# In search of conditioned pain

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# In search of conditioned pain: an experimental analysis

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## Abstract

There is an ongoing debate about whether pain can be classically conditioned, but surprisingly, evidence is scarce. Here, we report 3 experiments investigating this idea. In a virtual reality task, healthy participants were approached and touched near or on their hand with a coloured pen (blue or yellow). During acquisition, participants learned that one of the colours of the pen (CS+) was predictive of a painful electrocutaneous stimulus (ECS) whereas the other coloured pen (CS−) was not. During the test phase, more frequent reports of experiencing an US when none was delivered ("false alarm") for the CS+ vs CS− qualified as evidence of conditioned pain. Notable differences between experiments were that the US was delivered when the pen touched a spot between the thumb and index finger (experiment 1; n = 23), when it virtually touched the hand (experiment 2; n = 28) and when participants were informed that the pen caused pain rather than simply predicting something (experiment 3; n = 21). The conditioning procedure proved successful in all 3 experiments: Self-reported fear, attention, pain, fear, and US expectancy were higher ($P < 0.0005$) for the CS+ than the CS−. There was no evidence for conditioned pain in experiment 1, but there was some evidence in experiments 2 and 3. Our findings indicate that conditioned pain may exist, albeit most likely in rare cases or under specific situations. More research is needed to understand the specific conditions under which conditioned pain exists and the underlying processes (eg, response bias).

**Keywords:** Classical conditioning, Pavlovian conditioning, Conditioned pain, Pain, Hallucination, Fear

## 1. Introduction

Chronic pain is a major health problem.[8,55] Despite decades of research, a comprehensive rationale for its development remains unclear. Numerous biological, psychological, and social factors have been explored, with mixed success.[27,34] One idea receiving renewed interest is that the development of chronic pain in the absence of organic pathology can be explained by classical conditioning.[14,23,29,38,41,43,49,59] According to this view, previously neutral events (conditioned stimulus: CS), such as movements, muscle tensions, or context elements, that precede pain, may begin to elicit pain by themselves (conditioned response: CR), even in the absence of the original cause of pain (unconditioned stimulus: US). The experience of pain therefore becomes the conditioned response (CR).

Historically, the idea of conditioned pain has been proposed by several scholars.[10,26,38,41,45,51,57–59,67] It is also widely adopted by clinicians.[44] Nevertheless, there is an ongoing debate about whether pain can actually be classically conditioned.[24,25,54,56] Surprisingly, there are not many experiments on this topic, and convincing evidence is currently lacking. Most studies are old and lack proper description of methods and results; see Ref. 1 For instance, Leuba[41] reported on their 10-year experience with conditioning sensations, which involved conditioning with painful stimuli under hypnosis to facilitate unconscious conditioning. On waking, 2 of the 4 participants reported feeling a prick when the CS was delivered alone. However, reporting is poor and likely favouring positive results. Indeed, a review of the historical evidence on conditioned pain concluded that the existing evidence is anecdotical and, hence, of low quality regarding the current and acceptable standards required of conditioning experiments.[14] More recently, Madden and colleagues (2015) systematically reviewed the empirical studies and identified only 3 studies. They also concluded that evidence for conditioned pain was inconclusive and insufficient.

The aim of this article was to test whether classical conditioning can result in the experience of pain in the absence of nociception or a painful stimulus. In this article, we report 3 experiments investigating this. We developed a flexible conditioning paradigm to be able to account for the possibly rare and extreme nature of conditioned pain. Indeed, as yet, the procedure of classical conditioning has proven to be a valid way to investigate fear and avoidance of impending pain,[47,48,65] but not to investigate conditioned pain. It is likely that conditioned pain only emerges under certain conditions. Therefore, we took the following hypotheses into account when designing the studies. Conditioned pain may be more likely (1) with low-intensity painful stimuli as the US[52]; (2) when there is not only a temporal but also a spatial contingency, that is, the CS and US are at the same location[9,60,61]; and (3) when the CS is being perceived as causing instead of predicting pain.[22]

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

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## 2. Experiment 1

### 2.1. Methods

#### 2.1.1. Participants

Twenty-six healthy participants from Ghent University were recruited. Inclusion criteria were age (between 17 and 35 years), normal or corrected-to-normal vision, and proficiency in Dutch and English. Exclusion criteria were the presence of self-reported psychiatric conditions, severe pain, current drug use that affects the central nervous system, current use of medication affecting somatosensory system, having cardiovascular problems or an electronic medical implant. These criteria were listed in the online recruitment system (SONA). Individuals fulfilling these criteria were invited to participate. Eligibility was rechecked on arrival in the laboratory. Three participants were excluded because of technical failure (n = 1), not understanding Dutch (n = 1), and failure to select an appropriate stimulus as the US during the calibration procedure (n = 1).

The final sample consisted of 23 participants (5 men; $M_{age}$ = 24 years, $SD$ = 3.5). All participants received €10 for participation. Ethical approval was obtained from the Ethics Committee of the Faculty of Psychology and Educational Sciences of Ghent University [2018/45/Geert Crombez/1]. The study protocol was registered on Open Science Framework (https://osf.io/5rm6w/?view_only=db36aea4e8e842b4a259277b903c9555).

#### 2.1.2. Apparatus and stimuli

##### 2.1.2.1. Electrocutaneous stimuli

Electrocutaneous stimuli (ECS; bipolar; 300 Hz; 100 milliseconds; instantaneous rise and fall time) were delivered by 2 constant current stimulators (Digitimer DS5 2000, Digitimer Ltd, the United Kingdom) through 2 pairs of Ag-AgCl electrodes (4-mm sensor; MedCaT BV) placed on the sensory territory of the superficial radial nerve of each hand.

Two individually calibrated ECS of low intensity were chosen to serve as the US. The first stimulus consisted of the ECS at the lowest level at which a participant experienced the stimulus as a pin prick. This level was individually calibrated for each hand for each participant using a simple staircase procedure (see below; right-hand average M = 0.55 mA, SD= 0.26; left-hand average M= 0.59 mA, SD= 0.28) and is labelled the "US threshold." The second stimulus was calculated by adding 20% to the US threshold and is labelled the "US suprathreshold." The choice for low-intense stimuli was based upon available models of pain and somatic experience,[21,40,52] which suggest that it is more plausible to find conditioned pain using US of lower intensities than US of higher intensities. Data collected from the quality of sensations questionnaire (see below) confirmed that the 2 USs were experienced as pricking and (to a lesser extent) stinging, sharp, tingling, and electrical (see the supplementary file available at http://links.lww.com/PAIN/B860). In addition, it was assessed and confirmed that the ECS was indeed painful through ratings in every block break. Furthermore, these values were consistent with previous studies in which the nociceptors were selectively activated and best described as "pricking".[13,50]

##### 2.1.2.2. Virtual reality

Virtual reality was presented using a HTC VIVE pro head-mounted display (HTC Corporation, Taoyuan, Taiwan) powered by a HP Omen 880 to 179 nd desktop. The VR environment was made in the Unity game engine (Unity technologies) and presented using the Steam Source engine (Valve Corporation, Bellevue, WA). During the task, participants wore headphones with noise-cancelling technology (QuietComfort, 35, II BOSE).

