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Studying the Effect of Expectations on High-Frequency Electrical Stimulation-Induced Pain and Pinprick Hypersensitivity

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Abstract: **Negative expectations can increase pain, but can they promote the development of central sensitization? This study used an inert treatment and verbal suggestions to induce expectations of increased high-frequency electrical stimulation (HFS)-induced pain and assessed their effects on pain ratings during HFS and HFS-induced pinprick hypersensitivity. Fifty healthy volunteers were randomly allocated to either a control group (N = 25) or a nocebo group (N = 25). Participants in both groups received a patch containing water on the right forearm. The nocebo group was told that the patch contained capsaicin that sensitized their skin, while the control group was told that the patch contained water that had no effect on skin sensitivity. Before and after patch attachment, single electrical stimuli were delivered to the area of the patch to measure the perceived intensity to these stimuli. After patch removal and after the participant rated expected pain and fear for HFS, HFS was delivered to the same skin site, followed by the assessment of pinprick sensitivity. The nocebo group rated the perceived intensity for the single electrical stimulus after removal of the patch as more intense compared with the control group, indicating that our manipulation worked. Yet, this effect did not transfer to expected pain for HFS, nor did it affect pain intensity ratings during HFS. HFS increased pinprick sensitivity but no group differences were found. Because of the lack of differences in expected pain and pain intensity ratings for HFS between groups, no firm conclusions can be drawn regarding their effect on pinprick hypersensitivity.**

Perspective: ***This study shows that sham treatment combined with verbal suggestions induces a nocebo effect but does not necessarily change expectations and experience of upcoming pain.***

Key words: *Expectations, pain, nocebo, high-frequency stimulation, secondary hyperalgesia*

Expectations about pain may impact pain experiences.[1-3] For instance, expectations that a treatment will produce pain relief can reduce pain, even when the treatment itself is inert (placebo effect).[4] On the other hand, expectations that a treatment will worsen pain can increase pain (nocebo effect).[4] Nocebo effects can be induced through verbal suggestions, but the combination of verbal suggestions and conditioning showed stronger nocebo responses on pain.[5,6] Imaging studies have shown that negative expectations, induced by a nocebo treatment, increase spinal cord activity that overlaps with the activity triggered by nociceptive stimulation.[7]

Central sensitization (CS), defined by the International Association for the Study of Pain as an "Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold input,"[8] is believed

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to play a role in persistent pain.[9,10] It is unclear if negative expectations about pain can promote CS.

The increase in mechanical pinprick sensitivity of the skin surrounding a cutaneous injury is considered a manifestation of CS.[10,11] Indeed, animal studies have demonstrated that pinprick stimuli applied after capsaicin or high-frequency electrical stimulation (HFS) to adjacent skin areas, elicit increased responses of spinal nociceptive neurons[12,13] without changes in the responsiveness of peripheral neurons.[14] If this is also the case in humans, these increased spinal responses may contribute to pinprick hypersensitivity.

To date, human studies investigating the effect of negative expectations on the development of pinprick hypersensitivity are scarce. Bedwell et al[15] investigated the effect of an inert treatment with verbal suggestions on HFS-induced pinprick hypersensitivity. However, their manipulation was not successful and no effect was found on pinprick hypersensitivity. More recently, Jaltare et al[16] used an inert pill with verbal suggestions to investigate the nocebo effect on HFS-induced pinprick hypersensitivity. They found no significant effect of the manipulation on pinprick hypersensitivity. Moreover, the experimenters were not blinded. Torta et al[17] used observational learning to investigate the effect of nocebo on HFS-induced pinprick hypersensitivity. Participants watched either a video of an actress showing intense pain during HFS ("high pain" group) or less pain ("low pain" group) before undergoing HFS. Participants in the "high pain" group reported more pain during the actual HFS compared with participants in the "low pain" group. Furthermore, HFS-induced pinprick hypersensitivity was on average higher in the "high pain" group compared with the "low pain" group. These findings suggest that expecting more HFS pain can result in experiencing more HFS pain and pinprick hypersensitivity. However, pain expectations regarding HFS after the videos and before receiving HFS were not assessed. Moreover, the experimenters were not blinded. Finally, the effects on HFS-induced pinprick hypersensitivity were weak and no effect on the spread of the area of increased pinprick sensitivity was observed.

The aim of the present study was to investigate how altering expectations related to HFS pain—specifically, expecting more pain during HFS—impacts on both HFS-evoked pain and pinprick hypersensitivity. To induce the expectation that HFS will be more painful, we used a combination of an inert treatment and verbal suggestions. To further reinforce this expectation, we applied nonpainful electrical test stimuli with increasing stimulation intensity, with the statement that these stimuli were of the same intensity, after the inert treatment. We kept the assessor blinded and we asked participants for their pain expectations after the manipulation and before applying HFS. We expected that expectations of increased HFS pain would increase spinal cord excitability via top-down descending facilitatory pathways[18] resulting in higher pain ratings during HFS and a larger increase and spread of HFS-induced pinprick hypersensitivity.

