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A highly cognitive demanding working memory task may prevent the development of nociceptive hypersensitivity

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Abstract

Whether, how, and which cognitive factors modulate the development of secondary hypersensitivity/hyperalgesia after central sensitization is not fully understood. Here, we tested, in 3 subsequent experiments, whether being engaged in non–pain-related cognitive demanding tasks: (1) lessens the amount of hypersensitivity developed after an experimental procedure sensitizing nociceptive pathways; and (2) modulates cortical responses to somatosensory stimuli (measured by electroencephalography, EEG). In the first experiment, we validated a novel model in humans using low-frequency stimulation of the skin and demonstrated that it was able to successfully induce hypersensitivity to mechanical pinprick stimuli in the area surrounding the sensitized site. In the second and third experiments, we engaged participants in tasks of increasing difficulty (the Eriksen Flanker Task in experiment 2, and a modified N-back task in experiment 3). We observed that hypersensitivity to mechanical stimuli still developed in experiment 2, that is, the pinprick stimuli applied on the sensitized arm were perceived as more intense after low-frequency stimulation. By contrast, no statistically significant enhancement of mechanical hypersensitivity was observed in experiment 3, indicating that, at the group level, being engaged in a difficult N-back task may interfere with the development of mechanical hypersensitivity. Contrary to previous studies, which have used different methods to induce sensitization, we did not observe any increase in the cortical response to somatosensory stimuli applied on the sensitized arm. We conclude that (1) the development of pinprick hypersensitivity is modulated by the concomitant execution of a difficult N-back task, and (2) the enhancement of cortical responses to somatosensory stimuli is related to the method used to induce central sensitization.

Keywords: Central sensitization, Cognition, Mechanical hypersensitivity, EEG

1. Introduction

The optimal balance between shielding goals and attending to dangerous signals is crucial for survival. Nociceptive stimuli are salient, signal potential danger, and capture attention.[5] This attentional capture is reduced when participants perform tasks requiring mental operations that are sufficiently engaging, difficult, and unrelated to pain.[12,13,19,29] Previous research has shown that cognitive load reduces pain reports and brain responses to brief transient nociceptive stimuli, and that it slows down reaction times to these stimuli.[13,16] Indeed, performing a task recruits cognitive resources that are no longer allocated to the concomitant incoming nociceptive stimulus, shielding the task performance from the disruptive effects of nociceptive input.[13,19] This possibility allows us to keep on pursuing our goals even in the face of pain.[29]

Animal studies have shown that repeated and/or intense peripheral nociceptive input triggers an increase in the excitability of spinal nociceptive neurons, a phenomenon referred to as central sensitization (CS) (eg, the *"increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold input*[11]). In humans, a direct measure of such excitation is not possible, and secondary hyperalgesia/hypersensitivity to mechanical stimuli (eg, the increased sensitivity developing, after tissue injury, in the surrounding uninjured skin) is taken as one of its manifestations. In this paper we will use the term hypersensitivity when the increased perception refers to nociceptive stimuli which are not perceived as painful at baseline, and hyperalgesia as the increased perception to stimuli which are perceived as painful at the baseline. See Ref. 30 for a discussion on this point. Whether, how, and which cognitive factors modulate the development of secondary hypersensitivity after CS is not fully understood. A few studies have addressed this key question by experimentally inducing CS in healthy volunteers. Their results suggest that positive expectations, induced through placebo manipulations, reduce the dimension of the area of hyperalgesia,[14] whereas negative expectations induced by verbal suggestion increase the amount of hypersensitivity/hyperalgesia.[31] Furthermore, it has been reported that brief sessions of pain-focused cognitive behavioral therapy, aimed at reducing negative cognitions, led to a smaller extent of the hyperalgesic site as compared to a non–pain-specific training.[17]

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

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It is unknown which cognitive mechanisms can interfere with the development of CS, and the increase in cortical responses to somatosensory stimuli observed after sensitization.[30,34,36–38] It can be hypothesized that shielding cognition from the sensitization procedure would lead to less attentional resources engaged in the perception of the intense/prolonged nociceptive stimuli, and possibly reduce both hypersensitivity and the increase in cortical responses. This would constitute evidence that attention directed to the sensitizing stimuli is a major contributor to the genesis of secondary hyperalgesia. To test this hypothesis, we performed 3 separate electroencephalographic (EEG) and behavioral experiments. In the first, we validated a novel protocol to induce hypersensitivity in humans by using low-frequency stimulation (LFS).[7] The same protocol was then used in the following experiments in which engaging and pain-unrelated cognitive tasks of different difficulty were administered during LFS.

2. Materials and methods

2.1. Participants

Participants were recruited at the KU Leuven and were naive to the aims of research. Their participation was rewarded with either course credits or money (20 Euros for a 2.30-hour experiment). Informed written consent was obtained before the beginning of the study, which had been approved by the university ethical committee (G-2016 11669). Sample size was calculated on the basis of previous studies and available literature.[31] By signing the exclusion criteria, participants confirmed that they did not suffer from cardiovascular or respiratory diseases, chronic pain, acute pain at the time of testing, hearing problems, and diagnosis of neurological and/or psychiatric syndromes. Participants were also excluded if they were pregnant, regular drug users, on stable medication (with the exception of contraceptive pill), significantly sleep deprived (slept less than 6 hours the night before the experiment), and if they had taken anti-inflammatory drugs <12 hours before the experiment.

Sixty-four healthy participants were enrolled; 4 stopped during the sensitization procedure due to unbearable pain (2 in experiment 1 and 2 in experiment 2). The final sample was composed of 60 participants: 20 took part in experiment 1 (14 women, 6 men; median age 22 years, range 19-37), 19 in experiment 2 (15 women, 4 men; median age 22 years, range 18-40), and 21 in experiment 3 (10 women, 11 men; median age 26, range 19-36). None of the participants took part in more than one experiment.

2.2. Measures

2.2.1. Questionnaires

Before the beginning of the experiment, participants filled in questionnaires assessing the level of intolerance of uncertainty, positive/negative affect and optimism, pain catastrophizing (eg, Intolerance of Uncertainty Scale,[3] Positive and Negative Affect Schedule,[41] Life Orientation Test-Revised,[18] and Pain Catastrophizing Scale[23]). Questionnaires are part of larger prospective ongoing study. Therefore, the results will be presented here only in a descriptive way. A description of the questionnaires is provided in the supplementary material (available at http://links.lww.com/PAIN/A968).

2.2.2. Stimuli

2.2.2.1. Low-frequency stimulation

Low-frequency stimulation was used to induce secondary mechanical hypersensitivity, a hallmark of CS.[28] It consisted of 2 minutes of electrical stimulation at 2 Hz (pulse width 2 ms).[7] The pulses were generated by a constant-current electrical stimulator (DS7; Digitimer Ltd, Welwyn Garden City, United Kingdom). The stimuli were applied by using a specifically designed electrode composed of 16 blunt stainless steel pins with a diameter of 0.2 mm, protruding 1 mm from the base.[9,38] The pins were placed in a circle with a diameter of 10 mm and served as cathode. The stainless steel reference electrode, the anode, was placed surrounding the cathode and had an inner diameter of 22 mm and an outer diameter of 40 mm.