#### 2.1.3. Study paradigm

##### 2.1.3.1. In vivo approaching objects task—virtual reality

The In Vivo Approaching Objects task—virtual reality (IVAO-VR) is a virtual reality adaptation of a task previously developed in our laboratory.[6] Participants were seated on a chair (individually adapted height), with their hands and palms facing down on a table. Their chin was positioned to rest in a chin rest. A camera (Logitech C 525 HD Pro), installed above both the hands, captured the hands and projected these in real time in the VR environment (**Fig. 1**). The position of the hands remained fixed on the same location during the entire experiment (ie, 30 cm from the front of the table and approximately 50 cm between the thumb and index fingers).

The VR environment depicted a white table (0.8 m in width and 0.75 m in depth) in the centre of a laboratory room, resembling the actual testing room. The participant was seated on a white table across from a female experimenter at a perceived distance of 1.75 m. There was a fixation cross at the centre of the table and participants were instructed to fix their gaze toward it throughout the experiment. The virtual experimenter was holding a blue or yellow pen (CS). In a typical trial, she smoothly moved her arm toward the participant and tapped a black square (1 cm × 1 cm in size; tap duration: 200 milliseconds) that was placed between the participant's thumb and index finger (movement duration: 1500 milliseconds) and moved the arm back to the starting position (movement duration: 1500 milliseconds). Tapping the square sometimes triggered the delivery of the ECS to that same hand. An example video of the trials can be viewed on OSF: https://osf.io/g3y4k/?view_only=822e6f154f074f1baddbfd3fffa151ec.

The presentation sequence and timings of stimuli presentation was programmed and presented using the INQUISIT Millisecond software package (Inquisit 5; Millisecond Software, Seattle, WA) on a Dell computer (Intel Core2 Duo P8600, 4096 MB) with a 60-Hz, 17-inch colour CRT monitor.

##### 2.1.3.2. Classical conditioning procedure

The experiment consisted of an acquisition phase and a subsequent test phase. In the acquisition phase, pairing took place between one of the 2 colours of the pen (conditioned stimulus; CS+) and the ECS (unconditioned stimulus; US). The other colour of the pen (CS−) was never followed by the US. The colour of the pen was counterbalanced across participants. In total, 20 trials were presented during the acquisition phase, consisting of 10 CS+ trials (6 trials with US suprathreshold, 2 trials with US threshold, and 2 trials with no US) and 10 CS− trials that were never followed by the US.

During the test phase, 4 blocks of 32 trials were presented (totalling 128 trials). Each block consisted of 16 CS+ trials (2 trials with US suprathreshold, 4 trials of US threshold, and 10 trials with no US) and 16 CS− trials that were never followed by the US. All trial types were equally balanced between both hands. The experiment took approximately 30 to 45 minutes.

#### 2.1.4. Self-report measures

After each trial, participants were instructed to orally indicate whenever they felt the ECS by saying the word "yes" (primary

**Figure 1.** In Vivo Approaching Objects task—virtual reality paradigm. The left image displays the laboratory setup. The right image displays the VR view of the participant. In this experiment, the black square was placed between the thumb and index fingers (Fig. 4).



outcome measure). In case a participant answered "yes," they were prompted to indicate the level of certainty ("definitely" or "maybe") of their experience ("*How sure are you that you felt a stimulus?*"). In case a participant did not say "yes," they were prompted to indicate the level of certainty ("definitely" or "maybe") of the absence of an experience ("*How sure are you that you did not feel a stimulus?*"). Finally, after each trial, participants were asked to indicate expectancy ("*To what extent did you expect to feel an ECS?*") on a scale of 0= "not at all" to 10= "very much."

There were also some specific questions at the end of each block. After each block, participants answered 11 questions on a Likert scale ranging from 0 (not at all) to 10 (very much). Questions pertained to the degree of pain after the presentation of both pens ("*On average, how painful was the stimulus following the blue pen?*" and "*On average, how painful was the stimulus following the yellow pen?"*), fear after the presentation of both pens ("*On average, how afraid were you of the blue pen?*" and "*On average, how afraid were you of the yellow pen?"*), attention after the presentation of both pens ("*To what extent did the blue pen capture your attention?*" and "*To what extent did the yellow pen capture your attention?*"), expectancy after the presentation of both pens ("*To what extent was the blue pen followed by a stimulus?*" and "*To what extent was the yellow pen followed by a stimulus?*"). We also assessed overall pain ("*On average, how painful was the stimulus?*"), concentration ("*How concentrated were you during the overall test block?*"), and fear ("*On average, how afraid were you of the stimulus?*").

### 2.1.5. Procedure

On entering the laboratory, participants were welcomed, requested to turn off and put away their phones. They were seated in a chair in the testing room. Participants filled out the eligibility criteria form, read an information sheet about the study, and provided written informed consent. Next, they completed a battery of self-report questionnaires on LimeSurvey (see OSF https://osf.io/5rm6w/?view_only=db36aea4e8e842-b4a259277b903c9555). These were collected for a secondary analysis on the role of individual differences and are not discussed here further. Next, the participant's skin on the hand was cleaned using skin pure gel (NuPrep). The electrodes were filled with conductive Signa electrode gel and attached to the hands between the thumb and index fingers using the tape. The intensity of the ECS was individually calibrated for each participant for both hands separately (side counterbalanced across participants). To do so, a series of ECS (starting at 0.2 mA, increasing in steps of 0.2 mA, then decreasing in steps of 0.1 mA, and then increasing or decreasing in steps of 0.04 mA) were delivered to the hand until the participant selected the lowest level at which they felt a pin prick (US threshold). Then, a suprathreshold stimulus (US suprathreshold) was calculated for both hands by adding 20% to the intensity of the US threshold stimuli. Next, participants filled out the quality of sensations questionnaire. This was a set of 8 questions pertaining to the experience of the US in (un) pleasantness (scale of +5 to −5), intensity (on a 4-point scale from light to highly unbearable), and the degree to which they felt stinging, pricking, sharp, tingling, and electric (on a 5-point scale from not to very strong), taken from the Dutch McGill Pain Questionnaire.[15,46,63] In addition, it was assessed and confirmed that the ECS was indeed painful and remained so by asking about its painfulness in every block break. After that, they received instructions for the IVAO-VR paradigm. During the experimental task, the experimenter remained in a separate room and entered the verbal responses of the participant into the computer. After the task finished, participants filled out the quality of sensations questionnaire again and were debriefed.