Methods

Participants

Fifty white right-handed healthy volunteers (23 men/27 women; ranging from 18 to 32 years old; mean age ± standard deviation (SD) = 22.74 ± 2.56) participated in the experiment. The healthy volunteers were recruited via study advertisement (flyer) ad valvas within UCLouvain University and via a Facebook site used to advertise experiments.

We based our sample size on the power calculated on the means and standard deviations pinprick ratings of the study of van den Broeke et al,[19] and by considering violations of the assumption of homoscedasticity and sphericity. The power analysis, based on a 2 × 2 × 2 ANalysis Of VAriance (ANOVA) (2 groups [control vs nocebo], 2 arms [control vs HFS], and 2 timepoints [pre vs post 3]), revealed an effect size of .23 and a power of .95 with N = 25 per group. For the calculation, an online software package was used (https://shiny.ieis.tue.nl/anova_power/).

Volunteers were eligible if they 1) were between 18 and 30 years old, 2) were able to understand spoken and written French, and 3) did not fulfill one or more of the following exclusion criteria: 1) evidence for a clinically significant alteration of the skin of the volar forearms; 2) pregnancy; 3) presence of a pacemaker or implanted cardiac defibrillator; 4) major neurological of psychiatric conditions; 5) taking medication (except contraception); and 6) participated in previous studies using HFS or capsaicin.

Approval for the experiment was obtained from the local ethical committee (B4032021000041). All participants signed an informed consent form and received financial compensation (20€) for their participation. The study hypotheses and analysis plan was preregistered at the Open Science Forum: https://doi.org/10.17605/OSF.IO/JZF75.

Design

In this mixed (Group [nocebo/control] × Arm [HFS/control]) experimental design (Fig 1A), participants received HFS onto the right forearm to induce pain and pinprick hypersensitivity.[12,20] Before HFS, participants were randomly assigned to either a nocebo or control group and received a patch containing water on their right forearm. In the nocebo group, participants were told that the patch contained capsaicin that would sensitize their skin to electrical stimuli, while in the control group, participants were told that the patch contained water that did not affect skin sensitivity (see experimental manipulation).

After the patch and before applying HFS, participants were asked to rate expected pain and their fear for HFS. After that, HFS was delivered to the right forearm, and participants were asked to rate their perceived pain intensity. Before (T0) and after applying HFS (T1: directly after applying HFS; T2: 30 minutes after applying HFS; T3: 35 minutes after HFS; and T4: 40 minutes after HFS), pinprick sensitivity of the skin surrounding the site of HFS and the homologous site at the contralateral arm was tested. At T2, T3, and T4, also the length of the area of increased pinprick sensitivity was measured.

Experimental Induction of Increased Pinprick Sensitivity

HFS consisted of 5 trains of 100-Hz electrical charge-compensated pulses that lasted 1 second each and were delivered in a 10-second intertrain interval. The trains were programmed in Matlab 2014b (The Mathworks Inc, Natick), sent via a digital-analog interface (National Instruments, Austin, TX) to a constant-current electrical stimulator (Digitimer DS5, Welvyn Garden City, UK), and delivered to the skin of the ventral forearm approximately 10 cm from the cubital fossa via a specially designed multipin electrode (Fig 1B).[21] The cathode of this electrode consisted of 16 blunt stainless-steel pins with a diameter of .2 mm, protruding 1 mm from the base and placed in a circle with a diameter of 10 mm. The anode was a stainless-steel ring with an inner diameter of 22 mm and an outer diameter of 40 mm.[21] HFS was applied to the right volar forearm approximately 10 cm distal to the cubital fossa with a fixed intensity at 3 mA. After each train, participants were asked to rate their perceived pain intensity on a numeric rating scale (NRS), ranging from 0 ("no pain") to 100 ("worst pain imaginable").

Assessment of Mechanical Pinprick Sensitivity

Pinprick hypersensitivity induced by HFS can be characterized by both a change in perceived intensity and area size. To assess changes in perceived intensity, at each measurement, 3 mechanical pinprick stimuli, delivered using a calibrated mechanical pinprick stimulator (128 mN, MRC Systems GmbH, Heidelberg, Germany), were applied to both forearms to the area adjacent to the site at which HFS was delivered (within a circle between .5 and 2 cm from the center of the HFS electrode) and to the homologous site of the contralateral control arm (Fig 1C). Each mechanical stimulus was applied perpendicular to the skin for approximately 1 second. The participants were instructed to provide an average rating of the perceived intensity of the 3 pinprick stimuli on an NRS, assessing pain, ranging from 0 ("no pain") to 100 ("worst pain imaginable"). To avoid peripheral sensitization due to repeated pinprick stimulation, the same skin site was never stimulated twice. The order of testing (control or HFS arm first) was counterbalanced across participants. The length of the area of increased pinprick sensitivity was taken as a measure for the spread of pinprick hypersensitivity. For this, repeated mechanical pinprick stimuli were applied, spaced 1 cm each along the midline axes of the forearm, from the most distal point of the forearm to the center of the HFS-stimulated area, and from the most proximal point of the forearm to the center of the HFS-stimulated area (Fig 1C). The areas to be stimulated were marked onto the skin with a pen at the beginning of the experiment. The participant was instructed to report verbally when a clear increase in pinprick sensitivity was felt between 2 points. Finally, the distance (cm) between this point and the center of the HFS-stimulated area was measured. During the mapping, participants were instructed not to look at their arm.