The intensity of stimulation was determined individually at 15 times the absolute detection threshold to a single pulse. The 15× threshold was established after running a pilot experiment assessing the compromise between feasibility and effectiveness of LFS using the 20× and 10× detection thresholds.

2.2.2.2. Mechanical hypersensitivity

Mechanical hypersensitivity was tested by using pinprick stimuli, which were applied using a calibrated stainless steel pinprick stimulator exerting a force of 128 mN (MRC Systems, Heidelberg, Germany) and having a 0.25-mm probe diameter.

2.2.2.3. Electrocutaneous innocuous stimuli

Electrocutaneous innocuous stimuli consisted of 0.5-ms constant-current square waves electrical pulses (generated by a DS7 stimulator; Digitimer Ltd). The stimuli were delivered using a bar stimulating electrode (Digitimer Ltd), which consisted of 2 durable stainless steel disk electrodes of a 8-mm diameter with 30-mm spacing. The electrode was held by means of a Velcro strap. Both mechanical and electrocutaneous stimuli were applied on the volar forearm, 1.5 cm from the LFS stimulated region (and the homologue region of the control arm).

2.2.3. EEG recording and analysis

The EEG was recorded at a 1-kHz sampling rate using a 129-channel amplifier and digitizer (Philips Electrical Geodesics, Inc, Eugene, OR). Analysis of the EEG data was performed using Letswave 6 (http://www.nocions.org/letswave). Extraencephalic channels likely to be contaminated by artifacts were excluded from subsequent analyses.[11] These included the following leads (E44, E43, E38, E128, E127, E48, E49, E119, E126, E120, E114, E113, E121, and E125). Continuous EEG recordings were re-referenced to the average of the remaining leads; a 50-Hz notch and a 0.5 to 30 Hz Butterworth zero phase filter were then applied. The data were segmented in 3-second epochs extending from −1 to +2 seconds relative to stimulus onset. Artifacts were removed from the signal using an independent component analysis.[8] Baseline correction was performed subtracting the signal from the −1 to −0.1 seconds prestimulus interval; a further artifact correction eliminating epochs exceeding 100 μV was performed. The obtained waveforms were then averaged to obtain for each participant and time point (T0, T1, and T2), 2 grand averages, one for the stimuli applied to the control arm and the other for the stimuli applied to the LFS arm. The latency and amplitude of the N1 and the P2 component of the somatosensory evoked potentials (SEPs) were identified at pooled electrodes around the vertex Cz (E129); pooled electrodes were E7, E31, E55, E80, E106, and E129 (Cz). The N1 was identified as the most negative peak between 0.07 and 0.2 seconds after stimulus, and the P2 as the most positive deflection after the N1 and occurring in an interval between 0.100 and 0.350 seconds. Waves were subsequently visually inspected to confirm the automatic procedure.

2.2.4. General experimental procedure

The 3 experiments shared the same experimental procedure. For the nature of the study, ie, we first needed to validate the LFS procedure, the experiments were performed consecutively on 3 separate groups of participants. On arrival, participants signed the informed consent and the declaration regarding the exclusion criteria. Then, they completed the questionnaires.

The detection threshold for electrocutaneous innocuous stimuli was then established using a staircase procedure. Low intensities were initially presented (starting from 0.1 mN) and increased by 0.1 mN until the first stimulus was detected; then, the intensity was lowered until no longer perceived, and then increased again. The threshold was established after 3 reversals. The intensity used during the experiments was twice the detection threshold. At such intensity, the stimuli do not elicit any painful sensation, and brain responses to them are considered recruiting mainly Aβ fibers.[24,26] We chose for low-intensity electrical stimuli to compare the effects of low-frequency stimulation (see later) to those of high-frequency stimulation (HFS) on brain responses to Aβ inputs. Indeed, previous reports[34] have observed that after HFS, brain responses to a variety of somatosensory inputs, even nonnociceptive ones, are enhanced. Furthermore, we always ensured that the elicited sensation was nonpainful, by asking for a rating on a scale ranging from 0 (no sensation) to 100 (the most intense pain imaginable). The rating of 50 constituted an anchor separating nonpainful (0-50) to painful (50-100) sensations.[15,33,36–38]

After establishing the threshold, the EEG net (Philips Electrical Geodesics, Inc) was mounted. Each participant performed 3 sessions, one before the sensitization procedure (ie, LFS) (T0) and 2 after, at 20 (T1) and 45 (T2) minutes after the end of LFS. These time points were in line with previous findings obtained with HFS,[36–38] and were confirmed by an initial pilot study, in which we tested for mechanical sensitivity from the end of LFS, each 5 minutes until 60 minutes. Low-frequency stimulation was applied to one arm only, the dominant or nondominant one; the arm was counterbalanced across participants. The other arm served as control. At each of the time points (T0, T1, and T2), participants received 3 mechanical pinprick stimuli on both the LFS and control arm, and they were requested to provide an average rating of its intensity on the previously described scale. Participants also received 30 low-intensity electrical stimuli on each arm to elicit SEPs. At the end of the 30 stimuli, a rating of intensity for these stimuli was also asked. The first kind of stimulus that was applied, either mechanical or electrical, and the first stimulated arm, either LFS or control, were counterbalanced across participants.

2.2.5. Experiment 1

In experiment 1, participants did not receive any specific instruction for what to do during LFS. Unbeknownst to them at the beginning of the stimulation, we asked for a rating of intensity of the LFS stimuli at the end of the 2-minute stimulation. We also enquired volunteers on whether they used specific strategies during LFS to cope with the painfulness of the stimulation.

2.2.6. Experiment 2

Participants in experiment 2 performed an engaging task during LFS, the Eriksen Flanker Task. During this task, participants were shown, on a Philips 32-inch monitor positioned at approximately 1 m, 5 arrowheads horizontally aligned and were instructed to indicate the direction towards which the central arrow pointed by either pressing the left or right mouse button. The mouse was held on the nonstimulated side. The 4 possible arrowhead combinations (<<<<, <<><<, >>>>>, or >><>>) were presented pseudorandomly. In each trial, the arrowheads were presented for 200 ms and replaced by a blank screen until either a response was given or the maximal allowed time (1000 ms) was elapsed. The intertrial interval varied randomly between 600 and 1000 ms (mean: 800 ms) (see Ref. 22). At the beginning of the experiment, participants performed 20 familiarization trials (5 for each of the 4 arrow combinations) during which they received a feedback about their performance. The feedback was not available during the actual experiment. The task started 90 seconds before LFS and continued for approximately 90 seconds after LFS. The instruction stressed the importance of both the speed and the accuracy of the response, and these 2 parameters were recorded and analyzed separately for the 3 time periods: pre, during, and post LFS. After the end of the task, we asked participants to judge how engaging and how difficult the task was on a scale from 0 (not difficult/engaging at all) to 10 (as difficult/engaging as possible). A rating of intensity of the LFS was also obtained. Given that a slightly different number of trials was presented to each participant (depending on the speed of the response), the accuracy was calculated in terms of percentage of correct responses.