### 2.1.6. Statistical analysis

Successful differential conditioning was investigated by performing 2 (CS type: CS+, CS−) X 5 (Phase: acquisition block, test block 1, test block 2, test block 3, and test block 4) repeated-measures (RM) ANOVAs for self-reported trial-by-trial US expectancy, and the following self-reports were measured after each block: US expectancy, pain, fear, and attention ratings. When sphericity was violated, Greenhouse-Geisser results were reported.

To test our primary hypothesis on conditioned pain, a Poisson regression (ZIP) analysis was performed with the number of false alarms in the presence of the CS+ and CS−, that is, the report of an ECS in the trials where no stimulus was given, as a dependent variable.[36,35,42] These analyses were chosen because false alarms have a low frequency (low in number, with many zeros in the data) causing a skewed distribution, which renders the use of linear models inappropriate.[64] Generalised linear mixed models were fitted with a random subject intercept to capture the dependency within participants. Four models were compared, that is, Poisson, negative binomial, zero-inflated Poisson, and negative binomial zero-inflated Poisson. The Akaike information criterion was used to select the best fit model. The CS type was added as a predictor. The regression coefficients were reported as rate ratios (RRs). RRs are a representation of the percentage increase ($RR > 1$) or decrease ($RR < 1$) in the expected frequency of false alarms for each one unit increase in the continuous predictor. In cases where the zero-inflated models fitted, an odds

ratio (OR) was reported to explain the odds of there being 1 vs 0s in the data. All count models were fitted using the package glmmTMB (Brooks et al., 2017) in R (version 3.6.1). The total number of CS+ and CS− trials was the same but some of the CS+ trials were reinforced whereas the CS− trials were not. Therefore, CS+ had a lower number of "no stimulus" trials than the CS− trials. The log of the number of CS+ (N = 40) and CS− trials (N = 64), in which no shock was applied, was included in the models as an offset variable. Next, we performed a secondary analysis on the certainty of the false alarms, whereby we expected more certainty for the false alarms made for the CS+ as compared withthe CS− trials. To investigate this hypothesis, we performed a mixed-effects logistic regression model with CS (CS+ vs CS−) as the independent variable and certainty (definitely vs maybe) as a dependent variable. Generalised linear mixed-effects models were performed with a logit link function, as implemented in the R package lme4.

Conditioned pain and certainty analyses were performed in R (version 3.6.1). All other analyses were performed using SPSS 25.0 (IBM SPSS Statistics for Windows, version 25.0; Armonk, NY, USA).

### 2.2. Results

#### 2.2.1. Manipulation check—classical conditioning

US expectancy: A RM ANOVA of mean trial-by-trial US expectancy indicated that acquisition (learning) was successful throughout the acquisition and test blocks. Overall, US expectancy for CS+ ($M = 6.39$, $SD = 1.56$) was significantly higher than for CS− trials ($M = 1.54$, $SD = 1.84$), $F(1,22) = 240.98$, $P < 0.001$. In addition, a main effect of phase was found, $F(1.95, 42.89) = 24.32$, $P < 0.001$, showing a decline over time (acquisition $M = 5.35$, $SD = 2.88$; test phase 1 $M = 4.17$, $SD = 2.88$; test phase 2 $M = 3.53$, $SD = 2.73$, test phase 3 $M = 3.52$, $SD = 3.01$, test phase 4 $M = 3.26$, $SD = 2.95$). No interaction effect was found between CS type and phase, $F(2.27, 50.08) = 1.17$, $P = 0.32$. Similar results were found for a RM ANOVA with block expectancy as the dependent variable indicating that acquisition was successful. US expectancy for CS+ ($M = 5.98$, $SD = 2.38$) was significantly higher than CS− ($M = 0.85$, $SD = 1.74$), $F(1,22) = 183.43$, $P < 0.001$. A main effect of phase was found, $F(1.57, 34.68) = 7.92$, $P < 0.005$, showing a decline over time (**Fig. 2**). In addition, a significant interaction was found between CS type and phase, $F(2.18, 48.10) = 4.34$, $P < 0.05$, indicating that there were significant drops in the ratings for the CS+ until the first test block, and then, there was a more marginal but steady decline over the test blocks, whereas the CS− ratings remained low from start to end.

Fear: A RM ANOVA of fear ratings indicated that participants were more fearful of the CS+ ($M = 2.81$, $SD = 2.45$) as compared with the CS− ($M = 0.58$, $SD = 1.27$), $F(1,22) = 39.85$, $P < 0.001$. There was neither a significant effect of phase, $F(2.33, 51.33) = 0.42$, $P = 0.69$, nor an interaction between Fear and CS type, $F(2.05, 45.09) = 0.99$, $P = 0.37$.

Pain: A RM ANOVA of pain ratings indicated that participants perceived the stimulus following the CS+ as more painful ($M = 2.43$, $SD = 2.25$) than the stimulus following the CS− ($M = 0.40$, $SD = 1.05$), $F(1,22) = 23.70$, $P < 0.001$. No significant effect of Phase, $F(2.95, 64.89) = 2.10$, $P = 0.10$ and interaction between Phase and CS type, $F(4,88) = 0.21$, $P = 0.93$ were found.

Attention: *A* RM ANOVA of attention ratings indicated that participants were more attentive to the CS+ ($M = 6.66$, $SD = 2.20$) than the CS− ($M = 3.28$, $SD = 2.33$), $F(1,22) = 65.02$, $P < 0.001$. There was also a significant effect of phase, $F(4,88) = 3.87$, $P < 0.01$, and a significant interaction between phase and CS type, $F(4,88) = 5.30$, $P < 0.001$. Attention for CS+ remained high throughout, while CS− steadily declined over blocks with a peak in the third phase (**Fig. 2**).

