INVESTIGATING THE EFFECT OF NEGATIVE EXPECTATIONS ON PAIN AND SECONDARY HYPERALGESIA

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Introduction

Intense peripheral nociceptive input can increase the responsiveness of spinal nociceptive neurons (central sensitization) leading potentially to pain amplification. Based on the results of animal studies, secondary mechanical hyperalgesia (SH) is considered a manifestation of central sensitization. An unexplored question is whether psychological factors, such as negative expectations, can facilitate the development of SH, that can be induced experimentally in humans by applying high-frequency electrical stimulation (HFS) onto the skin. The aim of this study was to investigate if negative expectations about pain would increase SH on the forearm. We hypothesized that expecting more pain would result in higher pain ratings during HFS and a larger spread and a higher magnitude of HFS-induced SH.

Methods

This double-blind study (**Fig 1.**) was performed on 50 healthy volunteers, allocated randomly to either the control group (n=25) or nocebo group (n=25). The test areas were the volar forearms (**Fig 2.A**)

- Baseline measurements: mechanical pinprick stimuli with a 128 mN pinprick probe on both forearms.
- 3 single electrical stimuli on the right forearm (3X 0.5 mA).
- Application of a neutral patch and instruction that it is “capsaicin that will sensitize the skin” or “water that has no effect on the sensitivity”, according to the group.
- 3 single stimuli on the right forearm. 3X 0.5 mA in the control group ; 0.5, 1, and 2 mA in the nocebo group in order to make them trust the procedure of sensitization.
- Assessment of the expected fear and the expected pain for HFS with an numerical rating scale ranging from 0 to 100 (NRS).
- Conditioning HFS (3mA, 100 Hz) on the right forearm and rating of each trains on the 0-100 NRS (**Fig 2.B**).
- Post measurements : mechanical pinprick stimuli with a 128 mN pinprick probe on both forearms and assessment of the length of secondary hyperalgesia.
- Assessment of the trust of the participants regarding the experiment on a 0-100 NRS scale.

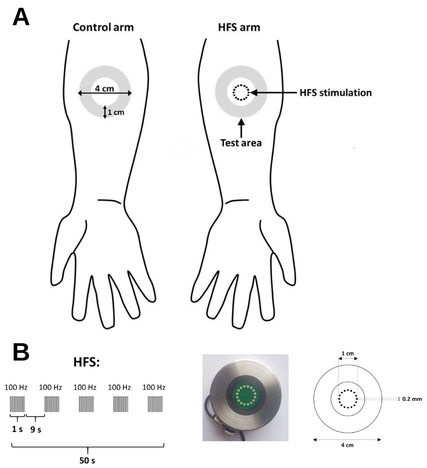

Figure 2.A High frequency electrical stimulation of the skin (HFS) was applied to the right volar forearm. Pinprick stimulation (128mN) were applied to the skin surrounding the area onto which HFS was applied as well as to the same skin area on the contralateral arm, which served as control. **B:** HFS was delivered at 100 Hz. The electrode used to deliver HFS consisted in 16 blunt stainless steel pins placed in a 10-mm diameter circle (cathode), surrounded by a concentrically-located stainless steel anode.

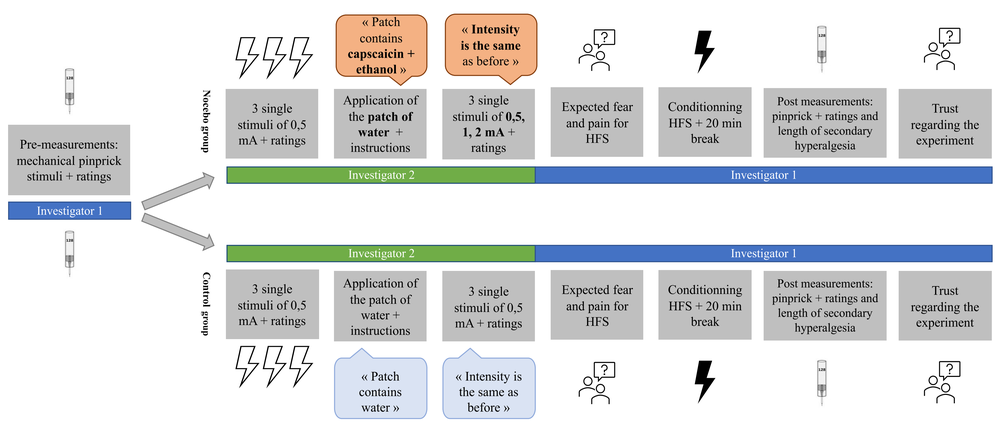

Figure 1. Timeline of the experiment.