2.2.7. Experiment 3

Participants in experiment 3 performed a modified version of an N-back task as used by.[21] They were shown, on the same screen used in experiment 2, a series of letters (A to E), each visible for 750 ms, and followed by a 750-ms blank screen. The task was to detect matches between the actual letter and one presented 2 letters before (2-back task). Each string was composed of 15 letters, and the number of matches was pseudorandomized. Participants were additionally requested to retain in memory the number of matches per string, and to report it at the end of the 22.5-second duration of the string. Before the experiment, participants performed a familiarization phase in which 5 strings were presented. During this phase, they received feedback about their performance; the feedback was not provided during the actual experimental phase. Four strings were presented, during the experiment in the "Pre" LFS period, 5 during LFS, and 4 in the "Post" LFS.

Figure 1 summarizes the setup.

2.3. Statistical analyses

Statistical analyses were conducted using IBM Statistics SPSS 19 (Armonk, NY: IBM Corp). Assumption of normality was tested using the Wilk–Shapiro test, and the Greenhouse–Geisser correction was used where appropriate.

Changes in the perceived intensity of mechanical pinprick and electrocutaneous stimuli, and in the magnitude of the SEPs (vertex N1 and P2) were assessed using 3 separate analyses of variance with the factors "*Time*" (3 levels, T0, T1, T2) and "*Side*" (LFS and control arm). The interaction "*Time*" × "*Side*" was used to investigate the effects of LFS. In case of significant interactions, follow-up t-tests were conducted, and the level of significance of the alpha adjusted by the number of comparisons.

The effect of the "*Phase*" (pre, during, and post LFS) was assessed on the accuracy of the response and reaction times in the Flanker task. The same effect of the "*Phase*" was used as

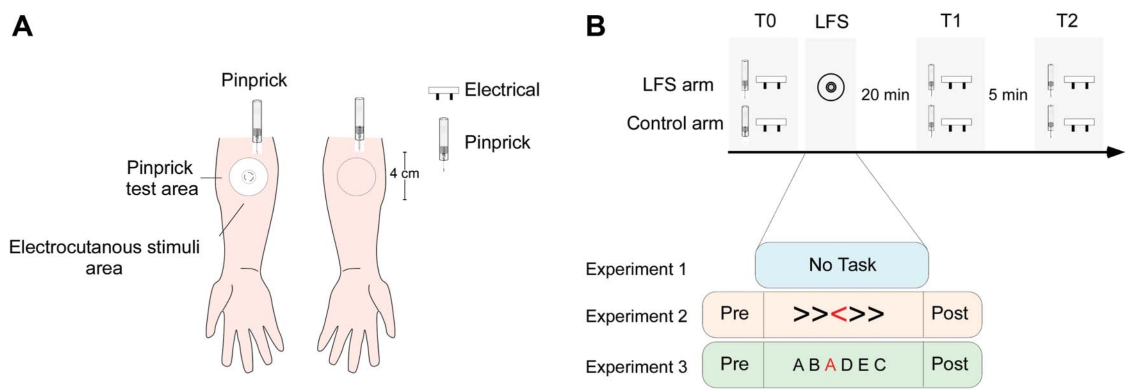

Figure 1. Experimental setup. (A) Participants received, on their volar forearm, 2 kinds of stimuli, before and after an experimental procedure inducing sensitization (ie, LFS of the skin). (B) Three blocks were run for each participant, one before LFS, and 2 after, at 20 minutes (T1) and at 45 minutes (T2) from the end of LFS stimulation. During LFS, participants performed different tasks, depending on the experiment. In experiment 1, no task was performed, in experiment 2 volunteers performed an Eriksen Flanker Task, and in experiment 3 they completed a modified N-Back task. These tasks started before the beginning of LFS and continued after its end. LFS, low-frequency stimulation.

factor for the N-back task; outcome variables were the accuracy of the response, and the deliberation time for the number of matches. Correlations were run using two-tailed Person's *r* on the pooled data of the 3 experiments.

3. Results

3.1. Questionnaires

Descriptive statistics for the questionnaires are summarized in **Table 1**.

3.2. Thresholds, intensity of stimulation and perceived intensity of low-frequency stimulation

The intensity of the LFS stimulation was 6.06 (±2.2), 7.41 (±2.06), and 8.11 (±3.21) mN, for experiments 1, 2, and 3, respectively. The intensity of the innocuous electrocutaneous stimuli was 1.70 (±1.52), 1.37 (±0.51), and 1.46 (±0.53) mN, for experiments 1, 2, and 3, respectively. Low-frequency stimulation was perceived on average as painful in all experiments (experiment 1: 65.30 ±13.43, experiment 2: 68.11 ± 19.14, and experiment 3: 66.48 ± 16.08).

3.3. Cognitive tasks

We debriefed participants at the end of experiment 1 to understand whether they have used cognitive strategies to cope with the painful sensitizing procedure. Nine participants reported having done so, more specifically: 2 participants tried to slow breathing, 3 counted (either to 8 or made a countdown for the time), 3 tried to rationalize and limit negative thoughts, and one sang a song in his/her head.

Due to a technical problem, data from one participant from experiment 2 were not recorded. Therefore, the data refer to 18 participants for experiment 2 and 21 for experiment 3. On the 0 to 10 scale investigating how engaging the task was, the Eriksen Flanker task was rated on average 7.61 ± 1.68, and the N-back 6.76 ± 1.51. This difference was not significant (Mann–Whitney test for independent samples $Z = -1.83$ $P = 0.067$). The N-back task was considered more difficult on the same 0 to 10 scale, being rated on average 6.76 ± 1.37 vs a 4.28 ± 2.24 for the Eriksen Flanker Task (Mann–Whitney test for independent samples $Z = 3.33$ $P < 0.001$) (see also Supplementary figure 1, available at http://links.lww.com/PAIN/A968).

The Flanker task accuracy was 91.07 ± 12.24%, 92.74 ± 11.11%, and 93.97 ± 12.37% in the pre, during, and post LFS phases, respectively, and the differences in accuracy in these 3 phases did not reach statistical significance $F(1,17) = 1.667$, $P = 0.204$; partial $\eta^2 = 0.089$. The reaction times for correct answers were of 529.91 ± 42.99 ms before, 494.36 ± 38.83 ms during, and 511.62 ± 43.06 after LFS. These values were significantly different $F(1,17) = 10.445$, $P < 0.001$. partial $\eta^2 = 0.381$. Participants became faster, without losing their accuracy *during* LFS as compared to before $t(17) = 4.108$, $P = 0.001$, Cohen's $d = 0.86$. Importantly, the reaction times increased significantly again *post* as compared to during LFS, $t(17) = -2.490$, $P = 0.023$, Cohen's $d = 0.42$, indicating that the effects were not simply due to training.

Reaction times for errors were 439.72 ± 62.19, 415 ± 55.36, and 366.63 ± 179.29 ms in the pre, during, and post LFS periods, respectively. This difference was not significant $F_{g\text{-}g}(1,13) = 0.294$ $P = 0.656$ partial $\eta^2 = 0.022$.

The N-back accuracy reached an average of 45.60 ± 35.89%, 32.14 ± 27.63%, and 44.04 ± 28.12% correct responses in the pre, during, and post LFS phases, respectively, with no

Table 1

Mean and SDs of the scores at psychological questionnaires.

