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The Effect of Observing High or Low Pain on the Development of Central Sensitization

Diana M. Torta,* Elke Meyers,* Klaartje Polleunis,* Sarah De Wolf,* Ann Meulders,*,†
and Emaneul N van den Broeke*,‡

*Health Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium, †Faculty of Psychology and Neuroscience, Experimental Health Psychology, Maastricht, The Netherlands, ‡Institute of Neuroscience, division Cognition and Systems, Faculty of Medicine, UCLouvain, Brussels, Belgium

Abstract: It is unknown whether watching other people in high pain increases mechanical hypersensitivity induced by pain. We applied high-frequency electrical stimulation (HFS) on the skin of healthy volunteers to induce pinprick mechanical hypersensitivity. Before HFS participants were randomly allocated to 2 groups: in the low pain group, which was the control condition, they watched a model expressing and reporting lower pain scores, in the high pain group the model expressed and reported higher scores. The 2 videos were selected on the basis of a pilot/observational study that had been conducted before. We tested the differences in perceived intensity of the HFS procedure, in the development of hypersensitivity and the role of fear and empathy. The high pain group reported on average higher pain ratings during HFS. The perceived intensity of hypersensitivity, but not the unpleasantness or the length of the area was higher in the high pain group. Our results suggest that watching a person expressing more pain during HFS increases one's own pain ratings during HFS and may weakly facilitate the development of secondary mechanical hypersensitivity, although this latter result needs replication.

Perspective: Observing a person in high pain can influence the perceived pain intensity of a procedure leading to secondary mechanical hypersensitivity, and has a weak effect on hypersensitivity itself. The role of fear remains to be elucidated.

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Keywords: Central sensitization, observational learning, pain, fear.

Introduction

Building on Bandura's observational learning theory,[2] previous research has found that the observation of others in pain is an important source for the development of pain beliefs and fear.[1,3,6,11-14,19,25,26,29,45] Indeed, several reports[1,6,9,22,25,26,45-47] have indicated that the observation of others in pain can affect experimentally induced pain perception, and may impart significant placebo- nocebo effects, via expectations, but also purportedly via modulation of pain-related fear.[11,12,15,29]

Experimental pain, such as the topical application or injection of capsaicin and electrical stimulation of the skin, induces mechanical pinprick hypersensitivity of the surrounding skin (secondary hyperalgesia), which is considered to be a manifestation of central sensitization, ie, the increased responsiveness of nociceptive neurons in the central nervous system.[17] It is believed that the central sensitization contributes to persistent pain conditions.[16,48] Whether observing a person in high pain can increase the secondary mechanical pinprick hypersensitivity (or central sensitization) is yet unknown.

To address this question we conducted a pilot study and an experiment. In a pilot/observational study we showed participants 5 videos of an actress undergoing High-Frequency electrical stimulation of the skin (HFS). HFS is a procedure that, besides being painful, induces consistently across volunteers a robust pinprick hypersensitivity of the skin adjacent to the site at which

HFS is applied. The videos differed on the perceived painfulness expressed and reported by the actress during HFS. After watching the videos, participants provided ratings of fear of HFS and expected pain intensity of the procedure. These results were then used to select, for the actual experiment, the 2 videos showing the largest differences on fear and expected painfulness, the high pain and low pain video. In this experiment, volunteers were randomly assigned to watch the low pain video, in which the actress demonstrated and reported mild pain ("low pain" group), or the high pain video, where the actress demonstrated reported intense pain ("high pain" group). After having seen the videos, the participants underwent HFS themselves, and were tested for 1) the presence and magnitude of pinprick hypersensitivity and its unpleasantness at several time points after applying HFS, 2) the vertical spread of pinprick hypersensitivity along the proximal-distal axis. Crucially, the videos only portrayed the actress in different degrees of pain *during* HFS, but did not provide any information about the subsequent development of pinprick hypersensitivity, which was our primary outcome. We hypothesized that the high pain video would induce more fear of HFS than the low pain video, leading to higher pain ratings during HFS and as a consequence to more pinprick hypersensitivity.

Additionally, we were interested in investigating the potential contribution of empathy to fear scores.[15,20] We hypothesized that the higher the empathy scores would lead to higher, the more the fear of pain ratings they would develop. In the pilot/observational study, we hypothesized that higher scores on the empathy scale would be associated with higher developed fear after watching a person in pain. In the experiment, since our main hypothesis regarded an increase of fear in the high pain video, we planned to use empathy scores as a potential moderator in case of a significant relationship between fear and hyperalgesia.

Materials and Methods

Participants

The pilot/observational study was performed online via Qualtrics XM[OS]. One-hundred participants were recruited via snowballing techniques, but only 83 participants fulfilled the inclusion criteria (17 participants were older than 40 years, see also later).

The experiment was performed in the laboratory. Forty-five participants were included. This number was based on a sample size calculation performed with MorePower 6.0.4[4] using Cohen's f effect size of 0.4 for the interaction, standard 0.05 alpha error probability, power of 0.80. The f effect size was derived from a previous report by van den Broeke and colleagues[33] on the role of negative expectations on pinprick hyperalgesia. One participant dropped out during HFS for excessive pain, resulting in a final sample of 44 volunteers (N = 22 per group). This experiment was pre-registered on the

Open Science Framework (https://osf.io/mxsa5) prior to data acquisition.

