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Temporal summation of second pain is affected by cognitive load

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Abstract

This work attempted to clarify the interaction of cognition and pain sensitization during a paradigm of Temporal Summation of Second Pain (TSSP). We analyzed pain ratings and electroencephalographic (EEG) activity obtained from 21 healthy participants during the presentation of four experimental conditions that differed in the manipulation of attention to painful stimuli or working memory load (Attention to hand & TSSP; 0-back & TSSP (low cognitive load); 2-back & TSSP (high cognitive load); 2-back (without pain)). We found that the TSSP was reduced when the attention was diverted and the cognitive load increased, and this reduction was accompanied by higher midfrontal theta activity and lower posterior alpha and central beta activity. Although it is well established that TSSP is a phenomenon that occurs at the spinal level, here we show that it is also affected by supraspinal attentional mechanisms. Delivery of painful repeated stimuli did not affect the performance of the 2-back task but was associated with smaller amplitudes of attentional event-related potentials (ERPs) after standard stimuli (not the target). The study of brain activity during TSSP allowed to clarify the role of top-down attentional modulation in pain sensitization processes. Results contribute to a better understanding of cognitive dysfunction in pain conditions and reinforce the use of therapeutic strategies based on distracting attention away from pain.

KEYWORDS
attention, cognitive load, event-related potentials (ERPs), global field power (GFP), temporal summation of second pain (TSSP), working memory

1 | INTRODUCTION

Temporal Summation of Second Pain (TSSP) is an increase in perceived pain intensity that can be reliably evoked by repetitive painful heat pulses applied to the skin, at frequencies at or above 1/3 Hz (Staud et al., 2006) and is a perceptual correlate of the phenomenon of increased neuronal sensitivity or "wind up," which involves facilitation of neuronal responses in pain-related pathways at the level of the spinal dorsal horn (Staud et al., 2006; Usichenko et al., 2018). To understand this phenomenon, it is essential to distinguish between

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"first pain," which is characterized by rapid onset, sharp localization, and short duration (transmitted mostly by myelinated A-delta fibers), and "second pain," which exhibits a slower onset, diffuse localization, and prolonged duration even after the cessation of the noxious stimulus (transmitted mainly by non-myelinated C fibers) (Staud et al., 2007). The TSSP provides insights into the mechanisms of pain amplification at the spinal cord level and shows alterations in patients suffering from several chronic pain pathologies (Maixner et al., 1998; Staud et al., 2001, 2008; Thompson et al., 2020; van Campen et al., 2021; Woolf, 2011).

Pain perception is reduced when attention is shifted away from nociceptive stimuli (Buhle & Wager, 2010; Legrain et al., 2011; Nakae et al., 2013). This finding has been well supported by neuroimaging studies (Bingel et al., 2007; Schweinhardt & Bushnell, 2010) and some authors have suggested that attention may modulate pain through two inhibitory descending pathways (Schweinhardt & Bushnell, 2010). Furthermore, research in this domain indicates that engaging in tasks demanding cognitive resources, such as working memory tasks, while experiencing nociceptive stimulation, may raise pain perception thresholds (Buhle & Wager, 2010; Nakae et al., 2013; Sturgeon et al., 2015).

The relation between pain perception and attention also occurs in the opposite direction: Several studies support that the delivery of painful stimuli impairs performance in working memory tasks (Buhle & Wager, 2010; Hood et al., 2013; Moore et al., 2012), although this was not always observed (Etherton, 2014; Legrain et al., 2011; Sturgeon et al., 2015). This interaction can be explained by the overlap between brain networks involved in pain perception and other cognitive processes (Apkarian et al., 2005; Moriarty et al., 2011). This overlap, in turn, may explain the cognitive deficits frequently reported by patients with chronic pain (Moriarty et al., 2011).

The use of brain activity measures may provide a better understanding of the mechanisms involved in the interaction between pain and cognition. With a millisecond resolution, the EEG is sensitive to both perceived pain intensity and attention and working memory load manipulation. Event-related potentials (like N1 or P3) are good for assessing attentional and cognitive resources allocated to discrete stimulus presentation (Luck et al., 1990); also, the spectral power of three prominent EEG frequency bands, Theta (4–7 Hz), Alpha (8–13 Hz), and Beta (14–29 Hz), consistently shows modulation by both nociceptive input and cognitive load (Colon et al., 2017; Hu et al., 2013; Michail et al., 2016; Ploner et al., 2017; Ploner & May, 2018).

Previous research on the relationship between cognition and nociception, as well as on the analysis of the associated brain activity, has been based on static measures of experimental pain (using single discrete nociceptive stimuli and pain thresholds indices); little is known about how attention and working memory affect a plastic process of pain amplification that presumably occurs at the spinal cord level, as is the case of the TSSP, nor about the possible electrophysiological correlates of that effect.

Therefore, in this work, our main objective was to evaluate how attention and working memory load affect the TSSP, analyzing both pain ratings and brain activity during repetitive nociceptive stimulation. A second objective was to assess how experimental pain affects cognitive performance (using behavioral and ERP attentional indices). To this end, we recorded EEG from young healthy participants under four conditions, using a TSSP paradigm for pain delivery: A: Attention to hand & TSSP; B: 0-back & TSSP (low cognitive load) pain; C: 2-back & TSSP (high cognitive load) pain; and D: 2-back (without pain). We hypothesized that diverting attention from pain and increasing cognitive load would reduce the TSSP effect, with concomitant changes in the spectral power of theta, alpha, and beta EEG oscillations. We also predicted that the presence of nociceptive stimulation would impair the performance of a 2-back task and affect ERP attentional components linked to the processing of the standard and target stimuli.

The exploration of the reciprocal influence of the pain experienced in a TSSP paradigm and cognitive processes may contribute to the understanding of supraspinal influences on TSSP and on the mechanisms of pain modulation in clinical and non-clinical populations.

Significance

This study enhances our understanding of how attention diversion and cognitive load interact with pain perception, assessed using a Temporal Summation of Second Pain (TSSP) paradigm. Our results highlight that the TSSP phenomenon is not solely driven by spinal mechanisms but also involves attention-dependent top-down inhibitory processes. Interpretations of increased TSSP in individuals with chronic pain should consider the influence of these attentional and cognitive factors, suggesting that interventions should target these aspects to modify sensitization processes. These findings highlight the importance of using attention and distraction techniques for practical applications in pain treatment.

2 | METHOD

2.1 | Participants

The sample consisted of 22 participants (10 men and 12 women), with an age range between 18 and 30 years (mean age = 23 years; *SD* = 1.91); one subject was eliminated due to inability to discriminate painful stimuli, so the final analysis was done with 21 participants. All were healthy participants, right-handed, with no history of chronic pain, and were required not to consume alcohol in the 24 h prior to the study; not to consume other drugs or medication (especially analgesics) in the 3 days prior to the study; not to have symptoms of COVID-19 or contact with a person with COVID-19; and having slept at least 7 h the night before. All participants signed an informed consent form prior to the experiment, and a COVID protocol was conducted to ensure the safety of the participants. To avoid any bias in the assessment of

painful stimuli, they were not informed of the purpose of the experiment. Participants' data were coded for pseudonymization. This study was approved by the Research Ethics Committee of Santiago-Lugo with code 2020/093 and conducted in Galicia (NW of Spain) in the period from December 2020 to January 2021.