	IUS total score	PANAS (positive)	PANAS (negative)	LOT-R dispositional	PCS total
Experiment 1	55.11 ± 21.46	31.83 ± 4.99	21.11 ± 4.89	16.83 ± 4.21	17.11 ± 8.20
Experiment 2	57.82 ± 17.98	30.24 ± 7.21	19.94 ± 7.40	13.71 ± 3.56	14.71 ± 9.78
Experiment 3	55.14 ± 17.24	31.62 ± 7.39	19.81 ± 6.12	15 ± 4.29	14.48 ± 7.78

A description of the questionnaires is available in the supplementary material (available at http://links.lww.com/PAIN/A968).
IUS, Intolerance of Uncertainties[3]; LOT-R, Life Orientation Test-Revised[18]; PANAS, Positive and Negative Affect Schedule[41]; PCS, Pain Catastrophizing Scale.[23]

statistically significant differences amongst them; F(1,20) = 1.593, $P = 0.216$; partial $\eta^2 = 0.074$. Indeed, 6 of 21 participants significantly *improved* their performance during LFS. Deliberation times for correct answers were 2771 ± 753, 2232 ± 804, and 2197 ± 781 ms, and 2775 ± 1358, 2364 ± 820, and 2372 ± 895 ms for incorrect trials. There were no statistically significant differences for incorrect trials F(2,30) = 0.691, $P = 0.509$ partial $\eta^2 = 0.044$. Conversely, deliberation times for correct trials significantly differed (F(2,30) = 3.690, $P = 0.042$, partial $\eta^2 = 0.270$). More specifically, deliberation times decreased from pre to post t(13) = 3.109 $P = 0.008$, Cohen's d = 0.54.

Figure 2 summarizes all these findings.

3.4. Mechanical hypersensitivity

3.4.1. Experiment 1

A "*Time*" × "*Side*" interaction (F(2, 38) = 11.722, $P < 0.001$ partial $\eta^2 = 0.382$) was observed on the perceived intensity of mechanical pinprick stimuli. Follow-up *t*-tests showed that stimuli applied on the LFS arm were rated as more intense at T1 (t(19) = 2.950 $P = 0.008$, Cohen's d = 0.52) as compared to T0. The increase at T2 did not survive the correction for multiple comparisons (Bonferroni-corrected alpha 0.012) (t(19) = 2.068 $P = 0.053$, Cohen's d = 0.33). By contrast, the ratings for the stimuli applied on the control arm remained unchanged from T0 to T1 (t(19) = −0.629 $P = 0.537$, Cohen's d = 0.08). A mild habituation, not surviving Bonferroni correction, was observed at T2 (t(19) = −2.313 $P = 0.032$, Cohen's d = 0.28). Including sex as between factor in exploratory analyses did not significantly change the "*Time*" × "*Side*" interaction (F = 11.416, $P < 0.001$ partial $\eta^2 = 0.438$).

3.4.2. Experiment 2

The results of experiment 2 were similar to those obtained in experiment 1. We observed a "*Time*" × "*Side*" interaction F(2, 36) = 11.168, $P < 0.001$ partial $\eta^2 = 0.383$), explained by an increase in ratings for the stimuli applied at the LFS arm at T1 as compared to T0 (t(18) = 3.129 $P = 0.006$, Cohen's d = 0.32), but no difference for stimuli applied on the control arm (t(18) = 1.010 $P = 0.326$, Cohen's d = 0.07). No difference between T2 and T0 was found (LFS arm t(18) = 1.997 $P = 0.061$, Cohen's d = 0.22; control arm t(18) = −1.355 $P = 0.192$, Cohen's d = 0.14). Overall, these findings suggest that the cognitive manipulation was ineffective in preventing the development of hypersensitivity at T1. Similar to experiment 1, exploratory analysis including sex as a between factor did not significantly change the "*Time*" × "*Side*" interaction (F = 9.673 $P <$ 0.001 partial $\eta^2 = 0.363$).

3.4.3. Experiment 3

By contrast, in experiment 3, no "*Time*" × "*Side*" interaction was observed (F(2,38) = 2.358, $P = 0.108$ partial $\eta^2 = 0.110$), suggesting that when a high cognitive load working memory task is performed during sensitization, no statistically significant hypersensitivity to mechanical stimuli is developed on the LFS arm at the group level. Also, in this case, exploratory analysis including sex as between factor did not change the results (F = 2.082 $P = 0.264$ partial $\eta^2 = 0.104$).

Figures 3 and 4 summarize the results. The complete statistics are reported in the supplementary materials (available at http://links.lww.com/PAIN/A968).

3.5. Mechanical hypersensitivity: additional analyses

The frequentist statistical approach did not allow drawing conclusions about the null hypothesis (H0). To support our conclusion that the probability that there was no interaction effect was larger than the probability there was an interaction effect, we used the Bayesian analysis approach. Bayesian statistics have the advantage of comparing the evidence for the null (H0) and

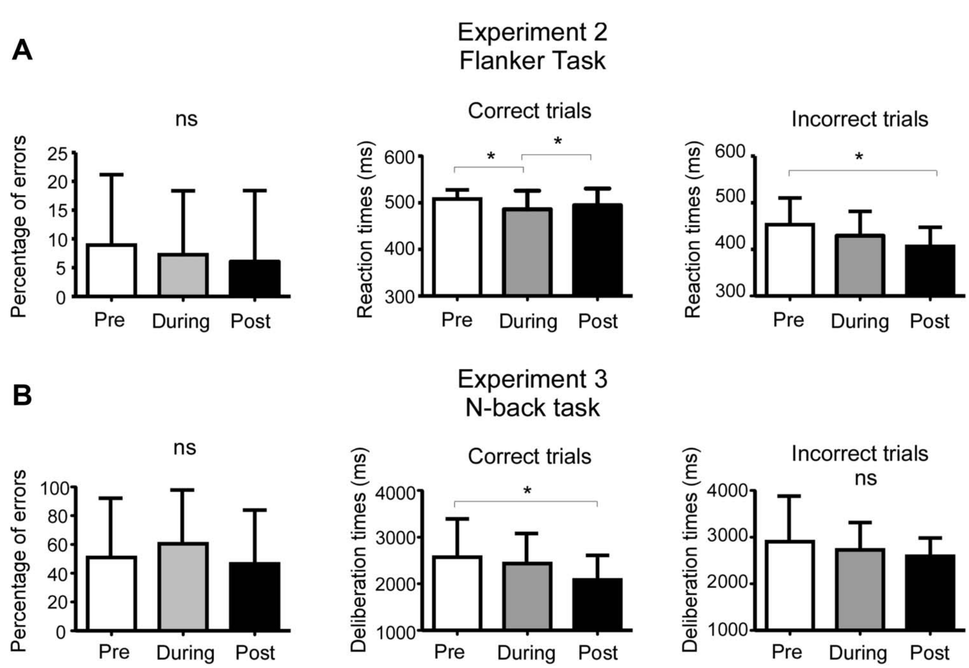

Figure 2. Performance at the tasks. (A) Participants were significantly faster during LFS as compared to before and after for correct trials. Reaction times to incorrect trials diminished across phases. (B) The performance at the N-back task was unchanged during LFS, whereas deliberation time decreased over time. LFS, low-frequency stimulation.

