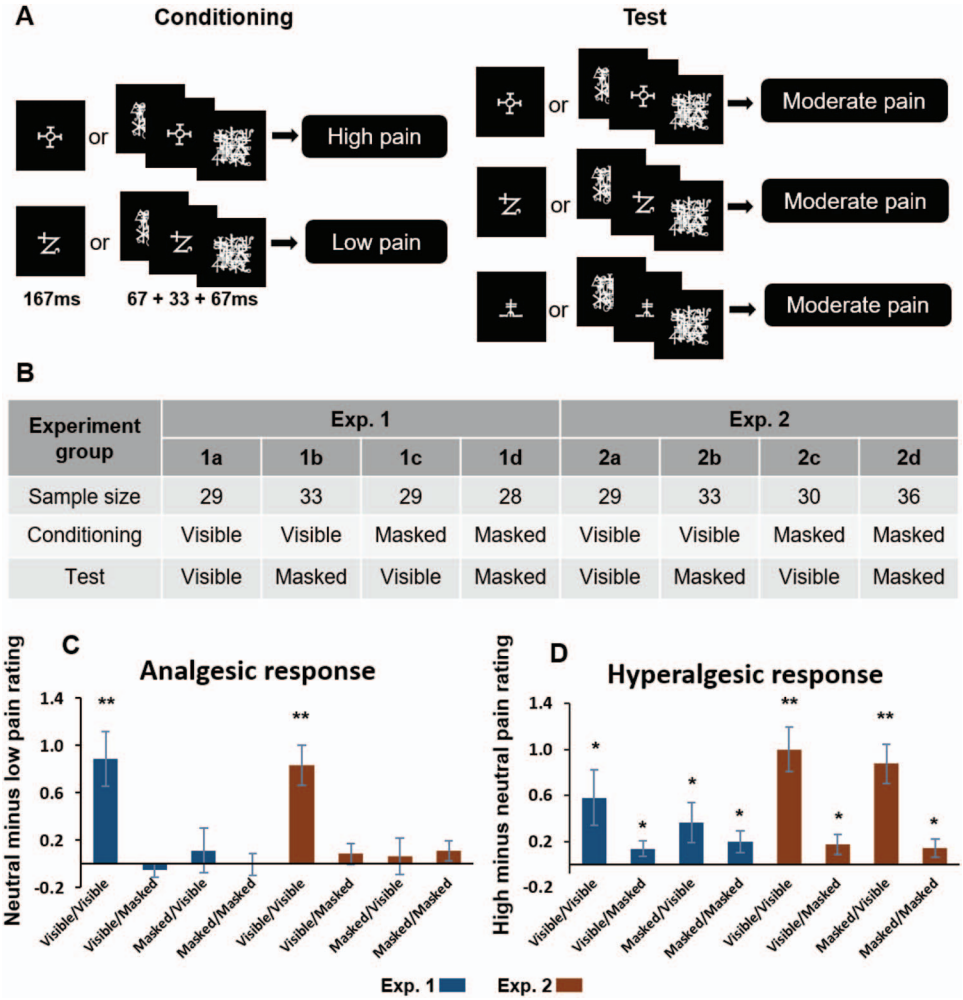

Experiment group	Exp. 1				Exp. 2			
	1a	1b	1c	1d	2a	2b	2c	2d
Sample size	29	33	29	28	29	33	30	36
Conditioning	Visible	Visible	Masked	Masked	Visible	Visible	Masked	Masked
Test	Visible	Masked	Visible	Masked	Visible	Masked	Visible	Masked

Figure 1. Experimental protocol and results. (A) Each experiment involved a conditioning phase and a test phase, using either visible (presented for 167 ms) or masked (presented for 33 ms with backward- and forward-masks for 67 ms) cues. In the conditioning phase, two abstract cues were consistently associated with a high or low electric current stimulus. In the test phase, the high cue, low cue, and a new cue were all paired with identical moderate electric stimuli. Participants were asked to rate their pain intensity after each electric stimulus. (B) Experiment 1 used a delay conditioning procedure in which cues overlapped with shock stimuli. Experiment 2 used a trace conditioning in which there was a 2-s interval between cues and shock stimuli. There were four combinations of cues presented visibly or subliminally in conditioning and test phases for each experiment. (C) Analgesic pain response and (D) hyperalgesic pain response in the test phase (one-tailed *t* tests compared to zero, with FDR adjusted for multiple comparisons). * $p < .05$. ** $p < .001$. Error bars represent standard errors. See the online article for the color version of this figure.

Materials. Electric stimulations were square pulses delivered to the right volar forearm by a Grass SD9 stimulator (Warwick, RI) with two 0.75 cm diameter electrodes. The experiment was conducted in a quiet room with a temperature of 24 °C. Three symbol images were used as cues and two fractal images were used as pre- and postmasks. A 60-Hz, 17-in. CRT monitor was used for visual presentations and the masked image presentations were synchronized at a refresh rate of 16.7 ms. Two of the three cues were first used during the conditioning phase: The "high" cue was coupled with a high pain level and the "low" cue was coupled with a low pain level. During the test phase, moderate pain stimuli were associated with high, low, and neutral cue images. The neutral cue was not shown during the conditioning phase (i.e., it first appeared during the test phase). The specific assignment of cues to a given trial type was fully counterbalanced across participants. All stimuli were presented using the Eprime 2.0 software (Version 2.0.8.22, http://www.pstnet.com).

Experimental procedures. The experiment consisted of four stages: (1) calibration, (2) supraliminal/subliminal conditioning, (3) supraliminal/subliminal test, and (4) manipulation check.