Experimental Manipulation of Expectations

A patch was applied for 5 minutes, on the right ventral forearm at the site where HFS would be applied,

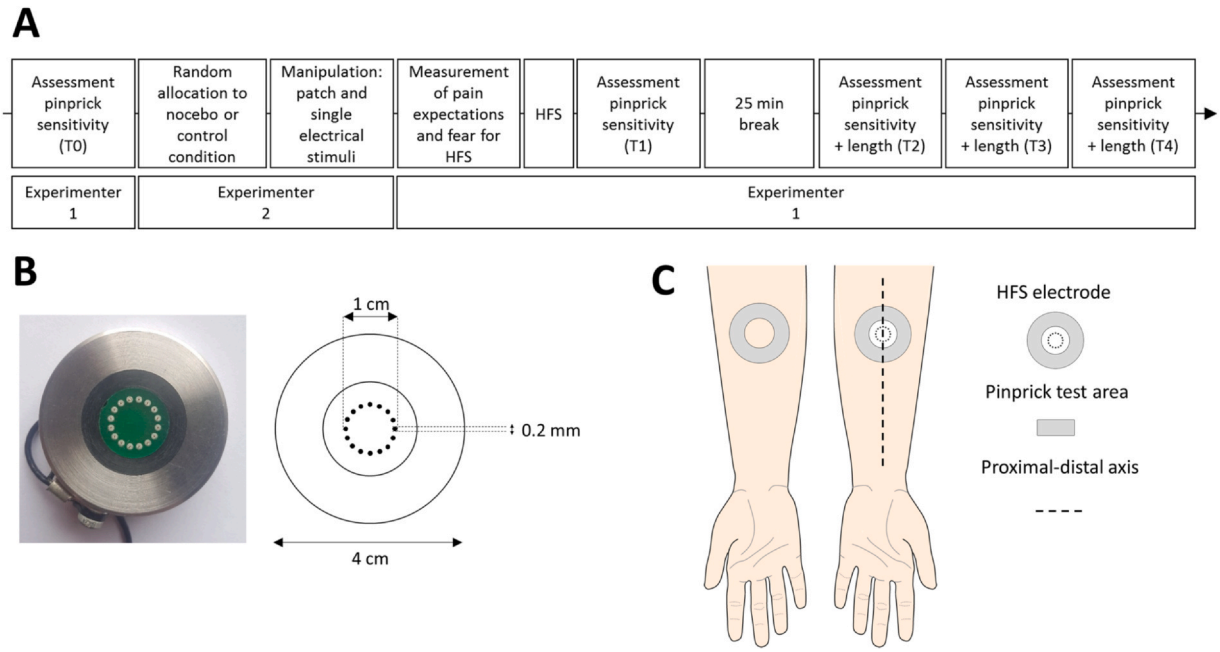

Figure 1. (**A**) Timeline of the experiment. T0 is the baseline measurement (before the manipulation and before applying HFS), T1 is the measurement directly after applying HFS, T2 is approximately at 30 minutes after HFS, T3 is 35 minutes after HFS, and T4 is 40 minutes after HFS. (**B**) Characteristics of the HFS electrode. (**C**) The area at which the pinprick stimuli were applied is shown as well as the proximal-distal axis (dotted line) for the measurement of the length of the area of increased pinprick sensitivity.

and consisted of a medical adhesive patch with a squared cotton attached. To prepare the patch, the cotton was sprinkled with water, using a pipette, from one of the 2 bottles that were put in front of the participant on the table. One bottle was transparent, and the water was clearly visible. The other bottle was a brown bottle normally used for liquid drugs. At the front of the brown bottle, a sticker was attached with the name "Capsaicin" on it and the logo of the University Pharmacy.

The patch of the participants of the nocebo group was sprinkled with the water from the brown bottle. The participants were told that they would receive a patch with capsaicin (dissolved in ethanol) that would sensitize their skin and make it more sensitive for electrical stimuli. To increase the credibility of the manipulation (application of capsaicin), the experimenter wore a white medical coat and gloves.[22]

The patch of the participants of the control group was sprinkled with the water from the transparent bottle, and the participants were told that they receive a patch containing pure water, as a control for the experimental condition, which would not affect their skin sensitivity for electrical stimuli.

