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The brain in pain: A multidimensional approach

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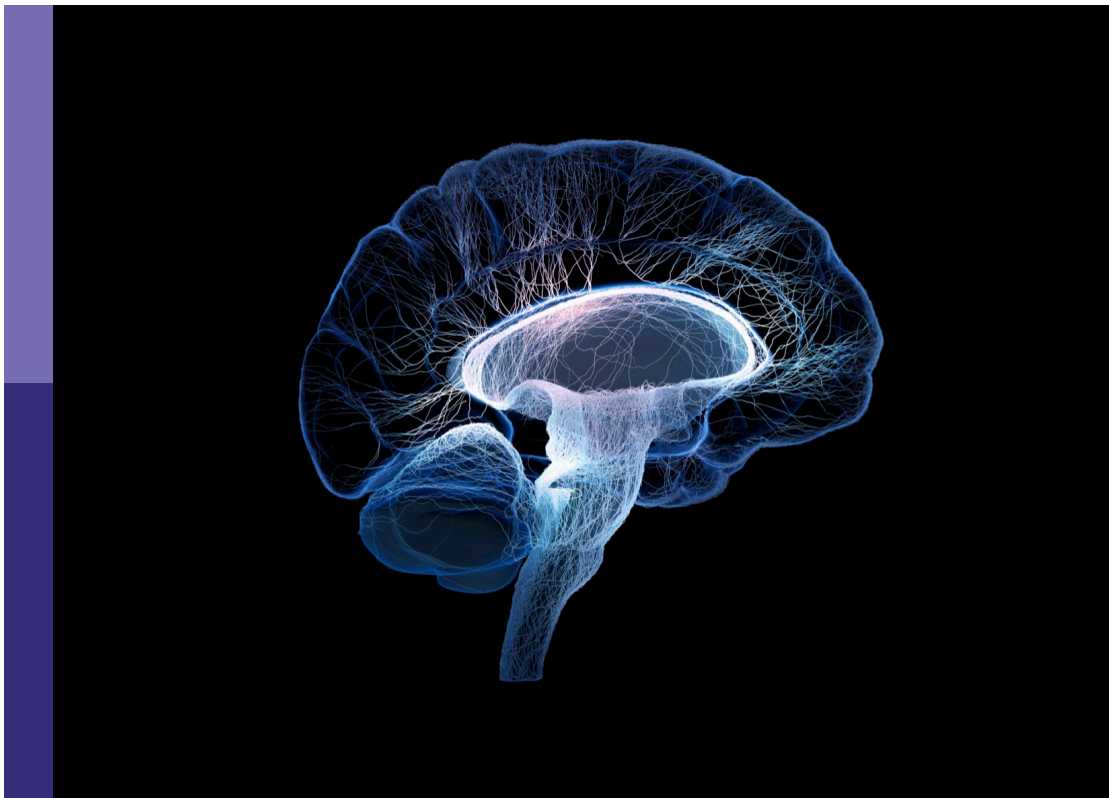

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The brain in pain: A multidimensional approach

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Editorial: The brain in pain: a multidimensional approach

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KEYWORDS

pain, empathy, Event-Related Potentials (ERPs), Near-InfraRed-Spectroscopy (NIRS), Magnetic Resonance Imaging (MRI), meta-analysis

Editorial on the Research Topic
The brain in pain: a multidimensional approach

Introduction/background

The aim of the Research Topic "*The brain in pain: a multidisciplinary approach*" is to collect the latest quality research on the subject, focusing on the multiple facets of pain in humans, from its neural substrates to its possible expressions and modulation.

We have published papers by a total of 63 Authors, affiliated to research institutions located in five countries in three different continents, employing a variety of techniques, from behavioral, psychological and sensory testing, to Event-Related Potentials (ERPs), Near-InfraRed-Spectroscopy (NIRS) and functional Magnetic Resonance Imaging (fMRI), and including meta-analysis of previous research. Some of the studies dealt with specific chronic pain patients, others with different modulatory factors in healthy volunteers.

Overview of the articles in this Research Topic

Primary dysmenorrhea (PDM) is a very common cause of pelvic pain in women during their fertile years, with severe consequences for their quality of life (Ferries-Rowe et al., 2020). The study by Lee et al. demonstrates that young Asian PDM females, who, differently from Caucasian PDM patients, do not express pain hypersensitivity, during acute noxious heat stimulation show reduced response and de-coupling of the Default Mode Network (DMN), but only in the painful menstrual phase. Another study by the same research group (Hsu et al.) reveals an influence of the A118G polymorphism of the OPRM1 gene on white matter features, especially of the motor network, but only during the painful menstrual phase, possibly with a maladaptive role. These results offer interesting contributions to the discussion of ethnic, genetic and hormonal influences both on pain perception and on its neural mechanisms.

Two studies focus on fibromyalgia (FM), another chronic pain condition, mostly affecting women (Ruschak et al., 2023). Bao et al. investigated the relationship between fibromyalgia and long-term opioid use, revealing that, quite unexpectedly, temporal

summation does not significantly change in FM patients, but negatively correlates with pain ratings, whereas higher opioid dosage correlates with higher heat pain sensitivity. On the other hand, Xin et al. performed a metanalysis of voxel-based morphometry (VBM) studies in FM, including updated data with respect to previous studies (see, e.g., Dehghan et al., 2016). They found changes in gray matter (GM) in FM patients, namely, increased GM in right postcentral gyrus and left angular gyrus, and decreased GM in right cingulate gyrus, right paracingulate gyrus, left cerebellum, and left gyrus rectus, i.e., brain regions involved in different (somatosensory, affective, cognitive) functions. These findings suggest both structural and functional adjustments, in a complex pain syndrome such as fibromyalgia.

Two more studies dealt with different forms of neuropathic pain: Du et al. adopted functional near-infrared spectroscopy (fNIRS) to detect cerebral changes in patients with cervical spondylosis. During acute pain stimulation, they found substantial increases in oxyhemoglobin concentrations in the frontal pole and dorsolateral prefrontal cortex, which significantly decreased in stimulation trials following analgesic procedures; these results add to our knowledge about the role of DLPFC in chronic pain conditions and about its potential as a therapeutic target (Seminowicz and Moayedi, 2017). In the study by Bu et al., spinal cord stimulation not only effectively reduced pain and other anomalies, such as sleep disorders, in patients affected by postherpetic neuralgia, but it also induced both static and dynamic brain resting state activity changes, which in some regions correlate with clinical characteristics.

Pain can be modulated by several factors, including physical exercise and training, although the underlying mechanisms are not yet well understood (Lesnak and Sluka, 2020). Peier et al. compared endurance athletes to non-trained individuals, and identified a pain-resistant population, especially numerous among athletes, who show some peculiarities in their EEG pattern during pain perception (i.e., reduced global power spectra in the beta bands, as opposed to the increase found in non-resistant non-athletes); it is worth pointing out that the characterization of pain responses might lead to a personalized, and therefore more efficient, pain management.

Pain empathy is a powerful means to improve interpersonal communication and prosocial behavior (see, e.g., Smith et al., 2020). The study by Li et al. reveals ERP changes depending on the moral judgment given by the participant on the person experiencing pain, namely, smaller mean wave amplitude of positive 300 (P3) and late positive potential (LPP) for painful pictures of individuals deserving a low moral judgement, and vice versa for people deserving a high moral judgement; notably, the study puts these results in relationship with the issue of violence against healthcare operators, a reason of globally increasing alarm (Banga et al., 2023).

Finally, two studies investigate the intriguing relationship between pain and language (Borelli et al., 2021). Gilioli et al. investigated the electrophysiological correlates of implicit processing of words with pain content using an affective priming paradigm. The study indicates that valence and semantics of a stimulus interact to produce specific emotional responses. This research increases our knowledge of how pain-related words impact cognitive processing and emotional reactions, providing insights into the complex interplay among pain, affective priming, and cognitive mechanisms. Lastly, the study by Borelli et al. presents an event-related fMRI study that aimed to compare brain activity related to perceiving nociceptive pain and processing semantic pain, and specifically, words related to either physical or social pain. The results show that words associated with social pain activate regions linked to affective-motivational aspects of pain perception; conversely, words related to physical pain trigger activity in regions associated with sensory-discriminative aspects of pain perception; the degree of activation in specific regions vary depending on the type of pain being processed. This study sheds light on how words associated with physical and social pain influence the brain networks involved in pain perception.

In conclusion, the present Research Topic, "*The brain in pain: a multidimensional approach*", brings together cutting-edge research and diverse perspectives to increase our understanding of how the brain perceives, processes, and responds to pain. By doing so, it both advances our knowledge on the neuroscience of pain, and offers new perspectives for innovative approaches to pain management and treatment.

Author contributions

FB: Writing—review & editing, Writing—original draft, Project administration, Conceptualization. AM-H: Writing—review & editing, Project administration, Conceptualization. CAP: Writing—review & editing, Supervision, Conceptualization. FL: Writing—review & editing, Writing—original draft, Supervision, Project administration, Conceptualization.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of doctor–patient news-induced moral judgments on pain empathy for doctors and patients in China

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Objective: Pain empathy's preferential nature tends to trigger prejudice and intergroup conflicts. Given the current degree of proliferation of doctor–patient conflict news in China, this study aims to determine whether readers of doctor–patient news-initiated moral judgments prefer pain empathy for doctors or patients.

Materials and methods: This study utilized localized doctor–patient news with high or low moral performance (based on morality ratings of patients' behaviors) as moral-judgment-eliciting materials, and painful pictures as pain empathy-eliciting materials. The event-related potential (ERP) technique was utilized to assess moral judgment's effect on the cognitive empathy component and to investigate electroencephalogram signals' accuracy in classifying four brain response patterns when facing doctor or patient is experiencing or not experiencing pain.

Results: Under low moral text material, participants exhibited smaller mean wave amplitude of positive 300 (P3) and late positive potential (LPP) to painful pictures than non-painful pictures when facing patients; under high moral text material, participants exhibited larger mean wave amplitude of P3 and LPP to painful pictures than non-painful pictures when facing doctors. Electroencephalogram (EEG) signals' classification accuracy was significant in 0–1,000 ms in both high and low moral judgments, but the classification accuracy was higher in low moral judgments in some cognitive empathy stages (0.51, 0.53–0.55, 0.66–0.79, and 0.88–1 s).

Conclusion: Under low moral judgment, individuals pay less attention to the patient's (perpetrator's) pain; under high moral judgment, individuals empathize with the doctor (the person praised), showing that news-induced

moral judgment can sway readers' empathy for different social groups. In cognitive empathy, individuals' brain representations are more discriminatory under low than high moral judgments when confronted with pain by doctors and patients, which provides insight into objectively recognizing group bias.

KEYWORDS

moral judgment, pain empathy, ERP, SVM, doctor–patient relationship

Introduction

Arguably, the doctor–patient relationship—that is, the interaction between the care provider and service recipient (Harbishettar et al., 2019)—is influenced by the general public's empathy in response to the media coverage of doctor–patient conflicts (Stefanello, 2022). Currently, in China, the doctor–patient relationship is turbulent, and news covering doctor–patient conflicts is rapidly proliferating, predominantly focusing on negative reporting of patients harming doctors (Sun et al., 2018). Indubitably, some media outlets consciously broadcast news regarding harmonious doctor–patient relationships to compensate for the general one-sided reporting tendencies (Zhou et al., 2021); however, the measures implemented thus far have been either insufficient or ineffective (The Lancet, 2020).

Empathy is defined as an individual's ability to experience others' emotional states and mirror similar states in themselves (Michaels et al., 2014), which, in turn, enhances interpersonal communication efficiency (Singer and Lamm, 2009) and promotes individuals' pro-social behavior (Wang et al., 2018; Smith et al., 2020). Pain empathy–a type of empathy–refers to the ability to empathize with observed as well as imagined pain (Fitzgibbon et al., 2010). Prior studies have demonstrated that pain empathy is preferential. For example, people exhibit stronger pain empathy for close friends than for strangers (Zhou et al., 2019), and for people with the same ethnicity than for those with another ethnicity (Fabi and Leuthold, 2018). Furthermore, people can distinguish the moral level of others' behavior during pain empathy and exhibit higher pain empathy levels toward people who engage in ethical behavior (Cameron et al., 2022). A recent study demonstrated that people are more likely to subject strangers who are "harming others" to physical pain than strangers who are "not helping others." This finding suggests that human pain empathy is influenced by moral judgments (Yang et al., 2022).

Moral judgment is about how "blameworthy" a behavior is, in other words, is to assess whether an act is blameworthy (Siegel et al., 2017). News-induced moral opinions precipitate empathy and facilitate individuals' choice to empathize with different entities after making different moral judgments (Zaki, 2019b). However, empathy may pose a danger when the media use empathy to trigger bias and hatred (Bloom, 2017). Importantly, such biased empathy is narrow, and its unfairness makes people overlook those genuinely needing help, which, in turn, intensifies intergroup conflict (Fowler et al., 2021). Empathy that considers all people equal has greater social value and aids in the maintenance of social harmony and stability. Therefore, this study investigates the pain empathy mechanism after individuals' exposure to common doctor–patient conflict news, to reveal how such news' selection and description may reduce public prejudice against doctor or patient groups, which can help improve doctor–patient relationships.

Unfortunately, existing commonly used subjective assessments are time-intensive and fail to detect progressive changes in pain empathy. Moreover, human subjective ratings' sensitivity is inadequate to identify the empathy process' specific nuances and underlying mechanisms (Xiao et al., 2016). By contrast, utilizing event-related potential (ERP) techniques with high temporal resolution refines pain empathy's neural mechanisms in more naturalistic contexts (Coll, 2018). Pain empathy is categorized into bottom-up emotional and top-down cognitive empathy (Kopiś et al., 2020). The former represents the ability to spontaneously experience others' inner emotions. Prior research has indicated that N1, N2 can distinguish between pain and non-pain stimuli and can be considered a marker of the automatic activation of emotionally salient stimuli (Li et al., 2020), however, a recent meta-analysis has shown that N1, N2 may not be a reliable index of pain empathy (Coll, 2018). The latter refers to the analysis and understanding of others' internal states and involves stimuli processing rooted in knowledge and experience (Fan and Han, 2008; Ibáñez et al., 2011). This induces late ERP components, such as positive 300 (P3) and late positive potential (LPP), thereby triggering the cognitive evaluation of others' pain (Coll, 2018). Therefore, we used P3 and LPP as late-ERP components. Further, explicit moral appraisals were found to induce LPP which is related to emotion, cognition, and motivation (Yoder and Decety, 2014). Thus, the following questions arise: Given that moral judgments are rooted in later cultivation (Kim and Park, 2019), do moral judgments influence cognitive empathy which is also based on later cultivation (the P3 and LPP components)?

Although empathy measurement is progressing, decoding human empathic perceptions, expressions, and behavior through the measurement results is relevant, but still in its infancy. Moreover, simultaneous advances in signal processing and machine learning techniques enable researchers to identify empathy in multimodal data and, consequently, provide objective assessments (Xiao et al., 2016). Machine learning has been applied to empathy classification and prediction, and

patterns of resting-state fMRI connectivity of resonance and control networks have been shown to predict trait empathic concern (EC) (Christov-Moore et al., 2020), empathic ingroup preferences translating into behavior, and neural activation in their associated regions predicting pro-social behavior (Hein et al., 2010; Christov-Moore et al., 2017). The first single machine learning model for neural activation on pain empathy for comparing ingroups and outgroups was developed by Vaughn et al. (2018). This model showed that human empathic classification of ingroups and outgroups was 72% accurate, thus postulating that neural networks are sufficient and necessary conditions to distinguish between ingroups and outgroups (Vaughn et al., 2018). People tend to classify those with desirable moral performance as ingroup (Van et al., 2012); hence, individual neural responses' ability to distinguish between doctor or patient pain under doctor–patient news-induced moral judgments can lend a theoretical basis for neural responses to predict pain empathy group preferences and provide criteria for group bias diagnosis.