Stage 1: Calibration. Upon entering the laboratory, participants were told that the purpose of the experiment was to investigate the influence of learning on pain perception. Since individuals differ in their pain sensitivity, the threshold and tolerance to

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electric stimuli for each participant was calibrated. Calibrations were manipulated via ascending voltage of the electric currents with a fixed delivering duration of 80 ms. Participants were asked to rate their pain intensity on a 9-point self-report Numeric Rating Scale (NRS, 1 = *a little pain*, 5 = *moderate pain*, and 9 = *unbearable pain*). After finding the physical voltage that participants rated around 3 (*low pain*), this parameter kept constant in further procedures. The determined average electric voltage was 25.82 ± 3.42 V across participants.

The next step was to find electrical parameters that would elicit low pain at ≈3 rating, high pain at ≈7 rating and moderate pain at ≈5 rating on the NRS for each participant. With a previously determined constant voltage, we increased the stimulation time of electric currents, starting from 80 ms to 800 ms (increasing in sequence at multiples of 80 ms), to increase participants' feeling of pain. Participants were given 2 s to rate on the NRS by pressing the corresponding buttons on the keyboard. Once the low, moderate and high pain levels for each participant were determined, the participants were tested for rating response consistency. A random sequence of three low- and three high-intensity pain stimuli was administered. If participants could reliably rate the high stimuli as more intense than the low stimuli, with the rating difference between the high and low shock stimulation to be at least 3 on the 9-point NRS, they would proceed to the next step of the experiment. The calibration lasted for 5 to 10 min. The calibrated shock durations used for subsequent procedures are reported in Table S1 in the online supplemental materials.

Stage 2: Conditioning. The specific procedure and visual exposures for the conditioning stage are shown in Figure 1. Each trial started with the presentation of a fixation cross, which remained on the screen for 4 s. For the supraliminal conditioning groups, visual cues had a duration of 167 ms. The transient electric current stimulus was delivered 100 ms after the onset of the cue, resulting in an overlap of the cue and shock. For the subliminal conditioning groups, the cue was presented for a shorter duration of 33 ms and the same two masking patterns (one displayed before the cue and the other after the cue for 67 ms, respectively) were used to render the cues invisible. The shock was delivered after the end of the cue, overlapping with the backward masks. Participants were informed that the cues would flash by swiftly and it is normal not to be able to recognize the symbols, After the electric stimulation, participants rated the level of pain they felt using the same 9-point NRS.

In total, there were 40 trials during the conditioning sequence: 20 for the high-pain cue and 20 for the low-pain cue. The cues were counterbalanced across participants. The conditioning sequence was divided into two blocks of ≈7 min each, with a break of around 1.5 min in between. Shock stimuli were applied to the right volar forearm and the position of the probe was changed for every session. During the whole experimental procedure, an experimental assistant was seated on a chair near the desk that the monitor was on, facing the side of the participant. The placement of the assistant allowed for constant monitoring to make sure that participants were facing the screen and not looking in other directions. The sequence of trial types is listed in Table S2 in the online supplemental materials.

Stage 3: Test. There were three cues in the test stage: the cue previously associated with high pain (high-pain cue), the cue previously associated with low pain (low-pain cue), and a new cue that participants had not seen before (neutral cue). Half of all participants were presented with supraliminal cues (for 167 ms), while the other half was presented with subliminal cues (for 33 ms, masked by fractals before and after it). The shock was delivered in the same way as in conditioning stage. Participants then rated the intensity of pain stimulus using the same 9-point NRS. Unknown to participants, the cues were all paired with identical moderate electric shocks. This test stage consisted of 45 trials: 15 high-pain cues, 15 low-pain cues, and 15 neutral cues. There was a chance for participants to rest during the test stage, allowing them to maintain a high level of alertness and to lessen the strain on their eyes. The position of the stimulator probe was changed during the test.

Similar to previous studies, six "booster trials" were added to the test stage (K. B. Jensen et al., 2012; K. B. Jensen, Kirsch et al., 2015). Specifically, three high-pain cues and three low-pain cues were paired respectively with their original electric currents. As all electric current stimuli were at the same level of intensity in the test stage, the booster trials served to prevent habituation and extinction and to ensure participants remain vigilant. These booster trials were not included in the statistical analysis of analgesic and hyperalgesic effects. The sequence of trial types is listed in Table S3 in the online supplemental materials.

Stage 4: Manipulation check. To verify that the masked stimuli were truly subliminal, a discrimination task and a detection task were conducted after the test stage. The orders of the two tasks were counterbalanced across participants. Participants in the supraliminal conditioning and supraliminal test group did not perform the tasks because the cues were presented clearly throughout the whole experimental procedure.

The discrimination test consisted of three types of masked images: two of them were cues associated with high pain and low pain respectively in the conditioning stage, and the third image is the novel cue. In each trial, two sandwich-masked cues were displayed successively on the computer screen with a 1,500 ms interval, and participants were asked to judge whether the two cues were the same or not (based on any criteria). There were 36 trials in total and half of them were same-cues trials. This task lasted for 5 min in total.

The detection test consisted of two cues that were paired with high pain and low pain respectively in the conditioning stage. The cues were displayed through sandwich masking and participants were asked to judge whether the cue shown was associated with a high or low pain level as in the previous conditioning stage. There were 30 trials in total, lasting for 4 min.