Both the pilot/observational study and the experiment had been approved by the Social and Societal Ethics Committee of KU Leuven (G-2019 12 1893) and were conducted according to the Helsinki Declaration. Before the beginning of each study a written informed consent was obtained from each participant. Inclusion criteria were: 1) being female, 2) being 18 years of age or older but younger than 40, and 3) being a native or fluent Dutch speaker. Exclusion criteria were: 1) having participated in a study using High or Low Frequency stimulation of the skin, 2) having used paracetamol or other anti-inflammatory and/or painkiller <12 hours before the experiment, 3) having heart and vascular problems, 4) having respiratory or neurological diseases, 5) suffering from pain of a duration of 3 months or longer (chronic pain), 6) having a pacemaker or another electronical implant, 7) having uncorrected hearing and/or vision problems, 8) having psychiatric disorders, 9) being under regular medication use (except anticonception), 10) being pregnant or sleep deprived (<5 hours) at the moment of testing. Additional exclusion criteria for experiment 2 were: 1) having scars or tattoos on their ventral forearms and 2) presenting symptoms of Covid-19. We chose to recruit only women in order to prevent potential gender effects as both the experimenters (SdW and KP) and the model in the video were women.

Design of the Study

Pilot/Observational Study

In this pilot/observational study, participants were asked to watch and evaluate 5 online videos (see https://osf.io/mxsa5). On the day of testing, participants received a link to participate and were asked to fill in their demographics including age and level of education. After that, they were presented with the 5 videos; the presentation order was counterbalanced across participants.

In all videos the same female model (a young Caucasian amateur actress in her early 20s) pretended to undergo HFS on one of the two ventral forearms (see 2.3 for a description of HFS). HFS, when delivered at an intensity corresponding to 20 x the electrical detection threshold to a single pulse, is experienced as painful in the majority of people[39] and induces increased pinprick sensitivity of the skin surrounding the site at which HFS is applied.[31-39,42-44] In reality the actress received only very mild stimuli. The 5 videos differed on the perceived intensity of HFS pain as expressed by different facial expressions and bodily reactions to the stimulation and the pain ratings reported after each train. Each train was rated on a scale ranging from 0 (did not feel anything) to 100 (the most intense pain possible) with 50 being the anchor for the transition from non-painful to painful sensations. In the low pain videos (videos 1 and 2) the actress expressed mild reactions to the 5 trains, which were rated as 60-60-55-55-55. In the high pain videos (videos 4 and 5), she displayed intense pain and

provided 80-80-85-85-85 as ratings. Video 3 was used to test the effects of a neutral expression associated with low ratings (as in videos 1 and 2), and meant to be an additional control condition. All videos lasted approximately 1 minute and were filmed in the same room where the exeriment took place. After watching each video, participants answered the questions "*How afraid would you be should you have to undergo this procedure*" and "*How painful do you expect the stimulation to be?*" on a scale from 0 to 4, where 0 was not fearful/not painful, 1 was slightly fearful/painful, 2 was medium fearful/painful, 3 was very fearful/painful, 4 was extremely fearful/painful. In order to investigate whether these scores were more influenced by the facial and bodily expressions or by the ratings of the actress we further asked: "*To what extent did the following aspects have an effect on your answers: The facial/bodily expressions that the woman showed, the pain ratings that the woman provided.*" Answers were given by moving a scroll bar from 0 to 10 for each of the two elements (facial/bodily expressions and ratings). Finally, participants were asked to fill in the Interpersonal Reactivity Index (IRI) questionnaire,[7,8] an empathy scale.