Therefore, we collated localized news materials to elicit moral judgments, used pain-picture materials to elicit pain empathy, and collected ERP data. Through ERP analysis, we explored high vs. low moral judgments' electrophysiological effects on cognitive empathy between doctor and patient groups during pain empathy. Through support vector machines (SVMs), we explored whether electrophysiological responses are differentiated in the treatment of patients vs. doctors experiencing or not experiencing pain, and if so, whether the degree of this differentiation is influenced by moral judgment.

Materials and methods

Research design

This study used a three-factor mixed design of 2 (high moral text material/low moral text material) × 2 (imagined subject as doctor/imagined subject as patient) × 2 (painful pictures/non-painful pictures); herein, high and low moral ratings were between-subject factors, and the remainder were within-participant factors. This study was approved by the Ethics Committee of Wenzhou Medical University (2022-017). All participants voluntarily participated in the study and signed an informed consent form. Participants were informed that they could withdraw from the study at any time if they no longer intended to participate. The research structure is shown in **Figure 1**.

Participants

The sample size was calculated using G-Power, which indicated that 24 participants (Effect size $f = 0.25$, $\alpha = 0.05$, $1\text{-}\beta = 0.8$, number of groups = 2, number of measurements = 4, Corr. among rep measures = 0.5, non-sphericity correction = 1) were required; eventually, 30 participants were included (20 women). The mean age was 21.23 (SD = 2.42) years. All the patients were right-handed and exhibited normal or corrected visual acuity.

Materials

Commonly used search engines in China (Baidu and Sogou) were used to retrieve 30 news articles. The keywords used were "doctor–patient," "conflict," "news," and "relationship." Two articles having excessively numerous words were excluded, the remained 28 textual materials had an average length of 509.39 ± 85.72 words each. Overall, the 28 textual materials were randomly divided into four groups, and 122 participants (61 women) who did not participate in the formal experiment were recruited and randomly divided into four groups as well. The mean age was 21.48 (SD = 0.94) years. Each group of textual materials was rated on a scale of 1–9 by one of the groups of participants. The rating dimensions were as follows: patient moral level (1 = low moral level, 9 = high moral level), pleasantness (1 = very unpleasant, 9 = high pleasantness), arousal (1 = fairly calm, 9 = fairly agitated), and dominance (1 = being dominated, 9 = dominating). The three highest and lowest moral-level patient ratings were selected as high moral text initiation material ($M = 8.32$, SD = 1.03) and low moral text initiation material ($M = 1.21$, SD = 0.49), respectively, $t(119) = 114.23$, $p < 0.001$ (see Appendix A for further details).

We used 40 fully scored pain and non-painful pictures (Meng et al., 2012) as pain-empathy-inducing stimuli. The painful pictures' content included injury to a human body part–such as cutting or needling; the non-painful pictures' content replaced the previous injury-related content–for example, replacing the needle with a cotton swab. All pictures were close to those of daily life, easy to understand, and unambiguous (see Appendix B for details on the material).

The Interpersonal Reactivity Index-C (IRI-C) was used to measure participants' empathic abilities. The original version was developed by Davis in 1980, and the Chinese version was developed by Chan in 1987. The scale comprises four dimensions: perspective-taking (PT), fantasy (FS), EC, and personal distress (PD). The IRI-C exhibits a split-half reliability of 0.734, test–retest reliability of 0.737, and a variance rate of 46.342%, across the questionnaire's four factors (Meng et al., 2012). Its reliability is good, and it demonstrates considerable validity in measuring participants' empathy.

Procedure

The experimental environment was a standard electroencephalogram (EEG) laboratory with soundproofing and no external noise disturbance. The light was bright and soft,

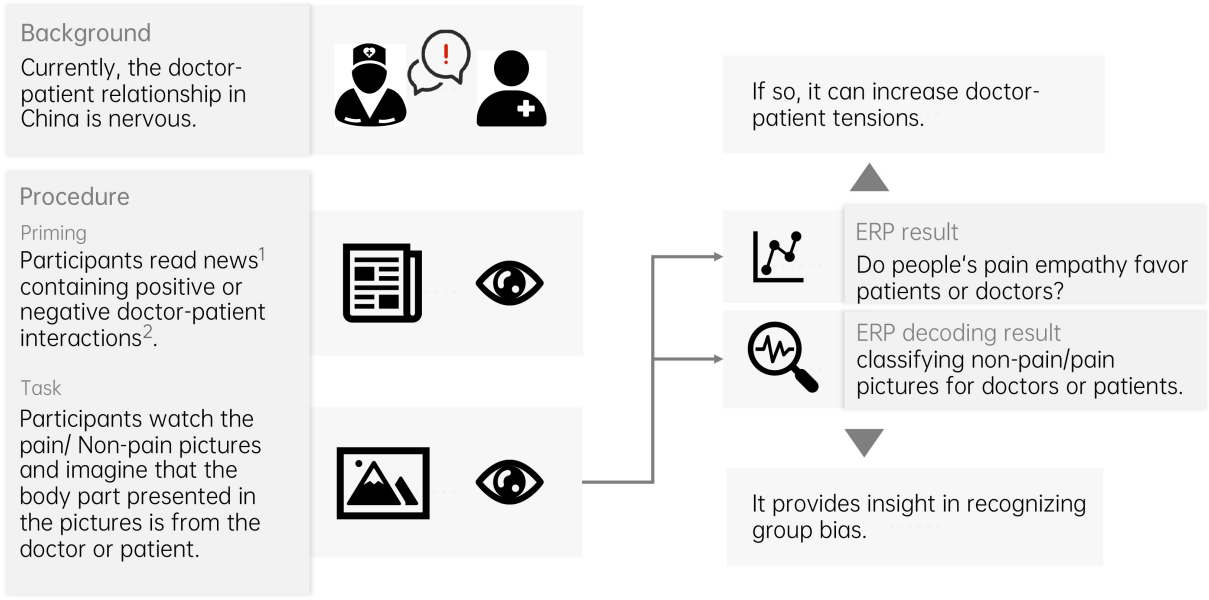

FIGURE 1
The research structure. [1]News materials are selected through a rigorous scoring process. [2]The degree of positive or negative doctor–patient interaction is determined by the level of morality exhibited by the patient's behavior.

and the room temperature was appropriate. The participants' eyes were approximately 80 cm away from the computer screen, and their viewing angle was less than 10°.

Prior to conducting the formal experiment, the participants were prompted to adjust their sitting posture and place their hands on the corresponding keys on the keyboard. To prevent artifacts in the electrophysiological data, they were asked to avoid making any sound and refrain from moving body parts irrelevant to the experimental response.

The experimental procedure comprised an exercise and formal experiment. The exercise involved the random presentation of 20 pictures from the Pain Empathy Gallery (Meng et al., 2012); There are two types of pictures, pain and non-pain. The participants were asked to identify the types of pictures by pressing the "F" or "J" picture. Each identification provided correct, incorrect, or no response feedback to help participants become familiar with the keystrokes of the formal experiment. None of the pictures presented during the exercise were presented in the formal experiment.

The experimental procedure was divided into two categories–high and low ethics–according to the content of the priming text materials. Each block began with a short text on the doctor–patient relationship in which participants were asked to read at their own speed.

After reading, participants were instructed to rate patient moral level (1 = low moral level, 9 = high moral level) and then perform an imagery task when pictures were presented, imagining that the body part in the stimulus presented next belonged to the doctor or patient in the text. The imagined subjects were randomly prompted before each of the 40 trials with either "Please imagine that the part presented in the picture is a doctor in the text" or "Please imagine that the part presented in the picture is a patient in the text."

To ensure active attention to the content of the pictures during the experiment, the participants were asked to classify the presented stimuli as pain or non-painful pictures by pressing the key "F" or "J" in keyboard. The correct rate of classification was used to determine whether the participants could understand the content of the pictures, and the stimulus pictures were presented twice to ensure that participants are able to notice the picture content. The experimental procedure is shown in Figure 2.

Statistical analysis

Event-related potential data recording

The EEG data were recorded using a 64-channel EEG analysis system (ANT Neuroscan). The average value of the bilateral mastoid positions was used as a reference, with a filtered bandpass of 0.1–30 Hz and a sampling frequency of 500 Hz. The scalp impedance of each electrode was less than 5 kΩ .

Event-related potential data analysis

The ERP data were processed offline using EEGLAB 8.30 and ERPLAB 8.30 in MATLAB 2020b. The average value of the bilateral mastoids was taken as a reference, and horizontal electrooculography was automatically corrected. Waveform

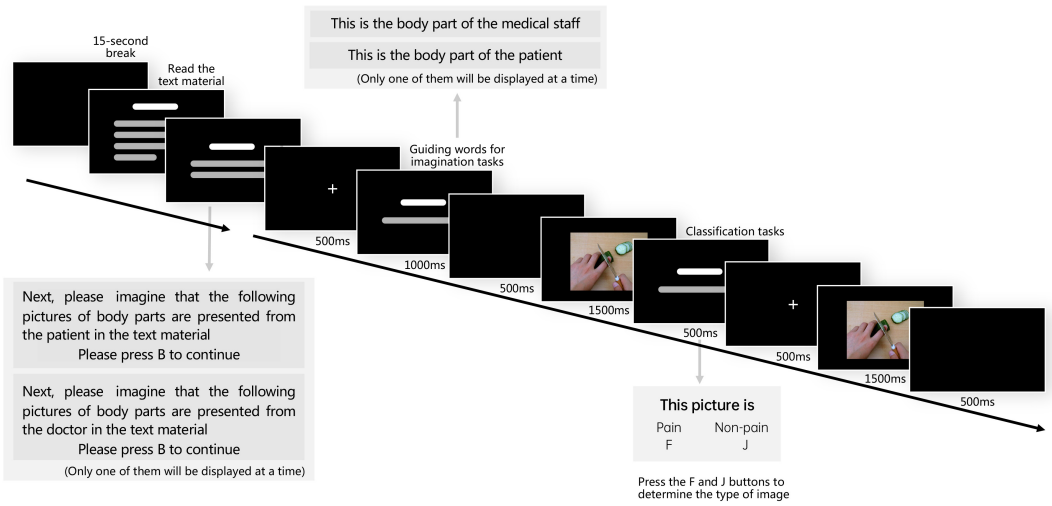

FIGURE 2
Flow diagram of experimental procedure. The experiment had two parts: reading text and viewing pictures; the low moral judgment group read low moral text and the high moral judgment group read high moral text.

data with amplitudes greater than ±80 μV were considered artifacts and were rejected. The 200 ms before stimulus presentation was used as the baseline, 1,000 ms after stimulus presentation was used as the response period, and the analysis duration was 1,200 ms.

Based on the aim of this study and previous studies (Campanella et al., 2002; Hajcak et al., 2007; Meng et al., 2012; Cheng et al., 2017), P3 (350–450 ms) and LPP (time window of 400–700 ms) was selected as the late component of empathic pain processing. The electrode sites selected for the P3 and LPP components were FCz, Cz, Pz, C3, C4, Cp3, and Cp4 (distributed in the parietal lobe and near the central region). A four-factor repeated measures ANOVA with 2 (textual material moral level: high moral/low moral) × 2 (imagined subject: medical care/patient) × 2 (picture type: painful pictures/non-painful pictures) × 7 (electrode points: FCz, Cz, C3, C4, Pz, Cp3, and Cp4) was performed for the mean wave amplitude and peak latency, respectively, using SPSS 23.0.

Event-related potential decoding

Commonly used machine learning methods to evaluate empathy include linear regression, SVMs, and dynamic Bayesian networks. SVMs (Xiao et al., 2016) are a class of generalized linear classifiers that perform binary classification of data in a supervised learning manner. Its decision boundary is the maximum-margin hyperplane of the learned sample solution, which is powerful in its ability to learn data classification patterns with balanced accuracy and reproducibility. SVM has become a widely used classification tool with high generality and has been extended to several data science scenarios (Pisner and Schnyer, 2020).

Using SVM, we performed time-point-by-time quadratic decoding of high- and low-moral text material groups characterized by mean wave amplitude, that is, imagining pain or non-painful pictures where the subject was a doctor or a patient and derived decoding performance above the time point of chance (random level of 0.25).

First, a three-dimensional data matrix was obtained for each participant, including trial (240 trials per category) and electrode location (62 scalp positions) dimensions. After traversing all participants' data, the low moral judgment group of 14 people was assembled into four dimensions (14, 240, 62, and 850), and the high moral judgment group of 16 people was assembled into four dimensions (16, 240, 62, and 850), corresponding to the label of each trial.

Decoding is then performed point-by-point using the function named "tbyt_decoding_kfold" under the decoding module of NeuroRA (Lu and Ku, 2020). The five trials of each class were averaged and decoded every five time points, followed by 10 triple-fold cross-validations. In the threefold cross-validation, 2/3 of the randomly selected trials were used to train the classifier, and the remaining 1/3 of the trials were used to evaluate the performance of the classifier. The evaluation process in each case was that the trained classifier predicts which of the four categories is the label of the test set at the current time point. Finally, the results were smoothed.

The function named "plot_tbyt_decoding" under the decoding module of NeuroRA was used for plotting. The cluster-based permutation test was used to determine whether there were differences in the mean wave amplitudes of different picture types for different imagined subjects. If differences

existed then the time series of these differences were analyzed with the time interval set to 0.01 s, the time range from −0.2 to 1.0 s, and p set to.05.

After decoding the two groups separately on a time-point-by-time basis, an independent samples t-test was used to analyze whether there was a significant difference in the classification accuracy between the two groups of high and low moral text materials at each time point.

Results

Moral ratings

The results of the ratings of patients' moral level showed that the independent sample t-test for high moral news (M = 8.25, SD = 1.06) vs. low moral news (M = 1.24, SD = 0.53) was $t(88) = -38.73$, $p < 0.001$, indicating that the participants were able to significantly distinguish between the moral levels of the two types of news.

Interpersonal Reactivity Index-C

Table 1 reveals no significant difference between the high and low moral text material groups in terms of empathy in general and no significant difference in terms of different dimensions of empathy.

Accuracy and reaction time

The accuracy rates and reaction times for each condition are presented in Table 2. All participants had significantly higher correct response rates for the picture types, indicating that they could effectively discriminate between the two picture types. The ANOVA results for reaction time showed a significant interaction between textual morality level and picture type (F (1, 29) = 1.049, $p < 0.001$, $\eta^2 = 0.306$). Simple effects analysis indicated that the reaction time for looking at painful pictures after reading high morality news (M = 418.596, SD = 5.171) was shorter than that for non-painful pictures (M = 465.459, SD = 5.373). The reaction time to look at painful pictures after reading low moral text material was shorter (M = 410.588, SD = 5.680) than that for non-painful pictures (M = 434.068, SD = 6.663). This is consistent with previous research (Cui et al., 2016; Cheng et al., 2017; Galang et al., 2017), people will tend to prioritize painful pictures that contain threat-related information (Clauwaert et al., 2019).

TABLE 1 The Interpersonal Reactivity Index-C result.

Dimension	High morality (M ± SD)	Low morality (M ± SD)	t	Sig.
Perspective taking	19.29 ± 4.30	18.07 ± 3.47	0.82	0.42
Fantasy scale	17.64 ± 2.27	18.71 ± 2.33	−1.23	0.65
Empathy concern	18.14 ± 2.25	19.36 ± 1.82	−1.57	0.21
Personal distress	15.14 ± 3.68	16.64 ± 3.18	−1.16	0.71
Total	54.64 ± 10.56	57.21 ± 11.74	−0.61	0.92

TABLE 2 Accuracy and reaction time result.