Results

Pain ratings in conditioning stage. Pain ratings during the conditioning phase are reported in Figure 2A. We conducted a 2 × 2 × 2 mixed-model ANOVA with electric stimuli type (high/low) as the within-subjects factor and acquisition/conditioning type (subliminal/supraliminal) and activation/test type (subliminal/supraliminal) as the between-subjects factors. The ANOVA revealed a significant main effect of stimuli type on pain ratings [$F(1, 115) = 962.24$, $p < .001$, $\eta_p^2 = 0.89$]. Specifically, participants across all groups rated high pain stimuli (mean ± *SE*, 6.73 ± 0.08) significantly higher than low pain stimuli (mean ± *SE*, 3.66 ± 0.09) on the numeric response scale ranging from 1 to 9. The

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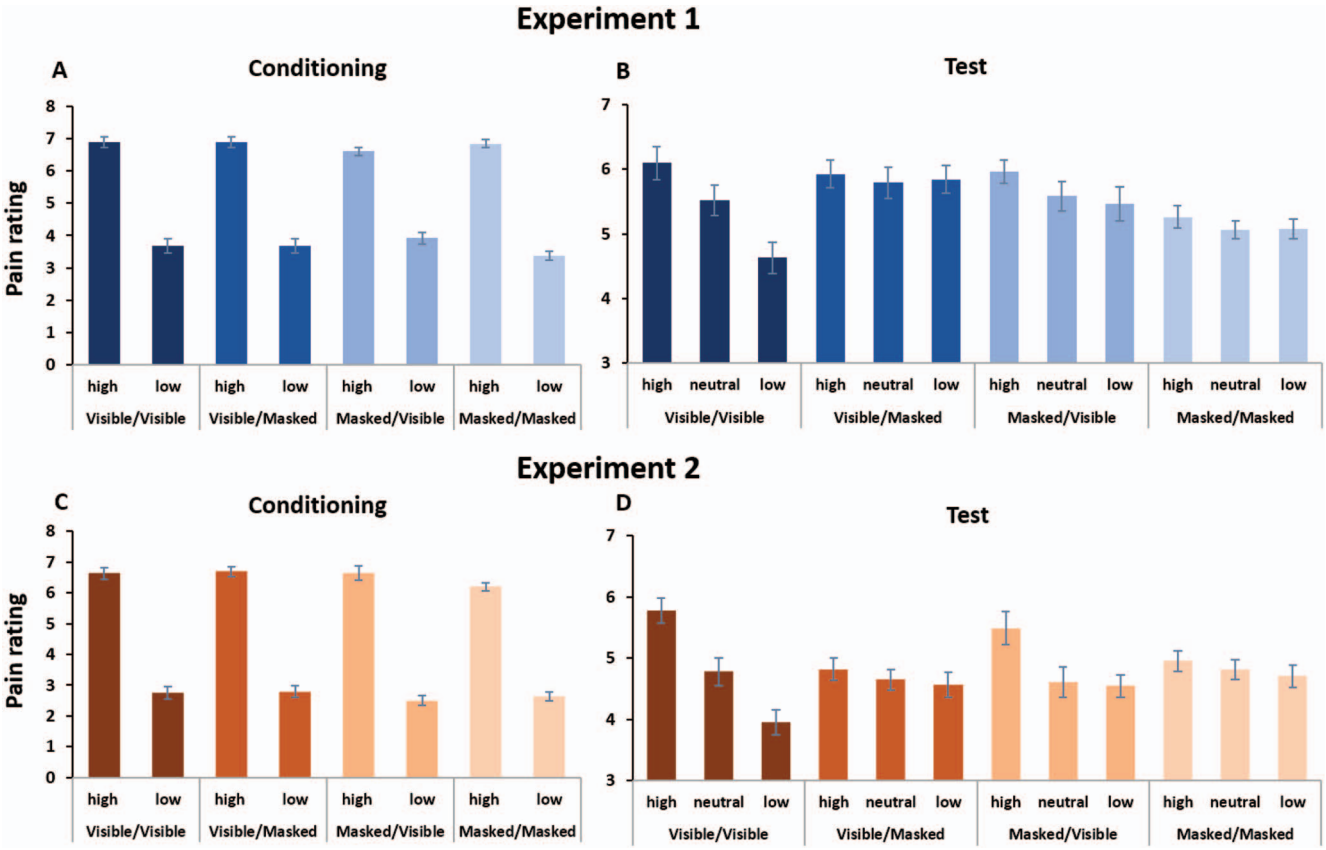

Figure 2. Pain ratings in response to high pain and low pain during the conditioning stage, and moderate electric stimuli associated with high, neutral, and low cues during the test stage in Experiment 1 (A and B) and Experiment 2 (C and D). Error bars represent standard errors. See the online article for the color version of this figure.

interaction between electric stimuli type and test type was also significant [$F(1, 115) = 7.86$, $p = .006$, $\eta_p^2 = 0.06$], with slightly higher pain rating in subliminal test (mean ± *SE*, 6.87 ± 0.11) than in supraliminal test (mean ± *SE*, 6.59 ± 0.11) for high pain stimuli ($p = .064$) while no difference between supraliminal test (mean ± *SE*, 3.80 ± 0.13) and subliminal test (mean ± *SE*, 3.53 ± 0.13) for low pain stimuli ($p = .146$). The other main effects and interactions were not significant (p values $> .1$).

