The Effect of High Versus Low Cognitive Load on the Development of Nociceptive Hypersensitivity: The Roles of Sympathetic Arousal, Sex, and Pain-Related Fear

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Previous research has mainly focused on cognitive load effects on the perception of acute painful stimuli. Yet this study extends our understanding by investigating cognitive load effects on the development of long-lasting secondary hypersensitivity, a common aspect in numerous persistent pain conditions. We test the long-lasting effects of cognitive load by presenting cognitive tasks during a painful procedure that induces secondary hypersensitivity. Additionally, we used psychophysiological measurements to explore potential underlying mechanisms involving limited attentional resources and sympathetic arousal.

Abstract

Background: According to limited-capacity theories of attention, less attentional resources remain available when engaging in a high versus a low demanding cognitive task. This may reduce the perceived intensity and the evoked cortical responses of concomitant nociceptive stimuli. Whether and how the competition for limited attentional resources between a cognitive task and pain impacts the development of long-lasting hypersensitivity is unclear.

Methods: Eighty-four healthy participants were randomized into a low or high cognitive load group. Low Frequency electrical Stimulation (LFS) of the skin was used to induce secondary hypersensitivity. We hypothesized that performing the high load task during LFS would reduce the development of hypersensitivity. We examined whether painfulness, non-pain-related sympathetic arousal, or sex related to hypersensitivity, by assessing intensity and unpleasantness of mechanical pinprick stimulation. During task execution, we recorded steady-state evoked potentials evoked by LFS, and skin conductance level for sympathetic arousal. Afterwards, participants reported task difficulty and LFS-related fear. For the primary outcomes, we used mixed ANOVAs.

Results: The results confirmed the difference in cognitive load. Although LFS successfully induced hypersensitivity, the high load task did not reduce its development. Next, the steady-state evoked potentials did not differ between groups. Hypersensitivity correlated positively with pain-related fear and negatively with skin conductance level before LFS, despite the lack of group differences in skin conductance level. We did not find any sex differences in hypersensitivity.

Conclusions: These results do not confirm that high cognitive load or sex modulate hypersensitivity, but show associations with pain-related fear and non-pain-related sympathetic arousal.

1. Introduction

Research has shown that performing a cognitive task during acute nociceptive stimulation attenuates pain perception (Petrovic et al., 2000; Romero et al., 2013; Valet et al., 2004; Verhoeven et al., 2011). Indeed, cognitive load (Bantick et al., 2002; Deldar et al., 2021; Legrain et al., 2005; Moore et al., 2017; Seminowicz et al., 2007; Veldhuijzen et al., 2006; Wagenaar-Tison et al., 2021; Wiech et al., 2005) and working memory (Buhle & Wager, 2010; Deldar et al., 2018; 2019; Do et al., 2020; Legrain et al., 2011a; 2011b; 2013) may contribute to pain reduction, by shielding attention from the nociceptive input. This would be in line with limited-capacity theories of attention (Broadbent, 1958; Kahneman, 1975; Lavie et al., 2004; Norman & Bobrow, 1975): The more attentional resources performing a cognitive task requires, the less resources remain available to process concomitant nociceptive stimuli.

Our knowledge about whether, how, and which cognitive factors affect the development of secondary hyperalgesia (Kóbor et al., 2009; Matre et al., 2006; Torta et al., 2020; Wiech et al., 2005) is limited. Furthermore, the contribution of autonomic arousal and sex remain unclear.

Secondary hyperalgesia[1] is considered as an indirect measure of central sensitization (Ali et al., 1996, Baumann et al., 1991; Klein et al., 2004; LaMotte et al., 1991; Raja et al., 1984; Simone et al., 1991; Woolf, 2011), contributing to persistent pain (Arendt-Nielsen et al., 2018; Woolf et al., 2011) (however see Cayrol et al., 2020; van den Broeke, 2018; van den Broeke et al., 2019 for a debate regarding the use of the term *central sensitization*), and can be experimentally induced using Low Frequency electrical Stimulation (LFS) of the skin (Torta et al., 2020). Torta et al. (2020) showed that performing a high cognitive load task during LFS results in less hypersensitivity, whereas this was not the case for a low cognitive load task. The robustness of this cognitive modulation, the conditions in which it appears, and the underlying mechanisms remain to be confirmed and elucidated. Here, we compared the role of high versus low load.

As more demanding cognitive tasks usually require greater effort, autonomic arousal increases with cognitive load, (Kahneman, 1975; Mandrick et al., 2016; Mehler et al., 2012; Nourbakhsh et al., 2012). Houzé et al. (2021) showed that a distraction task that increased autonomic responses resulted in pain reduction.

[1] As a note, since technically *hyperalgesia* refers only to the increased sensitivity to nociceptive stimuli that are perceived as painful at baseline, we will use the term *hypersensitivity* to refer to nociceptive stimuli that are not perceived as painful at baseline (for a discussion see van den Broeke et al., 2016).

Therefore, it can be hypothesized that higher non-pain-related arousal during cognitive tasks also results in less hypersensitivity.

Finally, relatively little is known about how sex relates to hypersensitivity. The literature shows mixed findings, with Rolke et al. (2006) indicating that females show lower pain thresholds before sensitization and enhanced hypersensitivity after sensitization than males, whereas another study could not confirm this (Jensen & Petersen, 2006). Torta et al. (2020) did not find evidence for a role of sex in the cognitive modulation of hypersensitivity, but their sample size was limited, and results await replication.