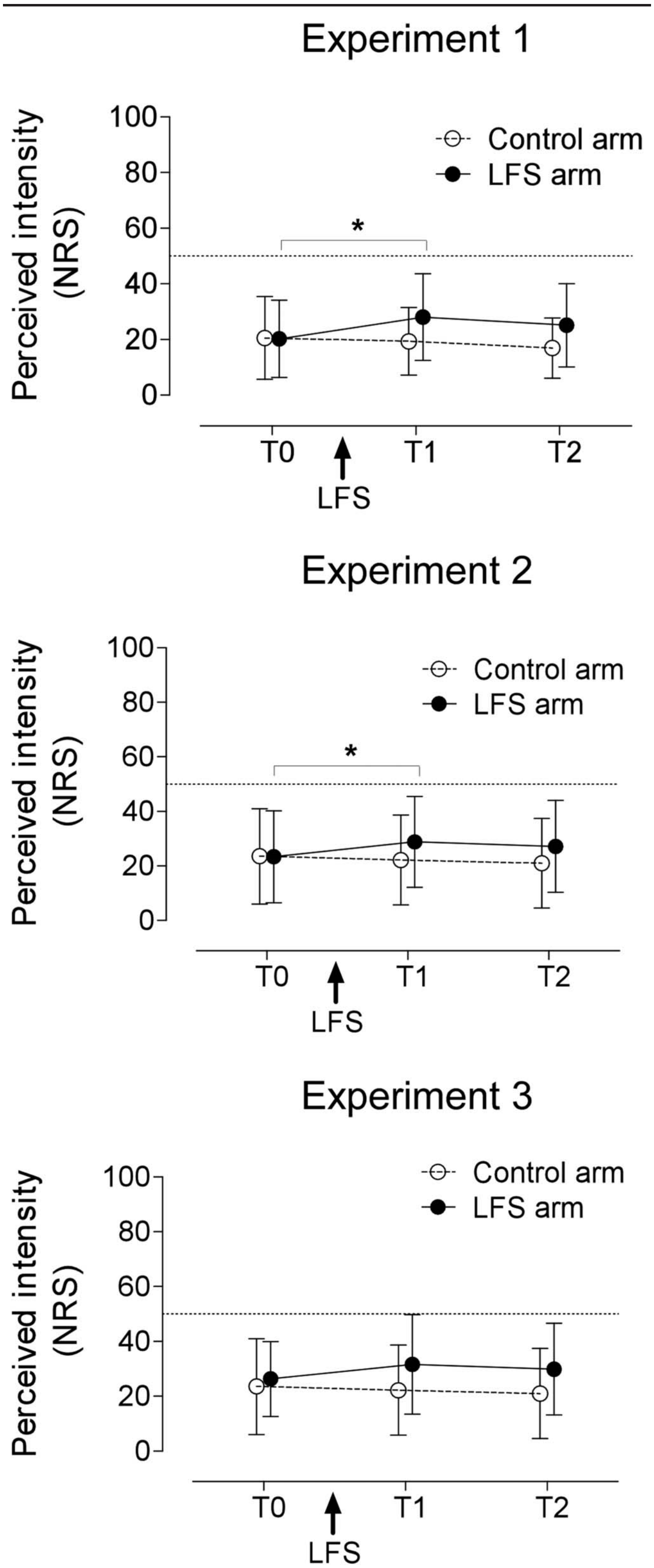

Figure 3. We found a significant Time × Side interaction in the first 2 experiments driven by a significant increase in the ratings to stimuli applied on the LFS but not on the control arm. By contrast, such interaction was not present for experiment 3. Error bars represent SDs. The dotted line at 50 represents the transition from a nonpainful to a painful domain of sensation. LFS, low-frequency stimulation; NRS, Numerical Rating Scale.

alternative (H1) models.[39,40] Therefore, to further elucidate our results, we performed additional Bayesian analyses focusing on the interaction effects. The analyses were performed by using JASP (version 0.11) and a default Cauchy prior of 0.707. Bayesian statistics return a Bayes factor for the H0 (B01) and one for the H1 (B10). To understand the contribution of the interaction, one compares the values of the full model (including the main effects and the interaction) to that including only the main effects. The value that is returned can be conventionally interpreted as follows: values between 1 and 3 indicate "anecdotal" evidence, from 3 to 10 "moderate," from 10 to 30 "strong," and above 30 "very strong." The evidence for the interaction was 5.36 in experiment 1, 6.37 in experiment 2, and 0.45 in experiment 3. In other terms, in experiment 3, unlike in experiments 1 and 2, there was substantial evidence against the interaction. The full Bayesian statistics are reported in the supplementary material (available at http://links.lww.com/PAIN/A968).

3.6. Tactile sensitivity

In none of the experiments, a "*Time*" × "*Side*" interaction was observed (experiment 1 $F(2,38) = -1.925$, $P = 0.160$ partial $\eta^2 = 0.092$; experiment 2 $F(2,34) = -0.080$, $P = 0.923$ partial $\eta^2 = 0.005$; experiment 3 $F(2,40) = -0.611$, $P = 0.548$ partial $\eta^2 = 0.030$), indicating that LFS had no effect on the reported intensity of innocuous stimuli (**Fig. 5**).

3.7. Somatosensory evoked potentials

3.7.1. N1 latency and amplitude

In none of the 3 experiments, a statistically significant "*Time*" × "*Side*" interaction was observed on the latency and amplitude of the N1 component.

3.7.2. P2 latency and amplitude

Likewise, no statistically significant "*Time*" × "*Side*" interaction was observed across experiments. The full statistics are provided in the supplementary material (available at http://links.lww.com/PAIN/A968), and **Figure 6** illustrates the results.

3.8. Correlations

After pooling all data from the 3 experiments together to increase the numerosity of the cases, we observed a statistically significant correlation between the intensity of the LFS stimulation and the amplitude of the N1 at the LFS arm at T1 ($r = -0.303$, $P = 0.030$, $R^2 = 0.092$). The correlation at T2 was of $r = -0.274$, $P = 0.051$, $R^2 = 0.075$. No such correlation was found for the P2 (T1; $r = 0.129$, $P = 0.364$, $R^2 = 0.016$; T2: $r = 0.149$, $P = 0.295$, $R^2 = 0.022$). The amplitude of the N1 at the LFS arm at T1 and the pinprick perception were also uncorrelated ($r = -0.161$, $P = 0.258$, $R^2 = 0.026$). Finally, whereas we found no relationship between the intensity of LFS stimulation and the amount of developed hypersensitivity ($r = 0.180$, $P = 0.204$, $R^2 = 0.032$), we did observe a correlation between *the perceived* intensity of LFS and the amount of hypersensitivity, both at T1 ($r = 0.394$, $P = 0.002$ $R^2 = 0.155$) and T2 ($r = 0.415$, $P = 0.001$ $R^2 = 0.172$). Nevertheless, heteroscedasticity was identified in the some of the data (**Fig. 8**). This calls for a cautious interpretation of the significant linear relationship. Indeed, a reliable linear relationship seems to exist between the perceived intensity of LFS and the development of lower hypersensitivity scores. However, for higher perceived LFS intensity scores, such linear relationship is disrupted.

Figures 7 and 8 summarize the results.