Experiment

In this between-subject experiment, participants watched either the high pain or low pain video (selected from the pilot/observational study) before they received HFS on one ventral forearm. The day before their participation, participants were requested to fill in the following questionnaires online via Qualtrics; the Interpersonal Reactivity Index (IRI), the State-Trait Anxiety Inventory (STAI),[23,41] the modified Differential Emotions Scale (mDES),[10] the Pain Catastrophizing Scale (PCS),[24,30] and the Fear of Pain Questionnaire-III (FPQ-III).[18,21] A description of the questionnaires can be found in the Supplementary material. The questionnaires were presented to control for potential psychological differences in the low and high pain groups. On the day of testing, at the beginning of the experiment, participants received a written standardized instruction (see Supplementary material) describing the procedure. After that, the baseline pain sensitivity (perceived intensity and unpleasantness) to mechanical pinprick stimuli was assessed on both forearms (measurement T0, see also 2.5). The arm that was stimulated first was counterbalanced across participants. The assessment of pinprick sensitivity was followed by the establishment of the detection threshold to a single electrical pulse (see also 2.4). After these baseline measurements, participants were randomly assigned to either a high pain or low pain group. In both groups, participants were told that before receiving HFS they first would watch a video showing the HFS procedure. The participants in the high pain group watched the high pain video selected in the pilot experiment (video 4) and the low pain group watched the low pain video (video 2). After watching the video, HFS was applied to one of the two ventral forearms (see 2.3) and participants were instructed to rate their perceived pain intensity for each train on the same scale as the one used by the model in the pilot/observational study. The arm at which HFS was delivered (dominant or non-dominant) was counterbalanced across participants. After applying HFS, mechanical pinprick sensitivity was assessed immediately after HFS (T1) and 10 (T2), 20 (T3) and 45 (T4) minutes after HFS at the skin surrounding the site at which HFS was applied and at the same skin area at the contralateral control arm (see Fig 1). Following the last measurement of pinprick
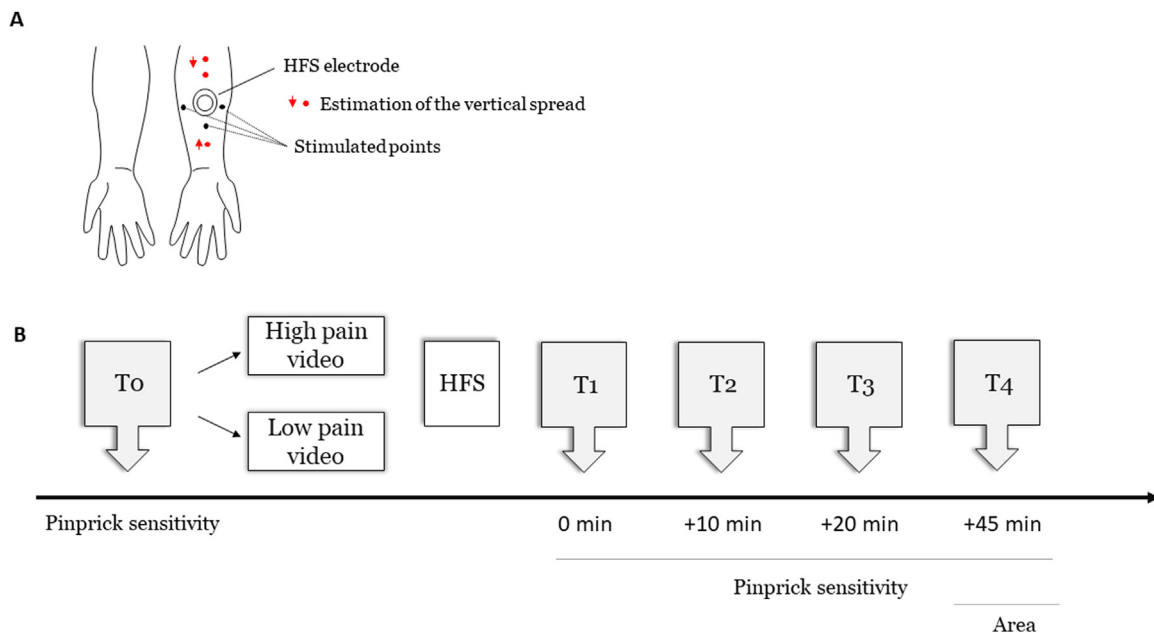

Figure 1. Timeline of the experiment. Panel **A**. The black dots depict where the 3 stimuli used to calculate mechanical hypersensitivity were applied. The red dots illustrate how the vertical spread was estimated.

sensitivity the spread of pinprick hypersensitivity was established by measuring the distance (in cm) between the proximal and distal borders of hypersensitivity from the center of the concentric electrode. Finally, participants filled in an exit questionnaire, assessing fear ratings for HFS, the credibility of the model, for the influence of the model's facial expression and posture in the video, and the influence of the pain scores given in the video.

High-Frequency Electrical Stimulation (HFS)

HFS consisted of 5 trains of 100 Hz electrical stimuli (pulse width 2 ms) lasting 1s each and repeated in a 9 second inter-train interval. HFS was delivered at an intensity corresponding to 20 x the individual detection threshold (see later.) to a single electrical pulse (pulse-width 2 ms). The HFS protocol was programmed in Matlab, generated with a DS5 (Digitimer) electrical stimulator and delivered to the skin via a custom-build concentric electrode. The electrode consisted of 16 blunt stainless steel pins with a diameter of 0.2 mm protruding 1 mm from the base. The pins formed a circle of 10 mm and constitute the cathode. The anode, made also of stainless steel, surrounded concentrically the anode, and had an inner diameter of 22 mm and an outer diameter of 40 mm.[28,39,40]

Electrical Detection Thresholds

Single electrocutaneous stimuli (2ms) were administered one by one, starting at 0.1 mA with increasing steps of 0.1 mA. Once the stimulus was detected, stimuli were presented in decreasing steps of 0.05 mA until the stimulus was no longer perceived, after which the intensity increased again in steps of 0.025 mA. After three reversals, the detection threshold was established.

Mechanical Pinprick Sensitivity

To assess the mechanical pinprick sensitivity a calibrated hand-held 128 mN pinprick stimulator (MRC Systems GmbH, Mannheim, Germany) was used.