#### 2.2.2. Primary outcomes—conditioned pain

False alarms: False alarms were reported by 26% (6 of 23) of the participants. The overall rate of false alarms was low. Of all the test trials without the US (2392 trials), false alarms occurred in only 14 of those trials, that is, 0.59% (8 false alarms for 920 no stimulus CS+ trials [0.87%] and 6 false alarms for 1472 no stimulus CS− trials (0.41%); **Figure 3**). To compare the presence of false alarms between both CSs, a zero-inflated Poisson model had the best fit, with the count part of the model showing no significant difference in the number of false alarms between CS+ and CS− trials [*RR* = 1.06, 95% *CI* (0.37, 3.08)].The zero-inflation part of the model, modelling the "excess zeros" and describing the odds of observing no false alarms vs at least one false alarm, found that the estimated odds of having no false alarms was 0.0,000,003, times lower for CS+ than for CS− [*OR* = 0.0,000,003, 95% *CI* (0.000,000,000,001, 0.11), $P = 0.02$]. However, when interpreting the latter finding, one has to keep in mind that the number of the participants reporting a false alarm was low (n = 6) and the total number of false alarms was also low (n = 14), possibly leading to an unusual (less reliable) low OR.

Certainty of false alarms: False alarms for the CS+ (*Definitely* = 5, *Maybe* = 3) were not significantly higher in certainty (definitely vs maybe) than for the CS− (*Definitely*= 3, *Maybe* =3) [*OR* = 1.69; 95% CI (0.10, 33.3), $P = 0.70$].

### 2.3. Conclusion

The differential conditioning between CS+ and CS- was successful because participants reported higher levels of US expectancy, pain, fear, and attention for the CS+ than the CS−. We found no reliable difference in the rate of false alarms for CS+ vs CS− trials. Therefore, this study does not support the hypothesis that pain can be conditioned. Note that results should be interpreted with caution given the limited number of participants who reported a false alarm (N = 6) and the small number of trials with false alarms (N = 14). This lack of false alarms may be due to the fact that conditioned pain may only emerge if the CS is experienced as causing instead of merely predicting pain.[22,53] In experiment 2, we attempted to facilitate such a causal inference by increasing the spatiotemporal contingency.[60,61] More specifically, the pen now touches the hand instead of a place near the hand (**Fig. 4**).

## 3. Experiment 2

### 3.1. Methods

#### 3.1.1. Participants

Twenty-nine healthy participants were recruited. Inclusion, exclusion, and compensation were identical to experiment 1. One participant was excluded due to technical failure as their hands were sweating too much for the electrodes to stay attached, resulting in a final sample of 28 participants (7 men; $M_{age}$ =21; *SD* = 3). Ethical approval was obtained from the Ethics Committee of the Faculty of Psychology and Educational Sciences of Ghent University [2018/45/Geert Crombez/3]. The study protocol was registered on Open Science Framework (https://osf.io/rtkn9/?view_only=8d2f6954de824c8aa761cc1e42e7c4c1).

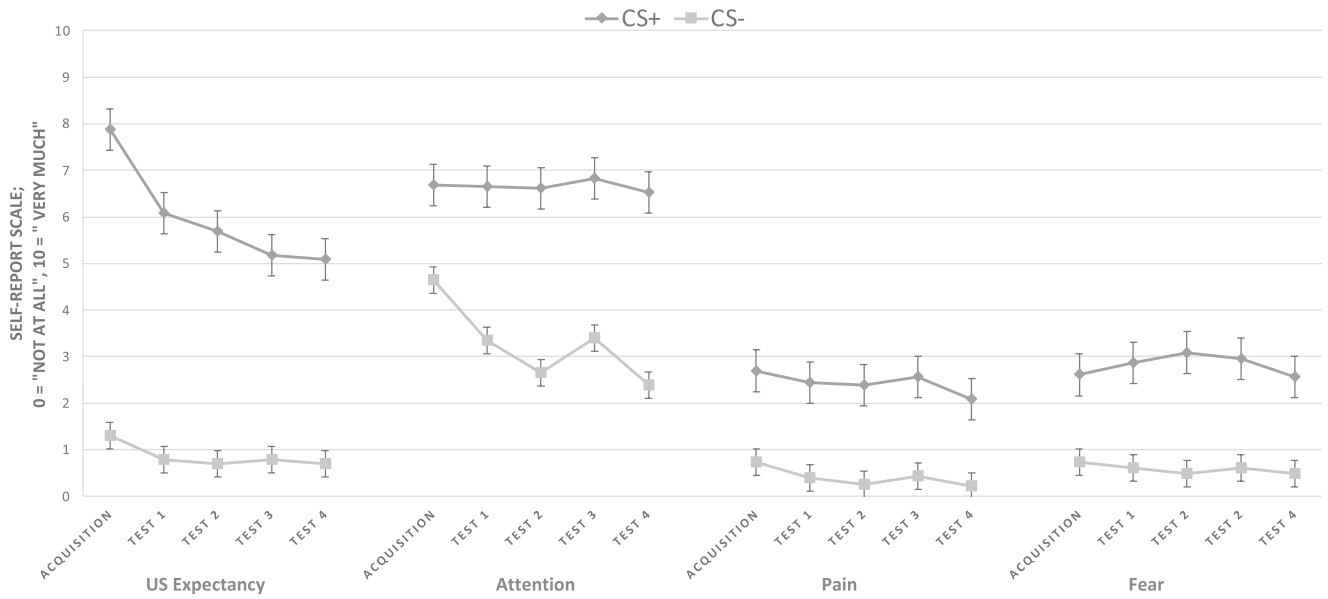


**Figure 2.** Graphical representation of the self-reported US expectancy (block), attention, pain, and fear ratings given for the CS+ and CS− during the block breaks in all 5 phases in experiment 1.

### *3.1.2. Apparatus and stimuli*

Apparatus and type of stimuli presented to induce pain and present a virtual reality setting were identical to experiment 1. The US threshold was individually calibrated for each hand for each participant using the same procedure as the last study (right-hand average M = 0.50 mA, SD = 0.30, left-hand average M = 0.46 mA, SD = 0.31).