Before the application of the patch and directly after its removal, participants received 3 single electrical stimuli delivered through the HFS electrode at the area of the patch and where HFS would be applied. The electrical stimuli (rectangular pulse width of 2.0 ms) were triggered by a custom-written MATLAB script and generated by a constant-current electrical stimulator (Digitimer DS5, Welvyn Garden City, UK). After each electrical stimulus, participants were asked to rate the perceived intensity on an NRS ranging from 0 ("not detected") to 100 ("maximal intensity imaginable").

The intensity of the 3 electrical stimuli delivered before the application of the patch was fixed at .5 mA and was the same for both groups. Directly after removal of the patch, the stimulation intensity of the 3 single electrical stimuli delivered in the control group was the same as the one before application of the patch (.5 mA), while the stimulation intensity of the electrical stimuli delivered in the nocebo group was gradually increased across the 3 stimuli (.5, 1.0, and 2.0 mA). The gradual increase in stimulation intensity across the 3 single stimuli after removal of the patch, combined with the instruction that the intensity was the same as before the patch, in the nocebo group, was intended to strengthen the suggestion that the skin had become more sensitive to electrical stimuli. The single electrical stimuli were not perceived as painful.

Procedure

The experiment was conducted in a quiet laboratory room at the Institute of Neuroscience of UCLouvain, Brussels, Belgium. To keep the experimenter blinded to the condition of the participants (nocebo or control) during the assessment of mechanical pinprick sensitivity, the experiment was conducted by 2 experimenters (experimenter 1 and 2). At the beginning of the experiment, participants were informed about the purpose of the study by experimenter 1. They were told that the aim of this study was to investigate the effect of capsaicin, a substance that sensitizes peripheral cutaneous nociceptors when applied onto the skin, on pain elicited by intense electrical stimulation (HFS). They were further told that they would be assigned to either the experimental group in which they would receive the patch with capsaicin or to a control group, in which the patch contained water that served as control for the experimental group. Then, the same experimenter performed the baseline measurement of mechanical pinprick sensitivity (T0). After that, experimenter 1 left the room and experimenter 2 entered. Experimenter 2 then randomly assigned the participant to either the nocebo group or control group and continued with the experimental manipulation of expectations.

After the manipulation, experimenter 2 explicitly instructed the participants not to inform experimenter 1 about their condition (nocebo or control) and left the room. Experimenter 1 entered again and started assessing the expected pain and fear for HFS. After that, a short explanation of the HFS protocol followed. This included the number of stimuli, the nature of the stimulation (painful electrical stimuli), and the instruction to provide a rating directly after each HFS stimulus (see Supplementary materials). Then, HFS was applied to the right ventral forearm and at different timepoints (T1, T2, T3, and T4), the perceived pinprick sensitivity was measured at both arms as well as the length of the area of increased pinprick sensitivity at the HFS arm at T2, T3, and T4. At the end of the experiment, participants were verbally asked 1) what they thought would be the hypothesis of this experiment; 2) how credible the information given during the experiment was, measured on a NRS ranging from 0 ("not credible") to 100 ("fully credible"); and 3) how honest they thought the experimenters were, ranging from 0 ("not honest") to 100 ("fully honest"). Participants were debriefed after the experiment.

Data Analyses

Manipulation Checks

To confirm if our manipulation of the expectations of HFS painfulness was successful, we compared the scores of expected painfulness of HFS (NRS 0–100) between the 2 groups. We also compared the perceived intensity elicited by the first single electrical stimulus after removal of the patch between the 2 groups.

Primary Outcomes

The primary outcomes of this study were 1) the difference in perceived mechanical pinprick intensity (NRS), averaged across 3 post measurements (T2, T3, and T4), between the 2 arms (corrected for the baseline measurement) and between the 2 groups; and 2) the difference in proximal-distal length (cm) of the area of increased pinprick sensitivity, averaged across T2, T3, and T4, at the HFS-treated arm between the 2 groups.

The reason for choosing the average of 3 post measurements (T2, T3, and T4) is to increase accuracy in the estimation of pinprick hypersensitivity.

Secondary Outcomes

The secondary outcomes in this study were 1) the perceived pain intensity (NRS 0–100) elicited by HFS, 2) the subjective fear intensity (NRS 0–100), 3) the difference in perceived mechanical pinprick intensity (NRS 0–100) measured directly after HFS between both arms (corrected for the baseline measurement) and groups, 4) the perceived credibility of the information given during the experiment (NRS 0–100), and 5) the perceived honesty of the experimenters (NRS 0–100).

Statistical Analyses

Data were analyzed using the statistical package SPSS version 28 (SPSS Inc, Chicago, IL). The critical *P* value was set at .05 (2-sided).

Manipulation Checks

Expected pain for HFS. To confirm that our manipulation of expectations was effective, we performed an independent sample t-tests on the expected painfulness of HFS scores measured before HFS.