Pain ratings in the test stage. Pain ratings during the test phase are displayed in Figure 2B. We conducted a 3 × 2 × 2 mixed-model ANOVA with cue type (high/control/low) as the within-subjects factor and acquisition/conditioning type (subliminal/supraliminal) and activation/test type (subliminal/supraliminal) as the between-subjects factors. The ANOVA revealed a significant main effect of cue type on pain ratings [$F(2, 230) = 24.15$, $p < .001$, $\eta_p^2 = 0.17$]. Pairwise comparisons with Bonferroni correction revealed that participants rated the moderate pain stimuli more painful in high cue condition (mean ± *SE*, 5.81 ± 0.11) compared to neutral cue condition (mean ± *SE*, 5.49 ± 0.10), $p < .001$, and low cue condition (mean ± *SE*, 5.25 ± 0.11), $p < .001$. They also rated the moderate pain stimuli more painful in neutral cue condition than in low cue condition, $p = .007$. These differences in pain ratings indicated that effects exist in both analgesic and hyperalgesic directions. The main effect of conditioning type [$F(1, 115) = 1.38$, $p = .242$, $\eta_p^2 = 0.012$] and the main effect of test type [$F(1, 115) = 0.06$, $p = .803$, $\eta_p^2 = 0.001$] were not significant. Importantly, there was a significant interaction among the three variables [$F(2, 230) = 6.15$, $p = .003$, $\eta_p^2 = 0.05$], which suggested that pain ratings were jointly determined by cue type and awareness in both the conditioning and test phases. We further decomposed the 3-way interaction to two interactions to examine the analgesic and hyperalgesic pain responses separately.

Effects of conscious awareness on analgesic responses. The analgesic response was reflected by a lower pain perception for moderate pain stimuli in the test phase that were paired with low-pain predictive cues in the previous conditioning phase. It could be measured by the pain rating difference between neutral-pain predictive cue condition and low-pain predictive cue condition (Figure 1C).

For analgesic pain response, we conducted a 2 (Conditioning type: subliminal/supraliminal) × 2 (Test type: subliminal/supraliminal) ANOVA using the pain rating difference between the control and low cue condition as dependent variable. The main effect of conditioning awareness was significant [$F(1, 115) = 5.52$, $p = .020$, $\eta_p^2 = 0.05$]. There was a larger analgesic response when conditioning stage was supraliminal (mean ± *SE*, 0.42 ±

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0.11) than when it was subliminal (mean ± *SE*, 0.06 ± 0.11). The main effect of test type was also significant [$F(1, 115) = 12.02$, $p = .001$, $\eta_p^2 = 0.10$]. There was a larger analgesic response when test stage was supraliminal (mean ± *SE*, 0.50 ± 0.11) than when it was subliminal (mean ± *SE*, −0.03 ± 0.11). Moreover, there was an interaction between conditioning type and test type [$F(1, 115) = 7.11$, $p = .009$, $\eta_p^2 = 0.06$]. The analgesic response was larger in the supraliminal test group (mean ± *SE*, 0.89 ± 0.16) than in the subliminal test group (mean ± *SE*, −0.05 ± 0.15), $p = .001$. No such difference was found when conditioning was subliminal ($p = .822$). These findings suggested that consciousness is needed during both conditioning and testing stages to produce analgesic responses.

Furthermore, one-sample *t* tests of analgesic response, with false discovery rate (FDR) correction for multiple *t* tests, showed significant analgesic effect only in the supraliminal conditioning and supraliminal test group (Figure 1C: 1a), confirming the importance of consciousness in placebo analgesia. There was no effect in the other three groups (Figure 1C: 1b, 1c, and 1d).

Effects of conscious awareness on hyperalgesic responses. The hyperalgesic pain response was reflected by a higher pain perception for moderate pain stimuli that were paired with high-pain predictive cues. It was measured by the pain rating difference between high-pain predictive cue condition and neutral-pain predictive cue condition.

For hyperalgesic pain response, we conducted a 2 (Conditioning type: subliminal/supraliminal) × 2 (Test type: subliminal/supraliminal) ANOVA using high-minus-neutral pain rating difference during the test phase as dependent variable. The main effect of test type was significant [$F(1, 115) = 3.96$, $p = .049$, $\eta_p^2 = 0.03$]. Pairwise comparisons demonstrated a larger hyperalgesic response in the supraliminal test (mean ± *SE*, 0.48 ± 0.11) than in the subliminal test (mean ± *SE*, 0.16 ± 0.11). The main effect of conditioning type was not significant [$F(1, 115) = 0.22$, $p = .643$, $\eta_p^2 = 0.002$], suggesting that hyperalgesic pain response was independent of conditioning awareness (subliminal/supraliminal). The interaction between conditioning type and test type was also not significant [$F(1, 115) = 0.72$, $p = .398$, $\eta_p^2 = 0.006$]. The stronger hyperalgesic response in the supraliminal test than in the subliminal test indicated a modulatory role of test consciousness on hyperalgesic response.

One-sample *t* test of hyperalgesic response, with FDR correction for multiple tests, showed significant hyperalgesic effects in four groups respectively (Figure 1D: 1a, 1b, 1c, and 1d), suggesting that stimuli consciousness in either conditioning phase or test phase is not necessary for producing nocebo effects. However, the supraliminal test produced stronger hyperalgesic response than the subliminal test.

To examine the effects of conscious awareness on analgesic/hyperalgesic responses without confounding by pain rating bias across participants, we conducted the same analyses after standardizing the pain ratings within participants. The results after standardization were similar to those of previous findings. The standardized results are reported in the online supplementary material.