### *3.1.3. Study paradigm*

#### *3.1.3.1. In vivo approaching objects task—virtual reality*

The IVAO-VR paradigm was identical to experiment 1, except the spatial contingency between the CS and US was changed. Indeed, in experiment 2, the black square that was approached by the pen placed on the top of the hand where the electrodes were attached between the thumb and index fingers (**Fig. 4**). Furthermore, 2 booster trials (ie, a reinforced CS+ and an unreinforced CS−; randomised for order and hand) at the start of each phase to ensure that participants are aware of the contingency which remains the same during each test phase despite the break between blocks. In doing so, the experiment consisted of 158 trials (20 acquisition trials, 128 test trials, and 10 booster trials). To further ensure that the contingency remained similar to the acquisition phase, verbal instructions were added before each test block, that is, "*Remember what you learnt in the first block. One of the 2 coloured pens (blue pen or yellow pen) will be predictive of something.*"

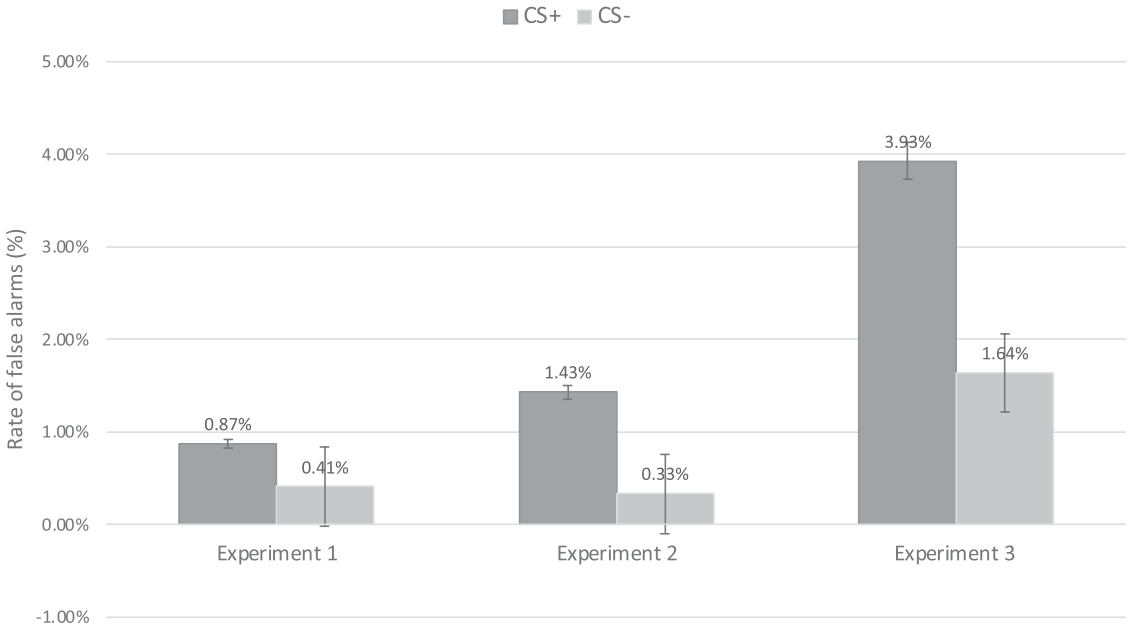


**Figure 3.** Rate of false alarms (percentage) made in the no US trials for the CS+ and CS− (Error bars: percentage) in all 3 experiments.

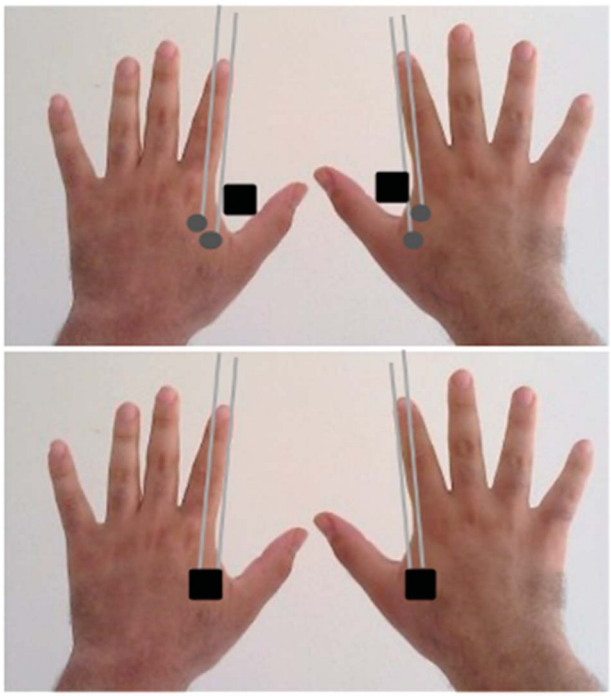

**Figure 4.** Improved spatial contingency. The image at the top represents the spatial contingency from experiment 1 and the image at the bottom represents the spatial contingency from experiment 2 and experiment 3.

#### *3.1.4. Self-report measures*

Participants were instructed to continue to indicate "yes" when they felt the US but to say nothing if they did not feel the US (primary outcome measure). In case a participant answered "yes," they were prompted to answer the questions "*Was it a pin prick?*" (yes or no) and "*How sure are you that you felt a stimulus?*" (definitely or maybe). In case a participant indicated they did not feel an ECS, no follow-up questions were presented, that is, no certainty question was asked if they did not say "yes." US expectancy was not measured during trials. Questions at the end of each block were identical to experiment 1.

#### *3.1.5. Statistical analysis*

In the previous experiment, self-reported US expectancy was collected after each trial and after each blocks. The results show that the 2 expectancy ratings are highly correlated (supplementary file available at http://links.lww.com/PAIN/B860). Therefore, trial US expectancy was dropped and the analysis was only performed for the block US expectancy.

In addition, certainty ratings were only collected for trials where participants said "yes" to feeling the US. The analysis was only performed on the certainty of false alarms.

### *3.2. Results*

#### *3.2.1. Manipulation check—classical conditioning*

US expectancy: A RM ANOVA for US expectancy indicated that acquisition was successful throughout all phases as overall US expectancy for CS+ trials ($M = 5.47$, $SD = 2.09$) was significantly higher than for CS- trials ($M = 0.41$, $SD = 1.09$), $F(1,27) = 394.17$, $P < 0.001$. In addition, a main effect of phase was found, $F(3.14, 1) = 41.28$, $P < 0.001$, indicating a decline in US expectancy over the phases (**Fig. 5**). There was no interaction between phases and CS type, $F(1.70, 45.93) = 2.23$, $P = 0.12$.

Fear: A RM ANOVA for fear ratings indicated that participants were more fearful of the CS+ ($M = 2.43$, $SD = 2.50$) than of the CS− ($M = 0.33$, $SD = 0.62$), $F(1,28) = 34.02$, $P < 0.001$. Neither a main effect of phase, $F(3.25, 91.09) = 0.62$, $P = 0.61$, nor an interaction between phase and CS type was found, $F(2.76, 77.36) = 0.24$, $P = 0.24$.