Perceived Mechanical Pinprick Intensity and Unpleasantness

Participants were asked to rate 3 mechanical pinprick stimuli applied at 1.5 cm from the center of the concentric electrode on a scale ranging from 0 ("no sensation at all") to 100 ("extremely painful") with 50 being the anchor for the transition from non-painful to painful sensations. The perceived unpleasantness of the sensation was rated on a scale ranging from 0 ("not unpleasant at all") to 100 ("as unpleasantness as possible"). Afterwards, the average of the three ratings was calculated for the analysis.

Determining the Spread (Vertical Length) of Increased Pinprick Sensitivity

To map the spread of increased pinprick sensitivity after HFS, the pinprick stimulator was applied onto the skin every 1 cm from the wrist and cubital fossa towards to center of the concentric electrode until the point at which the participant noticed a clear increase in pinprick sensitivity. The proximal and distal borders of increased pinprick sensitivity induced after HFS have shown excellent reliability.[5]

Statistical Analysis Overview

The statistical analyses were performed in SPSS (version 28, IBM Statistics).

Pilot/Observational Study

To test for statistically significant differences in the ratings of fear and expected pain intensity across the 5 videos we conducted a non-parametric Friedman test due to the ordinal nature of the scale. Significant tests were followed up with a Wilcoxon signed-rank test. We used a 2-tailed Spearman's Rho correlation to unveil a potential relationship between empathy scores and fear ratings. Empahty scores, calculated as total scores of the IRI, were correlated to fear ratings for each video, and a correction for multiple comparisons was applied.

Experiment

Primary outcomes. The statistical analyses for the experiment were conducted according to our pre-registered statistical plan (see https://osf.io/mxsa5). For the first 2 primary outcome measures, the perceived intensity and perceived unpleasantness of the mechanical pinprick stimuli, we conducted two separate repeated measures (RM) ANOVAs with "TIME" (T0, T1, T2, T3 and T4) and "SIDE" (HFS arm vs control arm) as within-subject factors and "GROUP" (low pain vs. high pain) as between-subject factor. We hypothesized a statistically significant TIME x SIDE x GROUP interaction revealing a larger increase in mechanical pinprick sensitivity after HFS at the HFS-treated arm for the high pain group compared to the "low pain" group. Regarding the second primary outcome measure, the proximal-distal length of the spread of increased pinprick sensitivity after HFS, we hypothesized that the high pain group would show on average a larger proximal-distal length compared to the "low pain" group. To test this we performed a one-tailed independent sample t-test on the proximal-distal length.

Secondary outcomes. As secondary outcomes we tested whether the high pain group rated the HFS trains as more painful compared to the low pain group. For this, we conducted a 1-tailed independent samples t-test on the average of the pain ratings obtained after each train in both groups. We further tested if there was a relationship between the fear of HFS as measured by fear ratings and the increased pinprick sensitivity induced by

HFS, and whether this potential relationship was moderated by empathy scores. The increased pinprick sensitivity was calculated as the difference between the difference score (post minus pre HFS) of the 2 arms per time point.

The 2 groups were also compared in terms of scores on the exit questionnaire by using the non-parametric Mann-U Whitney test and psychological questionnaires by using independent sample t-tests.

Results

Pilot/Observational Study

Empathy

The average total score ($\pm$ SD) of the Interpersonal Reactivity Index (IRI) questionnaire was 88.06 ($\pm$ 7.81) (range 28 −140).

Fear of Pain

Overall, participants reported a median score of 2 (moderately) for both low pain videos and the neutral video, and of 3 for both high pain videos.

The difference was also statistically significant ($X^2 = 252.84$, $P < .0001$). More specifically, differences were observed between the low and high pain videos 1 versus 4: Z = -7.641, $P < .0001$; video 1 versus video 5 Z = -7.786, $P < .0001$; video 2 versus video 4: Z = -8.674, $P < .0001$; and video 2 versus video 5 Z = -8.587 $P < .0001$. There was no statistically significant difference between videos 1 to 3 and the videos 4 and 5.

Expected Painfulness

Participants reported a median score of 2 for both low pain videos, and the neutral video and of 4 for both high pain videos. The difference was significant ($X^2 = 327.5$, $P < .0001$), with again videos 1 and 2 differing from 4 and 5 (video 1 vs video 4: Z = -8.468, $P < .0001$; video 1 vs video: 5 Z = -8.276, $P < .001$; video 2 vs video 4: Z = -8.732, $P < .001$, video 2 vs video 5 Z = -8.636 $P < .0001$).

Please note that these differences remained statistically significant even after randomly choosing 15 or 20% of the original sample. This was due to ensure that

statistical differences held also for smaller sample sizes as those that we planned to use for the experiment.

Considering the lack of difference between the low pain videos and the neutral video both in fear and expected painfulness, we decided to select only one high and one low pain video for the actual experiment.