Manipulation check of awareness. In the discrimination task, the grand mean accuracy of discrimination was 0.51 ± 0.09 (mean ± *SD*), which is equivalent to the chance level of 0.5, $t(89) = 0.65$, $p = .515$, confirming that the symbols were indeed unrecognizable. A d' sensitivity analysis, which takes the "hit" versus "false alarm" rate into account when qualifying the accuracy of participants' answers, indicated that participants performed at chance level [d' score (mean ± *SD*): 0.003 ± 0.60, $t(89) = 0.05$, $p = .959$]. Moreover, there was no significant correlation between the discrimination d' score and hyperalgesic effect across participants, $r(90) = .089$, $p = .403$, confirming that the hyperalgesic effect we found in subliminal groups was not due to the potential perception of the stimuli in some trials.

In the detection task, the grand mean accuracy of detection was 0.50 ± 0.11 (mean ± *SD*), which is equivalent to chance level of 0.5, $t(89) = 0.29$, $p = .774$. The d' score was also not different from 0 [d' score (mean ± *SD*): 0.08 ± 0.76, $t(89) = 0.94$, $p = .349$]. Moreover, there was no significant correlation between the detection d' score and hyperalgesic effect across participants, $r(90) = .051$, $p = .634$.

The findings of both discrimination and detection tasks suggest that the three groups of participants were unable to see the masked cues involved in the subliminal manipulation.

Summary

Experiment 1 demonstrated that conscious awareness of conditional stimuli determined the magnitude of analgesic and hyperalgesic pain responses in a delay conditioning procedure. The analgesic effect was only significant when stimuli were supraliminal in both conditioning and test phases, suggesting that awareness is needed in producing analgesic responses. Although the hyperalgesic response was conditioned and activated irrespective of stimuli awareness (supraliminal/subliminal), the magnitude of response was larger when stimuli were supraliminal in the test stage. These results highlight the distinct roles of consciousness in analgesic and hyperalgesic responses and show that the hyperalgesic response is more pronounced than the analgesic response. As high-pain cues are threat-related, automatic and rapid responses to subliminal exposures of aversive stimuli may reflect a valuable evolutionary adaption to dangers in the environment.

Experiment 2

Experiment 2 used a trace conditioning paradigm in which there was a 2-s interval between cues and shock stimuli. Here we explored whether trace conditioning exhibited a similar pattern of analgesic and hyperalgesic response as observed in Experiment 1 for delay conditioning.

Method

Method was the same as in Experiment 1 except for the following differences.

Participants. Four out of 132 healthy volunteers failed to distinguish between high pain and low pain in the conditioning phase, therefore only 128 participants were retained for analysis (mean age ± *SD*: 21.15 ± 1.79). Participants were randomly assigned to one of four experimental groups: supraliminal conditioning/supraliminal test group (2a, $n = 29$); supraliminal conditioning/subliminal test group (2b, $n = 33$); subliminal conditioning/supraliminal test group (2c, $n = 30$); and subliminal conditioning/subliminal test group (2d, $n = 36$).

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Experimental procedures. In previous studies as well as in Experiment 1, booster trials (CS + paired with the US) were used in the test stage to prevent extinction ("steady-state" generalization test; K. B. Jensen et al., 2012; K. B. Jensen, Kirsch et al., 2015). These steady-state ("booster" trials) reinforcement procedures are intended to extend the length of time over which responding can be measured and offset the effects of extinction and habituation (Dunsmoor, Mitroff, & LaBar, 2009; Lim & Pessoa, 2008; Smith, Most, Newsome, & Zald, 2006).

Participants may learn associations from booster trials alone. To rule out this possibility, we added a preconditioning test procedure in which three new cues were always associated with moderate pain (that is, Cue A paired with moderate pain in 15 trials, Cue B paired with moderate pain in 15 trials and Cue C paired with moderate pain in 15 trials; Figure S1 in online supplemental materials). In addition, another six trials were added in which Cue A was paired with high pain in three trials and Cue B was paired with low pain in another three trials. This preconditioning test was presented after the calibration sequence and before the formal conditioning sequence. Overall, the procedure of this preconditioning test was similar with the test stage. The only difference was whether there was a conditioning stage prior to the pretest. If individuals did exhibit analgesic/hyperalgesic effects in this preconditioning test measurement without the formal conditioning stage, this indicates that these six booster trials alone could affect participants' expectancy and pain ratings.

Conditioning and test stages were the same as Experiment 1, except that a preconditioning test was added and there was a 2-s interval between cues and shock stimuli for all phases. Booster trials were also included during the test phase.

Given that the discrimination task and detection task used in Experiment 1 gave similar results, participants in Experiment 2 underwent only the discrimination task after the test stage.

Results

Pain ratings in preconditioning test stage. A repeated-measures ANOVA on the preconditioning baseline measurement of pain ratings revealed no significant effect of cue type (high/control/low) for any group (p values $> .05$). These findings suggested that the six booster trials used in the test stage would not elicit analgesic or hyperalgesic responses.

Pain ratings in conditioning stage. Pain ratings during the conditioning phase are reported in Figure 2C. The 2 (Electric stimuli: high/low) × 2 (Conditioning type: subliminal/supraliminal) × 2 (Test type: subliminal/supraliminal) ANOVA revealed a significant main effect of stimuli type on pain ratings [$F(1, 124) = 1426.18$, $p < .001$, $\eta_p^2 = 0.92$]. Specifically, participants across all groups rated high pain stimuli (mean ± SE, 6.55 ± 0.09) significantly higher than low pain stimuli (mean ± SE, 2.67 ± 0.09). The other main effects and interactions were not significant (p values $> .05$).