Types of text material	Imagine subject	Picture type	ACC (M ± SD)	RT (M ± SD)
High morality	Doctor	Painful	0.96 ± 0.03	428.54 ± 154.72
		Non-painful	0.91 ± 0.06	476.89 ± 166.12
	Patient	Painful	0.96 ± 0.05	408.65 ± 145.22
		Non-painful	0.94 ± 0.07	454.03 ± 166.5
Low morality	Doctor	Painful	0.95 ± 0.04	405.39 ± 177.34
		Non-painful	0.91 ± 0.07	446.15 ± 178.79
	Patient	Painful	0.90 ± 0.09	415.79 ± 170.33
		Non-painful	0.94 ± 0.05	421.99 ± 185.01

Electrophysiological data

Positive 300

The mean wave amplitude main effect of textual material morality level (F (1, 29) = 37.209, $p < 0.001$, $\eta^2 = 0.045$), imagined subject (F (1, 29) = 5.817, $p = 0.016$, $\eta^2 = 0.007$), picture type (F (1, 29) = 9.312, $p = 0.002$, $\eta^2 = 0.012$) was significant. Lower morality level (M = 2.845, SD = 0.173), imagining doctor (M = 2.407, SD = 0.168), non-painful picture (M = 2.483, SD = 0.168) induced a greater wave amplitude than higher morality level (M = 1.397, SD = 0.162), imagining patient (M = 1.835, SD = 0.168), and painful picture (M = 1.759, SD = 0.168).

The mean wave amplitude interaction of the moral level of textual material, imagined subject, and picture type was significant, F (1, 29) = 4.914, $p = 0.027$, $\eta^2 = 0.006$; Pairwise comparison showed that after reading low morality materials, participants had smaller amplitudes of patients' pain pictures (M = 1.882, SD = 0.347) than non-pain pictures (M = 3.242, SD = 0.324); after reading high morality materials, had greater amplitudes of doctors' pain pictures (M = 2.258, SD = 0.347) than non-pain pictures (M = 1.116, SD = 0.324). No other analysis yielded significance.

The peak latency main effect of picture type (F (1, 29) = 3.957, $p = 0.047$, $\eta^2 = 0.005$) was significant, painful picture (M = 542.902, SD = 3.518) induced longer latency than

non-painful picture (M = 534.823, SD = 3.527). No other effect reached significance.

Late positive potential

The mean wave amplitude main effect of textual material morality level (F (1, 29) = 11.824, p = 0.001, η^2 = 0.015), imagined subject (F (1, 29) = 4.527, p = 0.034, η^2 = 0.006), picture type (F (1, 29) = 8.553, p = 0.004, η^2 = 0.011) was significant. Lower morality level (M = 2.546, SD = 0.174), imagining doctor (M = 2.390, SD = 0.168), and non-painful picture (M = 2.485, SD = 0.168) induced a greater wave amplitude than higher morality level (M = 1.729, SD = 0.162), imagining patient (M = 1.885, SD = 0.168), and painful picture (M = 1.790, SD = 0.168).

The mean wave amplitudes at the different electrode sites differed significantly (F (1, 29) = 3.619, $p < 0.05$, η^2 = 0.024): CP4 (M = 1.460, SD = 0.315) than FCz (M = 2.878, SD = 0.315), Cz (M = 2.996, SD = 0.315), C3 (M = 2.345, SD = 0.315), and C4 (M = 2.477, SD = 0.315) were lower; Pz (M = 1.112, SD = 0.315) was lower than FCz (M = 2.878, SD = 0.315), and Cz (M = 2.996, SD = 0.315), C3 (M = 2.345, SD = 0.315), and C4 (M = 2.477, SD = 0.315) were low. The interaction between text material morality level, imagined subject, and picture type was significant, F (1, 29) = 4.889, p = 0.027, η^2 = 0.006. Pairwise comparison showed that after reading low morality materials, participants had smaller amplitudes of patients' pain pictures (M = 1.620, SD = 0.347) than non-pain pictures (M = 2.959, SD = 0.347); after reading high morality materials, had greater amplitudes of doctors' pain pictures (M = 2.529, SD = 0.325) than non-pain pictures (M = 1.426, SD = 0.325). No other effect showed any significance.

Peak latencies differed significantly at the morality level (F (1, 29) = 13.460, $p < 0.001$, η^2 = 0.017), longer for those initiated by high moral text material (M = 548.0, SD = 3.407) than for low moral text material (M = 529.725, SD = 3.634). No other effect reached significance.

The total mean and topographic maps of ERP evoked by pain and non-pain stimuli under the initiation of high moral text material and low channel text material are shown in **Figure 3**.

Correlation analysis

A correlation analysis was done between IRI-C scores and the mean wave amplitude of P3 and LPP to painful pictures, and it was found that IRI-C scores were positively correlated with the mean wave amplitude of P3 (r = 0.148, $p < 0.01$) and LPP (r = 0.121, $p < 0.05$) to painful pictures, i.e., the stronger the empathic ability of the participants, the higher the wave amplitude of P3 and LPP to painful pictures.

Event-related potential decoding data

The cluster-based permutation test suggested that both high and low ethical text material groups were significant in 0–1.0 S; an independent samples t-test found that the low ethical evaluation group's classification accuracy was significantly greater than that of the high ethical evaluation group in 0.51 S, 0.53–0.55 S, 0.66–0.79 S, and 0.88–1.00 S, as shown in **Figure 4**.

Discussion

This study investigated the effect of doctor–patient relationship news on pain empathy in readers. Textual material at different moral levels was used to initiate participants' moral judgments, and an imagery task was interspersed to allow participants to empathize with pain for specific objects in the textual content.

Unexpectedly, this study found that after making low moral judgments of patients, individuals had lower P3 and LPP wave amplitudes for the patient's pain than in the absence of pain. And individuals had longer peak latencies in LPP after reading high moral material than after reading low moral material. Studies have shown that after some things induce negative emotions, people's pain empathy level decreases, and the neural representation of empathy when observing others' pain is inhibited to a certain extent, such as participants have significantly smaller parietal P3 amplitudes for painful pictures than neutral pictures. This is because individuals divert their own attention from previous pain experiences by reducing their attention to other people's pain stimuli and increasing their attention to neutral stimuli that are not related to pain (Li et al., 2017; Fan et al., 2021). As negative news, low-morality text materials may induce people's anger, sadness and other negative emotions to a certain extent. Individuals have already experienced pain during the reading process. After that, they are unwilling to bear more pain, as a result, they pay less attention to pain stimuli.

Moreover, both P3 and LPP are neural indicators for the stage of cognitive processing and evaluation of others' pain (Fan and Han, 2008; Yoder and Decety, 2014). Behaviors reflecting low morality have been shown to reduce the LPP amplitude (Chiu Loke et al., 2011), suggesting that moral judgment may have an impact on the top-down processing of pain empathy and that patients' antisocial behavior reduces pain empathy in readers. Therefore, readers may avoid pain stimuli after reading sad news with low morality, and the patient's harmful behavior may further reduce the readers' attention to the patient's pain. Worse yet, readers may even think that the patient should suffer from pain, thus causing even lower P3 and LPP amplitudes for patients suffering from pain than for neutral stimuli.

Another gratifying finding was that after reading high-morality news, individuals had higher amplitudes of P3 and LPP

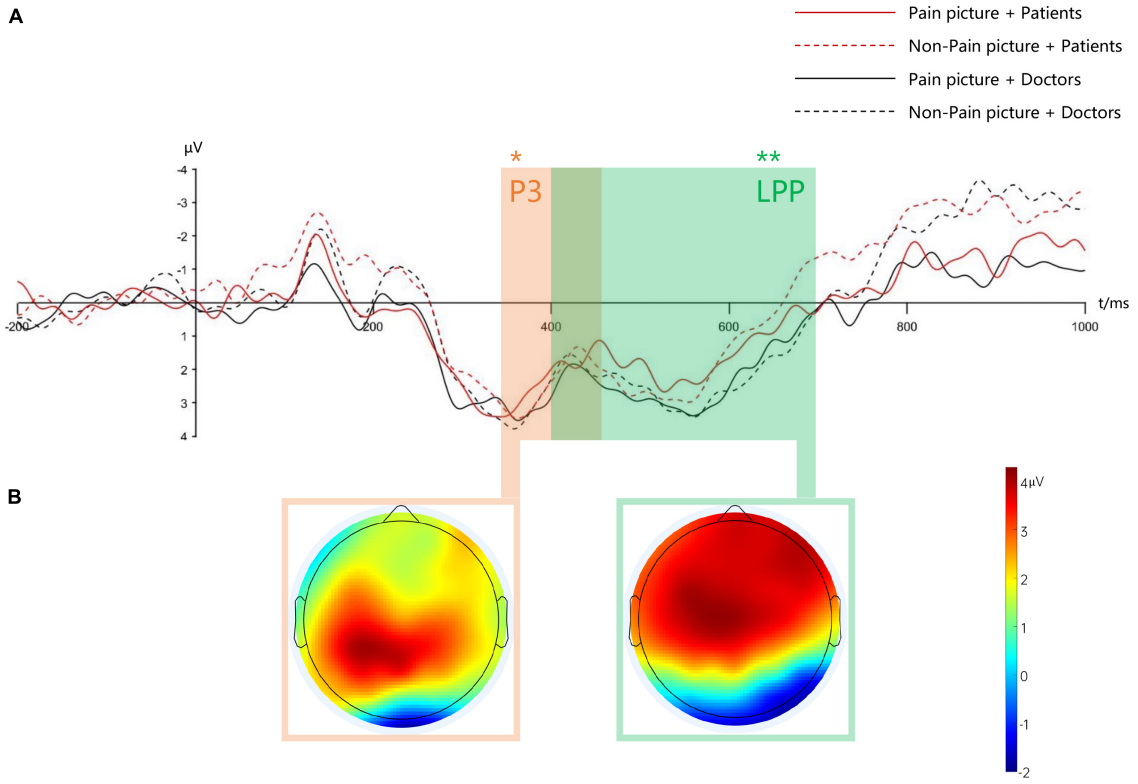

FIGURE 3
Mean waveform and mean topographic map under low moral text material. Panel **(A)** shows the mean waveforms of positive 300 (P3) and late positive potential (LPP) (selected electrode points are FCz, Cz, Pz, C3, C4, CP3, CP4), respectively, * indicates $p < 0.05$; ** indicates $p < 0.01$; panel **(B)** shows the mean topographic map of P3 (350–450 ms) and LPP (400–700 ms) for a specific time window.

for doctors' painful picture than those non-painful, indicating that individuals developed pain empathy for doctors. In high-morality news, both doctors and patients are subjects with positive images: Patients are grateful; doctors are positively recognized and highly commended by patients. Individuals may choose to empathy for higher-morality subjects through moral judgment (Smith and Frieze, 2003; Kirmani et al., 2017). Recently, a growing number of research works have focused on how objects' moral level affects participants' empathy for them. Compared with self-inflicted AIDS patients, people will show stronger empathy and willingness to donate to innocent AIDS patients (Guo et al., 2022); a fair person in pain causes increased activation of a brain region involved in empathy in the observer compared to an unfair person, for example, individuals have stronger P3 empathy responses to individuals who appear to be trustworthy, and even have negligible empathy responses to individuals who appear to be untrustworthy (Sessa and Meconi, 2015). Thus, moral judgments can facilitate the selection of appropriate social subjects to avoid social losses such as betrayal and deception by engaging with higher moral objects. In the process of empathy, the preference for "good people" stems from self-preservation, because people learn later in their upbringing that "good people" are less likely to betray them.

In summary, moral judgment influence pain empathy; however, do individuals respond differently to neuropathic pain empathy from different groups? In other words, is it possible that different brain response patterns characterize pain empathy differently between groups?

Individuals did not empathize with others indiscriminately, and the accuracy of individuals' classification of doctors or patients suffering from pain or not, was significantly greater than random levels on the whole-brain wave amplitude under high and low moral judgments. This indicates that individuals behave differently when they empathize with different groups suffering from pain. Individual empathy is moderated by group identity, such as social rank, and some researchers have established different social ranks by having participants perform a dot estimation task and by informing them of their achievement levels. The results showed that people had lower levels of pain empathy for higher-ranked individuals (Feng et al., 2016). In fact, people's empathy process is based on a social categorization model, i.e., they identify the social group to which the empathic target belongs during the empathy process (Read, 2021). In the present study, part of the reason for participants' differential empathy for doctors and patients may be the natural social identity division between doctors and patients.

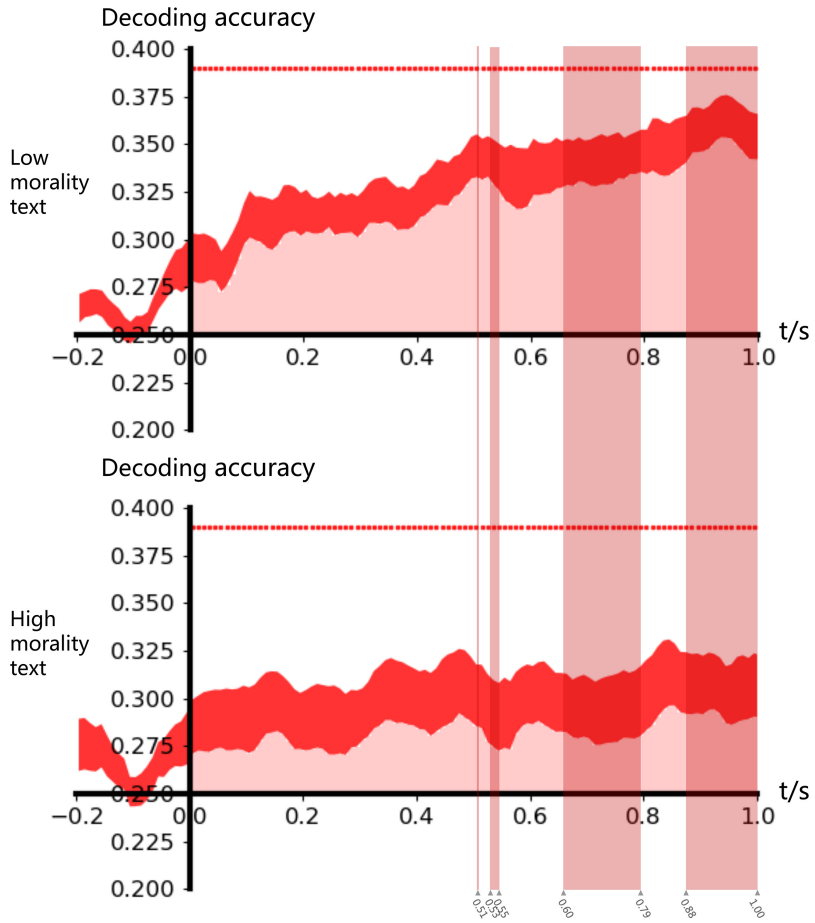

FIGURE 4
ERP decoding accuracy. In 0–1 s, the classification accuracy was significantly greater than the random classification level of 0.25. In 0.51 s, 0.53–0.55 s, 0.66–0.79 s, and 0.88–1 s, the classification accuracy under the influence of high moral text was significantly greater than that under the influence of low moral material ($p < 0.05$).

Notably, the classification accuracy was higher under low moral judgments than high moral judgments in the later components of ERP, suggesting that individuals' cognitive processing and evaluation of others' pain resulted in "differential" pain empathy for groups with different moral performance, supported by neural network patterns. Differences between explicit and implicit moral judgments exist mainly in the later stages of moral processing such as P3 and LPP (Zhan et al., 2018). This distinction is due to both the difference in social identity and the difference in assessment results at the moral level. Neural networks may be sufficient and necessary to distinguish between different groups (Vaughn et al., 2018), which may be equally applicable in pain empathy, suggesting that machine learning classification of brain representations could be used both as an intervention to reduce group bias and an objective diagnostic tool.