2.2 | Pain threshold measurement and TSSP protocol

Nociceptive stimuli were applied using the thermal cutaneous stimulator (TCS II.1.b; https://www.qst-lab.eu/tcs-technical-description). TCS II.1.b is a thermal contact stimulator that includes the Peltier elements (stimulation plates), which were placed over the skin of the subject to deliver thermal stimulation of predetermined duration and intensity. In this study, we used the T 08 probe (https://www.qst-lab.eu/probes), applying heat stimuli on the thenar eminence of both hands through stimulator plates 3, 4, and 5.

For pain threshold measurement, heat pulses of rising temperature (baseline: 32°, with a temperature increase of 1°C/s) were applied for 1 s. Participants were required to hold the stimulator with one hand and the response button with the other, and to press the response button just when they began to feel pain. The procedure was first applied three times on the right hand and then three times on the left hand, and the mean heat pain threshold of both hands was calculated. To be sure that the participants were holding the probe correctly, they were instructed prior to the tasks by the experimenter, with a thorough explanation of the area of application as well as the grip they were to make. The experimenter monitored that the probe was correctly positioned over the stimulated area.

In addition, prior to task execution, we conducted a brief training session to select the temperature to be used in the TSSP protocol and assess the ability of subjects to discriminate the intensity of different temperatures. During this training, participants were asked to verbally rate thermal stimuli applied to their right hand from 0 to 10 (being 0 not painful at all and 10 unbearable pain). Participants were instructed to pay attention to the "second pain," perceived as a stinging sensation that was prolonged in time, and that appeared just after the initial peak of pain provoked by the stimuli. They were assessed with a total of 10 stimuli at a variable temperature, with a duration of 1 s. The temperatures started at the pain threshold of each participant and were subsequently increased or decreased randomly in intensity relative to the individualized threshold, until a pain of 5/10 was reached, which would later be used for the TSSP protocol. To ensure that all the included participants correctly discriminated variations in temperature (performed in the training sessions), they were classified according to their degree of discrimination into three groups: "discriminates well" (>75% of the stimuli); "discriminates regularly" (75%–50%), and "discriminates poorly" (<50%). As stated, only one participant was eliminated due to a poor discrimination ability.

During the TSSP protocol, trains of 12 heat stimuli—with a duration of 1 s—were used. The interval between nociceptive stimuli was randomized, ranging from 1.5 to 2.3 s (except between the first and second stimuli, which were given the time necessary to rate pain). The temperature of the stimuli was adjusted for each participant individually, using the temperature scored as 5 out of 10 in the training procedure described above. Participants rated the pain caused by the first stimulus (S1) and the last stimulus (S12) of each series, using the mouse to respond on the computerized Numeric Rating Scale (NRS) with a range of 0–10. The magnitude of TSSP was calculated as the difference NRS-S12 minus NRS-S1.

2.3 | Tasks

Participants had to perform a task on the computer with four different conditions: A: Attention to hand & TSSP; B: 0-back & TSSP (low cognitive load) pain; C: 2-back & TSSP (high cognitive load) pain; D: 2-back (without pain). The first three conditions were presented with concomitant repetitive painful stimuli (TSSP protocol), while the last condition was presented without nociceptive stimulation. The instructions for each condition appeared on the screen at the beginning of each block, indicating the participant's assignment (attention to hand, 0-back or 2-back) and the hand with which they should hold the thermal stimulator. The hand with which they started the task was counterbalanced among the participants and was changing from right to left between each block. The participants were advised that they could experience painful stimuli of variable intensity (although all were of the same intensity) and that they should evaluate the pain experienced when the NRS scale appeared on the screen, even if they did not feel pain (in this case, they would score 0). The NRS to assess pain was presented just after S1 and S12. The presentation times of the painful stimuli and the visual stimuli (numbers and letters) were randomly distributed and could or not coincide at the same time. In the conditions B and C, the last stimulus of the cognitive task was presented at a random time between 2 and 2.8 before the onset of S12. A crucial point is that the participants were not required to perform any concomitant cognitive task during the NRS assessment of S1 and S12, to ensure that cognitive load did not affect pain assessment (i.e., the cognitive tasks were always presented during the 10 intermediate nociceptive stimuli of the TSSP protocol). All visual stimuli were presented at the center of a screen (resolution 1280 × 768 pixels) placed 1 m away from the participant, were white in color, and 5 × 8 cm in size.

Each of the four conditions is described in detail below (see also Figure 1):

A Attention to hand & TSSP. During this condition, participants were required to focus on the nociceptive stimuli (TSSP block) presented on their hands and evaluate their perceived intensity after S1 and S12. The word "hand" was presented at the top of the screen to let the participants know the ongoing condition.
B 0-back & TSSP. This condition consisted of the presentation of a series of visual stimuli (numbers from 0 to 9—standard stimuli—and letter X—target stimulus—randomly presented) and the