Correlation Between Empathy and Fear

We observed statistically significant correlations between empathy and fear ratings for both the low pain videos (1 and 2), and high pain videos (4 and 5) ($r_{s (video1)} = .216$ $P = .028$, $r_{s(video2)} = .190$ $P = .005$, $r_{s (video3)} = .118$ $P = .234$, $r_{s(video4)} = .219$ $P = .027$, $r_{s (video5)} = .294$ $P = .003$). Only the correlation for video 5 remained significant after correcting for multiple comparisons.

Correlation Between Pain Expectations and Fear

Strong statistically significant correlations were observed between scores of fear and expected pain in all conditions (video 1: $r_s = .608$, $P < .001$; video 2: $r_s = .638$, $P < .001$; video 3: $r_s = .662$, $P < .001$; video 4: $r_s = .662$, $P < .001$; video 5: $r_s = .720$, $P < .001$). All correlations survived the correction for multiple comparisons.

Experiment

Psychological Questionnaires

No statistically significant differences were observed regarding anxiety, fear of pain, pain catastrophizing, empathy, positive, and negative emotions between the 2 groups (see Table 1).

Electrical Detection Thresholds

The mean ($\pm$SD) electrical detection threshold were 0.28 $\pm$ 0.098 in the high pain group and 0.26 $\pm$ 0.08 in the low pain group. No statistically significant difference was observed for the electrical detection thresholds between the two groups (t(42) = -0.523, $P = .604$ Cohen's d = - 0.158).

Table 1. Mean ($\pm$SD) Scores and Statistical Comparison for Psychological Questionnaires

	LOW PAIN GROUP	HIGH PAIN GROUP	T-TEST VALUE	P VALUE	EFFECT SIZE (COHEN'S D)
IRI	77.45 (8.17)	75.63 (9.93)	0.646	.522	0.195
STAI	45.22 (9.46)	42.13 (10.59)	1.021	.313	0.308
mDES positive	39.50 (4.76)	39.40 (4.82)	0.063	.950	0.019
mDES negative	23.45 (6.83)	22.50 (6.06)	0.490	.627	0.148
PCS	18.81 (7.63)	17.27 (9.39)	0.599	.553	0.180
FPQ-III	14.95 (5.06)	16.13 (4.73)	− 0.799	.429	-0.241

Abbreviation: IRI, interpersonal reactivity index (global score, empathy); STAI (anxiety), mDES, modified differential emotions scale, PCS, pain catastrophizing scale; FPQ-III, fear of pain questionnaire.
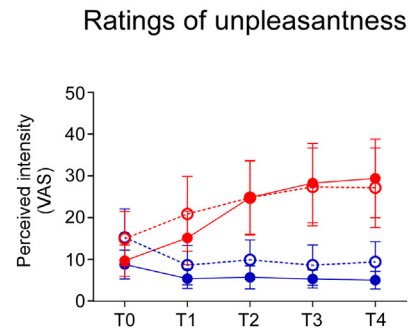Effect size is quantified with Cohen's d.
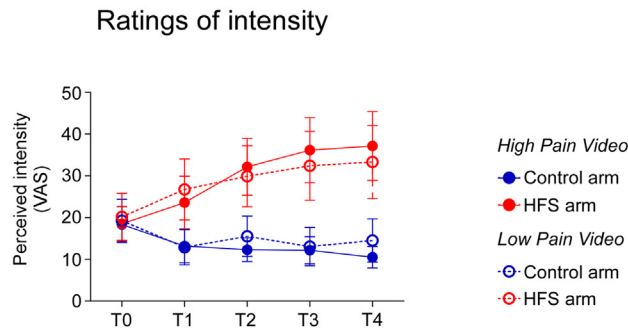
A   **B**

Figure 2. Mean and SD of the ratings of perceived intensity (Panel **A**) and unpleasantness (Panel **B**) for the 2 groups.

Perceived Mechanical Pinprick Intensity

The mean and SD perceived mechanical pinprick intensity measured before and after HFS at each arm for both groups are shown in Fig 2.

The RM ANOVA revealed a significant TIME x SIDE interaction F_{G-G} (2.33, 98.25) = 45.31, $P <$ .001, η_p^2 = 0.519 meaning that the mean perceived mechanical pinprick intensity was significantly different between the 2 arms across time. Posthoc tests showed that the mean perceived pinprick intensity was not significantly different between the 2 arms at baseline (T0), but significantly differed after HFS at T1 (t = 4.579, $P <$ .001; T2 t = 7.062, $P <$ .001; T3 t = 8.393, $P <$ .001; and T4 t = 8.750, $P <$ .001). These results confirm that HFS induced an increase in the perceived mechanical pinprick intensity.

The RM ANOVA also showed a significant TIME x SIDE x GROUP interaction (F_{G-G}(2.33, 98.25) = 3.048, P = .044, η_p^2 = 0.068), which means that the difference in perceived mechanical pinprick intensity after HFS between the 2 arms was significantly different between the 2 groups. Posthoc tests between the control and the HFS arm of the 2 groups (eg, $T1_{HFS}$ and $T1_{control}$ of the high pain video vs $T1_{HFS}$ and $T1_{control}$ of the low pain video) were not statistically significant. See Fig 2 and Table 2 for the details of the main results.