In this study, healthy volunteers were randomized into two groups, stratified by sex, to examine whether performing a high load task, versus a low load task, during LFS 1) attenuated the development of mechanical hypersensitivity, 2) reduced the attentional capture by LFS, reflected by the power of the steady-state evoked potentials, 3) increased sympathetic arousal. Next, we investigated 4) the contribution of the contribution of sympathetic arousal to the development of hypersensitivity, and 5) sex differences in the cognitive modulation of hypersensitivity. We hypothesized that 1) LFS would induce less hypersensitivity in the high versus the low load group, 2) LFS would capture less attention, indirectly estimated by the power of the steady-state evoked potentials, in the high versus the low load group, 3) sympathetic arousal, reflected by skin conductance level, would be higher in the low versus the high load group, 4) greater sympathetic arousal, reflected by skin conductance level, would predict less hypersensitivity, and 5) females would show more hypersensitivity than males.

2. Methods

2.1 Participants

Eighty-four healthy participants between 18 and 40 years (42 males and 42 females[2]; M_{age} = 23.33, SD_{age} = 4.62 years) were recruited at KU Leuven via the Experiment Management System, social media, printed advertisements, and word-of-mouth. The preregistered sample size was calculated a priori using G*Power (version 3.1; Faul et al., 2009) (2 x 2 x 2 mixed ANOVA for perceived intensity and unpleasantness of mechanical pinpricks as primary outcomes, using as within factors *time* [T0, T1] and *side* [control arm,

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[2] As a note, all participants reported to be cisgender, i.e. their gender identity corresponded with their birth sex.

stimulated arm], and as between factor *group* [low load group, high load group], η^2_p = .09, α error probability = .05, power = .8). To minimize the effects of confounding variables, we documented participants' age, sex, and for female participants also the current phase of their menstrual cycle as well as the use of hormonal contraception, and the room temperature. Participants were asked not to use caffeine up to four hours before the experiment and regular medication or drug use as well as sleep deprivation were part of our exclusion criteria. Participants received either a monetary compensation of eight euros or one research participation credit per hour. The informed consent form was signed before the start of the study. Exclusion criteria were: having already participated in a study using the n-back task, analgesic medication intake up to 12 hours before the experiment, caffeine intake up to four hours before the experiment, heart and vascular diseases, respiratory diseases, neurological diseases, acute or chronic pain, pacemaker or other electronical implants, hearing or eye problems, psychiatric diseases, regular medication use (except contraception), pregnancy, regular drug use, and sleep deprivation. The study was approved by the Social and Societal Ethics Committee of KU Leuven (SMEC registration numbers: G2016 11 669, G-2022-5147).

2.2 Low Frequency Electrical Stimulation (LFS) of the Skin

LFS of the skin was used to induce secondary hypersensitivity to mechanical pinpricks (as in Torta et al., 2020). LFS comprised a single train of 240 stimuli, 2 ms pulse width, delivered at 2 Hz frequency for a total of two minutes. LFS was administered through a specific electrode (Torta et al., 2017; 2018; 2020; van den Broeke et al., 2010; 2012; van den Broeke & Mouraux, 2014) consisting of 16 blunt stainless steel pins with a diameter of 0.2 mm protruding 1 mm from the base, generated by a constant current electrical stimulator (DS5, Digitimer, Welwyn Garden City, England). As the task was executed with the dominant hand (see paragraph on the working memory tasks), the electrode was placed on the non-dominant forearm to prevent any interference to LFS due to task-related movements (i.e. mouse clicking). The stimulus intensity was individually calibrated at 15 times the detection threshold to a single pulse, established by a staircase procedure as used in Torta et al. (2020). LFS at such an intensity is generally perceived as painful (Torta et al., 2020). More specifically, single electro-cutaneous stimuli were presented one by one (starting at 0.1 mA) in an ascending manner (by 0.1 mA) until a stimulus was detected. Then, the stimuli were presented in a descending manner (by 0.5 mA) until a stimulus was no longer perceived, after which the intensity increased again (by 0.25 mA). The threshold was established after three reversals. LFS was preferred over other methods to induce hypersensitivity as we aimed to compare our results with those by Torta et al. (2020). Torta et al. (2020) confirmed that LFS effectively induced hypersensitivity. Moreover, LFS could be administered continuously for two minutes, in contrast to high frequency electrical stimulation which seems too painful to tolerate for the total task duration. This allowed us to present a task during the electrical stimulation. In vitro studies (Ikeda et al., 2006) have also shown that LFS at 2 Hz for 2 minutes is effective in increasing post-synaptic potentials in the spino-PAG pathway.