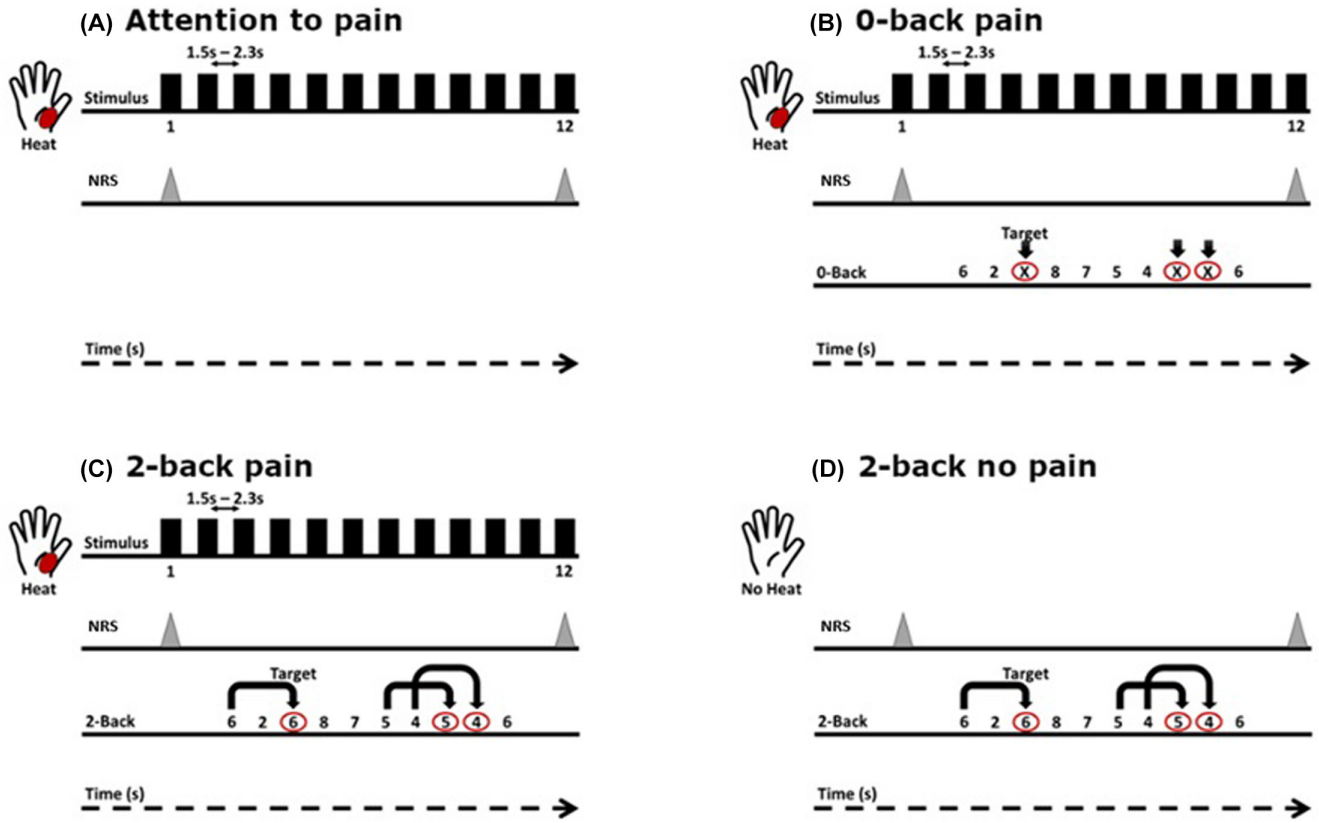

FIGURE 1 Visual representation of the experimental conditions. (A) Attention to hand & TSSP; (B) 0-back & TSSP (low cognitive load); (C) 2-back & TSSP (high cognitive load); (D) 2-back (without nociceptive stimulation). Nociceptive stimuli were presented in conditions A, B, and C. A numeric rating scale (NRS) was presented after the first (S1) and last (S12) nociceptive stimuli to assess pain levels. NRS had to be completed even in condition D, where no nociceptive stimulation was present. During B and C conditions, a working memory task with different cognitive loads (either 0-Back or 2-Back) had to be performed with concomitant nociceptive stimulation. Stimuli of the cognitive task were always presented after the first and before the last nociceptive stimulus.

participants had to respond (in a response box) when a letter X appeared on the screen. At the top of the screen the phrase, "respond to X" was displayed. Ten blocks of 10 visual stimuli each were presented: The stimulus duration was 500 ms, the inter-stimulus interval between 2 and 2.8 s, and each block could have two, three, or four target stimuli (the probability of having 2 was 16.7%; 3 = 50%; and 4 = 33.3%). A series of 12 painful stimuli as described above was applied concomitantly to the cognitive task.

C 2-back & TSSP. In this condition, a series of visual stimuli (numbers from 0 to 9) was presented on the screen and participants had to press a button when the number presented was identical to the number presented two positions back (referred to as the "target stimulus"; all the other stimuli were considered "standard stimuli"). At the top of the screen, "2-back" was indicated. The number of blocks, duration of stimuli, interval between stimuli, probability of target stimuli within each block, and concomitant delivery of the TSSP protocol were identical to Condition B.

D 2-back. This condition only differed from Condition C in that no nociceptive stimuli were delivered. Despite the lack of painful stimulation, to equate the parameters of this condition with those of the other conditions, participants had also to assess their pain in the NRS before and after the 2-back working memory block and had to hold the heat stimulation probe with their hand.

The complete task had 40 blocks divided into two series, with an approximate duration of 17 min each and a 5-min break in between. Each series was composed of 20 blocks, with five repetitions of each of the four conditions. There were four different orders of conditions (counterbalanced across participants): 1-BCADACBACBCDBCABCADC; 2-DACBACBDCBDABDACDACB; 3-CBDABDACDACBACBDCBDA; 4-ADBCDBCABCADCADCADBC. Each participant was assigned an order, kept for both series but changing the stimulated hand (i.e., if they started the first series with the right hand, they would start the second series with the left hand). Subjects with even codes started on the right hand, and odd codes started on the left hand. The task was programmed using Psychopy2 software (Peirce, 2007).

2.4 | EEG recording and analysis

EEG activity was recorded via 62 active electrodes inserted in an electrode cap (ActiChamp system; Brain Products Inc.). The electrodes were placed according to the 10–20 International System,

with the reference electrode in the tip of the nose and the ground electrode located in FPz. Horizontal eye movements were registered using two additional surface electrodes at the outer cants of both eyes. Vertical eye movements and blinks were registered using an active electrode placed approximately 2 cm below the right eye and subsequently referenced to the FP2 electrode during preprocessing of the EEG. Impedances were kept below 10 KΩ. The signal was digitized at 500 Hz and filtered with an on-line band-pass filter (.1–100 Hz) and a notch filter (50 Hz).

The EEG data were analyzed using the EEGlab V2021.1 toolbox (Delorme & Makeig, 2004). The EEG was re-referenced to an average reference. Noisy segments of the EEG—produced by eye movements or other contaminants—were rejected by visual inspection. Electrodes with high noise levels were removed and reconstructed using spherical spline interpolation. An average of 2.2 (*SD*: 2.2) electrodes were interpolated per participant. The data were digitally filtered using a .5-Hz high pass filter and a 40-Hz low pass filter, using the eeglab function "pop_eegfiltnew"—filter order of 3300 for .5 Hz and 166 for 40 Hz. Epochs were extracted from 1 s pre-stimulus to 2.2 s post-stimulus, time-locked to either somatosensory (heat painful pulses) or *n*-back visual stimuli (target and standard). Baseline correction was applied from −200 to 0 ms. An extended Independent Component Analysis algorithm (ICA) was applied to the electrophysiological data and components related to ocular or muscular activity were removed after visual inspection.

Power spectral density (PSD) was calculated by applying the EEGlab function "pop_spectopo" for the epochs locked to the nociceptive stimulus, using an interval from 200 to 1900 ms after stimulus presentation. The mean PSD values were measured from 4 to 7 Hz over Fz electrode (theta), from 9 to 11 Hz over PO7 and PO8 electrodes (alpha), and from 16 to 20 Hz over C1 and C2 electrodes (beta). The selection of the electrodes was made based on visual inspection as these are the areas where these frequencies were most prominent, irrespective of any difference in conditions (under the constraint that theta would be in mid-frontal locations, alpha in posterior locations, and beta over the Rolandic area). The alpha band was selected for showing higher power at those frequencies, while for theta and beta, no such clear peak was observed, so we used similar ranges to previous works (González-Villar et al., 2022; Luu et al., 2004; Pfurtscheller et al., 2002). The mean number of epochs (and their standard deviation; *SD*) used in this analysis for each condition was as follows: Attention to hand &TSSP (*M*: 91.5; *SD*: 10.3); 0-back & TSSP (*M*: 92.5; *SD*: 10.4); 2-back & TSSP (*M*: 92.5; *SD*: 10.4).