Pain ratings in test stage. Pain ratings during the test phase are displayed in Figure 2D. The 3 (Cue type: high/neutral/low) × 2 (Conditioning type: subliminal/supraliminal) × 2 (Test type: subliminal/supraliminal) ANOVA revealed a significant main effect of cue type on pain ratings [$F(2, 248) = 73.22$, $p < .001$, $\eta_p^2 = 0.37$]. Pairwise comparisons with Bonferroni correction revealed that participants rated the moderate pain stimuli more painful in high cue condition (mean ± SE, 5.26 ± 0.10) compared to neutral cue condition (mean ± SE, 4.71 ± 0.10), $p < .001$, and low cue condition (mean ± SE, 4.44 ± 0.10), $p < .001$. They also rated the moderate pain stimuli more painful in neutral cue condition than in low cue condition, $p < .001$. The main effect of conditioning type [$F(1, 124) = 0.28$, $p = .601$, $\eta_p^2 = 0.002$] and the main effect of test type [$F(1, 124) = 0.35$, $p = .558$, $\eta_p^2 = 0.003$] were not significant. Importantly, there was a significant interaction among the three variables [$F(2, 248) = 6.18$, $p = .002$, $\eta_p^2 = 0.05$]. The analgesic and hyperalgesic pain responses were analyzed separately to further clarify the three-way interaction effect.

Effects of conscious awareness on analgesic responses. For analgesic pain response, the 2 (Conditioning type: subliminal/supraliminal) × 2 (Test type: subliminal/supraliminal) ANOVA showed a main effect of conditioning awareness [$F(1, 124) = 8.85$, $p = .004$, $\eta_p^2 = 0.07$]. There was a larger analgesic response when conditioning stage was supraliminal (mean ± SE, 0.46 ± 0.09) than when it was subliminal (mean ± SE, 0.09 ± 0.09). The main effect of test type was also significant [$F(1, 124) = 8.00$, $p = .005$, $\eta_p^2 = 0.06$]. There was a larger analgesic response when test stage was supraliminal (mean ± SE, 0.45 ± 0.09) than when it was subliminal (mean ± SE, 0.10 ± 0.08). Moreover, there was an interaction between conditioning type and test type [$F(1, 124) = 10.15$, $p = .002$, $\eta_p^2 = 0.08$]. The analgesic pain response was larger in the supraliminal test group (mean ± SE, 0.83 ± 0.13) than in the subliminal test group (mean ± SE, 0.09 ± 0.12), $p < .001$, regarding supraliminal conditioning. No such difference was found when conditioning was subliminal ($p = .798$). Consistent with the findings in Experiment 1, consciousness was needed in producing analgesic responses in trace conditioning.

One-sample t tests with FDR correction also showed significant analgesic effect only in the supraliminal conditioning and supraliminal test group (Figure 1C: 2a) while there were no effects in other three groups (Figure 1C: 2b, 2c, and 2d).

Effects of conscious awareness on hyperalgesic responses. For hyperalgesic pain response, the 2 (Conditioning type: subliminal/supraliminal) × 2 (Test type: subliminal/supraliminal) ANOVA showed a main effect of test type [$F(1, 124) = 33.51$, $p < .001$, $\eta_p^2 = 0.21$]. Pairwise comparisons demonstrated a larger hyperalgesic response in the supraliminal test (mean ± SE, 0.94 ± 0.10) than in the subliminal test (mean ± SE, 0.15 ± 0.09). The main effect of conditioning type was not significant [$F(1, 124) = 0.35$, $p = .558$, $\eta_p^2 = 0.003$]. The interaction between conditioning type and test type was also not significant [$F(1, 124) = 0.11$, $p = .741$, $\eta_p^2 = 0.001$]. The findings show that stimuli consciousness during the test stage modulated the hyperalgesic response with larger effect in the supraliminal test than in the subliminal test.

Consistent with Experiment 1, one-sample t tests with FDR correction showed significant hyperalgesic effects in all four groups respectively (Figure 1D: 2a, 2b, 2c, and 2d), suggesting that stimuli consciousness is also not necessary for hyperalgesic response in trace conditioning procedure. The pattern of results after standardizing the pain ratings (see the online supplementary material) was similar to those of previous findings.

Manipulation check of awareness. In the discrimination task, the grand mean accuracy of discrimination was 0.51 ± 0.08 (mean ± SD), which is equivalent to chance level of 0.5, $t(98) = 0.79$, $p = .429$. The d' score was also not different from 0 [d' score (mean ± SD): 0.07 ± 0.59, $t(98) = 1.20$, $p = .232$]. Moreover,

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there was no significant correlation between the discrimination d' score and hyperalgesic effect across participants, $r(99) = -.042$, $p = .681$. Thus, participants were unable to discriminate between the different masked cues when they were displayed subliminally.

Summary

Using a trace conditioning procedure, Experiment 2 showed consistent findings with Experiment 1 suggesting that consciousness modulates pain perception in the same way in both delay and trace conditioning.

General Discussion

We systematically explored the role of awareness in conditioned analgesic and hyperalgesic pain responses using both classical delay conditioning and trace conditioning procedures. In two experiments, we found that analgesic and hyperalgesic responses were differentially sensitive to consciousness. Specifically, the analgesic response was only significant when stimuli were supraliminal in both conditioning and test phases. Although the hyperalgesic response was conditioned and activated irrespective of consciousness (supraliminal/subliminal), the magnitude of response was larger when stimuli were supraliminal in the test stage. Our results indicate that while the hyperalgesic response is more sensitive to conscious activation, the analgesic response requires both conscious conditioning and conscious activation.