2.3 Mechanical Pinpricks

Hypersensitivity to mechanical pinpricks was tested using a 128 mN pinprick stimulator (MRC Systems, Mannheim, Germany), with a flat cylindrical tip of 250 µm within an area of 4 cm^2. Three stimuli were applied approximately 1.5-2 cm around the stimulated area (Torta et al., 2017; 2018; 2020; van den Broeke et al., 2010; 2012; 2014) and on the homologous location on the control arm at two timepoints, i.e. before LFS (T0) and 20 minutes after LFS (T1). The order of the stimulated arm (LFS arm or control arm) was counterbalanced across participants. Participants were asked to look away from the arm stimulated during the pinprick procedure. Participants rated the perceived intensity of mechanical pinpricks on a VAS ranging from *not at all* (0) to *extremely* (100), with 50 referring to the pain threshold. They also rated the perceived unpleasantness of the mechanical pinpricks on a VAS ranging from *not at all* (0) to *extremely* (100). The average perceived intensity and unpleasantness of the three mechanical pinpricks per arm was calculated and used to analyze the development of secondary hypersensitivity. At T1, the vertical length of increased sensitivity to mechanical pinpricks was measured on the stimulated arm: Pinpricks were applied from the wrist and cubital fossa towards the center of the stimulated area in steps of 1 cm, at a pace of 1-s stimulation and 1-s interval, until the participant reported to perceive an increase in pinprick sensitivity (see FigureS1). The distance between the two points of increased sensitivity to mechanical pinpricks served as a measure of the area of hypersensitivity.

2.4 Working Memory Tasks

The tasks were programmed in the Affect software (Clarysse, 2019). Participants were stratified by sex and randomly assigned to a high load group and a low load group using the randomization function in Excel. Participants of the high load group performed a 2-back task, which is a modified version of the n-back task

(Sprenger et al., 2012; Torta et al., 2020) whereas those assigned to the low load group performed a 0-back task (Jonides et al., 1997) (Fig. 1). We opted for a 0-back task instead of a 1-back task to keep the load to a minimum. Moreover, we opted not to include a control condition in which no task was performed during LFS, as our aim was to investigate the effect of *high cognitive load,* rather than a task itself, on the development of hypersensitivity. For the 2-back task, 13 series of 15 letters (A-E) appeared on the screen, each visible for 750 ms and followed by 750 ms of a blank screen. After each series of letters, participants were instructed to report the number of matches they detected between the actual letter and the one presented two letters before. Participants only received feedback on their performance during the practice phase, which consisted of five strings. Similar to the high load group, the low load group received the same 13 series of 15 letters on the screen, each visible for 750 ms and followed by 750 ms of a blank screen during LFS. In this case, participants were instructed to report how many times they detected the letter *E*. Again, participants only received feedback on their performance during the practice phase, which consisted of five strings. The tasks were presented for a total of six minutes, two minutes before LFS (pre-LFS phase), two minutes during LFS (during-LFS phase), and two minutes after LFS (post-LFS phase). Each phase consisted of approximately 4 series of 15 letters.

Fig. 1

2.5 Skin Conductance Recording and Analysis

Electrodermal activity was recorded at a sampling rate of 1 kHz as a measure of sympathetic arousal. Two disposable 8 mm Ag/AgCl electrodes (Biopac Systems Inc, Goleta, CA, US), attached on the non-dominant palm, were connected to an isolated skin conductance coupler (Coulbourn Instruments, Lehigh Valley, PA, US), after which the signal was digitized by a 16-bit AD-converter (National Instruments, Austin, TX, US). The skin conductance recording started approximately 10 minutes after attaching the electrodes, while the researcher remained in the control room during the recording. We recorded the skin conductance level before (pre-LFS phase), during (during-LFS phase), and after (post-LFS phase) LFS, throughout the six minutes of the task execution. The skin conductance signal was analyzed offline using PsPM (Bach, 2020) with a 5 Hz low pass Butterworth filter to eliminate high-frequency noise. The filtered signal was then segmented into three epochs based on the phase: pre-LFS phase, during-LFS phase, and post-LFS phase. The average skin conductance levels served as indications of sympathetic arousal per phase. As the electrocutaneous stimuli were presented every

500 ms and skin conductance responses have a relatively long latency (1-5 s; Boucsein, 2012), we opted for skin conductance level.

2.6 EEG Recording and Analysis

Continuous EEG signals during LFS were recorded at a 1 kHz-sampling rate using a high density EEG system with 129 sensors (EGI, Eugene, OR, US). Since we used continuous electrical stimulation at 2 Hz, we expected the appearance of steady-state evoked potentials at 2 Hz and harmonics (Colon et al., 2012; Mouraux et al., 2011; Regan, 1966; Verhoeven et al., 2010). We tested whether the power of steady-state evoked potentials was reduced during the high load condition, indicating reduced bottom-up attentional capture by LFS (Kastner et al., 2015; Wieser & Keil, 2011; Wieser et al., 2016).

Letswave (Nocions, Leuven, Belgium) was used to process the EEG data. For the analysis, the continuous recording was offline re-referenced to the average of all channels and filtered with a first notch filter (49-51 Hz) and a second bandpass filter (0.3-30 Hz). Independent component analysis (Jung et al., 2000) was performed to remove artifacts. The signal was segmented into a 120 s epoch, based on markers at the start and at the end of LFS, i.e. the during-LFS phase. A fast Fourier transformation was applied to convert the signal to the frequency domain. Finally, the central electrodes of interest (E6, E7, E13, E30, E31, E37, E54, E55, E79, E80, E87, E106, and E129) were pooled together and the average signal was extracted for each individual.