Perceived Mechanical Pinprick Unpleasantness

The mean and SD perceived mechanical pinprick unpleasantness measured before and after HFS at each arm for both groups are shown in Fig 2 (see Figure S1 for the individual data).

The RM ANOVA revealed a significant TIME x SIDE interaction (F_{G-G} (2.1, 88.41) = 36.7, $P <$ .001 η_p^2 = 0.466), meaning that mechanical pinprick stimulation was perceived as more unpleasant on the HFS arm than on the control arm as a function of time. Posthoc tests showed that the participants did not report pinprick stimuli to be more unpleasant on the HFS arm compared to the control arm during baseline, but this difference emerged at T1 and remained significant during T2, T3, and T4 T1 t = 4.579 $P <$ .001; T2 = 7.062 $P <$ .001; T3 t = 8.393 $P <$ .001; and T4 t = 8.750 $P <$ .001. These results confirm that HFS induced an increase in the perceived mechanical pinprick unpleasantness.

The RM ANOVA did not show a significant TIME x SIDE x GROUP interaction (F_{G-G}(2.1, 88.41) = 1.511, P = .226, η_p^2 = 0.035), meaning participants in the 2 groups did not differ in the perceived unpleasantness of mechanical stimulation on the two arms after HFS.

Table 3 reports the full statistics, Fig 3 a graphical representation. Supplementary figures S1 and S2 show the individual data.

Table 2. Results of the 3-Way ANOVA on the Perceived Intensity of Mechanical Stimuli

	F Test Value	P Value	Effect Size (η_p^2)
Time	8.569	<.001	0.169
Time x Group	0.523	.625	0.012
Side	66.677	<.001	0.614
Side x Group	0.573	.453	0.013
Time x Side	45.312	<.001	0.519
Time x Side x Group	3.048	.044	0.068
Group	0.009	.923	<0.001

Significant *P*-values are highlighted in red. Because the sphericity assumption was violated, the Greenhouse-Geisser correction was applied. Effect sizes are indicated as partial eta square.

Table 3. Results of the 3-Way ANOVA on the Perceived Unpleasantness of Mechanical Stimuli

	F Test Value	P Value	Effect Size (η_p^2)
Time	15.513	<.001	0.270
Time x Group	2.471	.068	0.056
Side	47.608	<.001	0.531
Side x Group	0.453	.504	0.002
Time x Side	36.698	<.001	0.466
Time x Side x Group	1.511	0.226	0.035
Group	0.646	0.426	0.015

Significant *P*-values are highlighted in red. Effect sizes are reported as partial eta square.
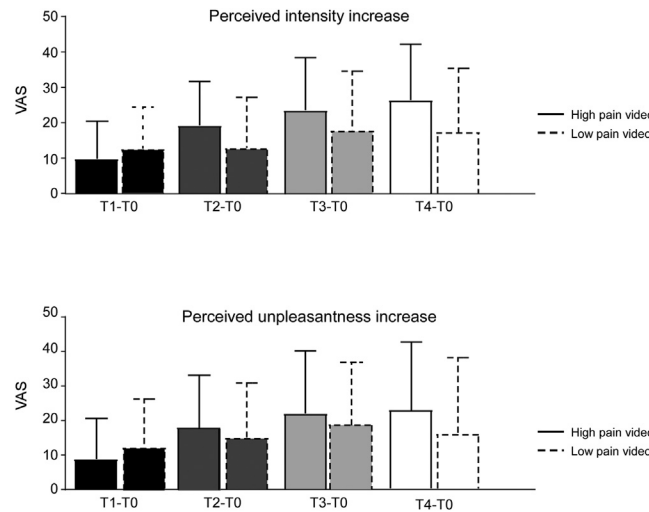
Figure 3. Increase in perceived intensity and unpleasantness of pinprick stimul applied at the stimulated arm at each time point in the two groups, after accounting for the ratings obtained for stimuli on the control arm (substraction HFS arm-Control arm per each time point).

Spread of the Area of Increased Pinprick Sensitivity

The mean and SD proximal-distal length of increased pinprick sensitivity were for the high pain video group 11.24 ± 2.2 cm and for the low pain group 10.53 ± 3 cm. An independent sample t-test did not show a statistically significant difference in the proximal-distal length between the 2 groups (t(42) = - 0.879, P = .192, Cohen's d = -0.265). See Fig 4.

Perceived Pain Intensity During HFS

The mean $\pm$ SD pain ratings were 85.03 ± 10.27 for the high pain video group and 79.44 ± 8.22 for the low pain video group. The one sided t-test revealed that participants in the high pain group perceived HFS as more intense on average than the low pain group t(42) = - 1.992 P = .026, Cohen's d = -0.601. Fig 5 shows the mean

and SD and individual perceived pain intensity scores elicited by HFS.

Exit Questions

Contrary to our hypothesis, we did not observe a difference in the reported fear in the 2 groups U = 189, P = .170. In contrast, the high pain group reported a greater influence of painfulness scores reported by the actress on their pain scores U = 129.5 P = .008. There was no difference in the credibility scores between the 2 groups U = 283.5 P = .320.