To analyze how nociceptive stimuli affect cognitive task information processing, we first extracted the ERPs from both target and standard stimuli epochs (−200 to 1000 ms) and then computed the global field power (GFP), calculated as the standard deviation of the voltages of the ERPs using all the scalp electrodes. This computation was performed at each time point of the ERP epochs. Despite its lack of spatial specificity, GFP is more robust to spurious findings by increasing the signal-to-noise ratio and reducing false positives compared to measuring ERP components in single electrodes. We analyzed the GFP corresponding to visual N1 component (measured as the mean value in a window from 140 to 190 ms) for the standard and target stimuli, and to P3 component (measured as the mean value from 300 to 500 ms) for the target stimuli. P3 was not evaluated for the standard stimuli because this component is significantly evoked only in the face of target trials. The time windows were selected because they capture the time points where these components were most clearly observed (Polich, 2007). The mean number of epochs used in this analysis for each condition in standard trials was: 0-back & TSSP (*M*: 62.8; *SD*: 7.1); 2-back & TSSP (*M*: 62.1; *SD*: 7.1); 2-back (*M*: 54.9; *SD*: 4.8). The number of epochs used for target trials was: 0-back & TSSP (*M*: 29.0; *SD*: 4.5); 2-back & TSSP (*M*: 26.6; *SD*: 5.0); 2-back (*M*: 28.7; *SD*: 3.6).

2.5 | Statistical analysis

We obtained the NRS-S12 minus NRS-S1 difference for each block and computed the average of the TSSP values obtained in the 10 blocks of each condition (A, B, and C).

Descriptive statistics were performed for all the variables, and it was confirmed that the data had a normal distribution. The data were also checked for sphericity and, when this was not confirmed, the Greenhouse–Geisser correction was used. To test whether there was a TSSP effect and whether this was modulated by attention and working memory load (objective 1), we performed one-way repeated measures ANOVA with the intra-subject factor "Condition" ("attention to hand & TSSP", "0-back & TSSP", "2-back & TSSP") for the magnitude of the TSSP effect (NRS-S12 minus NRS-S1). For the mean theta, alpha, and beta PSD values, one-way repeated measures ANOVAs with the intra-subject factor "Condition" ("attention to hand & TSSP", "0-back & TSSP", "2-back & TSSP") were performed. To test the effect of nociceptive stimulation on working memory performance and associated ERP indices (objective 2), we calculated mean reaction times (RTs) as well as percentages of hits and omissions for each working memory task. One-way repeated measures ANOVAs were performed with "Condition" ("0-back & TSSP", "2-back & TSSP" and "2-back") as intra-subject factor for each of the behavioral indices obtained in the three conditions (RTs, % hits, % omissions) and for the GFP means corresponding to N1 and P3 components. Holm correction was applied in the post hoc comparisons when an effect was found significant. Moreover, all the data were analyzed using the Bayesian approach to assess evidence for and against the effects. To describe the Bayes factors, we used the classification scheme of Lee & Wagenmakers (Quintana & Williams, 2018). Data analysis was performed with the statistical package JASP.

3 | RESULTS

We found one participant who discriminated temperature intensities poorly and was eliminated from the analyses.

3.1 | Objective 1: Effects of attention and working memory load in TSSP

3.1.1 | Behavioral results

Repeated measures ANOVA showed a significant effect of condition ($F_{(1.46,32.28)}=14.66$; $n=21$; $p<.001$; $\eta^2=.40$) for the magnitude of the TSSP (NRS-S12 minus NRS-S1). This result is supported by Bayesian analysis, which indicates extreme evidence for the alternative hypothesis (BF10 = 1300.27) for the condition effect (see Table 1) (see also Figure 2).

Post hoc frequentist analysis determined significant differences between conditions A and B, and A and C (see Table 1), with, respectively, strong (BF10 = 27.34) and very strong (BF10 = 114.21) evidence for the alternative hypothesis in their Bayesian counterparts. However, the difference between conditions B and C was not significant. Bayesian analysis indicates anecdotal evidence for a difference between these two conditions (BF10 = 1.09).

3.1.2 | EEG results

Repeated measures ANOVAs using the mean PSD values from 4 to 7 Hz (theta) ($F_{(2,40)}=13.02$; $n=21$; $p<.001$; $\eta^2=.39$), from 9 to 11 Hz (alpha) ($F_{(1.09,21.92)}=8.06$; $n=21$; $p<.008$; $\eta^2=.28$), and from 16 to 20 Hz (beta) ($F_{(1.55,31.07)}=7.34$; $n=21$; $p<.005$; $\eta^2=.27$), showed a main effect of condition. Bayesian analysis indicates extreme evidence for the alternative hypothesis for theta (BF10 = 444.29) and strong evidence for alpha (BF10 = 27.48) and beta (BF10 = 17.61) (see Table 2). Post hoc pairwise comparisons showed higher theta power and lower alpha power for condition B than A, and C than A, but no significant differences between B and C. For beta, post hoc pairwise comparisons showed lower power for C than A and C than B, but no differences between A and B (see also Figure 3).

3.2 | Objective 2: Effect of nociceptive stimulation on working memory performance

3.2.1 | Behavioral results

For the three *n*-back task conditions, repeated measures ANOVA showed a significant main effect for the mean of all three behavioral indices: reaction time ($F_{(2,44)}=11.63$; $n=21$; $p<.001$; $\eta^2=.35$), % of correct responses ($F_{(1.19,26.17)}=6.78$; $n=21$; $p=.011$; $\eta^2=.24$), and omissions ($F_{(1.22,27.04)}=8.13$; $n=21$; $p<.006$; $\eta^2=.27$). These results are supported by the Bayes factor with extreme evidence for the alternative hypothesis for reaction time (BF10 = 268.01) and strong

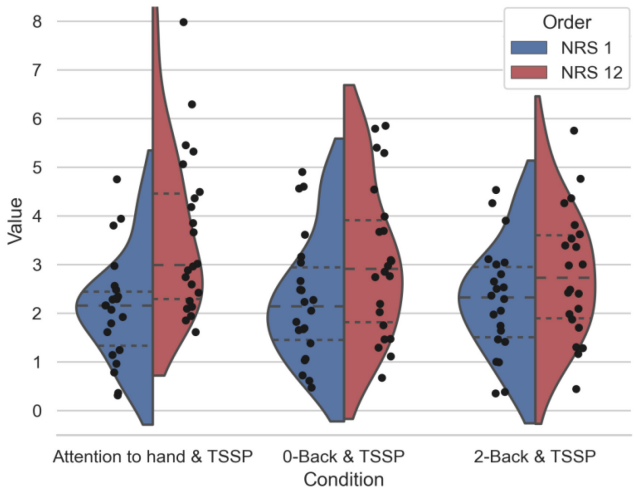

FIGURE 2 TSSP effect magnitude across the three conditions. Pain ratings after the first (NRS-S1) and last (NRS-S12) heat stimuli in the three conditions with TSSP. As may be seen, no difference across the three pain conditions is observed for NRS-S1. On the contrary, NRS-S12 (i.e., the TSSP effect) is reduced as attention is diverted from the painful stimuli and cognitive load increased. NRS, Numeric Rating Scale; TSSP, Temporal Summation of Second Pain.

TABLE 1 Mean magnitudes of the Temporal Summation of Second Pain (TSSP) effect (NRS-S12 minus NRS-S1) for each condition with nociceptive stimulation (A: Attention to hand & TSSP; B: 0-back & TSSP; C: 2-back & TSSP). Results of repeated-measures ANOVA (*F*) and post hoc comparisons for the Condition (A, B and C) effect. Bayes factor (BF10) for the condition effect.