2.7 Procedure

Participants were invited to the Health Psychology lab of KU Leuven. Before the start of the experiment, the EEG net was mounted and the skin conductance electrodes were attached. The experiment started with the measurement of the baseline sensitivity to mechanical pinpricks at T0. Once the LFS electrode was placed on the non-dominant forearm, the calibration procedure followed. Subsequently, participants in both groups engaged in the 0-back task or in the 2-back task depending on the group (Fig. 2). Participants rated its difficulty (“How difficult did you find the task?”), perceived painfulness of LFS (“How painful did you find the electrical stimulation?”), and fear of LFS (“How fearful were you of the electrical stimulation?”) on a VAS ranging from *not at all* (0) to *extremely* (100). These questions were presented at the end of the task as participants were instructed to remain engaged in the task during LFS. In addition, participants answered a question regarding the locus of their attention (“Did you focus your attention primarily on the electrical stimulation or on the task?"). Before the second application of the mechanical pinpricks (T1), a 20-minute break was scheduled during which participants were free to do whatever they preferred, but they were asked to remain seated. Finally, participants were debriefed and compensated for their participation. The experiment lasted approximately 1.5 hours.

Fig. 2

2.8 Data Analysis

Statistical analyses were conducted using IBM SPSS Statistics (version 27) and additional Bayesian analyses were performed in JASP (version 0.16.4). All statistical tests were considered significant at $p < .05$. When normality or homoscedasticity assumptions were violated, Mann-Whitney *U*-tests (with *Mdn* and effect size *r*) were used instead of independent samples *t*-tests (with *M, SD,* and effect size Cohen's *d*) for comparing groups or sexes, a Wilcoxon signed-rank *T*-test (with *Mdn* and effect size *r*) was used to compare skin conductance level between the three phases, and two-tailed Spearman's *r* correlations (with a 95% confidence interval (CI)) were performed instead of Pearson's *r* correlations (with a 95% CI). Spearman's *r* correlations were also used instead of linear regressions in case the assumptions were violated. A Greenhouse-Geisser correction was applied when the sphericity assumption was violated. Values were identified as outliers based on the interquartile rule, which states that values below or above the interquartile range multiplied by 1.5 are outliers. Outliers are included in the reported results unless the results significantly changed due to exclusion of outliers, in which case both results are reported.

2.8.1 Manipulation Checks

As manipulation checks, we performed 1) an independent samples *t*-test comparing the perceived task difficulty, and 2) a mixed ANOVA with within factor *phase* (pre-LFS phase, during-LFS phase, post-LFS phase) and between factor *group* (low load group, high load group) comparing the response accuracy between and within groups. Follow-up Wilcoxon signed-rank *T*-tests were carried out to compare the response accuracy between the three phases within groups.

2.8.2 Primary Outcomes: Pre-Registered Analyses

The development of secondary hypersensitivity was compared between groups using two separate 2 x 2 x 2 mixed ANOVAs for perceived intensity and unpleasantness of mechanical pinpricks, with within factors *time* (T0, T1) and *side* (control arm, stimulated arm) and between factor *group* (low load group, high load group). Mann-Whitney *U*-tests were performed to compare the area of increased sensitivity to mechanical pinpricks as well as the power of steady-state evoked potentials between the two groups.

To compare the skin conductance level between the two groups, we opted for a 3 x 2 mixed ANOVA with within factor *phase* (pre-LFS phase, during-LFS phase, post-LFS phase) and between factor *group* (low load group, high load group) with the purpose of analyzing the evolution of skin conductance level across the phases as well as comparing the two groups. In case of significant effects we carried out follow-up Wilcoxon signed-rank *T*-tests. We also investigated whether skin conductance level per phase predict the *absolute* increase in perceived intensity and unpleasantness of mechanical pinpricks using Spearman's *r* correlations. These *absolute* values were obtained by subtracting the difference between the perceived intensity and unpleasantness of mechanical pinpricks on the stimulated arm and the control arm at T0 from the difference between the perceived intensity and unpleasantness of mechanical pinpricks on the stimulated arm and the control arm at T1 (absolute intensity = stimulated arm (intensity T1 – intensity T0) - control arm (intensity T1 – intensity T0; absolute unpleasantness = stimulated arm (unpleasantness T1 – unpleasantness T0) - control arm (unpleasantness T1 – unpleasantness T0).

We conducted 2 x 2 x 2 mixed ANOVAs to examine sex differences in the cognitive modulation of secondary hypersensitivity with within factors *time* (T0, T1) and *side* (control arm, stimulated arm) and between factor *sex* (males, females). Sex differences in the area of increase sensitivity to mechanical pinpricks were analyzed using a Mann-Whitney *U*-test. Although we did not measure individual forearm surface areas, we adjusted the analysis to account for sex differences in forearm size (Jensen & Petersen, 2006): We multiplied the measured areas in female participants by the indexed standard gender conversion-factor of 1310/1035 (with 1310 referring to the male and 1035 referring to the female mean standard forearm size in cm^2; Crawford et al., 2004).

2.8.3 Exploratory Analyses

Spearman's *r* correlations were performed between the power of steady-state evoked potentials and the absolute increase in perceived intensity and unpleasantness of mechanical pinpricks, and between the power of steady-state evoked potentials and the perceived painfulness of LFS.

Differences in the perceived painfulness and fear of LFS were assess using independent-samples *t*-tests, whereas a χ^2-test was used to assess differences in the locus of attention. Spearman's *r* correlations were used to investigate the relationship between the perceived painfulness and fear of LFS and to examine the relationship between the perceived painfulness and fear of LFS and the absolute increase in perceived intensity and unpleasantness of mechanical pinpricks.