Correlation Between Fear of HFS and Hypersensitivity

There was no statistically significant correlation between the fear of HFS and hypersensitivity, at any of the time points for intensity ($r_{s\ T1-T0}$ = .192 P = .211, $r_{s\ T2-}$
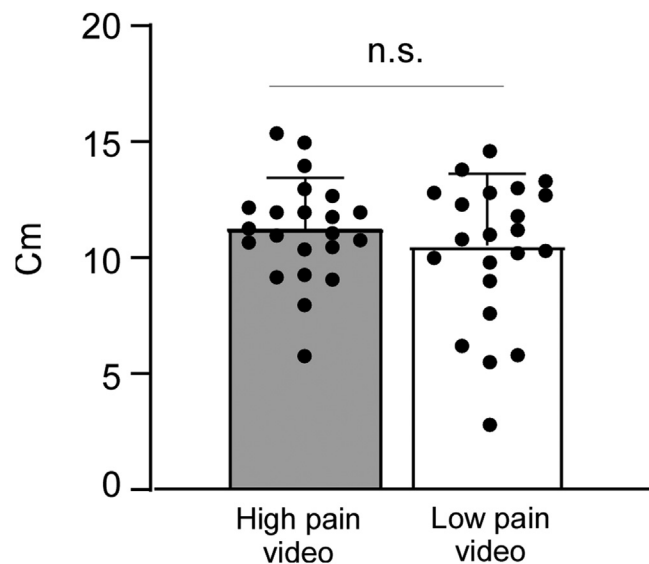

Figure 4. Mean and standard deviation of the length of the area of mechanical hypersensitivity in the 2 groups. Dots represent individual subjects.
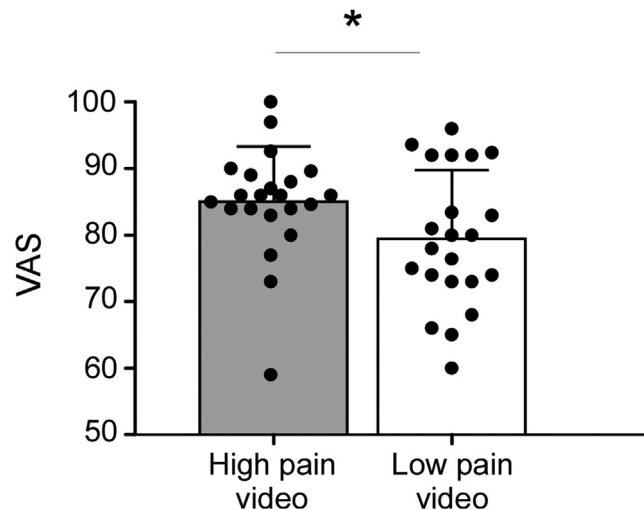
Figure 5. Mean and standard deviation of the perceived HFS intensity during the stimulation. The values in the two groups differed significantly * denotes a $P < .05$.

$_{T0} = .200$ $P = .193$, $r_{s\ T3-T0} = .201$ $P = .190$, $r_{s\ T4-T0} = .034$ $P = .825$). In contrast, whereas fear ratings did not correlate with hypersensitivity unpleasentness at T1 ($r_{s\ T1-T0} = .194$ $P = .208$) and at T4 ($r_{s\ T4-T0} = -0.091$ $P = .559$), they did at T2 ($r_{s\ T2-T0} = .375$ $P = .012$) and T3 ($r_{s\ T3-T0} = .399$ $P = .007$). Both values survived a Bonferroni correction for 4 comparisons.

Correlation Between Empathy and Fear

Contrary to the pilot experiment, there was no statistically significant correlation between the total IRI scores and fear of the HFS stimulation ($r_s = .121$, $P = .433$).

Correlation Perceived Intensity of HFS and Hypersensitivity

The perceived intensity of HFS correlated positively with hypersensivity scores (intensity ratings) at T2, T3, and T4 ($r_{s\ T2-T0} = .417$ $P = .005$, $r_{s\ T3-T0} = .483$ $P < .001$, $r_{s\ T4-T0} = .487$ $P < .001$), but not at T1 ($r_{s\ T4-T0} = .134$ $P = .387$). Unpleasantness scores correlated positively at T2 and T3 ($r_{s\ T2-T0} = .351$ $P = .020$, $r_{s\ T3-T0} = .418$ $P = .005$), but not at T1 and T4 ($r_{s\ T1-T0} = .243$ $P = .113$, $r_{s\ T4-T0} = .045$ $P = .770$).

Discussion

The present study was designed to investigate whether observing a model expressing high pain during HFS would lead to higher intensity pain ratings during HFS and more pronounced mechanical pinprick hypersensitivity, both in terms of intensity and unpleasantness, and in a larger spread. More specifically, we hypothesized that watching a video of a person expressing high pain during HFS would induce more fear of HFS as compared to watching a person showing less pain during HFS. We postulated that this increased fear would in turn lead to higher pain ratings for HFS and to a higher magnitude and a larger spread of pinprick

hypersensitivity induced by HFS. Our hypotheses were partially confirmed.