In general, news is a double-edged sword, individual pain empathy for doctors and patients is influenced by news-induced moral assessments to these two groups. People are more likely to empathize with ingroups than outgroups, and people may classify high moral individuals as ingroups and low moral individuals as outgroups based on their moral assessment of a person (Van et al., 2012), which may be the reason why moral assessments can trigger "differential" or even "biased" pain empathy. In this study, two representative news stories, "Patients Reward Doctors" and "Patients Harm Doctors," were selected. In the former, the doctor is a helper and commended by patients, which leave a good impression on the audience. In the latter, the patient is a perpetrator, which leads to indifference or even schadenfreude to the patient's pain. The doctor will feel respected and thus behave better; the patient may break down, which may exacerbate the disconnect between doctors and patients to some extent (Zaki, 2019a). When reporting, the media should weigh the positive and negative behaviors of doctors and patients. They should not label one as a victim or a victimizer to create public attention, gain more views, or generate traffic, and should instead clearly declare

the objective conflict of interest between doctors and patients (Al-Balushi, 2020).

This study only selected two representative types of doctor–patient news articles and moral judgment available was only for patients. Currently, most negative doctor-patient news articles depict patients causing physical harm to doctors, so most of the low-morality textual material in this experiment shows doctors who have been physically harmed, and such content may promote public empathy for doctors' pain. In the future, more ecological validity studies can be conducted from the perspectives of adding more types of doctor–patient news, expanding moral judgment to different subjects, producing globalized news materials, and further building mathematical models with large data samples to predict people's empathy for different groups after reading different moral performance news.

Conclusion

After low moral judgment of a patient, the individual is less concerned when the patient suffers pain; in the text where the doctor is thanked by the patient, the individual develops pain empathy for the doctor. Individuals' pain empathy for doctors and patients was more differentiated in "acquired" cognitive processing after low moral judgments of patients than after high moral judgments.

Individuals' pain empathy for the doctor–patient group was differentiated and moral judgments may have guided their biases.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary material**.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Wenzhou Medical University (2022-017). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HL, DZ, BY, and LY developed the original idea and the protocol and drafted the manuscript. YZ, HH, and HJ abstracted and analyzed data and improved the manuscript. HL, MC, QZ, and LY contributed to the critical revision of the manuscript for important intellectual content. MC provided guidance on research topics and design. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1037659/full#supplementary-material

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Adaptive neuroplasticity in the default mode network contributing to absence of central sensitization in primary dysmenorrhea

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Introduction: Primary dysmenorrhea (PDM), the most prevalent gynecological problem among women of reproductive age, presents as a regular pattern of cyclic menstrual pain. The presence or absence of central sensitization (i.e., pain hypersensitivity) in cases of PDM is a contentious issue. Among Caucasians, the presence of dysmenorrhea is associated with pain hypersensitivity throughout the menstrual cycle, indicating pain amplification mediated by the central nervous system. We previously reported on the absence of central sensitization to thermal pain among Asian PDM females. In this study, functional magnetic resonance imaging was used to reveal mechanisms underlying pain processing with the aim of explaining the absence of central sensitization in this population.

Methods: Brain responses to noxious heat applied to the left inner forearm of 31 Asian PDM females and 32 controls during their menstrual and periovulatory phases were analyzed.

Results and discussion: Among PDM females experiencing acute menstrual pain, we observed a blunted evoked response and de-coupling of the default mode network from the noxious heat stimulus. The fact that a similar response was not observed in the non-painful periovulatory phase indicates an adaptive mechanism aimed at reducing the impact of menstrual pain on the brain with an inhibitory effect on central sensitization. Here we propose that adaptive pain responses in the default mode network may contribute to the absence of central sensitization among Asian PDM females. Variations in clinical manifestations among different PDM populations can be attributed to differences in central pain processing.

KEYWORDS

primary dysmenorrhea, menstrual pain, central sensitization, pain hypersensitivity, default mode network, neuroplasticity, noxious heat, functional magnetic resonance imaging

Introduction

Affecting more than half of menstruating women worldwide, primary dysmenorrhea (PDM) refers to menstruation-related pain that is not associated with identifiable organic causes (Berkley, 2013). PDM subjects suffer from cramping pain cyclically emanating from the lower abdomen, beginning with the onset of menstrual flow and lasting 24–72 h (i.e., days 1–3 of each menstrual cycle). PDM also manifests as anxious and depressive symptoms and low self-rated quality of life (Lee et al., 2014). Researchers have proposed early-onset PDM as a plausible clinical precipitant for many chronic pain disorders that develop later in life, including irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, chronic low back pain, chronic headache, and fibromyalgia (Berkley, 2013).

Recent neuroimaging studies have revealed evidence suggesting that the brains of PDM females undergo reorganization (adaptive and maladaptive) in response to long-term dysmenorrhea. It is likely that maladaptive functional and structural alterations in the brain underpin the pathophysiology of PDM and corresponding sensory and affective elements of pain. They may also contribute to susceptibility to chronic pain disorders in later life (Tu et al., 2009, 2010; Wei et al., 2016a). In a previous study on the interaction of large-scale resting-state brain networks, we determined that among PDM females, the adaptive role of the default mode network (DMN) involves a dynamic transition from affective processing of pain salience to cognitive modulation of pain (Wu et al., 2016). In the context of interactions among large-scale brain networks, it appears that adaptive neuroplasticity may help to preserve the integrity of functional brain architecture, indicating a lack of overt psychosocial disturbances (Lee et al., 2018).

Central sensitization is defined as enhanced nociceptive signaling within the central nervous system causing hypersensitivity to pain (Woolf, 2011; Farmer et al., 2012). It can cause allodynia or hyperalgesia outside the referred area of pain (i.e., in remote or asymptomatic body sites) indicating pain amplification mediated by the central nervous system. The presence or absence of central sensitization in PDM is a contentious issue. Among Caucasians, the presence of dysmenorrhea is associated with elevated sensitivity to pain (regardless of location) throughout the menstrual cycle (Iacovides et al., 2015; Payne et al., 2017). Inconsistencies in the findings related to pain sensitivity among dysmenorrheic females can be partly explained by differences in experimental methodologies, such as the choice of noxious stimuli (thermal, electric, pressure, or ischemic pain), the location/tissue and the depth of experimental pain stimulation (somatic or visceral tissues), and outcome measures (thresholds or tolerance of pain) (Iacovides et al., 2015; Payne et al., 2017). In a previous study, we detected no evidence of central sensitization to cutaneous thermal pain among young Asian PDM females (Lee et al., 2014). This suggests that pain sensitivity may vary as a function of ethnic or psychosocial characteristics (Cardenas et al., 2004; Rahim-Williams et al., 2012). In the current study, we posit that variations in clinical manifestations among different PDM populations could be attributed to central processing and pain modulation in response to cyclic menstrual pain.

Pain is a complex, multidimensional experience with nociceptive, affective, and cognitive dimensions (Peyron et al., 2000; Garcia-Larrea and Peyron, 2013). Human neuroimaging studies have revealed a constellation of brain regions that are activated during the pain response, including the insula, the primary and secondary somatosensory cortices, the prefrontal cortex, thalamus, anterior and posterior cingulate, basal ganglia, and cerebellum (Coghill et al., 1999; Peyron et al., 2000; Hofbauer et al., 2001; Apkarian et al., 2005; Tracey, 2005; Schweinhardt and Bushnell, 2010). Note that these brain regions comprise the pain network. The tryptophan–kynurenine pathway and its metabolites also play an important role in neuroinflammation, which is intricately linked to the pathogenesis of chronic pain disorders. The tryptophan–kynurenine pathway provides a window by which to investigate the contribution of psychosocial and behavioral factors to central sensitization and the subsequent development of chronic pain disorders (Tanaka et al., 2021).

The mechanisms underlying central pain processing can be investigated by examining the brain responses evoked by inducing pain in an experimental setting (e.g., noxious thermal, electrical, pressure, or ischemic stimuli) while performing functional magnetic resonance imaging (fMRI). Neuroimaging studies have revealed that in several pain-related regions of the brain (e.g., the prefrontal cortex), the central processing of acute pain by patients with chronic pain disorders differs from that of healthy subjects (Apkarian et al., 2005; Schweinhardt and Bushnell, 2010). The prefrontal cortex is involved in the affective, cognitive, interoceptive, and memory components of the pain experience (Apkarian et al., 2005; Tracey, 2007), while the ventromedial region plays a causal role in the learning of fear as well as in the extinction of fear (Battaglia et al., 2020). One neuroimaging study on dysmenorrheic Caucasian females also reported that females with and without long-term menstrual pain differ in terms of the central processing of acute pain in the entorhinal cortex (part of the DMN) (Vincent et al., 2011).

In the current study, our aim was to investigate the brain responses evoked by heat pain to clarify the central mechanisms of pain processing among young Asian PDM females. We hypothesized that brain regions involved in pain processing/modulation and central sensitization may already have developed adaptive central mechanisms in response to cyclic menstrual pain. It is possible that central sensitization manifests as increased responsiveness to noxious stimuli in several pain-processing regions of the brain (Zambreanu et al., 2005). It has been suggested that central sensitization is maintained by the activity of the brainstem, such that any increase in the intensity of pain is reflected by activity in the primary somatosensory cortex (Lee et al., 2008). The DMN is generally not considered a part of the pain-processing network; however, it is integral to the dynamic pain connectome (Kucyi and Davis, 2015, 2017) and has been implicated in shaping individual differences in pain sensitivity (Emerson et al., 2014; Zhang X. et al., 2020). Our findings in previous work indicated that the DMN plays an adaptive role in the cognitive modulation of menstrual pain *via* interactions among the resting-state brain networks (Wu et al., 2016). Adaptive neuroplasticity in these brain regions may partly contribute to the absence of central sensitization and play a role in preserving the integrity of the functional brain architecture among young Asian PDM females (Lee et al., 2014, 2018).

Materials and methods

Subjects

The subjects in this study comprised a subset of the participants from our previous genetic/behavioral study of PDM (Lee et al., 2014), including those who were eligible for neuroimaging analysis

of evoked brain responses to heat pain. The inclusion criteria were as follows: (1) 20–30-year-old Asian (Taiwanese) female; (2) a regular menstrual cycle of approximately 27–32 days; (3) a history of menstrual pain longer than 6 months; (4) average menstrual pain under regular treatment with a rating higher than four on a verbal numeric rating scale (NRS, 0 = not at all, 10 = the worst imaginable pain) in the last 6 months; and (5) right-handedness, as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). The primary exception was the experience of menstrual pain intensity rated from none to mild (defined as NRS < 3). All PDM females were clinically examined and diagnosed in the gynecology clinic by the same certified gynecologist (H-TC) and underwent pelvic ultrasonography to exclude cases of secondary dysmenorrhea caused by organic pelvic diseases, such as endometriosis or adenomyosis. The inclusion criteria for healthy control females were similar to those for the PDM group, except that the subjects in the control group had no pain whatsoever during menses (NRS = 0). The exclusion criteria for all participants were as follows: (1) use of oral contraceptives, hormonal supplements, Chinese herbal medicine, or any centrally acting medication (e.g., opioid, anti-epileptics) within 6 months prior to the study; (2) pathological pituitary gland disease; (3) organic pelvic disease; (4) any psychiatric or neurological disorders (e.g., premenstrual dysphoric disorder); (5) previous brain surgery or head injury involving loss of consciousness; (6) immediate plans for pregnancy or a positive pregnancy test; (7) a history of childbirth; and (8) having a metal/pacemaker implant, claustrophobia, or any contraindications related to MRI. Note that no analgesics had been used by the subjects within 24 h prior to the study. The study was conducted in accordance with the Declaration of Helsinki under approval by the Institutional Review Board of Taipei Veterans General Hospital. All subjects signed a written informed consent form prior to participation in the study.

The initial enrollees included 106 PDM and 102 healthy control females who fulfilled the inclusion and exclusion criteria. Following enrollment in the neuroimaging experiments, 15 PDM and four control females were excluded due to incidental brain findings [e.g., normal brain variants, such as cavum septum pellucidum; and brain abnormalities, such as arachnoid cysts; for more details, see Li et al. (2015)], 9 PDM and two control females were excluded due to other physical conditions, 28 PDM and 39 control females were excluded because they did not complete neuroimaging experiments in both the menstrual and periovulatory phases, and 21 PDM and 21 control females were excluded for further neuroimaging analysis owing to significant head motion (translation >1.5 mm or rotation >1.5°) during the event-related fMRI scan. In addition, 2 PDM and four control females were excluded due to technical problems related to hormonal measurements. This resulted in the inclusion of 31 otherwise healthy females with PDM (age, 22.8 ± 2.67 years) and 32 education-matched, healthy control females (age, 23.4 ± 2.09 years) (see **Table 1** for demographic data and **Supplementary Figure 1** for the recruitment of subjects).

TABLE 1 Demographic data and baseline information of PDM and control groups.

	Control (n = 32)	PDM (n = 31)	P-value
Age (year)	23.4 ± 2.09	22.8 ± 2.67	0.098
Age at menarche (year)	12.4 ± 1.32	12.2 ± 1.35	0.801
Years of menstruation	11.0 ± 2.52	10.6 ± 3.09	0.498
Days of one menstrual cycle	29.5 ± 1.06	29.3 ± 1.37	0.750
Menstrual pain experience			
Years of dysmenorrhea history		8.6 ± 3.02	
Days of menstrual pain per cycle		2.2 ± 0.69	
Overall PRI (inception of study; range, 0–78)		34.4 ± 14.98	
Overall PPI (inception of study; range, 0–5)		3.0 ± 1.21	
Current PRI (MENS phase; range, 0–78)		30.0 ± 12.53	
Current PPI (MENS phase; range, 0–5)		2.7 ± 1.01	

PDM, primary dysmenorrhea; PPI, present pain intensity of the McGill Pain Questionnaire; PRI, pain rating index of the McGill Pain Questionnaire; MENS phase, menstrual phase. Data are presented as the means ± SD.

Experiment design

All of the subjects in the two groups underwent blood sampling for serum gonadal hormone assays, quantitative sensory testing, and brain MRI scans (T1 and event-related fMRI scanning of noxious heat stimulation) during the menstrual phase (i.e., painful phase, days 1–3 of the menstrual cycle) and periovulatory phase (i.e., non-painful phase, days 12–16 of the menstrual cycle). Ovulation was confirmed using a urinary luteinizing hormone test (Han Chiun Proper LH Rapid Test) to verify that the subjects were scanned during their periovulatory period.

Serum gonadal hormone assays

Sera extracted from blood samples drawn during the respective menstrual and periovulatory phases were stored for batch analysis using commercialized assays (UniCel DxC 800 Synchron Clinical Systems, Beckman Coulter, Inc., Brea, CA, United States). The total serum concentrations were determined using chemiluminescence immunoassays for estradiol and progesterone as well as radioimmunoassays for testosterone.

Quantitative sensory testing

Pain sensitivity throughout the menstrual cycle was quantitatively investigated by assessing thermal detection and pain thresholds in accordance with the established protocol (Rolke et al., 2006). Briefly, heat and cold stimuli were administered using a thermal stimulator (TSA 2001-II, MEDOC, Ramat Yishai, Israel) to bilateral periumbilical areas (T11-dermatome, referral area of menstrual pain) and forearm extensor areas (C7-dermatome, remote control area) during the menstrual and periovulatory phases. In each measurement, the baseline temperature of the thermode was set at 32°C. From this baseline temperature, all thresholds were obtained using the ramped stimulation method (1°C/sec). An ascending limit was used for heat simulation with the safety limit temperature set at 50°C for warm detection and pain. A descending limit was used for cold stimulation with the safety limit temperature set at 0°C for cold detection and pain. The temperature of the thermode increased or decreased to the target temperature (i.e., for the detection or pain thresholds) and returned to the baseline immediately. After determining the detection thresholds for cold

and warm first, we then determined the pain thresholds for cold and heat. Mean threshold temperatures were calculated by averaging three consecutive measurements.