2.8.4 Bayesian Statistics

We estimated Bayes factors (BF_{01}) using Bayesian information Criteria (Wagenmakers, 2007), i.e. a larger BF_{01} indicates more evidence in support of the null hypothesis. The Bayes factors were estimated for the two separate 2 x 2 x 2 mixed ANOVAs for the perceived intensity and unpleasantness of mechanical pinpricks, with within factors *time* (T0, T1) and *side* (control arm, stimulated arm) and between factor *group* (low load group, high load group), which compares the fit of the data under the null hypothesis (H_0 = *time* + *side* + *time* * *side*) and the alternative hypothesis (H_1 = *time* + *side* + *time* * *side* + *time* * *group* + *side* * *group* + *time* * *side* * *group*).

3. Results

3. 1 Final Sample

The data of three participants were excluded due to violation of exclusion criteria (two participants had scars on the volar forearm) or drop-out (one participant stopped the experiment because the stimulation felt too painful to endure), leading to a final sample of 81 participants (low load group: 20 males and 18 females; high load group: 21 males and 22 females) for the behavioral analyses. One non-responder participant was excluded from the skin conductance analysis. The EEG data of eight participants were not recorded and that of nine participants were excluded for technical problems related to markers, resulting in a total sample of 64 participants for psychophysiological and correlational analyses (low load group: 28 participants; high load group: 36 participants).

3.2 Manipulation Checks

The high load group (*M* = 62.95, *SD* = 19.94) rated the task difficulty significantly higher than the low load group (*M* = 27.79, *SD* = 19.16), $t(78) = -8.03$, $p < .001$, $d = -1.80$ (FigureS2).

We found a significant *group* effect on the response accuracy, with the high load group scoring significantly worse than the low load group (low load group: (*M* = 92.51% correct responses, *SD* = 12.45; high load group: 34.17% correct responses, *SD* = 19.45). There was also a significant *group* x *phase* interaction effect (Table 1, Fig. 3). Whereas the response accuracy did not differ significantly between the three phases within the high load group, within the low load group, the task performance improved from the pre-LFS phase to the during-LFS phase and decreased again to the post-LFS phase, while there was no significant difference between the pre-LFS phase and the post-LFS phase (TableS1).

Fig. 3

3.3 Detection Threshold and LFS Intensity

Mann-Whitney *U*-tests showed that the detection threshold to a single electro-cutaneous stimulus did not differ between the two groups (low load group: *Mdn* = 0.24 mA; high load group: *Mdn* = 0.24 mA; $U = 752$, $p = .54$, $r = 0.07$). Consequently, the actual intensity of LFS did not significantly differ between the two groups (low load group: *Mdn* = 3.53 mA; high load group: *Mdn* = 3.60 mA; $U = 756$, $p = .56$, $r = .06$).

3.4 Mechanical Pinprick Sensitivity

We found a significant *time* x *side* interaction effect for perceived intensity (Table 2) and unpleasantness (Table 3) of mechanical pinpricks, demonstrating that LFS effectively induced secondary hypersensitivity. Fig. 4 illustrates the non-significant *time* x *side* x *group* interaction effect for perceived intensity and unpleasantness. Similarly, we did not find a *group* effect on the area of increased sensitivity to mechanical pinpricks (low load group: *Mdn* = 10 cm; high load group: *Mdn* = 9.5 cm; $U = 844.5$, $p = .79$, $r = .03$; Fig. 5). There was no significant influence of the participants age, phase of menstrual cycle, and use of hormonal contraception on the results.

Fig. 4

Fig. 5

3.5 Steady-State Evoked Potentials

LFS successfully induced a peak of the signal at 2 Hz (Fig. 6). However, the power of steady-state evoked potentials did not significantly differ between the two groups (low load group: *Mdn* = 0.19 μV^2; high load group: *Mdn* = 0.17 μV^2; $U = 436.00$, $p = .36$, $r = -0.12$).

Fig. 6

3.6 Skin Conductance Level

Although skin conductance level did not differ between the two groups, skin conductance level increased significantly from the pre-LFS phase (*Mdn* = 17.65 µS) to the during-LFS phase (*Mdn* = 21.20 µS), $T = 3112$, $p < .001$, $r = .81$, and significantly decreased from the during-LFS phase to the post-LFS phase (*Mdn* = 19.37 µS), $T = 3106$, $p < .001$, $r = .83$ (Fig. 7, TableS2). Interestingly, skin conductance level significantly differed between the pre-LFS phase and the post-LFS phase as well, $T = 2134$, $p = .01$, $r = .28$. However, we did not find a significant *phase* x *group* interaction effect. We also found a significant negative association between the skin conductance level in the pre-LFS phase and the absolute increase in perceived intensity over the two groups, $r = -.23$, $p = .04$, 95% CI [-.43; .00] (Fig. 8, TableS3). The participants age, sex, phase of menstrual cycle, use of hormonal contraception, and room temperature did not impact the results.