Pain: A RM ANOVA for pain ratings indicated that participants perceived the stimulus following the CS+ as more painful ($M = 2.64$, $SD = 2.02$) than the stimulus following the CS- ($M = 0.24$, $SD = 0.67$), $F(1,27) = 55.11$, $P < 0.001$. There was a significant effect of phase, $F(4,108) = 2.54$, $P < 0.05$, such that pain ratings in acquisition and test 1 were significantly higher than the other test phases (**Fig. 5**). There was no significant interaction between phase and CS type, $F(4,108) = 0.41$, $P = 0.79$.

Attention: *A* RM ANOVA for attention ratings indicated that participants were more attentive to the CS+ ($M = 6.35$, $SD = 2.20$) than the CS− ($M = 3.12$, $SD = 2.46$), $F(1,28) = 82.73$, $P < 0.001$. There was also a significant effect of phase, $F(2.59, 72.59) = 14.26$, $P < 0.001$. Attention was higher in the acquisition and first test phase. There was no interaction between phase and CS, $F(2.80, 78.50) = 0.87$, $P = 0.45$.

#### *3.2.2. Primary outcomes—conditioned pain*

False alarms: False alarms were reported by 25% (10 of 28) of the participants. The overall rate of false alarms remained low. Of all the trials where no ECS was given (2912 trials), false alarms occurred in only 22 (0.76%) of all trials (16 of 1120 CS+ trials [1.43%] and 6 of 1792 CS− trials [0.33%]; **Figure 3**). To compare the number of false alarms between both CSs, a Poisson model showed the best fit, indicating that the incidence rate for false alarms for the CS+ trials was 4.27 times higher than for CS−, [$RR = 4.27$, 95% CI (1.67, 10.90), $P = 0.002$]. In other words, the expected number of false alarms was 327% higher for CS+ than for CS−.

Certainty of false alarms: False alarms for the CS+ (*Definitely* = 5, *Maybe* =11) were not significantly higher in certainty (definitely vs maybe) than for the CS- (*Definitely*= 1, *Maybe* =5) [$OR = 2.27$; 95% CI (0.26, 49.65), $P = 0.50$].

### *3.3. Conclusion*

In line with experiment 1, the differential conditioning between CS+ and CS- was successful. Of more importance is that this experiment provides some support in favour of the conditioned pain hypothesis. There were significantly more false alarms for the CS+ than for the CS−. Yet, some caution is warranted. The number of false alarms remained very low (0.76% of all test trials), also for the CS+ trials (1.43%). Furthermore, the confidence intervals were large, indicating an imprecise estimation. In addition, the results for the certainty analysis should be interpreted with caution as only 10 participants reported false alarms.

To further increase the chance of finding false alarms, the instructions were made pain-specific and causal. Hence, we changed the phrase "*predictive of something*" of experiment 2 into "*will cause you pain"*). 12,66

## 4. Experiment 3

### *4.1. Methods*

#### *4.1.1. Participants*

Twenty-two healthy participants were recruited. Inclusion, exclusion, and compensation were identical to experiment 1. One

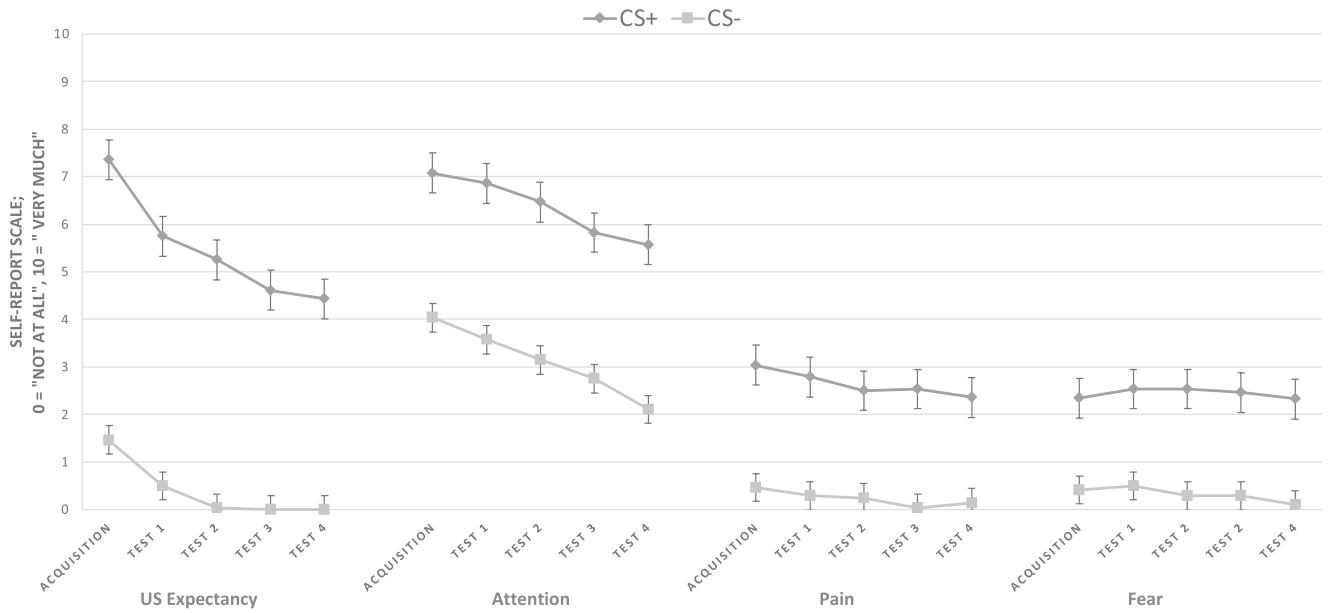


**Figure 5.** Graphical representation of the self-reported US expectancy (block), attention, pain, and fear ratings given for the CS+ and CS− during the block breaks in all 5 phases in experiment 2.



participant was excluded due to technical failure with the VR glasses. The final sample consisted of 21 participants (men = 4; $M_{age}$ = 21; *SD* = 4.5). The experiment was approved by the Ethical Committee of the Faculty of Psychology and Educational Sciences at Ghent University [2018/45/Geert Crombez/2]. The study protocol was registered in the Open Science Framework (https://osf.io/g3y4k/?view_only=822e6f154f074f1baddbfd3fffa151ec).

#### *4.1.2. Apparatus and stimuli*

Apparatus and type of stimuli presented to induce pain and present a virtual reality setting were identical to experiment 1. The US threshold was individually calibrated for each hand for each participant using the same procedure as the last study (right-hand average M= 0.37 mA, SD= 0.18, left-hand average M= 0.41 mA, SD = 0.20).