The distinct role of consciousness in analgesic and hyperalgesic responses between delay and trace conditioning corroborates the notion that analgesic placebo and hyperalgesic nocebo effects potentially operate via different mechanisms (Colloca, Sigaudo, & Benedetti, 2008; Freeman et al., 2015; Petrovic, 2008; Tu et al., 2019). For analgesic effect, its dependence on consciousness during both conditioning and test stages suggests that conditioning is not an entirely automatic process and conditioning interacts with cognitive components to bring about pain reduction (Finniss, Kaptchuk, Miller, & Benedetti, 2010). Our study provides further evidence reinforcing the expectancy theory, which states that the effect of conditioning on placebo analgesic response is mediated by awareness (Kirsch, 1985; Kirsch et al., 2014; Montgomery & Kirsch, 1997). Expectations can be induced by various forms of learning, such as typical conditioning procedure, verbal suggestion, and social observation. Across different types of learning, previous studies have provided evidence showing that expectations modulate the magnitude of placebo responses, highlighting the key function of consciousness in the placebo phenomena (Colloca & Benedetti, 2009; Colloca & Miller, 2011).

Nonconscious acquisition and activation of hyperalgesic response reinforce the idea of fast and automatic processing of subliminal threat-related information (Öhman, Carlsson, Lundqvist, & Ingvar, 2007). Indeed, people are more susceptible to acquire a conditional skin conductance response (SCR) to masked images of phylogenetic threats such as spiders (Öhman & Soares, 1998) or emotionally salient angry faces relative to positive images such as flowers or neutral/happy faces (Bekinschtein et al., 2009; Esteves, Parra, Dimberg, & Öhman, 1994; Killgore & Yurgelun-Todd, 2004; Öhman & Soares, 1994; Parra, Esteves, Flykt, & Öhman, 1997). Neuroimaging studies also suggest that masked fearful stimuli can be encoded by both subcortical and cortical brain structures (Kim et al., 2010; Liddell et al., 2005), and produce behavioral changes (LeDoux & Pine, 2016; van der Ploeg, Brosschot, Versluis, & Verkuil, 2017). Different from most fear conditioning studies that implement the threat itself to produce automatic and motor responses (Öhman et al., 2007), our study demonstrates the effect of hyperalgesic responses, even with neutral visual cues. As the neutral cues were associated with high pain, which is a threat-related signal, participants may be more ready to respond to these cues that could signal potential harms through conditioning, in comparison with cues that associated with low pain (Gross & Canteras, 2012; LeDoux, 2012; Maren, 2005; Raio et al., 2012). Therefore, hyperalgesic pain response may be triggered through rapid pathways involving a similar fear processing that does not require conscious awareness (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006; K. B. Jensen, Kaptchuk et al., 2015). This ability to unconsciously learn to predict potential threats reflects an adaptive function in humans.

It is interesting to note that supraliminal cues elicited stronger hyperalgesic response compared with subliminal cues in the test phase regardless of consciousness in acquisition phase. This finding indicates that consciousness might be particularly important in triggering conditioned hyperalgesic response. Nocebo effects can be triggered without consciousness, and conscious awareness of cues during the test stage further strengthen the effect. This finding again highlights the role of consciousness in pain modulation. However, it is unclear why consciousness of cues in the test stage rather than in the conditioning stage mediates nocebo effect. Our study highlights the need to distinguish the role of consciousness in the acquisition stage and test/measurement stage separately.

In our study, consciousness modulates pain perception in the same way in both delay and trace conditioning. It is surprising that nocebo hyperalgesia can still be subliminally conditioned in trace conditioning, given the critical role of consciousness posited for explaining trace conditioning (Clark et al., 2001, 2002; Clark & Squire, 1998; Knight et al., 2006). However, previous studies also found that both delay and trace conditioning elicited compatible eyeblink responses independent of outcome expectancy (Weidemann, Broderick, Lovibond, & Mitchell, 2012), suggesting that both delay and trace conditioning may emerge from the operation of an automatic learning system, which is distinct from conscious expectancy. Indeed, some researchers have proposed that there are no fundamental differences between the two conditioning procedures (Lovibond & Shanks, 2002). Our findings support the view that consciousness is not a necessity in trace conditioning as previously believed, at least in the context of pain perception.

Whether higher-level processes can operate unconsciously is a key question in understanding the nature of human thinking and reasoning. Increasing evidence shows that various forms of unconscious "high-level semantic integration" exist (Hassin, 2013; Mudrik, Faivre, & Koch, 2014). However, recent replication attempts and results reanalyses failed to find such effects, suggesting that unconscious higher-level processing is much more limited than previously thought (Biderman & Mudrik, 2018; Karpinski, Briggs, & Yale, 2019; A. Moors, 2016; P. Moors & Hesselmann, 2018; Rabagliati, Robertson, & Carmel, 2018). Our research shed light on the boundaries of consciousness. Our studies show that an unconscious placebo effect, if it exists, might not be as strong as was claimed in previous studies when compared with the conscious placebo effect. Consistent with the expectancy theory

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(Kirsch, 1985, 2018; Kirsch et al., 2014; Tracey, 2010), conscious awareness plays a crucial role in appetitive learning. Our findings further support the view that aversive learning is more automatic and relies less on conscious processes than appetitive learning (Martin-Soelch, Linthicum, & Ernst, 2007; Wunsch, Philippot, & Plaghki, 2003).