Fig. 7

Fig. 8

3.7 The Role of Sex

Males (*Mdn* = 0.30 mA) showed significantly higher detection thresholds than females (*Mdn* = 0.22 mA), $U = 1082.5$, $p = .01$, $r = .28$, resulting in higher intensities of LFS for males (*Mdn* = 4.5 mA) than for females (*Mdn* = 3.23), $U = 1087$, $p = .01$, $r = .28$. The results of the 2 x 2 x 2 mixed ANOVAs, with and without outliers, are presented in Tables 4-5 and TableS4-S5. The results indicate a significant *time* x *side* x *sex* interaction effect for perceived intensity (if outliers were excluded) and for perceived unpleasantness (with and without outliers)

(Fig. 9). However, when the detection threshold was included as a covariate the *time* x *side* x *sex* interaction no longer reached statistical significance for either the perceived intensity, $F(1,79) = 1.83$, $p = .18$, $\eta^2_p = .02$, or the perceived unpleasantness, $F(1,79) = 3.40$, $p = .07$, $\eta^2_p = .04$. The area of increased sensitivity to mechanical pinpricks, adjusted for sex difference in forearm surface areas, did not differ significantly between males (*Mdn* = 12 cm) and females (*Mdn* = 8.5 cm), $U = 827.5$, $p = .94$, $r = .01$. Again, the participants age, sex, phase of menstrual cycle, and use of hormonal contraception did not impact the results.

Fig. 9

3.8 Post-Task Ratings

There was no significant group difference in fear of LFS (low load group: $M = 42.97$, $SD = 25.73$; high load group: $M = 41.36$, $SD = 26.27$; $t(78) = 0.28$, $p = .39$, $d = .06$), perceived painfulness of LFS (low load group: $M = 56.11$; $SD = 16.52$; high load group: $M = 53.26$, $SD = 21.74$; $t(79) = 0.66$, $p = .26$, $d = .15$; *range* = 8-88), or locus of attention (mostly on the cognitive task instead of LFS), $\chi^2(1) = 0.001$, $p = .97$, $V = .00$.

To explore whether the perception of pain during LFS is crucial for the development of hypersensitivity, we repeated the 2 x 2 x 2 mixed ANOVAs for perceived intensity and unpleasantness of mechanical pinpricks, with within factors *time* (T0, T1) and *side* (control arm, stimulated arm) and between factor *group* (low load group, high load group) for the participants that rated the painfulness of LFS under versus above the pain threshold. The results showed that participants who perceived LFS as painful, but also participants who perceived LFS as non-painful, showed a significant *time x side* interaction effect on the perceived intensity (TableS10). However, the *time x side* interaction effect on the perceived unpleasantness was non-significant only for participants who did not perceive LFS as painful (TableS11).

3.9 Exploratory Correlations

We found a significant low positive correlation between fear of LFS and the absolute increase in perceived intensity, $r = .27$, $p = .02$, CI 95% [.04, .47], and unpleasantness of mechanical pinpricks, $r = .36$, $p = .001$, CI 95% [.15, .55]. The perceived painfulness of LFS showed a significant low positive correlation with the absolute increase in perceived intensity, $r = .27$, $p = .02$, CI 95% [.05, .47], but not unpleasantness, $r = .20$, $p = .07$, CI 95% [-.03, .41]. These correlations are illustrated by Fig. 10. Fear of LFS was positively correlated with the perceived painfulness of LFS, $r = .69$, $p < .001$, CI 95% [.54,.79].

The power of steady-state evoked potentials did not correlate significantly with the absolute perceived intensity, $r = -.12$, $p = .37$, CI 95% [-.37, .15], or unpleasantness of mechanical pinpricks, $r = .01$, $p = .91$, CI 95% [-.25; .27]. However, there was a significant positive correlation between the power of steady-state evoked potentials and the perceived painfulness of LFS when outliers were excluded, $r = .28$, $p = .03$, CI 95% [.02, .50].

Fig. 10

3.10 Bayesian Statistics

The estimated Bayes factors were between 20 and 150 (TableS13), reflecting strong evidence in favor of the null hypothesis for the perceived intensity and unpleasantness of mechanical pinprick stimuli (Raftery, 1995). For the perceived intensity, the data is 41.71 times more likely to occur under a model excluding the main and interaction effects of *group.* For the perceived unpleasantness, the data is 97.96 times more likely to occur under a model excluding the main and interaction effects of *group*.

4. Discussion

In the present study, we used LFS to examine whether engaging in a high load, in comparison with a low load, cognitive task attenuates the development of secondary hypersensitivity to mechanical pinpricks. In addition, we explored the roles of sympathetic arousal and sex. Our results show that cognitive load did not significantly impact 1) the development of hypersensitivity, 2) the attentional capture by LFS, or 3) sympathetic arousal, reflected by the lack of significant group differences. However, we found that 4) greater non-pain-related sympathetic arousal predicted less hypersensitivity. Finally, 5) sex differences in the cognitive modulation of hypersensitivity are partly related to the stimulation intensity.

4.1 The Effect of a High versus Low Load on the Development of Secondary Hypersensitivity

As we were interested in the effect of high versus low cognitive load on the development of hypersensitivity, we decided to include only two groups and not an additional control group in which participants did not perform a task. Group differences in task difficulty ratings and task performances indicated that the two tasks differed in cognitive load level. Nonetheless, we did not observe a significant difference in the development of hypersensitivity.