Perceived intensity elicited by the single electrical stimuli after the patch. To test if the first rating elicited by the single electrical stimulus directly after removal of the patch was significantly different between the 2 groups, we performed an ANalysis COVAriance (ANCOVA) with the first rating after removal of the patch as a dependent variable, "Group" as independent (fixed) factor, and the average of the 3 ratings before the application of the patch ("Baseline") as covariate.

Primary Outcomes

Perceived pinprick intensity. To test if the perceived intensity elicited by the mechanical pinprick stimuli was different after HFS between the 2 groups, we conducted a linear mixed model (LMM) (restricted maximum likelihood and Satterthwaite approximation) with the NRS ratings as a dependent variable, the factor "Arm" (control arm vs HFS arm) and "Group" (nocebo vs control) as fixed factors, the "Baseline Pinprick Ratings" as covariate, and the factor "SUBJECT" as random factor.

Length of the area of increased pinprick sensitivity. To test if there was a difference in the length of the area of increased pinprick sensitivity between the 2 groups, we performed an independent sample t-test on the total length in centimeters (averaged across T2, T3, and T4) between the 2 groups.

Secondary Outcomes

Independent sample t-tests were performed on the perceived pain intensity measured during HFS (average across the 5 trains) and the fear for HFS report measured before HFS.

To test if the first NRS rating elicited by the mechanical pinprick stimulus directly after the application of HFS was significantly different between the 2 groups, we performed a linear mixed model with the first mechanical pinprick rating after HFS as a dependent variable, "Arm" and "Group" as independent (fixed) factors, the "Baseline Pinprick Ratings" as covariate, and "Subject" as random factor.

Finally, to assess differences in the perceived credibility of the information given during the experiment and the perceived honesty of the experimenters between the 2 groups, we performed an independent sample t-test for each exit question.

The effect size in the LMM (η_p^2) was calculated using the EffectSize package in the free online available statistical software R. To calculate effects sizes for independent t-tests, we used Cohen's *d*.

Results

Sample Demographics

The mean + SD age was 23.2 ± 2.7 for the control group (12 women and 13 men) and 22.2 ± 2.4 for the nocebo group (15 women and 10 men).

Manipulation Check

Expected Painfulness of HFS

The independent sample t-test performed on the ratings of expected painfulness of HFS revealed no significant difference (t[48] = .036, $P = .971$, Cohen's $d = .01$) between the 2 groups ($M_{nocebo} = 42.88$ vs $M_{control} = 43.08$).

Ratings Elicited by the First Single Electrical Stimulus After Removal of the Patch

The ANCOVA revealed a significant effect of "Baseline" (F[1,47] = 65.707, $P < .001$, $\eta_p^2 = .58$), meaning that the average (across the 3 stimuli) baseline ratings elicited by the single electrical stimuli affected the ratings to the single electrical stimuli delivered after removal of the patch. We found a significant effect of "Group" (F[1,47] = 22.109, $P < .001$, $\eta_p^2 = .32$), meaning that the ratings elicited by the first single electrical stimulus after removal of the patch were significantly different between the 2 groups after correcting for the baseline ratings ($M_{control} = 12.22$ vs $M_{nocebo} = 23.78$, Fig 2A). Fig 2B shows the mean (+SD) ratings elicited by each single electrical stimulus before and after the patch.

Primary Outcomes

Perceived Pinprick Intensity After HFS

The linear mixed model revealed a significant main effect of "Baseline Pinprick Rating" (F[1,68.939] = 49.347, $P < .001$, $\eta_p^2 = .42$), meaning that the pinprick ratings after HFS were influenced by the pinprick ratings before HFS. We also found a significant main effect of "Arm" (F

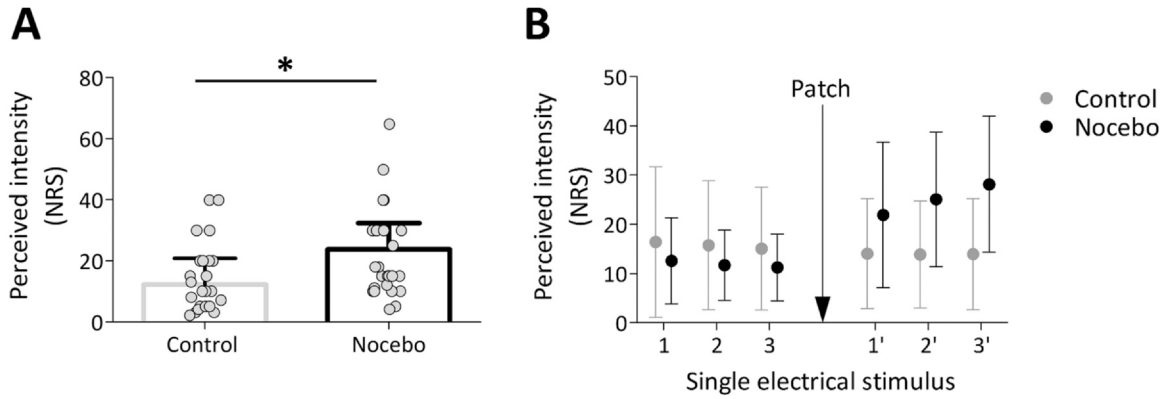

Figure 2. (**A**) Estimated marginal means (+SD) of the perceived intensity elicited by the first single electrical stimulus, delivered after removing the patch, for the control and nocebo group. Dots are representing individual data. (**B**) Mean ratings (+SD) of each single electrical stimulus applied before and after the patch.