Observing a Model Expressing More Pain Increases One's Own Pain Experience (During HFS)

We found that the HFS trains were perceived on average as more intense in the high pain group compared to the low pain group. The higher average pain rating to HFS between the 2 groups indicates that our manipulation was effective.

Is Watching a Model Expressing More Pain Associated With More Pinprick Hypersensitivity?

We found a significant TIME x SIDE x GROUP interaction. However, no follow up comparisons were statistically significant. These findings can be interpreted in 2 ways. On the one hand, they can be seen as suggestive that observing a model expressing more pain during HFS, not only increase one's own pain during actual HFS but also facilitates the development of pinprick hypersensitivity induced by HFS (central sensitization). On the other hand, one could argue that our triple interaction reflects a random finding. This would explain the lack of effect on the unpleasantness ratings and the vertical spread (see later) as well as the absence of significant follow up tests for the intensity ratings. To confirm the existence of the triple interaction, future studies should aim to replicate these findings with larger sample sizes taking into account the small effect size.

Importantly, the present study used a novel design to investigate the effects of observing high pain. Indeed, we opted for manipulating only the information regarding the painfulness of the HFS procedure, without instructing the participants about any potential change in the perceived intensity/unpleasantness of the pinprick stimulation. This was done in a previous study by van den Broeke et al,[33] in which the authors showed

that negative expectations about the pinprick stimulation after HFS (ie, that it would become painful) increased the development of HFS-induced pinprick hypersensitivity. Importantly, the aim of this study was to investigate whether watching a model in high pain would lead to higher pain ratings during HFS, but also more hypersensitivity after HFS. In this sense our control was the low pain condition. We acknowledge that an additional control condition without the video would be needed to characterize the effects of observational learning.

Observing a dissociation between the intensity and unpleasantness is not common in pain studies (for a systematic review see[27]). Nevertheless, it has to be noted that such differences were mainly reported for studies targeting acute pain but not for studies assessing the hypersensitivity induced by acute pain. We might speculate that the lack of significant effects on unpleasantness scores was related to the lack of statistically significant difference in fear reported by the two groups. Importantly however, the significant positive correlations that we observed between the perceived intensity of the HFS procedure and hypersensitivity would suggest that an increase in the perceived intensity of HFS leads to greater hyperalgesia. Such an effect replicates what we had already observed in a previous study, in which we used a different model to induce hypersensitivity (eg, Low Frequency Stimulation of the skin, LFS).[28] More than the actual intensity of stimulation, the perceived intensity seems to be related to the increase in hypersensitivity, confirming the role of top-down modulatory factors.

The lack of differences in the length of the area of pinprick hypersensitivity could be related to the use of a too high stimulation intensity for HFS (20 x detection threshold) that resulted in a ceiling effect in the spread of pinprick hypersensitivity. Or, as already mentioned before, watching a person with more pain does not affect the development of pinprick hypersensitivity.

The Role of Fear and Empathy

While in the pilot experiment the high pain video was associated with higher fear ratings, the statistical comparison in fear levels in the experiment failed to reach statistical significance. This results did not depend on the sample size as the same results were obtained in the pilot experiment when just a subset of participants was selected in order to match the required numerosity of the experiment. However, one substantial difference is that in the experiment the fear scores were obtained at the end of the experiment, after participants had experienced HFS, whereas in the pilot experiment they were obtained after watching the videos as no HFS was actually administered. It is therefore possible that in the experiment some participants made adjustments to their scores based on the actual experience. This would be also consistent with the results of Vögtle et al,[47] who did not find any correlation between the expectations and nocebo effects when the ratings were asked retrospectively.

Whether fear is potentially the main drive of differential effects based on observation remains therefore an open question. In the experiment, fear ratings did not correlate with the intensity of hypersensitivity, nor did the empathy scores. Of note, we used a Likert scale from 0 to 5 for fear ratings, and it can be argued that as such we potentially lost the necessary variability to disclose more subtle relationships. On the other hand, we did find a significant relationship between the fear ratings and unpleasentness scores (at two time points) and pinprick ratings.

The role that empathy has in observational learning is more controversial. Previous studies have found significant,[25] but mainly non-significant effects of empathy scores on placebo/nocebo effects imparted by observational learning.[45-47] It has been proposed[47] that the specific experimental conditions, namely the in person presence of the model or the presentation of a recorded video, may be part of the explanation. However, it should also be noticed that also Swider and Babel[25] discuss the relationship between empathy and nocebo effects cautiously as their results did not provide the strong support that had been initially proposed.[6] Moreover, the timing in which empathy scores were collected was different between the pilot/observational study and the experiment. Participants completed the IRI questionnaires in the same session in which they scored the videos in the pilot/observational experiment. Instead, they filled in all the questionnaires online one day before coming to the lab in the actual experiment.

Conclusion

Our results suggest that watching a person expressing more pain during HFS increases one's own pain ratings during HFS and may weakly facilitate the development of secondary mechanical hypersensitivity, although this latter result needs replication. It remains to be investigated whether fear is the main drive for this increase.

Disclosure

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2022.09.009.

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