The only other available study on the topic (Torta et al., 2020) found that a high load working memory task prevented the development of hypersensitivity at the group level. Our results do not corroborate these findings, but we also used different methodology. In contrast to the study of Torta et al. (2020), we randomized participants into two groups being therefore able to directly compare them while preventing any selection bias or accidental bias. Moreover, we included two tasks tapping on working memory, as such investigating the cognitive load more selectively: Perhaps the mere involvement of working memory is more important than cognitive load in the modulation of hypersensitivity. Our findings provide no evidence that high load reduces the development of hypersensitivity more than low load. Also, we speculate that perhaps task-related motivation plays a role in modulating hypersensitivity.

4.2 The Effect of a High versus Low Load on the Perceived Painfulness of LFS

The perceived painfulness of LFS did not differ between groups. This appears to contradicts the results of Deldar et al. (2021), showing that a high load task reduces pain more than a low load task. Importantly however, we used a 2-minute painful stimulation to induce hypersensitivity and we obtained only one assessment of the painfulness of LFS at the end of the task, which was 2 minutes after the end of LFS. The availability of one rating only might have hampered the appearance of more subtle differences. Additionally, higher perceived painfulness of LFS predicted greater hypersensitivity on the intensity dimension. This finding follows the results of Torta et al. (2022), which indicate that the perceived intensity of the electrical stimulation relates to the development of hypersensitivity, pointing towards a role of top-down modulatory factors. Interestingly, participants who did not perceive LFS as painful also developed hypersensitivity (but only on the intensity dimension). Whether reducing the perceived painfulness of LFS is crucial to observe effects on hypersensitivity remains an open question.

4.3 Lack of Difference in Cortical Responses to Repeated Electrical Stimulation

In contrast to our expectations, we did not observe a group difference in the power of steady-state evoked potentials. This could be explained by several arguments, and does not necessarily indicate that our cognitive manipulation was fallacious. First, we did not find a significant difference in the perceived painfulness of LFS between the two groups. Perhaps the attentional capture by LFS did not differ between the two groups, which may explain the lack of group difference in the power of steady-state evoked potentials. Second, one might argue that the power of steady-state evoked potentials does not reflect the attentional modulation by cognitive load. At present, there is no direct evidence supporting that high intensity electrical steady-state evoked potentials can be modulated by cognitive load. In addition, Adam et al. (2020) did not find any attentional modulation of visual steady-state evoked potentials responses. Third, it is possible that the design is not optimal to disclose difference in the power of steady-state evoked potentials. We only had a 2-minute recording of steady-state evoked potentials during painful stimulation, in contrast with classical studies using several repetitions of the stimuli (Wagenaar-Tison et al., 2021). Moreover, to the best of our knowledge, all other studies combining EEG and nociceptive stimulation used a number of discrete nociceptive stimuli (e.g. Legrain et al., 2013), rather than a 2-minute sequence of electrical stimulation. Therefore, it is difficult to directly compare our findings with previous studies. Finally, the two groups may have been equally motivated, which could have led to similar attentional engagement in the tasks (Torta et al., 2017; Van Damme et al., 2010; Van Ryckeghem et al., 2018; Verhoeven et al., 2010), and a similar effect of bottom-up stimuli.

4.4 Sympathetic Arousal

As a rise in task demands relates to an increase in sympathetic arousal (Kahneman, 1975; Mandrick et al., 2016; Mehler et al., 2012; Nourbakhsh et al., 2012), we expected that sympathetic arousal would be higher during the execution of the high load task compared to the low load task. However, skin conductance level did not differ between the two groups across the three phases, despite difference in cognitive load. We propose several explanations. First, task-related motivation may more important than task difficulty to increase sympathetic arousal: Sympathetic arousal may have increased similarly in the two groups because the two groups were equally motivated, and thus engaged, to perform well on the tasks. Second, the involvement of working memory may have increased sympathetic arousal similarly in both groups, independently of the task difficulty. Third, as participants were anticipating the incoming painful stimulation, pain-related fear may have increased sympathetic arousal more than the cognitive load. Indeed, previous studies examining the effect of cognitive load on sympathetic arousal did not include concomitant nociceptive stimulation (Mandrick et al., 2016; Mehler et al., 2012; Nourbakhsh et al., 2012).

Interestingly, the analyses revealed a negative correlation between skin conductance level in the pre-LFS phase and hypersensitivity (for the perceived intensity ratings). This might suggest that higher sympathetic arousal is associated with less hypersensitivity. As the task was executed without administration of LFS in the pre-LFS phase, it appears that greater non-pain-related sympathetic arousal, predicts less hypersensitivity. This builds on previous evidence showing that autonomic arousal elicited by cognitive stimuli does not only attenuate the acute pain perception (Houzé et al., 2021), but also reduces the development of hypersensitivity.

4.5 Pain-Related Fear

Higher ratings of pain-related fear significantly predicted higher ratings of painfulness of LFS as well as greater hypersensitivity. These results extend previous findings of positive associations between pain-related fear and pain reports (for a meta-analysis and systematic review see Markfelder & Pauli, 2020). Thus, pain-related fear appears to affect not only acute pain perception, but also hypersensitivity.