[1,46.043] = 53.681, $P < .001$, $\eta_p^2 = .54$), meaning that the pinprick ratings after HFS across all participants differed between the 2 arms after controlling for the baseline pinprick ratings ($M_{HFS\ arm} = 22.88$ vs $M_{control\ arm} = 9.887$). No significant main effect of "Group" (F[1,46.437] = .252, $P = .618$, $\eta_p^2 = .00$) or "Arm × Group" interaction (F[1,46.104] = .793, $P = .378$, $\eta_p^2 = .02$) was found. The estimated marginal means (+SD) of the perceived intensity elicited by the mechanical pinprick stimuli at each arm (control arm and HFS arm) in each group (control and nocebo) are shown in Fig 3.

Length of the Area of Increased Pinprick Sensitivity After HFS

An unpaired t-test performed on the individual length (averaged across timepoints T2, T3, and T4) between the 2 groups (t[48] = .068, $P = .946$, Cohen's $d = .02$) revealed no statistical significant difference ($M_{nocebo} = 8.95$ cm vs $M_{control} = 8.66$ cm, Fig 4).

Secondary Outcomes

Experienced Pain During HFS

The independent sample t-test performed on the ratings of pain elicited by HFS revealed no significant difference (t[48] = –.511, $P = .612$, Cohen's $d = –.15$) between the 2 groups ($M_{nocebo} = 67.46$ vs $M_{control} = 65.06$, Fig 5A). Fig 5B shows the mean (+SD) pain ratings elicited by each HFS train for both groups.

Fear for HFS

The independent sample t-test performed on the ratings of fear for HFS revealed no significant difference (t[48] = –.046, $P = .964$, Cohen's $d = –.01$) between the 2 groups ($M_{nocebo} = 27.20$ vs $M_{control} = 26.92$).

Perceived Mechanical Pinprick Intensity Directly After HFS

The linear mixed model revealed a significant effect of "Baseline Pinprick Rating" (F[1,93.376] = 64.804, $P < .001$, $\eta_p^2 = .41$), meaning that the pinprick ratings directly after HFS are influenced by the baseline pinprick rating. We also found a significant effect of "Arm" (F[1,52.538] = 32.862, $P < .001$, $\eta_p^2 = .38$), meaning that the pinprick ratings after HFS across all participants differed between the 2 arms after controlling for baseline pinprick ratings ($M_{Control\ arm} = 9.753$ vs $M_{HFS\ arm} = 15.527$). There was no significant effect of "Group" (F[1,54.354] = .798, $P = .376$, $\eta_p^2 = .01$) and "Arm × Group" interaction (F[1,52.627] = .259, $P = .613$, $\eta_p^2 = .00$).

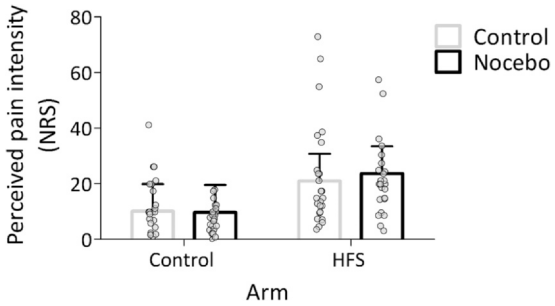

Figure 3. Estimated marginal means (+SD) perceived mechanical pinprick intensity after HFS and after controlling for baseline pinprick sensitivity for the control and HFS arm in the nocebo and control group. Dots are representing individual data.

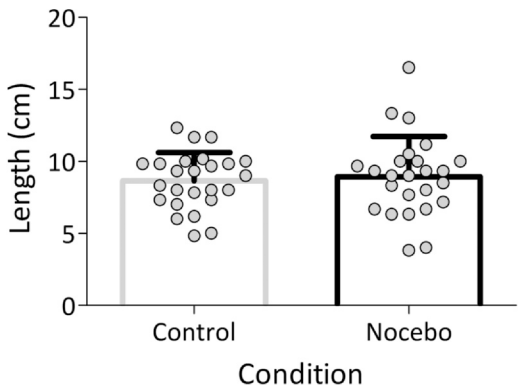

Figure 4. Mean (+SD) length (averaged across timepoints T2, T3, and T4) of the area of increased pinprick sensitivity. Length is expressed in centimeters (cm). Dots are representing individual data.