#### *4.1.3. Study paradigm4.1.3.1.*

#### *In vivo approaching objects task—virtual reality*

The IVAO-VR paradigm was identical to experiment 2, except for the instructions that were provided at the start of the experiment (ie, "*Pay close attention to the colour of the pen as one of them will cause you pain.*") and each experiment block (ie, "*Remember what you learnt in the first block-one of the 2 coloured pens (blue pen or yellow pen) will cause you pain.*"). In doing so, causal and pain-specific instructions replaced the predictive instructions.

#### *4.1.4. Self-report measures*

Questions at the end of each trial and at the end of each block were identical to experiment 2, except for the question "*Was it a pin prick*?" which was not used.

### *4.2. Results*

#### *4.2.1. Manipulation check—classical conditioning*

US expectancy: A RM ANOVA for US expectancy indicated that acquisition was successful and it remained so throughout all test phases as overall US expectancy for CS+ trials ($M$ = 5.64, $SD$ = 2.41) was significantly higher than for CS− trials ($M$= 0.51, $SD$= 1.27), $F(1,20) = 97.12$, $P < 0.001$. In addition, a main effect of phase was found, $F(4,80) = 16.56$, $P < 0.001$, wherein there was a steady and significant decline in US expectancy in each phase until test 3. There was a significant interaction between phase and CS, $F(2.67.53.52) = 11.32$, $P < 0.001$, wherein CS- remained low but CS+ started higher and slowly declined (**Fig. 6**).

Fear: A RM ANOVA for fear ratings indicated that participants were more fearful of the CS+ ($M$ = 2.32, $SD$ = 2.32) than for the CS− ($M$ = 0.45, $SD$ = 1.18), $F(1,20) = 15.94$, $P < 0.001$. There was no significant effect of phase, $F(2.35.47.12) = 1.11$, $P = 0.34$, and no interaction between phase and CS type, $F(1.94.38.91) = 3.18$, $P = 0.054$.

Pain: RM ANOVA for pain ratings indicated that participants perceived the stimulus following the CS+ ($M$ = 2.69, $SD$ = 2.30) as more painful than the stimulus following the CS− ($M$ = 0.16, $SD$ = 0.52), $F(1,20) = 28.18$, $P < 0.001$. There was a significant effect of Phase, $F(3.10.62.18) = 3.01$, $P < 0.05$, such that pain was reported significantly highest in the first phase. There was no interaction between Phase and CS type, $F(2.80.56.15) = 0.53$, $P = 0.64$.

Attention: RM ANOVA for attention ratings indicated that participants were more attentive to the CS+ ($M$ = 6.13, $SD$ = 2.10) than the CS− ($M$ = 3.68, $SD$ = 2.43), $F(1,20) = 31.74$, $P < 0.001$. There was also a significant effect of phase, $F(4,80) = 7.88$, $P < 0.001$. Attention was higher in the acquisition and first test phase then during later phases (**Fig. 6**). Again, no interaction was found between phase and CS type, $F(2.67, 53.41) = 2.53$, $P = 0.07$.

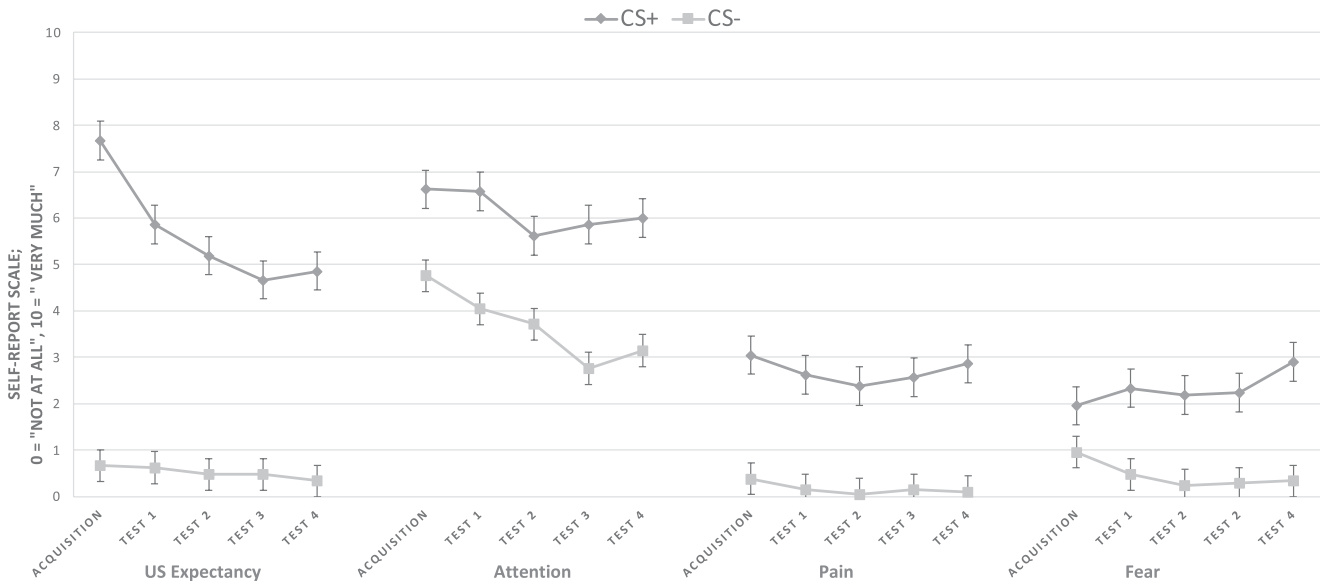


**Figure 6.** Graphical representation of the self-reported US expectancy (block), attention, pain, and fear ratings given for the CS+ and CS− during the block breaks in all 5 phases in experiment 3.



#### *4.2.2. Primary outcomes—conditioned pain*

False alarms: False alarms were reported by 62% (13 of 21) of the participants. Of all the trials where no ECS was given (2184 trials), false alarms occurred in 55 trials, that is, (2.52%) (33 for 840 CS+ trials [3.93%] and 22 for 1344 CS− trials [1.64%]; **Figure 3**). To compare the number of false alarms between both CSs, a Poisson model had the best fit, showing that the incidence rate for false alarms for the CS+ trials was 2.40 times higher than for CS− , [*RR* = 2.40, 95% CI (1.40, 4.12), *P* = 0.001]. In other words, the expected number of false alarms was 140% higher for CS+ than for CS- trials.

Certainty of false alarms: False alarms for the CS+ (*Definitely* = 15, *Maybe* = 18) were not significantly higher in certainty (definitely vs maybe) than for the CS- (*Definitely* = 9, *Maybe* = 13), [*OR* =0.44; 95% CI (0.07, 2.92), *P* = 0.39].