Determining the individual-defined temperature indicating moderate heat pain

A thermal stimulator (TSA 2001-II, MEDOC, Israel) was attached to the left inner forearm using Velcro straps. In the menstrual and periovulatory phases, ramped stimulation (0.5°C/sec ascending from 32°C) was used to determine the minimum temperature at which that participant would describe the sensation as moderate pain at the level of NRS = 6. When participants entered the MRI room to undergo brain scans, the temperature indicating moderate heat pain was retested to ensure that their perception of heat pain intensity was unaffected by the environment. Matching pain intensity (set at NRS = 6) allowed us to investigate possible alterations in the central processing of an identical pain percept across menstrual cycle phases in females with and without PDM (Kucyi et al., 2016).

Heat stimulation under fMRI

In the fMRI scanning session for evoked brain responses, non-painful warm stimuli (WARM; set at 38°C) and moderate heat-pain stimuli (PAIN; set at the defined temperature of moderate heat pain, i.e., NRS = 6) were applied to the left inner forearm of each participant. We employed an event-related design with a stimulus (WARM or PAIN) presentation of 2.5 sec and an inter-stimulus interval of 30 sec (BASELINE; set at a temperature of 32°C). In each session, 9 WARM and 9 PAIN stimuli were presented in random order with intervening BASELINE periods (see **Supplementary Figure 2** for paradigm of experimental heat stimulation). Each experiment comprised two fMRI sessions, each of which used the same order of stimuli presentation. Each session took roughly 10 min. After completing each session, the participants were asked to rate the average pain intensity and describe the characteristics of the heat pain.

Brain MRI scanning

Event-related fMRI images were acquired using a 3.0 Tesla MRI scanner (Magnetom Trio Tim, Siemens, Erlangen, Germany) *via* echo-planar imaging (EPI) with the following scanning parameters: repetition time (TR) = 2,500 ms, echo time (TE) = 30 ms, 40 axial slices/image volume with slice thickness = 3.4 mm, and flip angle = 90°. Each session of EPI scanning consisted of 260 volumes. All subjects were scanned with their eyes open in a supine and relaxed position. T1-weighted 3-dimensional structural images were acquired using a magnetization-prepared rapid-acquired gradient echo sequence (MPRAGE) with the following scanning parameters: TR = 2,530 ms, TE = 3.03 ms, inversion time (TI) = 1,100 ms, flip angle = 7°, field of view = 224 × 256 mm^2, matrix size = 224 × 256, number of slices = 192, and slice thickness = 1 mm. Head cushions and earplugs were respectively used to reduce interference from head motion and ambient noise.

Image preprocessing

All EPI images were preprocessed using Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom[1]) in MATLAB (The MathWorks, Inc., Natick, MA, USA), as follows: correction of slice timing, realignment for head motion correction (6-parameter rigid body transformation), and spatial normalization. The time course of head motion for each subject was obtained by estimating the translation and rotation along each axis for 260 consecutive EPI volumes. Head motion can have a profound influence on fMRI analysis (Van Dijk et al., 2012); therefore, we excluded subjects who presented significant head motion (translation > 1.5 mm or rotation > 1.5°) of any volume from further analysis. Among the subjects that were retained for fMRI analysis (31 PDM and 32 control females), we found no main effects of group (PDM vs. control), menstrual cycle phase (menstrual phase vs. periovulatory phase), or interaction between them in terms of the root mean squares of overall translation and rotation parameters of head motion (all $P > 0.05$). The EPI images were spatially normalized using the SPM's standard EPI template in the Montreal Neurological Institute (MNI) space and re-sampled to an isotropic voxel size of 2 × 2 × 2 mm^3. The normalized images were then spatially smoothed using a 3D Gaussian kernel with a full width at half-maximum (FWHM) of 8 mm.

First-level fMRI analysis

First-level parameter estimates were compared using linear contrast (*t*-contrast) with temporal derivatives. Timing parameters were set as follows: inter-scan interval = 2.5 sec and microtime resolution = 40 with onset = 21. Head motion parameters estimated from rigid-body realignment were added as regressors of no interest to reduce the influence of head motion on fMRI analysis (Van Dijk et al., 2012). The default high-pass temporal filter was applied in SPM (cut-off period: 128 sec; 0.0078 Hz) to attenuate noise. Note that noxious heat stimuli can elicit perceptions other than pain. To avoid potential confounding effects of administering heat (i.e., focus on pain-specific effects) (Duerden and Albanese, 2013; van den Bosch et al., 2013), we created a PAIN versus WARM contrast for use in second-level analysis.

Second-level fMRI analysis: Group comparisons

The evoked brain responses related to PAIN versus WARM contrast were computed using one-sample *t*-tests for the PDM and control groups in the menstrual and periovulatory phases. We performed between-group comparisons to address the *state* (control vs. PDM in the menstrual phase) and *trait* (control vs. PDM in the periovulatory phase) effects of cyclic menstrual pain on evoked brain responses to noxious heat. *State*-related effects are acute menstrual pain-primed, whereas *trait*-related effects exist even without acute menstrual pain. Gonadal hormones may have an influence on

1 http://www.fil.ion.ucl.ac.uk/spm

pain-related brain activation (Veldhuijzen et al., 2013), and trivial non-significant differences were noted between the individual-defined temperature of cutaneous heat stimulation in the PDM and control groups (Table 2); therefore, serum gonadal hormone levels (estradiol, progesterone, and testosterone) and temperature indicating moderate heat pain (NRS = 6) were entered as covariates in the statistical model of SPM to obtain pain-specific functional correlates. Significance was set at the uncorrected voxel level of $P < 0.005$, followed by a family-wise error rate-corrected cluster level of $P < 0.05$. The anatomic regions of cluster maxima that show significant differences in the evoked brain responses were labeled according to the Talairach Daemon database (Lancaster et al., 2000) and Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

Correlation between evoked brain responses and the temperature associated with moderate heat pain

The temperature of noxious heat can influence the magnitude and extent of brain activation in healthy controls (Becerra et al., 1999; Kong et al., 2010); therefore, we examined the relationship between the evoked brain response of significant clusters and the temperature associated with moderate heat pain in the control and PDM groups. The evoked brain response of each cluster that showed a significant difference for the between-group comparisons of noxious heat stimulation was extracted. Two-tailed partial correlation analysis was performed with serum estradiol, progesterone, and testosterone levels entered as covariates. The significance level for the partial correlation analysis was set at $P < 0.05$.

Statistical analysis

Two-sample *t*-tests or the Mann–Whitney *U* tests (if the data did not conform to normal distribution) were used to examine between-group differences in demographic data. In assessing serum gonadal hormone levels, quantitative sensory testing, and the individual-defined temperature of moderate heat pain during two menstrual cycle phases, general linear models with a repeated-measures design were used to examine the possible effects of group (PDM vs. control) and menstrual cycle phase (menstrual phase vs. periovulatory phase) as well as the interaction between them. SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, United States) was used for all statistical analysis. The data are presented as mean ± SD, and the results were considered significant at $P < 0.05$ (two-tailed).

Results

Demographic data

No significant between-group differences were observed in terms of age, age at menarche, years of menstruation, or the average duration of a menstrual cycle. The PDM group had a long history of cyclic menstrual pain (8.6 ± 3.02 years), with pain during a single menstrual cycle lasting 1–3 days (2.2 ± 0.69 days). The overall menstrual pain experience, as assessed by the pain rating index (34.4 ± 14.98) and present pain intensity (3.0 ± 1.21) of McGill Pain Questionnaire, confirmed that the PDM group experienced long-term cyclic menstrual pain of moderate to severe degree (Table 1).

Serum gonadal hormone assays

We observed a significant main effect of menstrual cycle phase, but no main effect of group or the interaction between group and menstrual cycle phase, on serum estradiol, progesterone, and testosterone levels. The serum estradiol, progesterone, and testosterone levels were significantly higher during the periovulatory phase than during the menstrual phase in both the PDM and control groups (Supplementary Table 1).

Quantitative sensory testing

In line with one previous report (Rolke et al., 2006), we observed no right-left differences in any of the measured thresholds of heat or cold pain. We therefore averaged the bilateral values of the corresponding dermatomes to perform group comparisons. The measured thresholds of heat and cold pain in our study cohort were similar to the values obtained among Caucasians (Rolke et al., 2006). No main effects of menstrual cycle phase, group, or interactions between them were observed in the measured thresholds of heat or cold pain in the respective T11- and C7-dermatomes (Table 2). In accordance with our previous report with a larger sample (Lee et al., 2014), we detected no regional or generalized hypersensitivity to cutaneous thermal pain among the young Asian PDM females.

Evoked brain responses to heat pain

We observed no main effects of menstrual cycle phase, group, or interaction between them in terms of the minimum temperature indicating moderate heat pain (i.e., the temperature that elicited heat pain of NRS = 6 during fMRI scanning) (Table 2). The stimulation paradigm of cutaneous heat pain revealed pain-related brain activation in the anterior and posterior cingulate gyrus, insula, postcentral and precentral gyri, cerebellum, thalamus, and basal ganglia associated with PAIN versus WARM contrast (at family-wise error rate-corrected cluster level of $P < 0.05$). Our findings were in line with a previous meta-analysis on the localization of heat pain-related brain activation (Duerden and Albanese, 2013). Average group responses to cutaneous heat pain in the menstrual and periovulatory phases are listed in Supplementary Tables 2–5 and Supplementary Figures 3–6.

In the menstrual phase (painful phase), brain responses to cutaneous heat pain in the PDM group in the left precuneus and right precuneus/posterior cingulate [i.e., posterior part of the DMN (pDMN)] were significantly lower than in the control group (Table 3 and Figure 1). In the periovulatory phase (non-painful phase), no significant differences were observed between the groups in terms of brain responses to cutaneous heat pain. PDM females experiencing acute menstrual pain presented a blunted pDMN response to experimental heat pain, which is

TABLE 2 Results of repeated-measures ANOVA of quantitative sensory testing and temperature of moderate heat pain: Effects of group and menstrual cycle phase.

			Main effect		Interaction
	Control (n = 32)	PDM (n = 31)	Group (P)	Phase (P)	Group*Phase (P)
Heat pain threshold–C7 (°C)					
MENS phase	45.0 ± 3.33	44.0 ± 3.55	0.329	0.868	0.606
POV phase	44.8 ± 3.51	44.2 ± 2.92			
Heat pain threshold–T11 (°C)					
MENS phase	43.9 ± 3.20	43.1 ± 3.15	0.243	0.101	0.554
POV phase	44.4 ± 3.08	43.4 ± 3.14			
Cold pain threshold–C7 (°C)					
MENS phase	9.1 ± 10.67	11.9 ± 10.52	0.458	0.887	0.355
POV phase	10.2 ± 10.73	11.1 ± 11.14			
Cold pain threshold–T11 (°C)					
MENS phase	11.0 ± 11.07	13.6 ± 11.45	0.681	0.872	0.097
POV phase	12.7 ± 10.98	12.2 ± 10.59			
Temperature of moderate heat pain (°C)					
MENS phase	45.2 ± 2.29	45.3 ± 1.98	0.700	0.072	0.643
POV phase	44.7 ± 2.88	45.0 ± 1.94			

ANOVA, analysis of variance; PDM, primary dysmenorrhea; MENS phase, menstrual phase; POV phase, periovulatory phase. Data are presented as the means ± SD.

TABLE 3 Significant reductions in evoked brain responses to cutaneous heat pain in the PDM group (menstrual phase).

Regions of reduced response	BA	Cluster size (voxels)	t score	z score	Peak MNI coordinate		
					x	y	z
Left precuneus	7/31	589	3.81	3.58	−10	−48	48
Right precuneus/posterior cingulate	31/7	255	3.79	3.56	12	−62	34

BA, Brodmann area; MNI, Montreal Neurological Institute; PDM, primary dysmenorrhea.

a phenomenon that is unlikely to occur without concomitant menstrual pain.

Correlation between evoked brain responses and the temperature of moderate heat pain

Evoked brain responses in clusters presenting significant between-group differences during the menstrual phase were extracted to examine their correlation with the temperature indicating moderate heat pain (NRS = 6). In the control group, the evoked pDMN response during the menstrual phase was positively correlated with the temperature of moderate heat pain (P = 0.012 and r = 0.440 in the left precuneus; P = 0.018 and r = 0.415 in the right precuneus/posterior cingulate) after controlling for fluctuations in serum gonadal hormone levels. This positive correlation is in agreement with a previous fMRI study, which reported a correlation between the temperature deemed noxious and the degree of activation in the posterior cingulate gyrus (Becerra et al., 1999). Note, however, that this positive correlation was not observed in the PDM group (P = 0.057 and r = 0.345 in the left precuneus; P = 0.060 and r = 0.342 in the right precuneus/posterior cingulate) (**Figure 2**). PDM females experiencing acute menstrual pain presented a de-coupling between the minimum temperature that elicited moderate heat pain and the brain responses evoked in the pDMN.

Correlation between evoked brain responses and PDM characteristics

We also investigated the influence of PDM characteristics on evoked brain responses to noxious heat by examining the correlation of the evoked pDMN responses that showed significant between-group differences with years of dysmenorrhea history as well as current menstrual pain experience in the PDM group. After controlling for fluctuations in serum gonadal hormone levels, we observed no significant correlation between evoked pDMN responses and dysmenorrhea history or pain rating index/present pain intensity of McGill Pain Questionnaire (all $P > 0.05$). The evoked responses to noxious heat in the pDMN were unrelated to the clinical characteristics of PDM, and the presence of acute menstrual pain *per se* is likely responsible for altered responses in the pDMN.

Discussion

In the current study [an extension of our previous work; (Lee et al., 2014)], we found no firm evidence supporting the presence

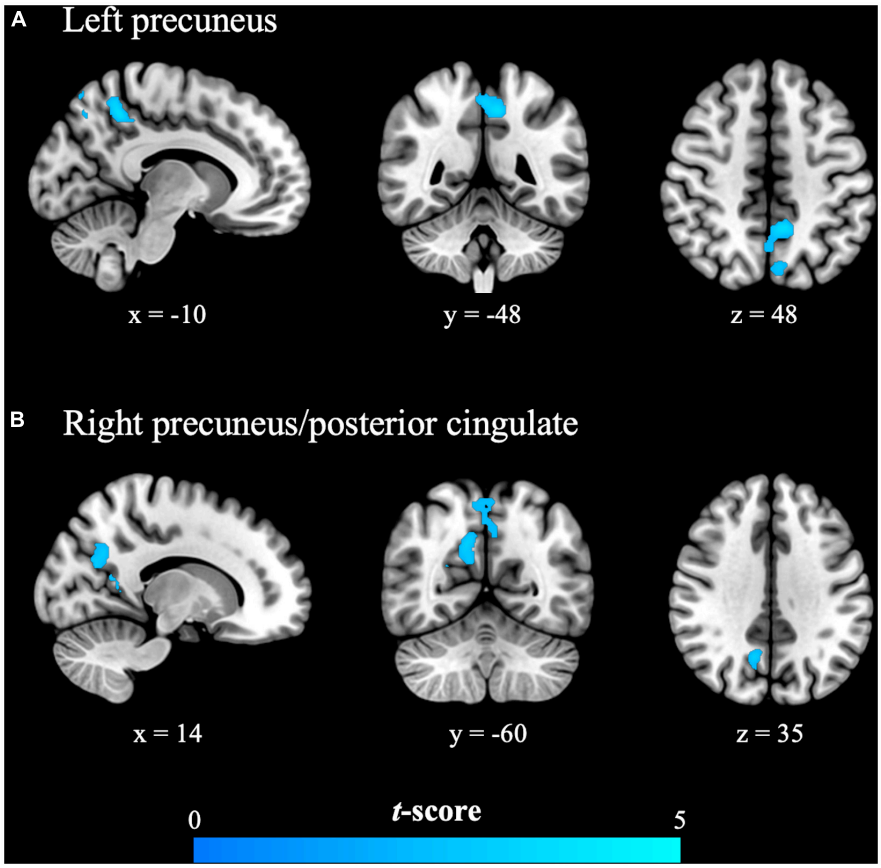

FIGURE 1
The primary dysmenorrhea group presented significantly reduced evoked brain responses to cutaneous heat pain in the **(A)** left precuneus and **(B)** right precuneus/posterior cingulate during the painful menstrual phase. Significance was set at the uncorrected voxel level of $P < 0.005$, followed by the family-wise error rate-corrected cluster level of $P < 0.05$. The cold color (blue) indicates the observed reduction in the evoked brain responses in females with primary dysmenorrhea.