Limitations

Limitations of the current study should be noted. First, we studied the analgesic and hyperalgesic pain responses using conditioning procedures without involving any inert substance or treatment. Whether the findings can be extended to clinical situations remains to be tested. Abundant research on placebo and nocebo effects use ointments, pills and infusions that constitute the placebos as conditional stimuli (Klinger, Soost, Flor, & Worm, 2007; Levine, Stern, & Koch, 2006; Peciña et al., 2014). Our conditioning procedure has no inherent ability to change the perception of pain. Although conditioning procedures did not include placebos, our current study, together with previous research using conditioning paradigms, does map well onto placebo and nocebo literature (K. B. Jensen, Kirsch et al., 2015). Second, our study did not use trial-by-trial online assessment of consciousness, which may underestimate participants' level of awareness in the tasks. The postexperiment forced-choice discrimination task, although frequently used as measures of awareness, may not be sensitive enough to measure consciousness. Such a postexperiment measure is susceptible to forgetting, interference, and reconstruction of events before the assessment of awareness. Concurrent measures of awareness should be used in future studies (Knight, Nguyen, & Bandettini, 2003; Lovibond & Shanks, 2002). Third, the current study used electric stimulation with varying duration of stimulation to induce different levels of pain experience. The difference of pain modality applied may also explain the discrepancy between studies, given that individuals respond differently across different pain modality (Hastie et al., 2005). In addition, it is worth noting that the pain rating scale we used is different from the 0–100 numeric rating scale in the two previous studies. The Numeric Rating Scales (NRS) with 9, 20, or 101 point are all commonly used (Hawker, Mian, Kendzerska, & French, 2011; Williamson & Hoggart, 2005). Previous studies have shown that subjects used multiples of 10 when using a 101-point scale and used the scale as if it had 11 points (M. P. Jensen, Turner, & Romano, 1994). Although it has been shown that 11-point scales are more than adequate for the assessment of pain (M. P. Jensen et al., 1994), future studies may further test whether scales that have more levels of discrimination are indeed more sensitive. Finally, the current study design did not allow a direct contrast between trace conditioning versus delay conditioning effects as groups were not randomly assigned into different conditions. A formal comparison between the delay and trace conditioning on placebo and nocebo effects is needed for future research.

Future Directions and Implications

Our findings contrast with the results of K. B. Jensen et al. (2012; K. B. Jensen, Kaptchuk et al., 2015; K. B. Jensen, Kirsch et al., 2015) showing that both analgesic and hyperalgesic responses can be acquired with and activated by cues that are not consciously perceived. One possibility underlying this difference is that, in K. B. Jensen et al.'s studies, the authors used neutral faces as conditioning stimuli. Indeed, a recent study investigating the effect of different CSs in pain conditioning has found that only face stimuli elicit a conditioning effect when stimuli were presented subliminally while abstract images and pseudowords do not produce conditioned responses (Egorova et al., 2017). Therefore, face-related associations to pain might be stronger than those elicited with nonsocial visual cues. Based on the above, it is premature to conclude the role of consciousness on analgesic and hyperalgesic responses in light of mixed findings. Future studies should directly compare the face and nonface CSs, and test how different types of CSs modulate the interaction between consciousness and placebo/nocebo effects.

The distinct role of consciousness between analgesic and hyperalgesic pain responses across delay and trace conditioning corroborate the notion that analgesic placebo and hyperalgesic nocebo effects are due to differential behavioral and neural mechanisms (Freeman et al., 2015; Petrovic, 2008). Such differential reliance on consciousness illustrates the mechanistic differences between the two forms of pain modulation. Medical treatments are significantly modulated by placebo effects in clinical settings. Our research, if transitioned from bench to bedside, might be used by clinicians to harness placebo effects to optimize treatment outcomes and reduce unintended nocebo effects. Further studies are needed to rigorously test unconscious analgesic/hyperalgesic effects across contexts.

In addition, there is a need to distinguish the role of consciousness in the acquisition stage and test/activation stage separately to tease apart the nature of unconscious learning. Previous studies on unconscious conditioning either focus on the consciousness of CS during the acquisition stage (Bunce, Bernat, Wong, & Shevrin, 1999; Esteves et al., 1994; Wong et al., 1997) or on the consciousness of CS during the test/activation stage (Egorova, Park et al., 2015; Egorova, Yu et al., 2015; Morris, Öhman, & Dolan, 1998; Olsson & Phelps, 2004; Tu et al., 2019). In a recent study with invisible CS during both acquisition and test stages, Raio et al. (2012) found that nonconscious fear is quickly acquired but rapidly extinguished. However, this study cannot dissociate whether it is the awareness in the acquisition or the activation stage that causes rapid extinction. Our study, for the first time, shows stage-dependent unconscious aversive learning of high-order associations.

Conclusions

While many aspects of human behavior operate outside of conscious awareness, exactly to what extent higher-order cognitive processes such as psychologically mediated pain responses work outside awareness remain elusive. In two experiments that were built on past research, we systematically examined how consciousness and type of conditioning influence analgesic and hyperalgesic effects at different stages. Our results indicate that whereas the hyperalgesic response is more sensitive to conscious activation, the analgesic response requires both conscious conditioning and conscious activation. This is the first study showing a differential role of consciousness in analgesic (placebo) and hyperalgesic (nocebo) responses in a systematic way (i.e., acquisition vs. activation stage and delay vs. trace conditioning). The present study enriches the

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theories on expectancy and conditioning, suggesting that nocebo effects do not appear to require consciousness to the same degree as placebo effects. It also adds evidence supporting the view that delay and trace conditioning may not be two distinct forms of learning, at least in the context of pain perception. Lastly, our findings underscore the importance of systematically comparing acquisition versus activation stages as well as salient versus nonsalient CSs in pain-related learning. Our findings demonstrate a nascent role of consciousness in learning of complex cognitive processes.

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