### *4.3. Conclusion*

Our differential conditioning procedure was successful again. We also observed an overall higher rate of false alarms than the 2 previous experiments, albeit the rate remained low (2.52%). Once again, the results for the certainty analysis should be interpreted with caution as only 13 participants reported false alarms.

Of note is that we found support for the conditioned pain hypothesis. There were significantly more false alarms for the CS+ than for the CS-.

## 5. General discussion

In a series of 3 experiments, we investigated whether pain can be a classically conditioned response. In each of the studies, differential conditioning between CS+ and CS− (acquisition) was successful. Of importance were the findings about reporting a stimulus when actually none was delivered (false alarm). We did not find evidence for conditioned pain in experiment 1. Study 2 and study 3, however, showed statistical evidence for conditioned pain.

We were able to demonstrate that classical conditioning may result in the report of pain in the absence of a painful or nociceptive stimulus (US). This is a remarkable finding due to its extreme nature. Indeed, there are various ways in which classical conditioning may affect pain. First, it is possible that the CS+ increased the experience of pain in the presence of a painful, noxious stimulus (US) (conditioned hyperalgesia). Second, it is possible that the CS+ elicits a painful experience but in the presence of a non-noxious stimulus instead of the original noxious stimulus (conditioned allodynia). Third, this is the focus in our study, the CS+ elicits a painful experience in the absence of any extra stimulus, which could be also labelled "conditioned hallucination".[43]

The idea of conditioned pain, in particular in the form of conditioned hallucination, has received much theoretical consideration in literature and has recently prompted discussion again[24,54,56] but has not yet been systematically tested. In that context, it is important to note that our conditioning procedure did not merely consist of a temporal relationship (contingency) between the CS+ and the US but also of a spatial relationship (contingency) between the CS+ and the US. This spatiotemporal relationship between CS+ and US was realized by delivering the US at the time that the coloured pen (almost) touched the hand. It has been proposed that such spatiotemporal contiguities lead to better conditioning and also better causal inferences.[22,33,60,61] In addition, providing causal information about the power of the pen to produce pain, we aimed to go beyond the typical predictive account of classical conditioning.[22] As of now, we do not know to what extent these factors are critical for our findings. Notwithstanding, our setup resembles the clinical observation that some patients may experience pain when a pen/syringe is nearing the body part of a patient and might cause pain. For example, Hoogenraad et al. (1994) reported the case of a 46-year-old man with ischaemic infarction of the right parietal cortex who reported feeling nothing when his arm was stimulated by a pin prick when his eyes were closed, but reported burning pain and quickly withdrew his arm on being approached by a pen-like stimulus with his eyes open.[32]

The mathematician Pierre-Simon LaPlace is credited with the following statement, which also holds true in our context: *"The weight of evidence for an extraordinary claim must be*

*proportioned to its strangeness."*[28,39,62] We must keep this in mind when considering our results. Our studies should not be considered as a definite answer to a thitherto largely unexplored question. It is a first step. One must also keep in mind that the rate of false alarms remained low across the 3 experiments and not every participant experienced false alarms. Overall, the findings across the 3 experiments indicate that participants were very sensitive to what happened to their body. As such, pain expectancies do not always seem to cause pain. Although a common idea in nocebo research[2,11,12,37] and prediction error theories[4,5,30,31] is that pain expectancies may cause pain, there is also research revealing that pain expectancies can easily be disconfirmed when no painful stimulus is delivered, both in healthy volunteers and in clinical studies.[3,16,17]

As yet, the possible processes underlying our results were not investigated. We can also not rule out the possibility of a response bias, the inclination to say "yes" during trials which are indeed more often accompanied by a painful stimulus, and not a genuine perceptual experience.[19] Follow-up studies may try to rule out this explanation. A potential solution may be to use strategic reinforcement schedules by punishing false alarms (conditioned hallucinations), rewarding correct responses, and allowing to give no response when unsure.[7] Another option may be to investigate to what extent the false alarms are accompanied by the presence of a specific pain signature in the brain.[25]

Our studies have several strengths. We report a series of 3 independent studies with nonoverlapping samples of participants in an open and transparent way. The study protocols were pre-registered, and the data are available for reanalyses and supplementary analyses. This series of studies has been successful in establishing a paradigm to test conditioned pain with a promising future. One of the advantages is the use of virtual reality. It allowed standardization of trials and movements and also made it possible to install a spatial and temporal contingency between the CS and the US. The paradigm can easily be adapted to various realistic contexts, such as a doctor's office. The CSs can also be easily varied, such as using a syringe or cotton swab.

Our studies also have limitations. First, the presence of conditioned pain is inferred using self-reports and may thus reflect a reporting bias. Second, we did not assess the intensity of the pain after each stimulus and were thus not able to directly infer that conditioned pain was experienced. The false alarms consisted of reporting the presence of a painful US when none was delivered. Third, we did not experimentally test the putative contributing role of factors influencing conditioned pain (eg, US-intensity, spatial contingency, and causal instructions), except for the CS+ and the CS−. We simply set or changed some background or control factors. In doing so, we adhere to some philosophical accounts of causality (John Mackie), positing that a causal factor (eg, experimentally manipulated factor) only works against a background of other causally relevant factors.[20] Future studies may aim to experimentally manipulate these other causally relevant factors. Fourth, our sample consisted of healthy students and not of individuals seeking health care for persistent pain. It is not sure to what extent conditioned pain can also be observed in clinical situations and whether it explains particular forms of chronic pain. Fifth, only a few participants showed evidence of conditioned pain. It may well be important to examine individual differences and to use designs that allow inferences at the level of a single case (eg, Ref. 18). Sixth, and relatedly, future studies might explore the role of individual differences. We have not performed this because our primary interest was to investigate whether pain could be classically conditioned. Furthermore, there were an insufficient number of participants reporting false alarms. Notwithstanding, participants filled out a list of questionnaires for this purpose: neuroticism (IPIP), imagery ability (QMI), bodily attention (BCQ), graded chronic pain (GCP), pain catastrophizing (PCS), PROMIS depression, anxiety, and sleep. Interested readers can contact us for these results or to perform additional analyses.

### 5.1. Note

The order in which the studies were conducted was experiment 1, experiment 3, and experiment 2. After experiment 1, experiment 3 was conducted with all the improvements together. Subsequently, experiment 2 was conducted to check if the results differ without the causal and pain-specific instructions and the pin prick question was added. Our studies, including a pilot study, were pre-registered on Open Science Framework.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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## Supplemental digital content

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