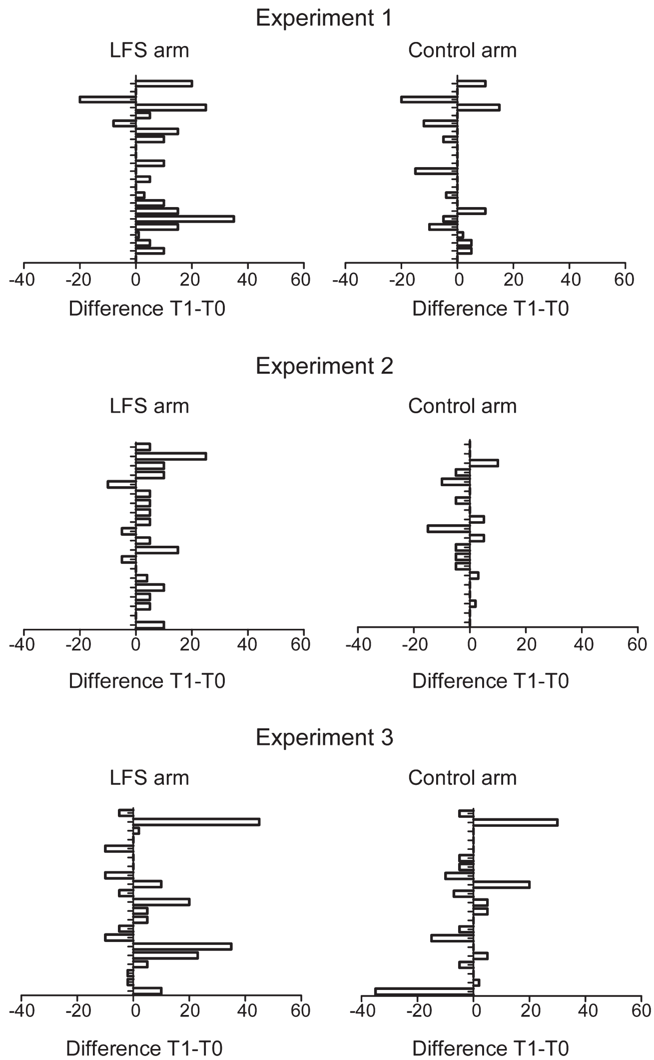

Figure 4. Details of the results at the individual level. Bars represent the scores provided for the pinprick stimulation. Negative values indicate lower scores at T1 as compared to T0.

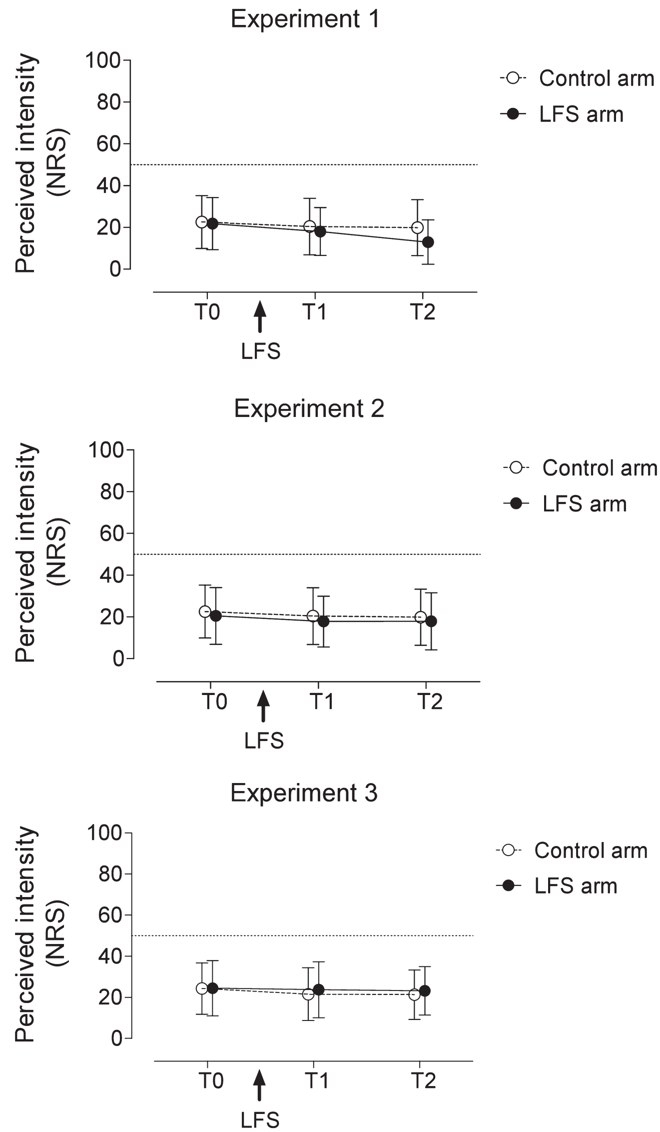

Figure 5. Low-frequency stimulation did not influence the ratings to innocuous electrical stimuli, as evidenced by the lack of interaction between Time and Side in all 3 experiments. Error bars represent SDs. The dotted line at 50 represents the transition from a non-painful to a painful domain of sensation. LFS, low-frequency stimulation; NRS, Numerical Rating Scale.

4. Discussion

Despite their clinical value, reports investigating whether, how, and which cognitive factors contribute to the development of hypersensitivity/hyperalgesia are still scarce.[14,17,31] Furthermore, the neural mechanisms of such effects, if they exist, largely remain to be elucidated.[10] In this study, we have tested, for the first time, in 3 separate studies, whether being engaged in non–pain-related cognitive tasks during sensitization results in the abolishment of the significant interaction Time × Side typically occurring after sensitization at T1 and T2. To achieve our aim, we have first validated, in humans, a novel protocol to induce hypersensitivity using LFS at 2 Hz for 2 minutes (experiment 1). Subsequently, in experiments 2 and 3, we have requested participants to engage in cognitive tasks of increasing difficulty while they underwent LFS. We have measured both the increase in perceived intensity of pinprick stimuli and brain responses to innocuous electrocutaneous stimuli (SEPs). Indeed, previous studies using HFS of the skin, another procedure that has shown to induce robust hyperalgesia, have reported that, after sensitization, the middle latency (120-200 ms) negative component of the event-related potentials measured at the vertex (Cz) was increased for a broad range of somatosensory and nonsomatosensory, ie, visual stimuli.[27,30,33,34,36]

Our results show that mechanical hypersensitivity can still develop when a moderately engaging response-inhibition task is performed during LFS. However, no significant *Time* × *Side* interaction was observed when a more difficult working memory task (an N-back task) was administered during sensitization. This evidence shows that the concomitant execution of certain cognitive tasks interferes with a significant development of mechanical hypersensitivity.

The present findings also do not support the possibility that LFS, in contrast with what is observed with HFS, induces an increase in the magnitude of the middle latency component of the event-related potentials. This, together with the lack of correlation between the N1 elicited by stimuli applied on the LFS arm at T1 and the perceived pinprick intensity for stimuli applied on the same arm also at T1, suggests that the increase in the middle latency component and the increase in perceived intensity of mechanical stimuli reflect 2 distinct processes.