Results

Primary outcomes were the length of the secondary hyperalgesia, and the magnitude of secondary hyperalgesia. Secondary outcomes were: expected HFS pain, fear for HFS and perceived pain intensity of each HFS train. At the end of the experiment, the level of trust about the given information during the experiment was asked to all the participants.

First of all, we noticed that the perceived intensity of the single electrical stimuli was significantly increased after the application of the patch for the nocebo group ($p<0.05$) (**Fig 3.A**), and as expected, HFS induced a significant increase of pinprick sensitivity across all participants ($p<0.0001$).

Regarding the primary outcomes, there were no significant differences in the longitudinal spread of secondary hyperalgesia and in the magnitude of the increased pinprick sensitivity induced by HFS between nocebo and control group (**Fig 3.B, 3.C**).

Regarding the secondary outcomes, we found no significant differences in the expected pain for HFS, in the level of fear for HFS, but also in the level of trust reported by the participants between the two groups. For the perceived pain intensity relative to HFS trains, no significant difference was observed between the nocebo and control group (**Fig 3.D**).

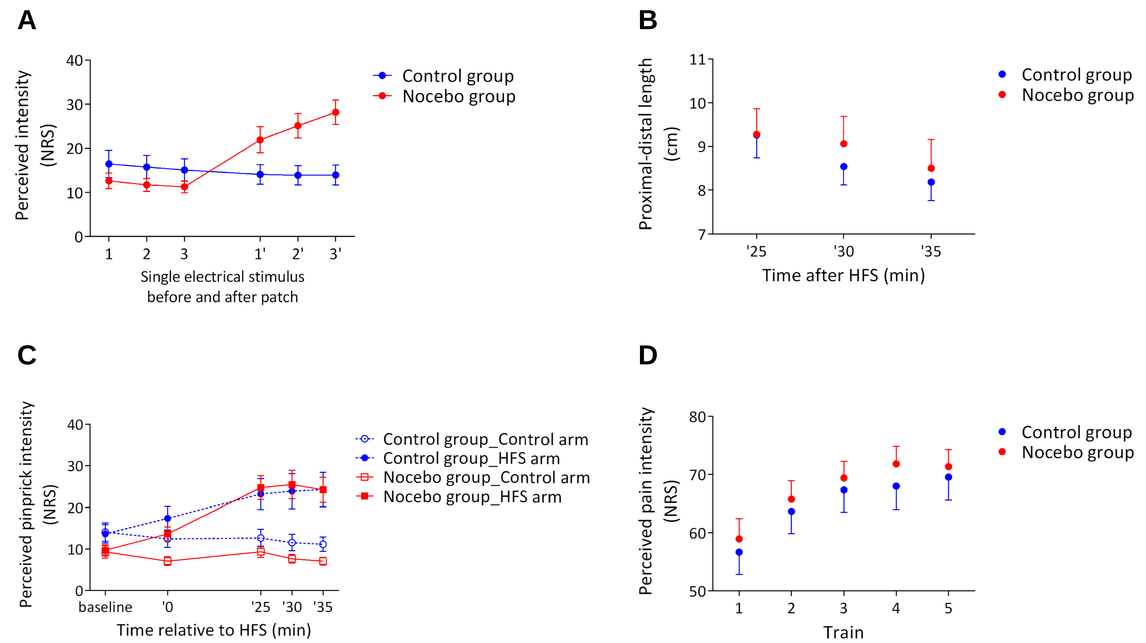

Figure 3.A: Mean and standard error of the perceived intensity of the three single electrical stimuli before and after the patch for control and nocebo group. **3.B**: Mean and standard error of the spread of HFS-induced secondary hyperalgesia. **3.C**: Mean and standard error pain numerical rating scale (NRS) scores observed in response to the mechanical punctate stimulation before and after HFS. **3.D**: Mean and standard error of the perceived pain intensity of each HFS trains during the conditioning stimulation.

Conclusion

The significantly higher perceived intensity elicited by the first single electrical stimulus after the application of the patch in the nocebo group indicates that we were successful in inducing the suggestion that the patch sensitized their skin to electrical stimuli. However, the nocebo suggestion was probably not strong enough to show differences in the primary and secondary outcomes of this study between the two groups. Nocebo effect appears to play a role in clinics, therefore, further studies are required to determine the relation between negative expectations and the development of secondary hyperalgesia.

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