Condition effect														
Mean (*SD*)														
A		B		C		*N*		*F* (*p*)			BF10		η^2	
1.48 (1.55)		.77 (1.11)		.53 (1.07)		21		$14.66^{a}_{(df:\ 1.46,32.28)}$ (<.001*)			1300.27		.40	
Post hoc comparisons														
A vs. B						A vs. C					B vs. C			
t (*p*)	BF10	Cohen's *d*	95% CI			*t* (*p*)	BF10	Cohen's *d*	95% CI		*t* (*p*)	BF10	Cohen's *d*	95% CI	
			Lower	Upper					Lower	Upper				Lower	Upper
$3.67_{df(22)}$ (.004*)	27.34	.57	.21	1.22		$4.34_{df(22)}$ (<.001*)	114.21	.75	.38	1.51	$1.95_{df(22)}$ (.192)	1.09	.18	−.07	.54

Abbreviations: BF, Bayes factor; *df*, degrees of freedom; *SD*, standard deviation.

[a]Sphericity correction Greenhouse–Geisser.

*Significant result.

TABLE 2 Mean of PSD values of the three frequency bands (theta, alpha, and beta) and results from repeated measures ANOVA (*F* and Bayes Factors) and post hoc analysis for the condition effect (A: attention to hand & TSSP; B: 0-back & TSSP; C: 2-back & TSSP).

Condition effect							
	Mean (*SD*)						
	A	**B**	**C**	***N***	***F* (*p*)**	**BF10**	η^2
Theta (4–7 Hz)	−.26 (2.47)	.36 (2.19)	.77 (2.27)	21	$13.02_{(df:2,40)}$ (<.001*)	444.29	.39
Alpha (9–11 Hz)	2.92 (5.18)	1.82 (3.56)	1.12 (3.32)	21	$8.06^{a}_{(df:1.09,21.92)}$ (.008*)	27.48	.28
Beta (16–20 Hz)	2.79 (.60)	2.77 (.60)	2.46 (.54)	21	$7.34^{a}_{(df:1.55,31.07)}$ (.005*)	17.61	.27

Post hoc comparisons															
	A vs. B					**A vs. C**					**B vs. C**				
				95% CI					**95% CI**					**95% CI**	
	***t* (*p*)**	**BF10**	**Cohen's *d***	**Lower**	**Upper**	***t* (*p*)**	**BF10**	**Cohen's *d***	**Lower**	**Upper**	***t* (*p*)**	**BF10**	**Cohen's *d***	**Lower**	**Upper**
Theta (4–7 Hz)	$-2.96_{df(20)}$ (.015*)	6.27	−.27	−1.16	−.07	$-5.50_{df(20)}$ (<.001*)	1090.98	−.44	−1.51	−.54	$-1.93_{df(20)}$ (.068)	1.08	−.18	−.96	.14
Alpha (9–11 Hz)	$2.43_{df(20)}$ (.039*)	1.79	.27	−.03	2.22	$3.98_{df(20)}$ (<.001*)	7.57	.44	.67	2.92	$1.55_{df(20)}$ (.128)	58.85	.17	−.42	1.153
Beta (16–20 Hz)	$-1.28_{df(20)}$ (.20)	.93	−.06	−.50	.16	$2.48_{df(20)}$ (.035*)	1.38	.12	−.00	.66	$3.76_{df(20)}$ (.002*)	21.50	.19	.17	.84

Abbreviations: BF, Bayes factor; *df*, degrees of freedom; *SD*, standard deviation.

[a]Sphericity correction Greenhouse–Geisser.

*Significant result.

evidence for % of correct responses (BF10 = 26.21) and very strong evidence for omissions (BF10 = 65.70). Post hoc pairwise comparisons showed a higher percentage of correct responses, fewer omissions, and lower reaction time for B than C and for B than D, but no significant differences between C and D (see Table 3). Therefore, the lack of differences between C and D suggests that the presence of pain does not seem to significantly affect the performance of a working memory task.

3.2.2 | ERP results

The mean GFP value related to N1 (in a window from 140 to 190 ms) shows a significant effect of condition, with differences for the standard ($F_{(2,40)} = 24.41$; $n = 21$; $p < .001$; $\eta^2 = .55$) but not for target stimuli ($F_{(1.39,27,83)} = .31$; $n = 21$; $p = .655$; $\eta^2 = .015$). The Bayes factor indicated extreme evidence for the alternative hypothesis for standard stimuli in N1 (BF10 = 81,549.49). Post hoc comparisons showed differences between the three paired comparisons for standard stimuli, with higher amplitude for D (2-back) trials, followed by C (2-back & TSSP), and the lowest amplitudes for B (0-back & TSSP). For the mean GFP value in the P3 time window (from 300 to 500 ms; only to target stimuli), the ANOVA showed a significant effect of condition ($F_{(1.34,26.88)} = 6.43$; $n = 21$; $p = .011$; $\eta^2 = .24$). Bayes factor showed a strong evidence for the alternative hypothesis (BF10 = 10.25). Post hoc comparisons showed differences between B and C, and B and D, but no differences between C and D (see Table 4) (see also Figure 4).

4 | DISCUSSION

In the present study, we assessed whether the TSSP is affected by attention and cognitive load, and if this effect may have neural correlates observed in EEG dynamics. We also analyzed the effect of nociceptive stimuli on a working memory task performance, using both behavioral and associated EEG activity. The TSSP was significantly reduced as attentional/cognitive requirements increased, and this reduction was associated with higher midfrontal theta, reduced posterior alpha and central beta power. Furthermore, working memory performance in the 2-back condition was not affected by the presence of repeated painful stimuli, although we found that pain reduced the amplitude of attention-related ERP components to standard stimuli, but not to targets.

TSSP is an increase in pain perception which is explained by the excitation of nociceptive neurons in the dorsal horn of the spinal cord (Staud et al., 2006; Usichenko et al., 2018). We observed the influence of supraspinal top-down attentional mechanisms on this process: by shifting attention away from the site where the painful stimulus was applied (the hand) and directing it to the performance of cognitive tasks, the pain sensitization effect was reduced. Previous research hypothesizes that pain processing and some cognitive processes share neural substrates, which may explain their reciprocal modulation (Moriarty et al., 2011; Moriarty & Finn, 2014). Another plausible idea is that this inhibitory process occurs primarily at the brain level, as a more localized "top-top" process, placing the brain as the ultimate site of action, which could exert its inhibitory control without the need to send signals to lower structures.