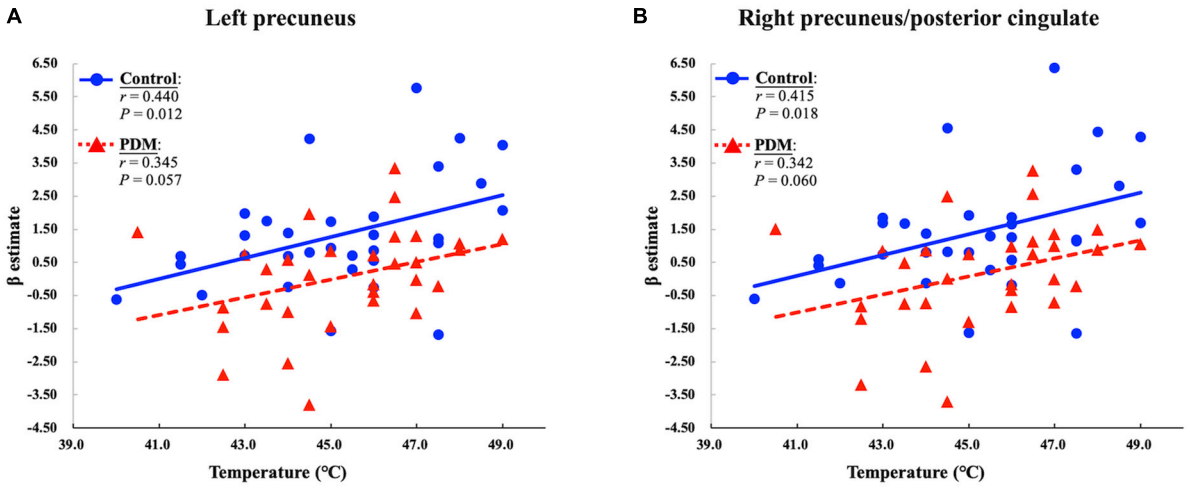

FIGURE 2
The primary dysmenorrhea (PDM) group presented a reduced positive correlation between the individual-defined temperature of moderate heat pain and the responses evoked in the **(A)** left precuneus and **(B)** right precuneus/posterior cingulate during the painful menstrual phase. *P* and *r* values for the partial correlation analysis in the control and PDM groups are presented.

of central sensitization to noxious heat stimulation among young Asian PDM females in terms of quantitative sensory testing or neuroimaging data. The subjects did not exhibit heightened pain sensitivity to cutaneous thermal stimuli (quantitative sensory testing or temperature of moderate heat pain), during either the painful menstrual or non-painful periovulatory phases. Compared to healthy

controls, the PDM subjects did not present elevated evoked responses (magnitude or spatial extent) in pain-processing brain regions or regions associated with central sensitization [e.g., brainstem and primary somatosensory cortex (Lee et al., 2008)] during the menstrual or periovulatory phases. Our findings are consistent with a recent study showing negative findings with respect to the sensitivity and neural processing of experimental visceral pain in PDM subjects (Böttcher et al., 2019).

During the menstrual phase, PDM females with acute menstrual pain exhibited significantly reduced responses to noxious heat in the pDMN. Note that in the menstrual phase, the positive correlation between evoked pDMN responses and the temperature of moderate heat pain in healthy controls was less pronounced in PDM females. These findings imply that young Asian PDM females experience a blunted response to the effects of noxious heat and a de-coupling of the pDMN during the painful menstrual phase (but not in the non-painful periovulatory phase). We speculate that this is an adaptive mechanism aimed at reducing the impact of cyclic menstrual pain on the brain, which may have an inhibitory effect on central sensitization. Brain regions of the pDMN are important mediators of pain in healthy subjects, which affect the relationships among stimuli intensity, pain rating/sensitivity, and evoked brain responses to noxious heat (Becerra et al., 1999; Atlas et al., 2014; Damascelli et al., 2021) or electric stimuli (Goffaux et al., 2014). Previous structural MRI studies also reported a correlation between changes in gray matter in the pDMN and sensitivity to noxious heat (Emerson et al., 2014; Zhang X. et al., 2020). This study provides further evidence that the pDMN is functionally engaged in the processing of noxious heat stimulation in healthy subjects (Becerra et al., 1999).

A secondary issue in the current study was resting-state neuronal activity in the clusters of pDMN presenting significantly reduced responses to noxious heat in PDM subjects (i.e., the left precuneus and right precuneus/posterior cingulate). This involved computing regional spontaneous neuronal activity using an amplitude of low-frequency fluctuation (ALFF) (Zang et al., 2007) and a fractional amplitude of low-frequency fluctuation (fALFF) (Zou et al., 2008) in conjunction with the local synchronization of resting-state brain activity using regional homogeneity (ReHo) (Zang et al., 2004). The average ALFF, fALFF, and ReHo values in the two pDMN clusters showed no significant between-group differences during the menstrual phase (**Supplementary Table 6**). These findings provide additional evidence that the altered responses to noxious heat cannot be ascribed to the altered resting activity in the pDMN. It further supports the assertion that pDMN plays an adaptive rather than maladaptive role in response to cyclic menstrual pain among PDM females.

Several studies have reported that PDM females exhibit functional and structural alterations in brain regions of the DMN. PDM females presented alterations in metabolism, spontaneous neuronal activity, cerebral blood flow, and functional connectivity in the precuneus and posterior cingulate cortex (Tu et al., 2009; Jin et al., 2017; Liu et al., 2017; Zhang et al., 2019; Zhang Y. N. et al., 2020). PDM females also presented alterations in gray matter volume and cortical thickness in the precuneus. Note that the extent of the alterations is correlated with the duration and menstrual pain experience of PDM (Tu et al., 2010, 2013; Liu et al., 2016). More importantly, previous studies on cross-network interactions have reported that the DMN exhibits adaptive responses to cyclic menstrual pain in PDM females (Wu et al., 2016; Dun et al., 2017). Reduced functional coupling of the DMN from the salience network implies that the interoceptive awareness of pain and attention to pain are inhibited (Wu et al., 2016; Dun et al., 2017). Furthermore, enhanced functional coupling between the DMN and the executive control network is an indication of adaptive functional reorganization enhancing the cognitive modulation of menstrual pain among these young Asian PDM females (Wu et al., 2016). In light of evoked brain responses to acute pain and resting-state cross-network interactions, this study provides important evidence supporting the assertion that the DMN plays an adaptive role in the clinical manifestations observed in young Asian PDM females. We speculate that the adaptive neuroplasticity of the DMN in response to cyclic menstrual pain in this and previous studies (Wu et al., 2016; Dun et al., 2017) helps to maintain the overall integrity of the resting-state functional brain architecture, leading to normal psychosocial outcomes (Lee et al., 2018).

It appears that ethnic and genetic characteristics may play roles in the clinical manifestations (e.g., pain sensitivity) observed among PDM females. Imaging genetics studies of functional connectivity have indicated that the intricate interactions between the descending pain modulatory systems and genetic polymorphisms, including *BDNF* Val66Met (Wei et al., 2016b) and *OPRM1* A118G (Wei et al., 2017), may underpin individual differences in susceptibility to pain among Asian PDM females. Note that descending pain modulatory systems (periaqueductal gray matter) and DMN (posterior cingulate cortex) may be functionally linked in the endogenous modulation of pain (Zyloney et al., 2010) and associated negative psychological effects (e.g., pain rumination) (Kucyi et al., 2014). In the context of genetics, we speculate that the adaptive responses of the pDMN in PDM females during the menstrual phase may influence descending pain modulation to inhibit pain hypersensitivity. In the future, it may be possible to use imaging genetics in combination with noxious stimulation to delineate the mechanisms underlying ethnic or individual differences in the experience of pain and to clarify the mechanisms underlying the presence or absence of central sensitization among PDM females.

Our findings on dysmenorrheic Asian females differ from those in a previous fMRI study on dysmenorrheic Caucasian females (Vincent et al., 2011). In that study, the dysmenorrheic subjects exhibited enhanced evoked responses to noxious heat stimulation in the left entorhinal cortex (part of the DMN) during non-menstrual phases, and the effects were positively correlated with the severity of acute menstrual pain. In terms of ethnic differences, it appears that differences in the central processing of noxious heat play a role in the contradictory manifestations of pain sensitivity (i.e., absence or presence of central sensitization) between Asian and Caucasian dysmenorrheic females. Note that the discrepancies between the previous findings and those in the current study may be attributed to differences in the analytic methods and demographic characteristics of recruited subjects. In the current study, we limited the study cohort to PDM subjects with a confirmed diagnosis by a gynecologist, whereas the previous study may have included subjects with secondary dysmenorrhea. The mean age of subjects in the current study (23–24 years) was also younger than in the previous study (30–32 years of age). In the current study, pain-specific effects were examined by analyzing evoked brain responses derived from the PAIN versus WARM contrast, whereas Vincent et al. (2011) investigated the evoked brain responses to noxious heat directly (i.e., without eliminating the effects of temperature). Nonetheless, both studies indicated the presence of altered DMN responses to pain among young women with long-term dysmenorrhea. It may

be necessary to perform longitudinal follow-up studies to track the functional and structural alterations of DMN in response to cyclic menstrual pain.

Several limitations and future direction should be considered in the interpretation of our findings. To begin with, we used only noxious heat stimulation to investigate the effects of cyclic menstrual pain on pain responses in the brain. Future studies should use other methods of pain provocation to verify the generalizability of the current findings. It has been suggested that cold stimuli can predispose the subject to menstrual pain (Wang et al., 2022); however, the psychophysical findings of cold stimulation-based experiments have been inconsistent, particularly among studies of central sensitization in dysmenorrhea (Slater et al., 2015; Payne et al., 2019). Second, the subjective experience of pain and sensitivity to temperature can vary considerably among individuals, and researchers have reported high inter-subject variability in brain responses evoked by noxious stimuli (Davis et al., 1998). Genetic, psychological, sensory-cognitive, neuroanatomical, and environmental (including cultural and ethnic) factors may all contribute to the individual differences in the experience of pain (Apkarian et al., 2005; Kupers and Kehlet, 2006; Norbury et al., 2007; Erpelding et al., 2012; Emerson et al., 2014; Zhang X. et al., 2020) and variations in the clinical manifestations of pain among different PDM populations (Tu et al., 2009, 2010, 2013; Wei et al., 2016a,b, 2017; Wu et al., 2016). In the current experimental study, we did not address the complex interdependence of these factors. These issues will have to be taken into consideration in future research.

Conclusion

This study observed a blunted evoked response to noxious heat and a de-coupling of the pDMN among PDM females experiencing acute menstrual pain. These results indicate the presence of an adaptive mechanism reducing the impact of cyclic menstrual pain on the brain. This mechanism may also have contributed to the absence of central sensitization observed among these young Asian PDM females. Variations in clinical manifestations among different PDM populations can be attributed to distinct central processing and pain modulation in response to cyclic menstrual pain. The findings in this preliminary report will have to be verified in neuroimaging studies of PDM using a large sample of subjects with different ethnic attributions and a wider range of sensory modalities for pain provocation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

L-CL: conceptualization, investigation, formal analysis, data curation, writing—original draft, and visualization. Y-YC: conceptualization, investigation, formal analysis, data curation, and writing—original draft. W-CL and IL: investigation and data curation. C-JY: investigation and formal analysis. C-HL: formal analysis. H-TC: investigation and resources. L-FC: conceptualization, methodology, resources, and funding acquisition. J-CH: conceptualization, methodology, resources, writing—review and editing, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1094988/full#supplementary-material

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Cerebral cortical hemodynamic metrics to aid in assessing pain levels? A pilot study of functional near-infrared spectroscopy

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Introduction: Establishing an accurate way to quantify pain is one of the most formidable tasks in neuroscience and medical practice. Functional near-infrared spectroscopy (fNIRS) can be utilized to detect the brain's reaction to pain. The study sought to assess the neural mechanisms of the wrist-ankle acupuncture transcutaneous electrical nerve stimulation analgesic bracelet (*E-WAA*) in providing pain relief and altering cerebral blood volume dynamics, and to ascertain the reliability of cortical activation patterns as a means of objectively measuring pain.

Methods: The participants (mean age 36.6 ± 7.2 years) with the cervical-shoulder syndrome (CSS) underwent pain testing prior to, 1 min following, and 30 min after the left point Jianyu treatment. The *E-WAA* was used to administer an electrical stimulation therapy that lasted for 5 min. A 24-channel fNIRS system was utilized to monitor brain oxyhemoglobin (HbO) levels, and changes in HbO concentrations, cortical activation areas, and subjective pain assessment scales were documented.

Results: We discovered that HbO concentrations in the prefrontal cortex significantly increased when CSS patients were exposed to painful stimuli at the cerebral cortex level. The second pain test saw a considerable decrease in the average HbO change amount in the prefrontal cortex when *E-WAA* was applied, which in turn led to a reduction in the amount of activation and the size of the activated area in the cortex.

Discussion: This study revealed that the frontal polar (FP) and dorsolateral prefrontal cortex (DLPFC) were linked to the analgesic modulation activated by the *E-WAA*.

KEYWORDS

blood volume dynamics, functional near-infrared spectroscopy, pain tests, wrist-ankle acupuncture, cervical-shoulder syndrome

1. Introduction

Pain, according to the International Association for the Study of Pain, is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Developing an accurate and quantifiable way to measure pain is one of the most significant issues in neuroscience and clinical medicine.

The reliability of current pain assessment strategies, which primarily rely on patient-reported information and medical evaluations, is questionable when applied to different types and sources of pain. In addition, the variability of pain scores and the difficulty of obtaining accurate patient feedback may conceal the severity of their condition, resulting in inadequate treatment for those affected, including those affected by stroke or dementia, as well as infants. The scientific credibility of clinical analgesic interventions is drastically reduced by this phenomenon.

Recently, due to researchers gaining better comprehension of pain's causes and the brain's associated neural pathways, as well as the emergence of more sophisticated neuroimaging methods, it has been established that a quantitative assessment of brain nociception in living organisms is possible (Ploner et al., 2017). The various techniques of functional neuroimaging, such as functional near-infrared spectroscopy (fNIRS) (Rojas et al., 2017), functional magnetic resonance imaging (fMRI) (Wager et al., 2013), and electroencephalogram (EEG), as shown in **Table 1**, are widely utilized. fMRI is the most reliable method of monitoring brain activity related to pain, however, the use of this technique necessitates physical limitations on the head and body, making it impractical for use in actual clinical settings. In comparison, fNIRS is capable of monitoring local cerebral blood flow by detecting the alteration of near-infrared light wavelengths between 650 and 1,000 nm (Ferrari and Quaresima, 2012), and it is equipped with a high temporal resolution (Mehta and Parasuraman, 2013), motion compatibility (Scarapicchia et al., 2017), portability, and the ability to detect pain in actual time in intricate clinical contexts (Basura et al., 2018).