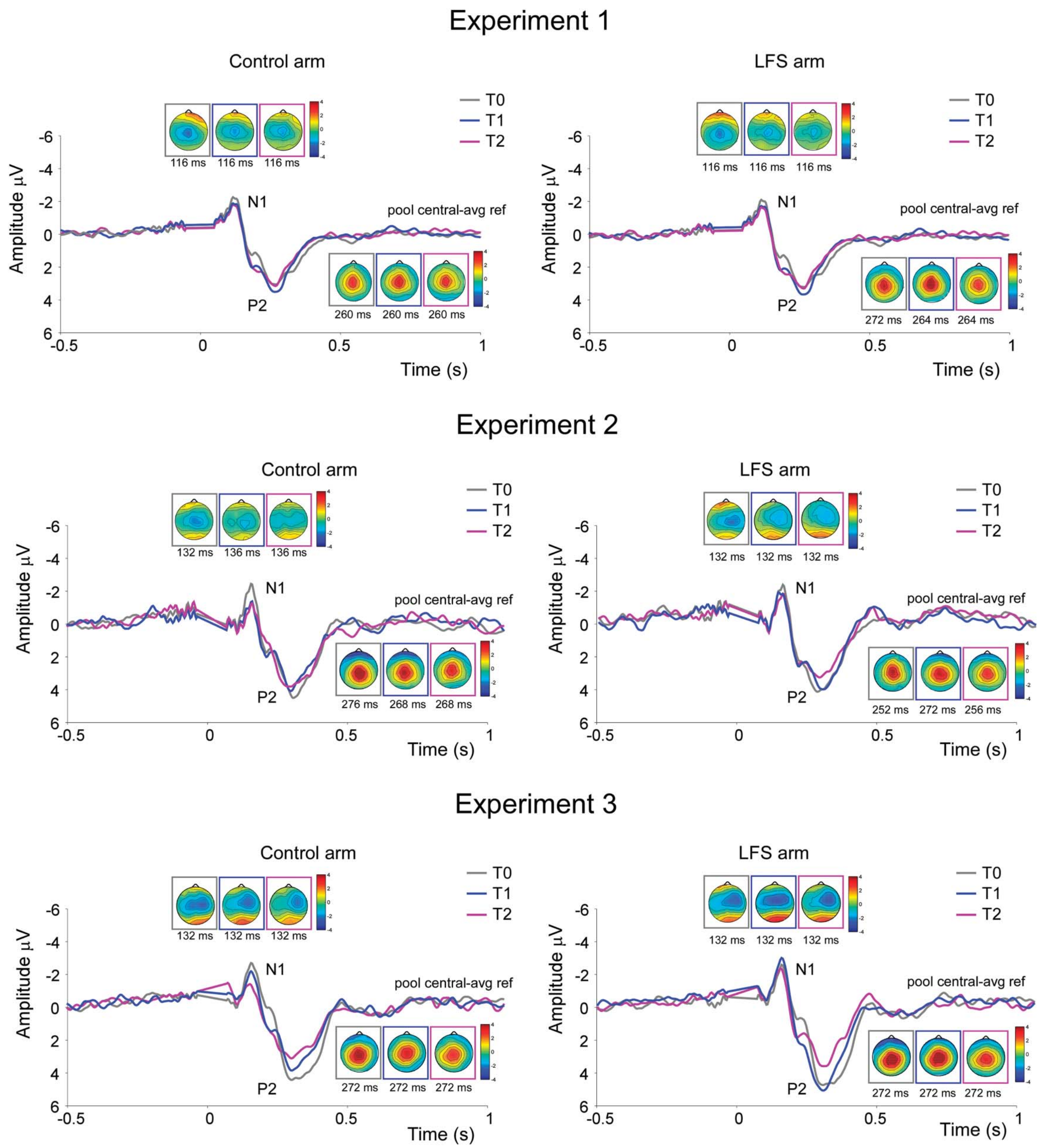

Figure 6. In contrast with previous studies using a different frequency to induce CS, we did not observe an increase of the N1 and P2 components of the SEPs. The electrical artifact around 0 seconds has been suppressed in the figure for visualization purposes. CS, central sensitization; SEP, somatosensory-evoked potential.

4.1. Low-frequency stimulation induces mechanical hypersensitivity

Electrical stimulation of the skin, as compared to capsaicin, has the advantage of inducing hypersensitivity without triggering an ongoing burning sensation that can per se capture attention. For its characteristics of brevity and intensity, HFS did not represent the best model to test top-down inhibitory effects as the whole procedure lasts 50 seconds, of which only 5 of intense painful stimuli. Therefore we validated, in humans, the protocol proposed by Ikeda et al.[7] The authors demonstrated, in vitro, that both HFS and LFS of the skin induce increased postsynaptic potential in nociceptive pathways, with LFS sensitizing the spinoperiaqueductal gray pathway instead of the spinoparabrachial pathway. We observed in humans that such a protocol, at 2 Hz for 2 minutes, is also capable of inducing a significant hypersensitivity to pinprick mechanical stimuli. This is also in line with other reports showing that, in humans, both LFS and HFS of the skin may result in a facilitation of nociceptive processing.[2,4] For instance, Biurrun-Manresa et al.[2] showed that LFS induced a long-lasting facilitation of the nociceptive withdrawal reflex, which is considered a measure of spinal nociceptive processing (however, for contradicting findings, see Ref. 9).

4.2. Low-frequency stimulation does not induce an increase of the vertex negative middle latency component

Somatosensory-evoked potentials were not enhanced after LFS. Accumulating evidence shows that the increase in SEPs coexists with, but is probably not a correlate of, hypersensitivity and hyperalgesia.[1] Indeed, albeit to a lesser extent, an enhancement

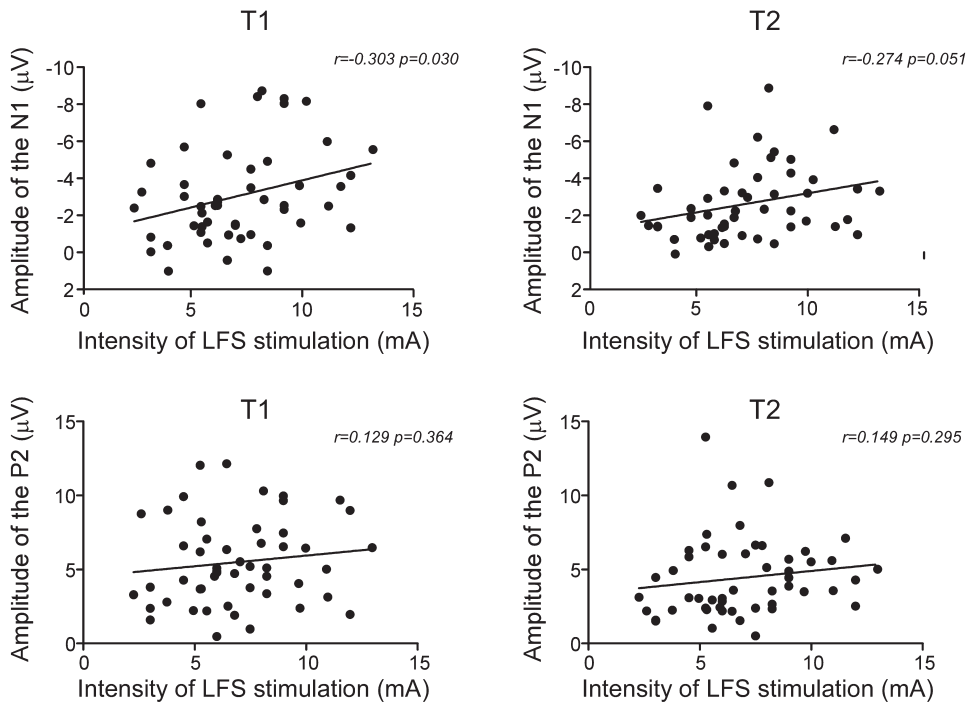

Figure 7. We observed significant correlations between the LFS intensity of stimulation and the amplitude of the signal (N1) at T1 and, marginally, at T2. No such correlation was observed for the amplitude of the P2. The correlations are calculated on the data of the 3 pooled experiments. LFS, low-frequency stimulation.