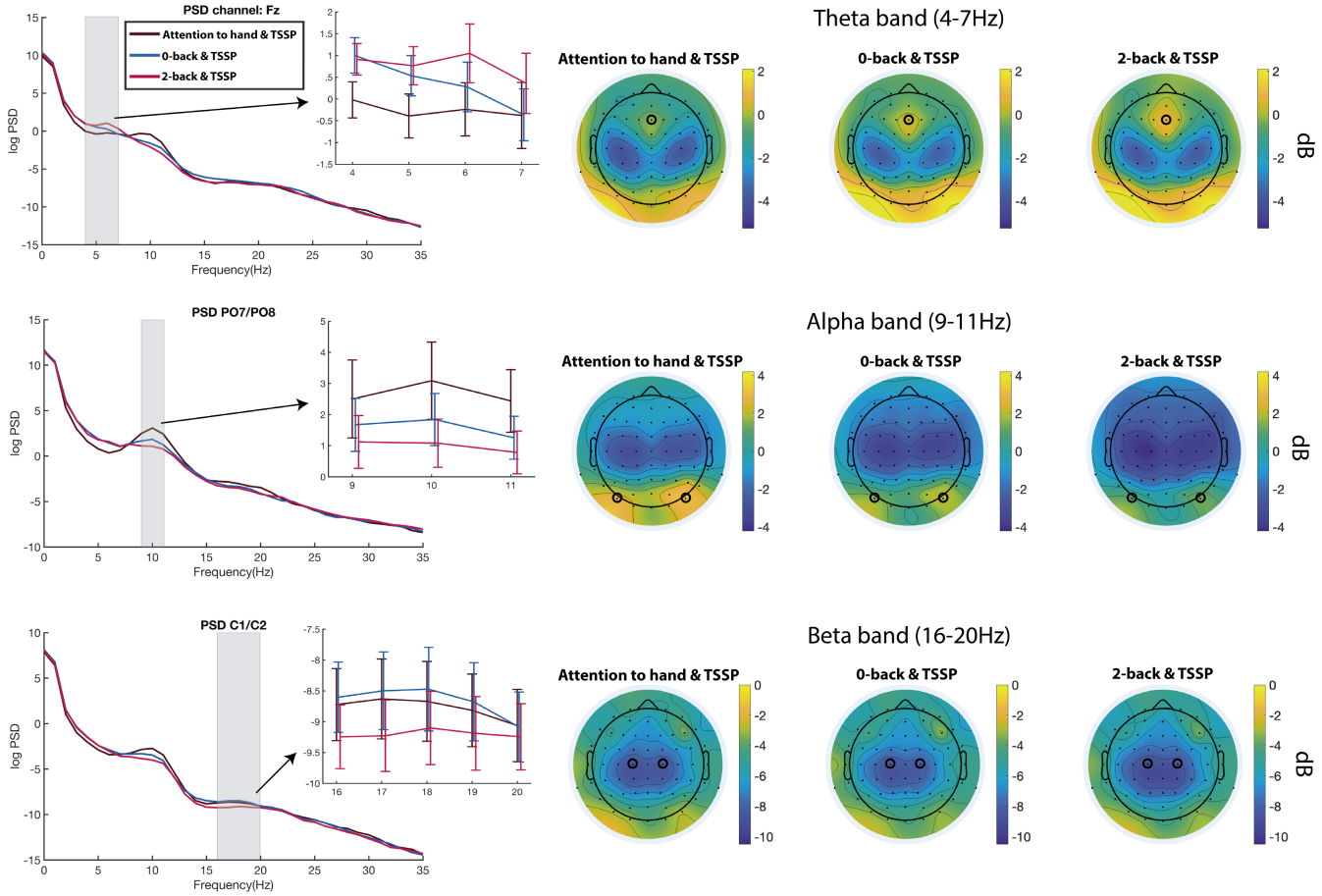

FIGURE 3 Power spectral density (PSD) of theta, alpha, and beta associated with heat painful stimuli for each condition (A, Attention to hand & TSSP; B, 0-back & TSSP; and C, 2-back & TSSP). Frequency bands of interest are shown magnified with standard error bars. Shaded areas show the frequency windows used to measure each band. The topographies of each frequency band in the three conditions are shown on the right side. The circled electrodes were used for power measurement.

We found a reduction in the magnitude of the TSSP effect in the high and low memory load conditions compared to the "attention to pain" task. In line with our results, other studies that used static measures of pain (mainly pain thresholds) found that performing cognitive tasks reduced the perception of pain administered continuously (Buhle & Wager, 2010; Nakae et al., 2013). Some authors pointed out that tasks of greater difficulty may be more successful in altering pain perception than easier tasks (Bushnell et al., 1999; Michail et al., 2016; Petrovic et al., 2000). In our case, even though a trend is observed (lower TSSP in the 2-back task than 0-back), no significant differences in the TSSP effect were seen between the low and high cognitive load conditions. Although the behavioral indices did show that the 2-back task was more difficult than the 0-back task (% of correct responses and omissions), this may be explained by the fact that participants were university students for whom the 2-back task could not be sufficiently demanding.

Previous studies using a secondary hyperalgesia paradigm, another indirect measure of central sensitization (Woolf, 2011), yielded conflicting results. While some authors argue that difficult tasks (such as *n*-back) (Torta et al., 2020) reduce the development of this phenomenon, others find no effect of working memory/cognitive load nor of spatial attention to the location, on the development of secondary hyperalgesia (Della Porta et al., 2022; Meyers et al., 2022, 2023). Although both phenomena are related to central sensitization, TSSP is a phenomenon independent of secondary hyperalgesia and with distinct underlying mechanisms (Woolf, 2011), and may therefore be affected differently by attention/cognitive load. In this case, using a protocol of repeated painful stimuli to assess central sensitization (TSSP), the evidence supports the interaction between pain and cognition.

At the electrophysiological level, we observed that the reduction of the TSSP effect in conditions with decreasing attention to pain (0-back and 2-back tasks) was accompanied by higher midfrontal theta power and reduced posterior alpha and central beta power. Theta oscillations over midfrontal scalp locations have been related to both pain processing and to other cognitive activities, such as conflict monitoring, novelty processing, and working memory (Cavanagh & Frank, 2014; Gevins et al., 1997; Michail et al., 2016; Taesler & Rose, 2016). Neuroimaging and EEG source reconstruction studies suggest that the anterior cingulate cortex is the main source of midfrontal theta activity (Kong et al., 2010; Michail et al., 2016; Treede et al., 1999). The anterior cingulate cortex is intrinsically related to pain perception

TABLE 3 Mean performance values obtained in each condition with *n*-back task (B: 0-back & TSSP; C: 2-back & TSSP; D: 2-back). Repeated measures ANOVA results (*F* and Bayes Factors) and post hoc analysis for the condition effect.

	Condition effect						
	Mean (*SD*)						
	B	C	D	*N*	*F* (*p*)	BF10	η^2
Reaction time	.42 (.07)	.54 (.54)	.54 (.18)	21	$11.63_{(df:\,2,44)}$ (<.001*)	268.01	.35
% Correct responses	99.87 (.62)	96.52 (3.35)	94.00 (9.52)	21	6.78[a] $_{(df:1.19,26.17)}$ (.011*)	26.21	.24
Omissions	0 (0)	1.78 (2.69)	1.13 (1.05)	21	8.13[a] $_{(df:\,1.22,27.04)}$ (.006*)	65.70	.27

Post hoc comparisons

	B vs. C					B vs. D					C vs. D				
				95% CI					95% CI					95% CI	
	t (*p*)	BF10	Cohen's *d*	Lower	Upper	*t* (*p*)	BF10	Cohen's *d*	Lower	Upper	*t* (*p*)	BF10	Cohen's *d*	Lower	Upper
Reaction time	$-4.56_{df(22)}$ (<.001*)	185.40	−.81	−.19	−.05	$-3.54_{df(22)}$ (.004*)	20.95	−.79	−.20	−.18	$-.11_{df(22)}$ (.91)	.22	−.02	−.06	.06
% Correct responses	$4.68_{df(22)}$ (.016*)	6.02	.00	.67	11.97	$4.67_{df(22)}$ (<.001*)	239.79	.57	.67	11.01	$1.42_{df(22)}$ (.168)	.53	.42	−2.06	7.13
Omissions	$-3.17_{df(22)}$ (.009*)	9.78	−.67	−1.70	−.55	$-5.12_{df(22)}$ (<.001*)	637.56	−.661	−1.70	−.017	$-1.34_{df(22)}$ (.19)	.46	−.39	−1.91	.60

Abbreviations: BF, Bayes factor; *df*, degrees of freedom; *SD*, standard deviation.