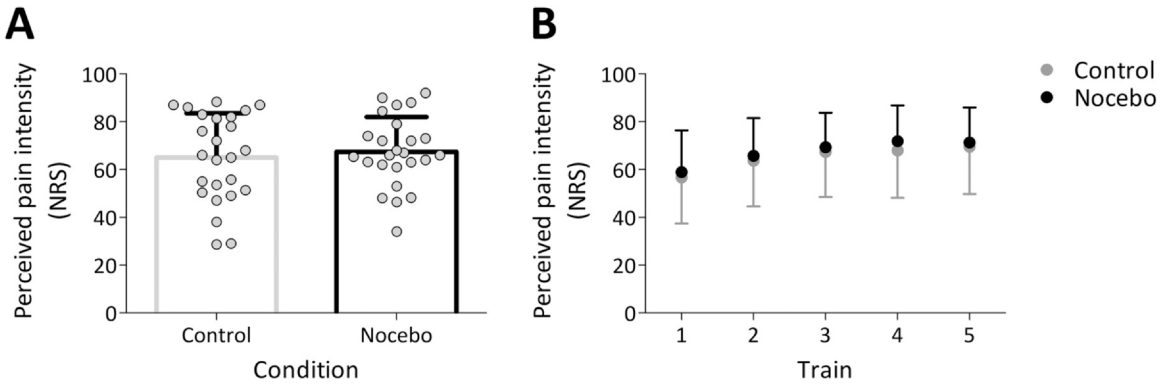

Figure 5. (**A**) Mean (+SD) of the experienced pain during HFS for the 2 groups (control and nocebo). Dots are representing individual data. (**B**) Mean (+SD) experienced pain for each train of both groups.

Perceived Credibility of the Information

The ratings of perceived credibility of information were high in both groups (M_{nocebo} = 96.60 vs $M_{control}$ = 98.20), meaning that people in both groups believed the information they received. An independent sample t-test showed that the level of credibility was not significantly different between the 2 groups (t[48] = .646, P = .521, Cohen's d = .19).

Perceived Honesty of the Experimenters

The ratings of perceived honesty of the experimenters were high in both groups (M_{nocebo} = 96.60 vs $M_{control}$ = 96.80), meaning that the participants perceived the experimenters as honest. An independent sample t-test showed that the level of honesty was not significantly different between the 2 groups (t[48] = .073, P = .942, Cohen's d = .02).

Exploratory Analysis

A significant and moderately strong correlation (Pearson r = .58, P < .01) was found between the expected painfulness of HFS and the actual reported pain during HFS (averaged across the 5 trains) across all participants (Fig 6).

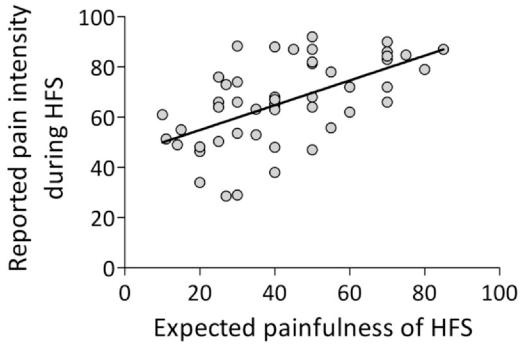

Figure 6. Correlation between the expected painfulness of HFS and the actual reported pain during HFS across all participants. Dots are representing individual data.

Discussion

The present study aimed to investigate if expecting more pain increases HFS-induced pain and pinprick hypersensitivity in healthy volunteers. We hypothesized that expecting more pain for HFS would increase pain ratings during HFS and would promote the development of pinprick hypersensitivity, resulting in a larger spread and more intense pinprick hypersensitivity.

During the manipulation, we found that the nocebo group reported a higher intensity rating to the first single electrical stimulus after removing the patch compared with the control group. Since the stimulation intensity of this electrical stimulus was the same for both groups, this finding indicates that the participants in the nocebo group felt the stimulus more intense and/or were convinced that their skin indeed had become more sensitive after the patch. Surprisingly, the nocebo group did not provide higher ratings for the expected painfulness of HFS compared with the control group and did not rate the pain during HFS as more intense compared with the control group. Hence, the expectation about the single stimulus did not transfer to the HFS stimuli, despite both being electrical stimuli.

Nevertheless, exploratory analyses showed a significant and moderate correlation between the expected painfulness of HFS and the actual pain intensity reported during HFS, suggesting that expectations may influence pain experiences.[1-3]

The threat that an intervention will increase pain may induce fear of pain and may facilitate the nocebo response.[23] In the present study, no differences were found in the reported fear for HFS between the 2 groups, indicating that the manipulation in the nocebo group did not induce more fear for HFS compared with the control group. A recent study found a mediating role of fear in nocebo hyperalgesia but only if high pain is experienced and not when it is merely anticipated.[24] The participants in the present study were naive regarding HFS and did not experience HFS before the manipulation. Future studies may include an example HFS train at the beginning of the experiment.