in the magnitude of cortical potentials in response to stimuli presented on the sensitized arm has been also observed for visual stimuli,[27] and changes in brain responses are uncorrelated with the changes in pain reports.[1] Currently, it remains unclear which processes lead to an increase in the magnitude of the brain response after HFS and capsaicin.[25,32,33,35] A previous study[25] investigated whether sensitization procedures (HFS in that case) would increase attentional allocation towards the sensitized arm, thereby resulting in a prioritization of stimuli presented on the sensitized arm over those presented on the control arm. Surprisingly, the findings did not uphold the hypothesis, questioning whether the increase in the middle latency component represents an indirect reflection of perceptual biases towards the sensitized arm.

4.3. Secondary mechanical hypersensitivity is reduced when a high load working memory task is performed concomitantly with the sensitization procedure

The main finding of the present study is that the amount of mechanical hypersensitivity that develops after LFS is modulated by the concomitant execution of a difficult cognitive task. In more detail, our data indicate that cognitive shielding against intense/prolonged stimuli inducing hypersensitivity is effective in some individuals. Previous studies have suggested that some individuals are better at remaining engaged in a task (attention types, A-types) while painful stimuli are presented, whereas others are more easily distracted by the pain (pain type, P-types).[6,20] An interesting possibility is that similar features play a role in the development of hypersensitivity as well. Of note, the present

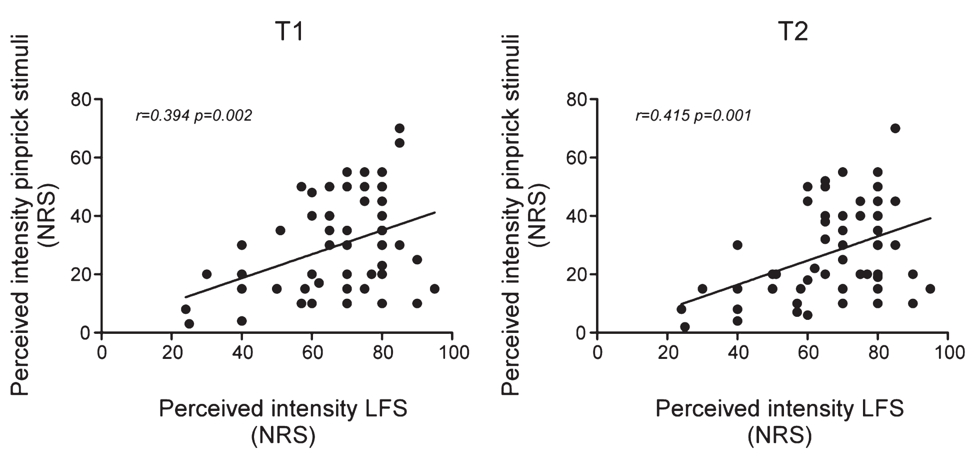

Figure 8. At both T1 and T2, the amount of hypersensitivity was associated with the perceived intensity of LFS during sensitization, rather than with the actual LFS intensity that was used. The correlations are calculated on the data of the 3 pooled experiments. LFS, low-frequency stimulation.

cognitive task was not individually tailored for difficulty; future studies may investigate whether cognition has a limited modulatory effect, ie, only "A-type" individuals may benefit from cognitive shielding or whether the proper balance between the perceived pain intensity and the difficulty of the task may contribute to exert analgesic effects in every participant. Moreover, considering the fact that we did not use the same task with increasing levels of difficulties, but 2 different tasks that were rated as having 2 different levels of difficulty, we cannot be certain of the underlying mechanisms that led to the lack of significant interaction in the group performing the N-back task. One possibility is that the N-back task had a higher cognitive load, and hence required more attention to be successfully performed. In line with this view, previous evidence showed that the execution of a high load working memory N-back task (the same we used) interferes more strongly with BOLD responses at the spinal level after the administration of a nociceptive heat laser stimulus,[21] as compared to a low-load version of the same task. An alternative possibility to explain our results is that working memory, but not response inhibition capacities, interferes with the development of mechanical hyperalgesia. Finally, it may be that not only an N-back task, but other difficult tasks as well, become arousing enough to impart "hypoalgesic" effects. Therefore, future studies are required to systematically examine the task specificity of cognitive load induction procedures.

Two caveats should also be put forward. First, due to the necessity to first validate the LFS procedure, the 3 experiments were conducted one after the other in 3 groups (between design), leading to our methodological choice of analyzing them separately. Second, our analysis of interest was the identification of a *Time* × *Side* interaction in the perception of mechanical stimuli, and this interaction did not reach the statistical significance in the third experiment. Nevertheless (see supplementary material, available at http://links.lww.com/PAIN/A968), a main effect of time was observed, driven by significant differences between the 2 arms at T1 and T2. This result indicates that hyperalgesia still developed in some individuals. Moreover, due to the methodological choice of analyzing the 3 experiments separately, we refrain from making direct comparisons across them. In this sense, we cannot conclude that more hyperalgesia developed in experiment 1 than in experiment 3. Nonetheless, we report all the individual results, and the likelihood of the H0 hypothesis in the 3 experiments using Bayesian statistics. These results support the possibility that the lack of significant interaction in experiment 3 is not merely due to lack of power. Replication studies using a randomized design are needed to further validate the present results.

4.4. Modulating hypersensitivity: different strategies, different mechanisms?

Two previous studies using repeated administration of heat painful stimuli to induce hypersensitivity/ hyperalgesia showed that placebo manipulations[14] as well as short sessions of repeated cognitive behavioral therapy over 8 days[17] were effective in reducing the amount of hyperalgesia. These results indicate that expectations play a major role in the development of hyperalgesia, as shown by a report by van den Broeke et al.[31] In this latter study, the authors demonstrated that a mere verbal suggestion was able, in a nocebo group vs a control group, to increase the perceived intensity of mechanical stimuli after HFS. The previous literature also indicated that reappraising the meaning of the pain experience, associating it with positive instead of negative thoughts, reduced unpleasantness ratings to painful stimuli and the extent of secondary hyperalgesia across sessions.[17] These latter effects were correlated with a reduction in pain catastrophizing.[17] Whether expectations, reappraisal, cognitive load, difficult of the task, cognitive abilities recruited by task, and/or arousal interfere with the development of hypersensitivity through the same or different mechanisms remains currently an open question. However, one important methodological difference is that both studies[14,17] included several sessions across days. By contrast, our study is the first one reporting that, at a group level, sensitivity to mechanical stimuli may not increase significantly when a difficult working memory task is performed during sensitization, suggesting that at least part of the development of hypersensitivity/hyperalgesia is modulated by mechanisms involved in the execution of a difficult N-back task.

To conclude, LFS can be used as an alternative method to induce hypersensitivity to mechanical stimuli, and the concomitant execution of a high load and difficult working memory N-back task can modulate such effects in certain individuals.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A968.

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