[a]Sphericity correction Greenhouse–Geisser.

*Significant result.

TABLE 4 Mean values for GFP for each component obtained in each condition with *n*-back task (B: 0-back & TSSP; C: 2-back & TSSP; D: 2-back). Repeated measures ANOVA and post hoc analysis for the condition effect.

Condition effect							
	Mean (*SD*)						
	B	C	D	*N*	*F* (*p*)	BF10	η^2
N1-Standard 140–190 ms	2.55 (1.23)	2.87 (1.43)	3.21 (1.46)	21	$24.41_{(df:2,40)}$ (<.001*)	81,549.49	.55
N1-Target 140–190 ms	3.13 (1.44)	3.23 (1.50)	3.26 (1.47)	21	.31[a] $_{(df:\,1.39,27.83)}$ (.655)	.16	.015
P3-Target 300–500 ms	4.04 (1.47)	3.42 (1.22)	3.39 (1.17)	21	6.43[a] $_{(df:\,1.34,26.88)}$ (.011*)	10.25	.24

Post hoc comparisons

	B vs. C					B vs. D					C vs. D				
				95% CI					95% CI					95% CI	
	t (*p*)	BF10	Cohen's *d*	Lower	Upper	*t* (*p*)	BF10	Cohen's *d*	Lower	Upper	*t* (*p*)	BF10	Cohen's *d*	Lower	Upper
N1-Standard 140–190 ms	$-3.30_{df(20)}$ (.005*)	12.16	−.23	−.57	−.06	$-7.51_{df(20)}$ (<.001*)	53,782.42	−1.64	−.88	−.42	$-3.45_{df(20)}$ (.005*)	16.36	−.25	−.59	−.08
N1-Target 140–190 ms	$-.49_{df(20)}$ (1.00)	.25	−.06	.62	.42	$-.69_{df(20)}$ (1.00)	.28	−.151	−.582	.339	$-.22_{df(20)}$ (1.00)	.23	−.049	−.281	.236
P3-Target 300–500 ms	$2.63_{df(20)}$ (.040*)	3.44	.575	.01	1.2	$2.71_{df(20)}$ (.040*)	3.93	.591	.02	1.27	$.26_{df(20)}$ (.791)	.23	.059	−.26	.11

Abbreviations: BF, Bayes factor; *df*, degrees of freedom; *SD*, standard deviation.

[a]Sphericity correction Greenhouse–Geisser.

*Significant result.

and working memory and forms part of one of the descending pathways of pain modulation, sending projections to the periaqueductal gray and the rostral ventral medulla, to descend to the dorsal horn of the spinal cord (Schweinhardt & Bushnell, 2010). Therefore, our finding that oscillatory activity at the theta range increases when the TSSP effects decrease can be related to the activation of the described top-down inhibitory mechanism. Concerning the alpha band, its suppression has been suggested as an objective indicator of cortical pain processing (Chouchou et al., 2021). We observed power reduction in the alpha band when the TSSP is weaker, an effect that was modulated

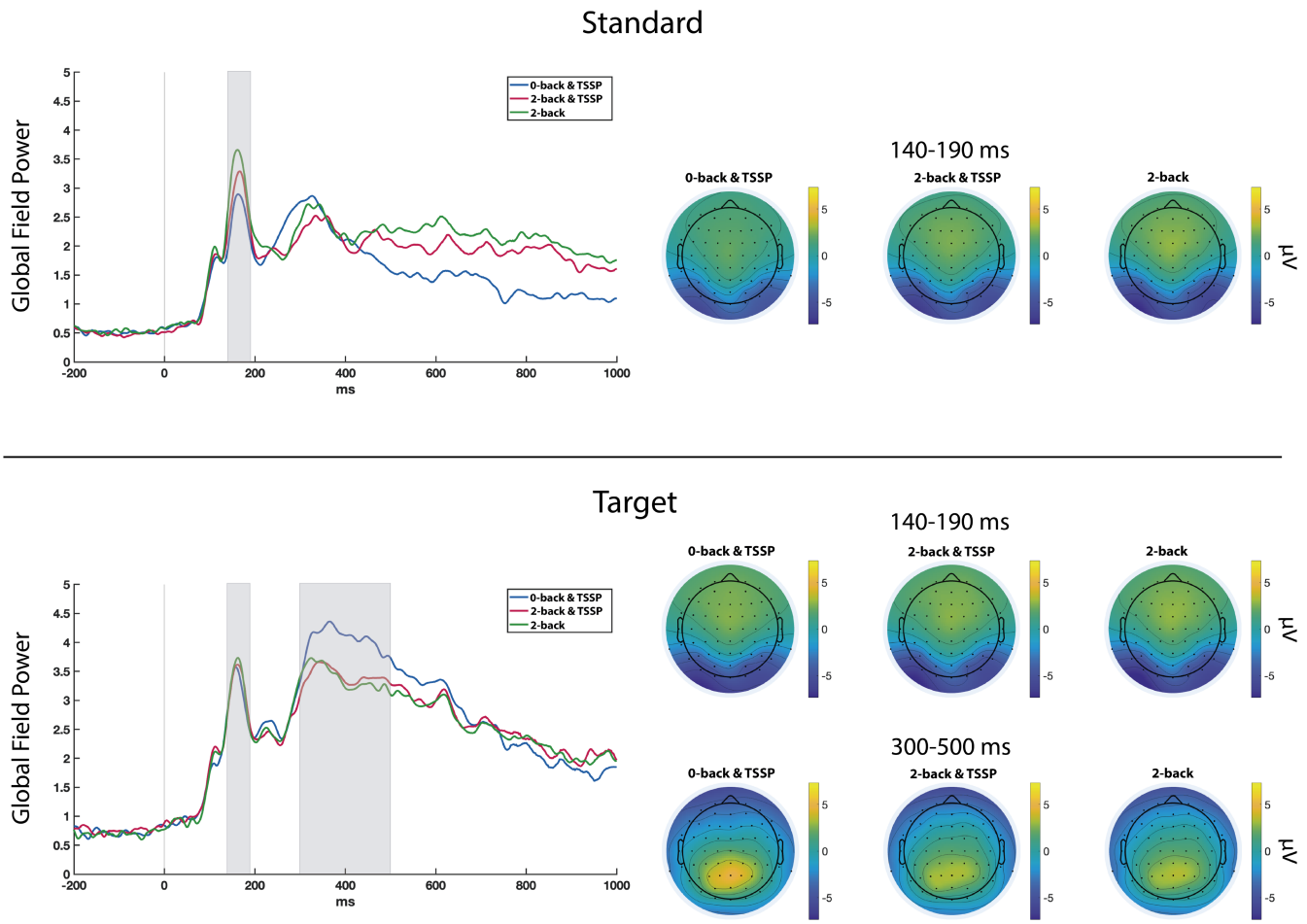

FIGURE 4 Global Field Power (GFP) evoked by standard visual stimuli (top) and by target visual stimuli (bottom) in the three conditions ("0-back & TSSP," "2-back & TSSP," and "2-back"). The shaded areas in the left panel show the time windows used to measure GFP (N1: 140–190 ms; P3: 300–500 ms), and the right side shows the associated topographies for each condition.