Research has indicated that fNIRS is a viable option for observing cortical hemodynamic changes in response to both experimentally and clinically induced pain in humans (Barati et al., 2013; Karunakaran et al., 2021). Studies involving pain have utilized fNIRS to measure the brain activity of newborns (Viola et al., 2014), healthy adults (Rojas et al., 2017; Han et al., 2018), and those with chronic pain (Xu et al., 2021) in response to unpleasant pain/stimuli. Studies have demonstrated that the introduction of unpleasant stimuli/pain to both healthy individuals and those with headaches is associated with an increase in prefrontal cortical activity (Brighina et al., 2011; Berger et al., 2019). Contrastingly, experiments on patients experiencing pain after a dental extraction (Derbyshire et al., 1999), people suffering from rheumatoid arthritis (Sandström et al., 2019), and even healthy participants (Sava et al., 2014) all demonstrated that painful stimulation causes a reduction in prefrontal cortical activity. The exact mechanism behind the prefrontal cortical activity caused by pain remains obscure, potentially being linked to the area of the body and the kind of pain experienced. A sizeable proportion of Chinese people suffer from cervical-shoulder syndrome (CSS), estimated to be between 8.1 and 19.1% (Lv et al., 2018), and this group was chosen as the sample for this research (Cai et al., 2016). Patients with CSS typically receive pharmacological and physical factor treatments in a clinical setting, which have been found to be effective in relieving their symptoms. Recently, a new method to wrist-ankle acupuncture-based electrical stimulation analgesic bracelet *E-WAA* has been made available, and is more popular among CSS patients due to its non-invasiveness, convenience, and effectiveness. The efficacy of medications such as morphine in relieving pain has been validated through objective techniques such as fMRI and fNIRS (Peng et al., 2018c). Despite this, the effectiveness of *E-WAA* has been demonstrated in several studies (Yang et al., 2019; Song et al., 2021; Du et al., 2022), its analgesic mechanism remains to be explored.

This study used fNIRS to assess the impact of *E-WAA* on cerebral blood flow and cortical activation patterns. We observed the fNIRS signals originating from the prefrontal area, which is an important part of pain perception, and examined how *E-WAA* impacted brain activity in our study. We delved deeper to determine if these hemodynamic shifts could be employed as a marker to measure the intensity of pain in CSS patients, thereby amplifying our knowledge of the hemodynamic answer to nociception in the prefrontal cortex of CSS patients.

2. Materials and methods

2.1. Participants

Participants were recruited from a representative sample of teachers and students affiliated with the University of Shanghai for Science and Technology, all of whom were members of a society of different ages. Previous studies have suggested that sex-related hormones may confound the relationship between pain and analgesic response (Fillingim and Ness, 2000; Mogil, 2020). Therefore, only males were selected as participants in the present study. All participants were right-handed to avoid changes in functional responses due to functional lateralization of the brain. We enlisted 20 male participants with CSS, with an average age of 36.6 years and a range of 7.2 years, who agreed to participate in the study after being informed of its details. All procedures were approved by the ChiRCT ethics committee.

2.2. Experimental devices

The point Jianyu was the most common pressure point in CSS patients, shown in **Figure 1A**, so we used the pressure pain at the point Jianyu as the pain model for this experiment (Amiri et al., 2021; Uysal et al., 2022). The degree of muscular tissue hardness is an objective indicator of the change in pain, and according to Chinese medicine theory, the higher the value of the acupoint tissue, the greater the degree of pain (Chen et al., 2007; Finocchietti et al., 2011). The criteria for pressure pain were that the same force (3–4 kg/cm^2) was applied to the patient to assess the patient's subjective visual analog scale (VAS) score, objective tissue stiffness, and objective cerebral blood flow changes under the same force. A rapid muscle measurement device (OE-220: Ito Corporation, Tokyo, Japan) was used to record the change in tissue stiffness at the participant's pain site before and after analgesia to reflect the change in pain.

Analgesic treatment is performed using a transcutaneous electrical nerve stimulation analgesic bracelet based on Chinese medicine wrist and ankle acupuncture (*E-WAA*) (Shi et al., 2020). It is a small portable non-invasive electrical stimulation device that can be worn on the wrist or ankle with Velcro to relieve or even

TABLE 1 Comparison of mainstream functional brain imaging techniques.

	fMRI	EEG	fNIRS
Detection parameters	BOLD signal	Neural activity	HbO
Detection depth	Superficial and deep cortex	Superficial cortex	Superficial cortex
Spatial resolution/cm	High	Low	Low
Temporal resolution/Hz	Low	High	High
Anti-motion interference	Low	Low	High
Anti-electromagnetic interference	–	Low	High
Application environment	Large, specialized instrument room and posture limitation	Not suitable for electromagnetic interference environment	No restrictions
Mobility	–	Low	High

treat pain in the human body, and its subjective analgesic effect has been demonstrated in several studies (Song et al., 2021; Du et al., 2022; Shi et al., 2022). The treatment site chosen for this experiment was the upper 5 area on the left hand, identified by the mechanism of WAA in traditional Chinese medicine (TCM) (**Figure 1B**). The upper 5 area is located in the middle of the palm surface between the two most prominent long palmar tendons and the radial carpal flexor tendon (Zhu et al., 2014). Due to the specificity of pain perception, the treatment parameters were self-adjusted: 0–100 V, 0–100 Hz.

To measure the changes in cerebral blood volume dynamics, we employed a continuous wave 24-channel fNIRS system (OXYMON MKIII; Artinis Co., Netherlands) using two wavelengths of near-infrared light (752 and 841 nm), as well as 24-channel probes (light sources and receivers). The distance between the light source and the receiver was 3 cm.

2.3. Experimental procedure

The study was conducted in an undisturbed laboratory where all lights were turned off (light intensity controlled below 100 lx). During the experiment, participants were expected to sit and remain as still as possible. The experimental procedures were performed by experienced traditional Chinese medical specialists.

The experimental procedure consisted of the first pain test-5 min of treatment-the second pain test-30 min of rest- the third pain test, with 1-minute rest intervals between blocks, as shown in **Figure 2**. The pain test consisted of 3 sets of 20 s of pressure pain and 20 s of rest. During the pain test, participants were simultaneously asked to score on a VAS. During the analgesic treatment, two output gold fingers of the *E-WAA* were placed on the participant's left hand in the upper 5 area for 5 min.

2.4. fNIRS and measurement items

Functional near-infrared spectroscopy calculates the variation of oxyhemoglobin (HbO) (Berretz et al., 2021) and deoxyhemoglobin concentrations according to the modified Beer–Lambert law (Hoshi, 2003). In the present experiment, HbO concentrations were used for analysis only because of their high signal-to-noise ratio (Lacerenza et al., 2020). Since the fNIRS signal acquired in this experiment was obtained by measuring through a head-mounted photopolar array cap consisting of 12 light sources and 8 detectors, the spatial position of each measurement channel was first calibrated during the analysis of the data. Five participants were first randomly selected as the base template for the fNIRS channel position alignment and used to estimate the prefrontal cortical area covered by the detectors. When the fNIRS photopolar array was placed on the participant's forehead, the positions of three cranial reference coordinates, namely the occipital ridge, the nasal root point, and the cranial capsule, were measured to translate the true stereotactic coordinates of the photopoles into the Montreal Neurological Institute (MNI) standard hemispheric regional coordinates used (Wagner et al., 2022). The locations of the 24 channels on the brain are shown in **Figure 3**.

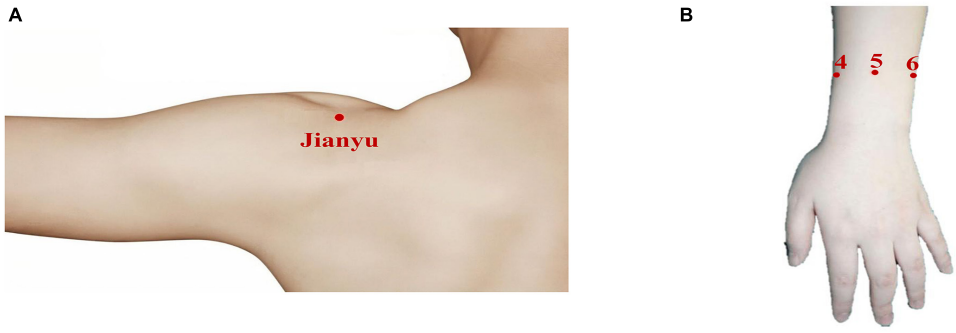

FIGURE 1
Schematic diagram of the positions of the experimental devices. **(A)** The pressure pain model—point Jianyu. Point Jianyu is situated on the front side of the shoulder blade, in the dip between the shoulder blade and the large protrusion of the arm bone (Tao et al., 2005). **(B)** The treatment site—the upper 5 area of the wrist. 4, 5, and 6 correspond to the upper 4 area, the upper 5 area, and the upper 6 area, respectively. The upper 5 area is located in the middle of the palm surface between the two most prominent long palmar tendons and the radial carpal flexor tendon.

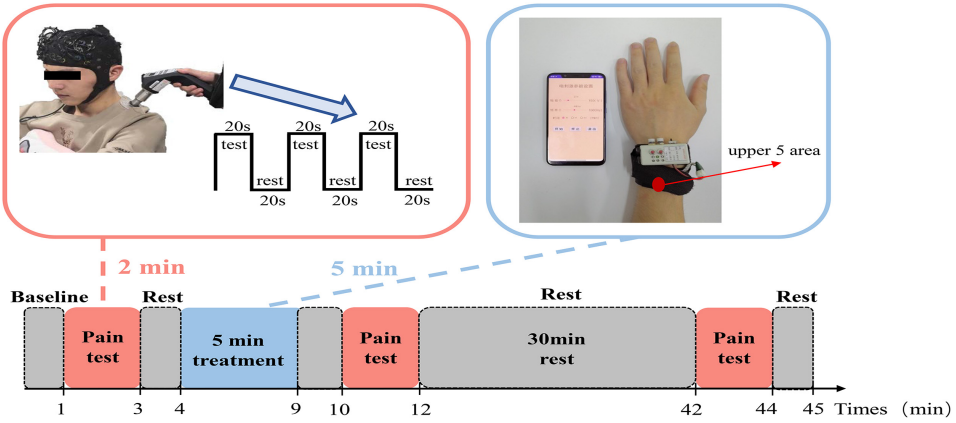

FIGURE 2
Experimental procedures.

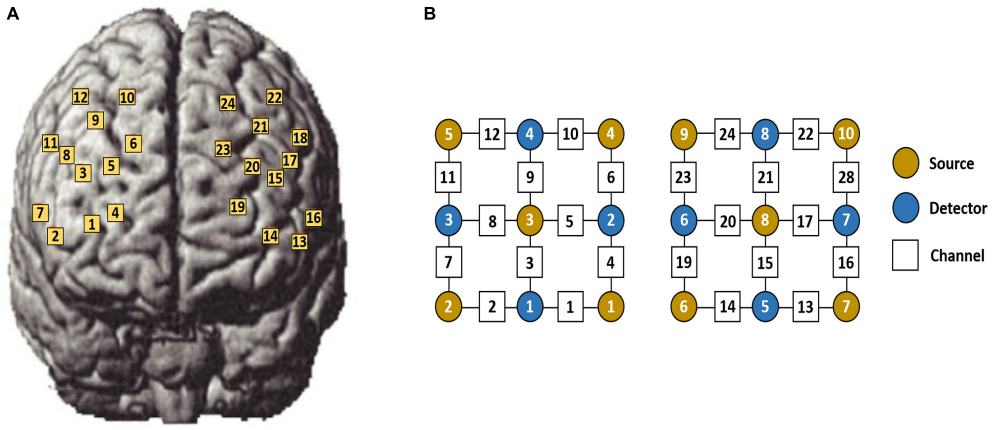

FIGURE 3
Functional near-infrared spectroscopy (fNIRS) photopole arrangement template. **(A)** Three-dimensional diagram of the distribution of 18 photopoles and 24 channels on the scalp surface. **(B)** Planar diagram of the photopolar template.

The initially acquired fNIRS data had more noise and interference and required further processing. The noise interference of the acquired cerebral blood oxygen signal mainly comes from (1) the Global drift of the baseline hemodynamic signal due to physiological activities such as heart rate (0.8–2.0 Hz) and respiration (0.13–0.33 Hz). (2) Spontaneous neural activities in the brain such as low-frequency oscillations (LFO, e.g., Mayer wave, 0.1 Hz) and ultra-low frequency oscillations (VLFO, 0.03 Hz). (3) Motion artifact interference. In this paper, wavelet analysis with higher frequency was used for noise and interference processing. Specifically, this study uses the hemodynamic response function (HRF) and wavelet-minimum description length algorithm (wavelet-MDL) to process the acquired fNIRS signal is processed (Jang et al., 2009; Tak et al., 2011) to remove low-frequency noise and motion artifact noise. Baseline fitting by least squares removes the baseline drift that may be caused by the device itself. We analyzed the hemodynamic response associated with the timing of painful stimuli to verify brain activation.

We performed spatial alignment of the acquired spatial data using NIRS_SPM (Ye et al., 2009), an open-source toolkit developed by the Korea Institute of Science and Technology based on Matlab scripts. Based on a probabilistic alignment algorithm, the channel coordinates of each participant were aligned to the MNI standard template space. The average MNI coordinates for the whole group were then calculated, and the spatial alignment results are shown in Table 2, including the MNI coordinates for each channel, as well as the corresponding neuroanatomical labeling (AAL) and Brodmann functional partitioning at the maximum probability for each channel. In this experiment, the frontal polar (FP) region and the dorsolateral prefrontal cortex (DLPFC) of the prefrontal cortex were the regions of interest (ROIs).

2.5. Statistical analysis

SPSS 21.0 statistical software was used for data analysis of VAS and tissue stiffness. The Shapiro–Wilk test was used to assess the normal distribution of the data. One-way repeated measures ANOVA with Bonferroni *post-hoc* test was performed on VAS and tissue stiffness parameters (expressed as mean ± standard

TABLE 2 The cortical locations corresponding to the channels.

Channels	MNI coordinates	BA	AAL	Channels	MNI coordinates	BA	AAL
1	(36, 65, 8)	10	Frontal_Sup_R-FP	13	(−51, 46, 3)	46	Frontal_Mid_R-DLPFC
2	(52, 48, 5)	46	Frontal_Mid_R-DLPFC	14	(−38, 63, 3)	10	Frontal_Sup_L-FP
3	(40, 55, 26)	46	Frontal_Mid_R-DLPFC	15	(−40, 54, 23)	46	Frontal_Mid_L-DLPFC
4	(26, 70, 13)	10	Frontal_Sup_R-FP	16	(−56, 33, 10)	45	Frontal_Inf_Tri_Lpars triangularis Broca's area
5	(29, 60, 29)	46	Frontal_Mid_R-DLPFC	17	(−46, 39, 30)	46	Frontal_Mid_R_R-DLPFC
6	(18, 60, 36)	9	Frontal_Sup_R-DLPFC	18	(−51, 26, 39)	46	Frontal_Mid_R_R-DLPFC
7	(58, 34, 12)	45	Frontal_Inf_Tri_Rpars triangularis Broca's area	19	(−25, 69, 13)	10	Frontal_Sup_L-FP
8	(47, 41, 32)	46	Frontal_Mid_R_R-DLPFC	20	(−29, 57, 28)	46	Frontal_Mid_L-DLPFC
9	(35, 42, 45)	9	Frontal_Mid_R-DLPFC	21	(−34, 42, 41)	9	Frontal_Mid_L-DLPFC
10	(22, 43, 51)	9	Frontal_Sup_R-DLPFC	22	(−40, 25, 52)	9	Frontal_Mid_L-DLPFC
11	(54, 24, 37)	46	Frontal_Mid_R_R-DLPFC	23	(−18, 61, 34)	9	Frontal_Sup_L-DLPFC
12	(41, 25, 53)	9	Frontal_Mid_R-DLPFC	24	(−21, 44, 50)	9	Frontal_Sup_L-DLPFC

TABLE 3 Comparison of VAS and tissue stiffness for three pain tests.