On the other hand, the participants in the study of Torta et al[17] also did not experience HFS before, but participants in the "high pain" group reported significantly higher pain ratings during HFS compared with the "low pain" group. Moreover, no significant difference in the self-reported fear between the 2 groups was found.

Fear generalization is when fear acquired to one stimulus transfers to another stimulus. Fear conditioning experiments have shown that this is the case for stimuli that are perceptually similar.[25] One possibility is that the single electrical stimuli applied after the patch are perceptually too different compared with the HFS, and therefore the acquired fear during the manipulation may not have transferred to the high-frequency stimuli.

Another possibility could be that expectations created for *nonpainful* electrical stimuli do not generalize to expectations for *painful* electrical stimuli, because of the different qualitative nature of the stimuli. This is supported by a recent study showing that nocebo effects on cowhage-evoked itch generalized to mechanically evoked itch but not to mechanically evoked touch.[26] Another study, conducted by the same group, showed that nocebo effects on pain may generalize within but not across stimulus modalities.[27] It would be interesting to repeat this experiment but using painful single electrical stimuli.

A recent study found that the effect of a cue has less effect on pain when the prediction error is large.[28] The expectation of HFS pain was on average 40 on the NRS, but the averaged pain intensity during HFS around 60. Any effect of the electrode (cue), through which the single electrical stimuli were delivered before and after the patch, could have been mitigated by the (large) difference between expected pain for HFS and the actual pain experienced during HFS.

Importantly, the perceived credibility of the information as well as the perceived honesty of the experimenters were on average very high and not different between the 2 groups, indicating that the participants trusted the information given during the experiment and the experimenters. On the other hand, these ratings were asked verbally and therefore it cannot be ruled out that they were affected by the experimenter demand effect.

Because we were not able to manipulate the expectations of HFS pain differently between the 2 groups, it is difficult to interpret the lack of changes in the HFS-induced spread and intensity of increased pinprick sensitivity.

Previous studies have shown an average increase in pinprick sensitivity after HFS of 20 points on the NRS when using an HFS stimulation intensity corresponding to 20× the detection threshold to a single electrical stimulus.[29,30] The average detection threshold for this type of electrode is usually around .3 mA.[29,30] The HFS stimulation intensity in the present study was 3 mA that corresponds to an intensity of 10× the individual detection threshold to a single electrical stimulus. In the present study, the increase in pinprick ratings after HFS was on average 10 points on the NRS (in the control group), which is half of the increase compared with HFS studies that used a 20× detection threshold HFS intensity. Based on this, we believe that the lack of difference in pinprick hypersensitivity after HFS between the 2 groups is most likely not due to a ceiling effect in the increase in pinprick ratings.

A previous study[31] found that expectations of pain reduction directed to 1 body part did not transfer to other body parts, suggesting that placebo effects are somatotopic-specific. In the present study, pinprick hypersensitivity was tested adjacent to the site at which expectations of pain increase were directed and could explain a lack of effect. However, it is unclear if somatotopic specificity is present for nocebo effects and how narrow the spatial specificity is.

When performing exploratory post hoc analyses, no associations between the averaged pain during HFS and the length or intensity of increased pinprick sensitivity were found. In contrast, Torta et al[17] found a significant correlation between HFS pain and the intensity of increased pinprick sensitivity. It is unclear why ratings of the painfulness of HFS are sometimes correlated and sometimes not to the increased pinprick sensitivity. Torta et al[17] also observed a higher average pain elicited by HFS in their experimental group compared with their control group, but no changes were observed in the length of the area of HFS-induced increased pinprick sensitivity. This latter suggests that experiencing more pain as a consequence of expecting more pain does not necessarily result in a larger spread of increased pinprick sensitivity. However, they did find a significant 3-way interaction between time, side, and group for the pinprick ratings, suggesting that the increase in mechanical pinprick sensitivity after HFS at the HFS-treated arm was larger in the "high pain" group compared with the "low pain" group. However, no follow-up comparisons were statistically significant, and the effect size was rather small; therefore, an alternative explanation could be that the significant 3-way interaction is a chance finding.

To conclude, despite the finding that participants in the nocebo group reported a higher perceived intensity to the single electrical stimulus after the patch compared with the control group, they did not expect HFS to be more painful and did not report more pain during HFS compared with the control group. Because the expectations about the HFS painfulness were not significantly different between the 2 groups, and no differences were observed in the pain ratings during HFS, it is difficult to interpret the lack of differences in HFS-induced pinprick hypersensitivity between the 2 groups. However, our data do provide evidence for an association between expectations and subsequent pain experiences.

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Appendix A. Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2024.104682.

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