by attention and cognitive load, as also reported in previous studies (Hauck et al., 2015; Michail et al., 2016). Finally, we found reduced beta power during the 2-back task. Beta oscillations are also related to pain processing, as well as to the functioning of motor cortex and cognitive and perceptual processing; specifically, they relate to endogenous top-down influences that override the effect of potentially novel or unexpected external events (Engel & Fries, 2010; Michail et al., 2016). Although in some experimental paradigms it has been observed that beta activity is mainly modulated by the intensity of the painful stimulus (bottom-up pathway) and not by attention levels (Hauck et al., 2015), here we found that it is also affected by cognitive/attentional load (top-down pathway; reduced beta power during 2-back task). Our results are in line with other studies, which indicate that beta activity could also be related to endogenous and top-down components (Engel & Fries, 2010; Kim & Davis, 2021).

Previous literature shows consistently higher TSSP in chronic pain patients than healthy controls (Legrain et al., 2013), which has been considered evidence of altered central sensitization mechanisms at the level of the spinal cord (Robinson et al., 2004). However, our study shows that these differences in TSSP can also be explained by supraspinal attention-related mechanisms. This fact supports the use of therapeutic alternatives, based on attention manipulation and distraction, such as mindfulness-based interventions (Majed et al., 2018) or virtual reality techniques, which have been effective in several types of chronic pain such as fibromyalgia (Botella et al., 2013) or migraine (de Tommaso et al., 2013).

Concerning the effect of painful sensations on cognitive performance, the results did not support our working hypothesis. Performance of the 2-back task was not affected by the presence of repeated painful stimuli. Previous results on the interference of pain in cognitive performance are also discrepant. Some studies report the effect of pain on the performance of simple visual tasks (Legrain et al., 2011), but not in working memory tasks such as the Working Memory Index (WMI) subtest of the WAIS-IV or the Sternberg task (Etherton, 2014; Legrain et al., 2011; Sturgeon et al., 2015). In contrast, other authors argue that experimental pain does affect working memory performance, both in a *n*-back task (Moore et al., 2012) and a letter-number sequence (Hood et al., 2013).

Thanks to the study of EEG, this work can throw light on the controversy about the effect of pain on working memory. Although pain did not affect observable task performance, the GFP index obtained at N1 latencies after standard trials suggests that, in some way, pain affects stimulus processing. The analyses showed higher GFP in the condition "2-back" than in "2-back & TSSP," and higher in the "2-back & TSSP" than in the "0-back & TSPP." This shows a gradation of the GFP index at N1 latencies modulated by both pain and attentional/cognitive resources. First, the highest GFP corresponds to the "2-back without pain" condition. The intermediate GFP value corresponds to the 2-back pain condition, suggesting that the presence of pain provokes distraction and attentional capture, and reduces the attentional resources devoted to the 2-back task (processing of standard stimuli). The lowest N1 GFP amplitude was observed for low cognitive load condition (0-back), suggesting a lower allocation of attentional resources to this less cognitively demanding task. Interestingly, N1 to target stimuli was not modulated by concomitant pain. Nociceptive stimuli did not affect either the GFP at P3 latency, which showed differences between the 0-back pain and 2-back pain conditions, but not between "2-back & TSSP" and "2-back" conditions. Overall, our results suggest that, although pain may divert attentional resources, participants are able to compensate for this deficiency when it is required for proper task performance.

It has been shown that patients with chronic pain present cognitive deficits and complaints in different areas such as attention and memory (including working memory) (Moriarty et al., 2011), and this has been explained by competence of neural resources devoted to pain processing and cognitive tasks (Eccleston & Crombez, 1999). Our result that pain delivery did not affect task performance does not support this explanation. However, these data should be interpreted with caution, bearing in mind that the participants were young healthy students and that we used medium/low pain intensities, so a ceiling effect may have occurred, explaining why the behavioral task performance was not impaired.

Our results should be interpreted in relation to the study's limitations. First, even though the individually selected temperature corresponded to a value of 5 out of 10 in NRS pain ratings, it was observed that the participants' assessments at the beginning of the TSSP procedure were slightly lower (this can be related to a lower uncertainty and a better knowledge of the characteristics of the nociceptive stimulus, or due to sensitization processes during threshold calibration). The use of stronger intensities could be more adequate to observe pain effects on performance in the 2-back task. Another aspect to consider is that we have compared the 0-back and 2-back tasks, which may represent a relatively low cognitive load for the students. It would be valuable to include more demanding tasks, such as 3- or 4-back tasks. Furthermore, since our sample was composed of young university participants, it would be interesting to use a sample with older participants and/or a more varied educational level. Given the subjectivity of the assessments, in future studies, it would be interesting to analyze the effect of cognitive processes on other pain modulation mechanisms, such as conditioned pain modulation (CPM).

Despite these acknowledged limitations, our study has notable strengths. We obtained robust results on the influence of attention diversion and cognitive load on pain perception, reinforced by the EEG data. Our study adds valuable information to the existing body of knowledge surrounding pain and cognition, thus providing a solid foundation for future research in this field. Our results suggest that interpretations of increased temporal summation in chronic pain patients should consider that this phenomenon depends on attentional and cognitive aspects, suggesting also that interventions addressing these aspects may modify sensitization processes. These findings hold promise for practical applications in pain treatment, especially regarding the use of attention and distraction techniques.

5 | CONCLUSION

In conclusion, our results suggest that the temporal summation of second pain is not exclusively dependent on mechanisms located at the dorsal horn of the spinal cord but is significantly modulated by supraspinal cognitive/attentional mechanisms: Higher cognitive load reduces the magnitude of the sensitization effect. This finding suggests that attention-dependent *top-down* inhibitory mechanisms could be modulating the nociceptive input at the spinal level. In addition, the presence of nociceptive stimuli did not worsen the performance in the 2-back task but seems to impair global attentional resources (as observed in the GFP at N1 latencies).

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*: M.T.C.D., L.R.O., A.J.G.V., and A.G.U.; *Methodology*: A.J.G.V., M.T.C.D., L.R.O., and A.G.U.; *Investigation*: L.R.O. and A.G.U.; *Formal Analysis*: L.R.O. and A.J.G.V.; *Resources*: M.T.C.D.; *Writing – Original Draf*: L.R.O.; *Writing – Review & Editing*: M.T.C.D., A.G.U., and A.J.G.V.; *Visualization*: L.R.O.; *Supervision*: M.T.C.D.; *Funding Acquisition*: M.T.C.D.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/jnr.25363.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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