4.6 Sex Differences

Although the pattern of hypersensitivity results seems to indicate that hypersensitivity after the task execution was higher for males than for females, the perceived painfulness of LFS did not differ. In addition, when the detection threshold (which determined the intensity of LFS) was taken into account, the development of hypersensitivity did no longer significantly differ. As males showed significant higher detection thresholds than females, which confirms previous findings (Rolke et al., 2006), the actual intensity of LFS was also higher for males than for females. This seem to indicate that the actual intensity of LFS contributed to the significant sex difference in hypersensitivity, highlighting the importance of the intensity of the input for the development of hypersensitivity. In other words, we did not find strong evidence for sex differences in our current cognitive modulation of hypersensitivity. These results add to the mixed evidence (Jensen & Petersen, 2006; Torta et al., 2020; Rolke et al., 2006) and highlight the need for more research investigating the role of sex in the development of hypersensitivity.

4.7 Strengths and Limitations

The present study is one of the first investigating the potential causal role of high cognitive load on the development of hypersensitivity using a mechanistic model. Moreover, we attempted a first psychophysiological investigation of the mechanisms underlying this effect. The study is however not free from limitations. As our aim was to compare the effects of high versus low cognitive load on the development of hypersensitivity on the basis of previous findings (Torta et al., 2020), we did not include a control condition in which participants did not execute a task during LFS. The lack of difference between the groups does not allow us to conclude whether high and low cognitive load have the same modulatory effect on hypersensitivity or whether they do not have any impact on hypersensitivity. Moreover, the introduction of a baseline recording of skin conductance level could have helped to calculate a relative increase in skin conductance level, possibly reducing the variability in the two samples.

4.8 Conclusions

The results of the present study do not support the hypothesis that different levels of cognitive load of a working memory task, performed during sustained pain, affect pain-induced hypersensitivity differently. Moreover, the study indicates that sex may not be critical in the cognitive modulation of hypersensitivity. However, non-pain-related sympathetic arousal as well as pain-related fear seem to contribute to the development of hypersensitivity.

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Author Contributions

The study was designed by EM and DMT and carried out by EM and AJP. EM, DMT, and AJP analyzed the data. EM and DM wrote the manuscript, while JWSV, ENVDB, AVL, and AJP provided critical feedback. All authors approved the final version of the manuscript.

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Figure Legends

Fig. 1. Working memory tasks. In each task 13 series of 15 letters (A-E) appeared on the screen, with an interstimulus interval (ISI) of 750 ms. After each series of letters, participants were instructed to report the number of *E*'s they detected in the 0-back task and the amount of matches between the actual letter and the one presented two letters before in the 2-back task. The tasks were presented for a total duration of 6 minutes.

Fig. 2. Experimental procedure. The task execution (0-back task or 2-back task depending on the group) included three phases: pre-LFS phase, during-LFS phase and post-LFS phase. Before (T0) and 20 minutes after LFS (T1), the sensitivity to mechanical pinprick stimuli was tested on both arms.

Fig. 3. Response accuracy in the low and high load groups throughout the three phases. The *phase* and *group* effects were significant, as well as the *phase* x *group* effect (*).

Fig. 4. Mechanical pinprick sensitivity in the low load group (a) and the high load group (b). The dashed lines illustrate the means, whereas the dotted lines illustrate the lower and upper quartiles.

Fig. 5. The area of increased sensitivity to mechanical pinprick stimuli in the low load group and in the high load group. The dashed lines illustrate the means, whereas the dotted lines illustrate the lower and upper quartiles.

Fig. 6. Steady-state evoked potentials (SSEPs) indicated by the power (μV^2) at 2 Hz of the grand averages of the low load group and the high load group. The grand average was calculated based on the central electrodes: E6, E7, E13, E30, E31, E37, E54, E55, E79, E80, E87, E106, and E129.

Fig. 7. Means and standard deviations of skin conductance level (µS) across the three phases in the low and high load groups. The *phase* effect was significant (*).

Fig. 8. Results of the correlation between skin conductance level (µS) in the pre-LFS phase over the two groups and the absolute increase in perceived intensity.

Fig. 9. Sex differences in the cognitive modulation of hypersensitivity for perceived intensity (a) and perceived unpleasantness (b) of mechanical pinprick stimuli on the stimulated arm. The dashed lines illustrate the means, whereas the dotted lines illustrate the lower and upper quartiles.

Fig. 10. Results of the correlations between fear of LFS versus. perceived painfulness of LFS, and the absolute increase in perceived intensity (a) and unpleasantness (b) of mechanical pinprick stimuli.

Table Legends

Table 1. Results of the mixed ANOVA (*phase* [pre-LFS, during-LFS, post-LFS] x *group* [low load group, high load group]) on the response accuracy. Results with $p < .05$ are shown in bold.

Table 2. Results of the mixed ANOVA (*time* [t0, t1] x *side* [control arm, stimulated arm] x *group* [low load group, high load group]) on the perceived intensity. Results with $p < .05$ are shown in bold.

Table 3. Results of the mixed ANOVA (*time* [t0, t1] x *side* [control arm, stimulated arm] x *group* [low load group, high load group]) on the perceived unpleasantness. Results with $p < .05$ are shown in bold.

Table 4. Results of the mixed ANOVA (*time* [t0, t1] x *side* [control arm, stimulated arm] x *sex* [males, females]) on the perceived intensity of mechanical pinprick stimuli. Outliers were included. Results with $p < .05$ are shown in bold.

Table 5. Results of the mixed ANOVA (*time* [t0, t1] x *side* [control arm, stimulated arm] x *sex* [males, females]) on the perceived unpleasantness of mechanical pinprick stimuli. Outliers were included. Results with $p < .05$ are shown in bold.