Indicator	*n*	The first pain test	The second pain test	The third pain test	*F*	*P*
VAS	20	5.33 ± 1.41	4.00 ± 1.12	3.78 ± 1.30	14.041	<0.001*
Tissue stiffness/%	20	57.63 ± 18.75	48.25 ± 8.49	47.67 ± 14.35	3.619	0.042*

*$P < 0.05$.

deviation) for three pain tests that obeyed normal distribution. $P < 0.05$ was considered a statistically significant difference.

In addition, we used the statistical parameter mapping NIRS-SPM (SPM 8) tool in NIRS-lab 2017.6 and the Shapiro–Wilk test to analyze and verify the normality of the fNIRS data. To quantify the prefrontal cortical hemodynamic response to pain tests, a general linear model (GLM) was first fitted to the fNIRS data, and then the values obtained from the GLM for pain stimulus intervals and rest intervals were interpolated and smoothed over the general human brain. The expected Eulerian feature method based on Lipschitz-Killing curvature was used to control for group errors. The degree of activation of each channel was expressed as a regression coefficient (β), and Bonferroni correction was then used for multiple comparisons. The differences between the values were ascertained by conducting an independent sample *t*-test, and then a one-way ANOVA was used to compare the groups, with a significance criterion of $P < 0.05$ for all analyses.

3. Results

The data in Table 3 reveals that there was a significant change in VAS and tissue stiffness between the three pain assessments, displaying a substantial divergence in VAS and tissue stiffness before and after treatment ($F = 0.041$, $P < 0.001$; $F = 3.619$, $P = 0.042$). The *post-hoc* tests showed that the differences between pre-treatment and 1-minute post-treatment, as well as 30 min post-treatment, were statistically significant, with $P < 0.05$. And the results of the tests between 1 and 30 min post-treatment had a *P*-value of 1.00, which is higher than 0.05, suggesting that there was no substantial variation. The present results confirm that we induced analgesia, as known from previous studies (Shi et al., 2022), *E-WAA* was able to significantly reduce participants' VAS and tissue stiffness.

A total of 24 channels of fNIRS signals were acquired, 4 of which were in the FP–Ch1, Ch4, Ch14, and Ch19–and the remaining 18 channels were situated in the DLPFC- Ch2, Ch3, Ch5, Ch6, Ch8–Ch13, Ch15, Ch17, Ch18, and Ch20–Ch24, respectively. Figure 4 illustrates the alterations in the average HbO concentration of the ROI-associated channels of the participants over the three pain tests. The graph indicates that the average HbO concentration had an impressive recurrent pattern over the three pain trials. When participants received a pain stimulus (represented by gray shading in the graph) the ROIs were activated, which was evidenced by a steadily increasing graph culminating in a peak. Following treatment with *E-WAA*, the average central HbO concentration in the second pain test (red curve) was notably lower than that of the initial pain test (blue curve) after 1 min. Following 30 min of rest, the average central change in HbO concentration for the third pain test (green curve) was comparable to the preceding two pain tests.

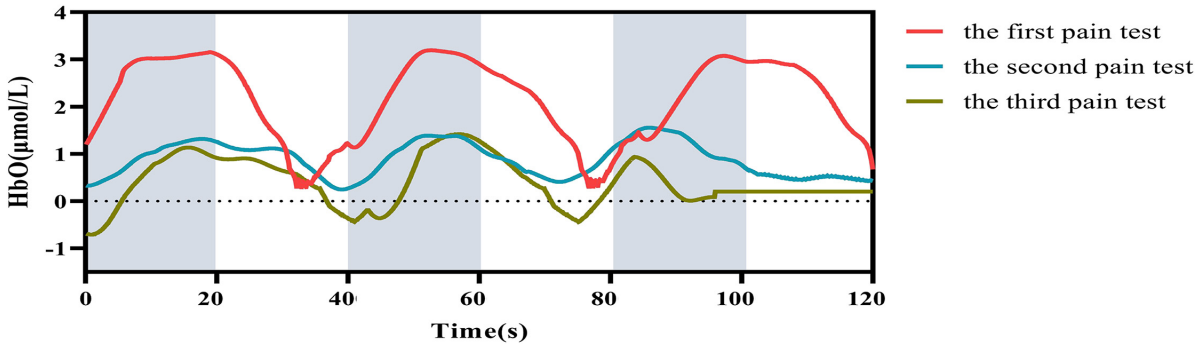

FIGURE 4
Time series of changes in mean HbO concentrations for three pain tests. The solid line indicates the average of the concentrations, red indicates the first pain test, blue indicates the second pain test, and green indicates the third pain test. The shaded part indicates the pain stimulation task, which lasted 20 s.

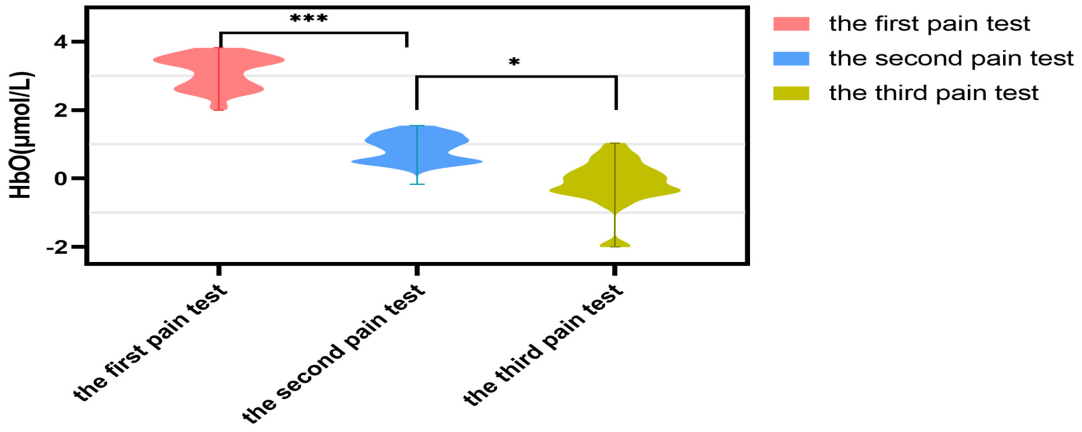

FIGURE 5
Differences in HbO levels between the three pain tests. *$P < 0.05$, ***$P < 0.001$.

Moreover, Figure 5 illustrates the contrast in the mean HbO concentrations for the ROI when subjected to the three pain tests. The ANOVA results revealed a notable reduction in mean HbO levels for participants in the second pain test when compared to the first one, which was statistically significant ($P = 0.001$). Despite this, the decline in HbO levels remained statistically significant when the third pain test was conducted compared to the second pain test ($P = 0.034$).

The prefrontal region of the brain is the primary focus of Figure 6, which shows the cortical activation outcomes of the participants' ROIs for the three pain tests. The findings revealed that during the three pain experiments, the participants' cerebral cortex exhibited a variety of activation degrees and ranges, distinguished by colors representing the intensity of the neural activation, from dark red to light yellow, signifying a progressive increase in activation. The initial experiment indicated that the FP and DLPFC areas of the brain were highly stimulated when the participants experienced pain in their point Jianyu (as seen in Figure 6A). Following electrical stimulation treatment, a second pain test was conducted 5 min later, which showed a considerable decrease in FP activation amongst the participants, whereas DLPFC had almost no detectable activation (Figure 6B). Upon the administration of the third stimulus, a limited region of FP was triggered within the prefrontal cortex of the individuals (Figure 6C). The results of the *E-WAA* treatment, combined with a period of recuperation, suggested that the participants' ROI was less responsive to painful stimuli, resulting in generally decreased activation levels.

In addition, Figure 7 displays the regression coefficients (β) for the 3 experimental conditions at the 2 ROIs, which were analyzed statistically. The β values of both ROI regions were consecutively lower for all three pain tests and the first two tests created considerable disparities in the stimulation intensities of the FP and DLPFC regions (FP: $P < 0.05$; DLPFC: $P < 0.001$).

4. Discussion

Most pain assessment methods are based solely on patient-reported responses, which clearly renders them subjective rather than objective. In this experiment, an OE-220 tissue hardness meter is employed to measure the alteration in muscle firmness in numerical terms, thus allowing for a relatively impartial evaluation of the impact of pain on muscle tension. The OE-220 takes the

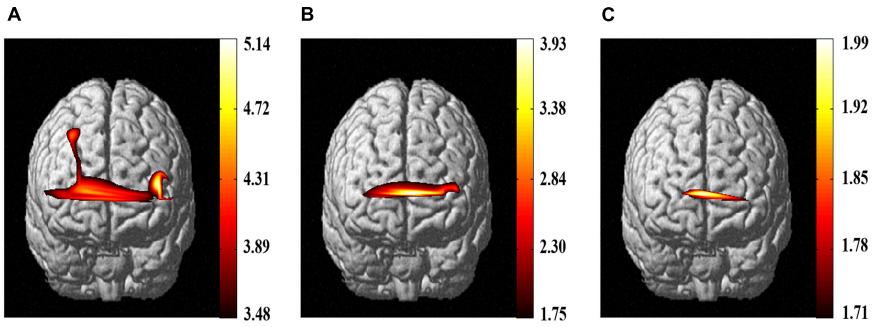

FIGURE 6
Outcomes of brain activity in response to three pain tests. **(A)** The first pain test. **(B)** The second pain test. **(C)** The third pain test. The colored bars on the right graph indicate *t*-values.

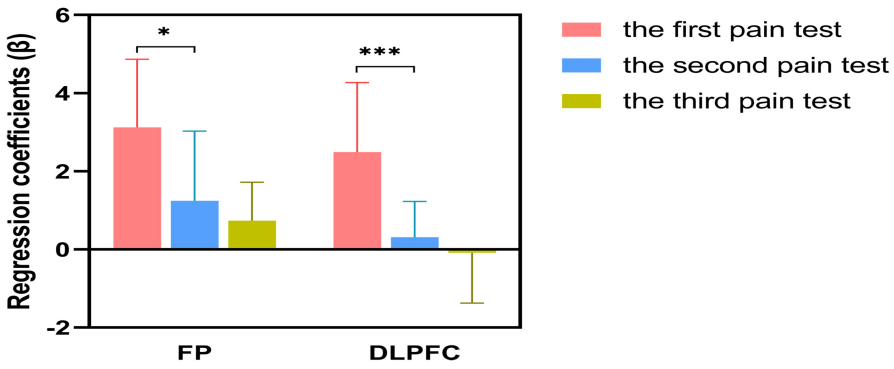

FIGURE 7
The β values of the regions of interest (ROI) were extracted from the results of the three pain tests. *$P < 0.05$, ***$P < 0.001$.

mean of three measurements to compensate for any potential momentary discrepancies in the readings. The data in Table 3 showing the single factor variance of VAS and tissue stiffness confirm previous findings that electrical stimulation therapy can provide immediate and efficient pain relief. Through the activation of nerve endings, electrical stimulation can induce a form of pain relief that is not dependent on its physical location. A pain patient's lesion site has a heightened sensory threshold, making them more sensitive to mild stimuli like electrical stimulation, which can lead to beneficial results such as reduced muscle spasms, improved circulation, and decreased pain when compared to a healthy individual. Conversely, the gate control theory of pain states that transcutaneous electrical nerve stimulation (TENS) stimulation leads to the activation of wide-diameter Aβ fibers and the inhibition of the painful feelings of the skin area nearby, which are generated by small-diameter, slow-conducting Aα and C fibers in the dorsal horn.

This research investigated the hemodynamic effects on the prefrontal cortex associated with the utilization of TENS analgesia as a means of furthering exploration into neural modulation. The prefrontal cortex is mainly connected to how the body and mind respond to pain. Various methods of alleviating discomfort have been identified, such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation, antidepressant medication, acupuncture, cognitive-behavioral therapy, mindfulness, music, exercise, assistance from a partner, empathy, meditation, and prayer (Ren et al., 2017). Previous research has elucidated the part that the prefrontal cortex plays in placebo analgesia, as well as the relationship between pain and depression, anxiety, and cognitive decline (Peng et al., 2018b). This experimental study examined the FP and DLPFC, two key regions of the prefrontal cortex. The results of Figures 4, 5 demonstrate that CSS sufferers were responsive to painful stimuli, as their HbO levels noticeably changed when subjected to pain. The HbO level of the FP and DLPFC rose drastically in response to the pain stimulus, yet their overall center levels decreased significantly after the three pain tests. The data from this experiment suggest that the pain stimulus caused an increased level of HbO in the FP and DLPFC, indicating that these areas were activated. This study demonstrated a decrease in VAS scores and muscle tissue hardness, which is in agreement with the previous research finding that the DLPFC is associated with a reduction in secondary hyperalgesia.

The brain imaging results in Figure 6 of this study provided a visual representation of the cortical activation level of ROIs in the pain test, and a marked difference was observed when *E-WAA* was administered to the participants. The *t*-value map demonstrated a marked contrast between the task and the other conditions, implying that the hemodynamic response of the participants altered during the experiment, and with the implementation of *E-WAA*, the participants were less responsive to the painful stimulus. After considering the limitations of the t-map in displaying the spatial activity of the relevant areas during the task, further examination

of the channel-directional hemodynamic response was conducted to evaluate the exact activity of FP and DLPFC; this is represented in **Figure 7**, which shows the mean activation level of both ROIs. The neural functional system's FP, which is responsible for self-referencing, attention regulation, working memory, decision-making, and salience detection (Peng et al., 2018a), has a vital cognitive function in handling pain, such as being able to properly direct attention, recognize pain and respond to it. Studies involving fNIRS have indicated that FP is active in the presence of experimental pain and clinical pain, as well as in response to analgesics. It is thought that the DLPFC, similar to the FP, plays a role in more complex cognitive processes and information processing, such as attending to tasks, maintaining information in mind, and inhibiting inappropriate responses (Seminowicz and Moayedi, 2017). Studies using fNIRS have demonstrated that the DLPFC is particularly active during experimental pain, and has been observed to be overactive in individuals with chronic pain conditions (Bandeira et al., 2019). The *E-WAA* treatment led to a substantial decrease in the activation of FP and DLPFC, which provides a partial explanation of how *E-WAA* produces its analgesic effects. The results of the *E-WAA* treatment which revealed a notable reduction in the DLPFC partially corroborate the research which suggests the prefrontal cortex is involved in the experience of pain and is a component of the pain regulation system (Hibi et al., 2020). Moreover, it has been suggested that activity in the DLPFC is inversely associated with the severity of experienced pain and distress, suggesting that the DLPFC has a role in the cognitive control of pain (Bristot et al., 2020), and the modulation of this region can help suppress or amplify the transmission of pain signals through the subsequent inhibitory pathway. *E-WAA* therapy lessened the activity of the nociceptors, resulting in a decrease in the brain's awareness of pain, relieving the brain tissue stimulation to some degree, and thus providing a measure of pain relief. Research has indicated that the decline in hemodynamic response could be connected to the production of endogenous opioids, and the contralateral hemisphere stress system will release a large amount of adrenocorticotropic hormone releasing factor, anti-peptides, and glutamate, leading to a lessening of the cortical hemodynamic response to pain. Subsequent to the application of *E-WAA* for a duration of 10 min, the activity levels of the two ROIs had not yet risen, leading to a dip in the release of dopamine from the brain's hemispheric edges. Consequently, the body was still in a state of low dopamine energy, which was clinically demonstrated by a significant decrease in pleasure, motivation, and natural exuberance. Even the hemodynamic response had not been restored to its former state, suggesting that the participants were receiving an anesthetic effect from *E-WAA*, instead of adapting to the pain (Harada et al., 2005).

Although this research has some positive aspects, its drawbacks should not be ignored. The fact that the study only included males and the observed dissimilarities in pain tolerance between genders implies that more research and larger sample sizes are needed to ascertain the hemodynamic effects of *E-WAA* for pain relief, taking into consideration gender. In addition, we cannot overlook the impact of psychological cues and pain habituation related to pain on the outcomes, necessitating the use of more rigorous psychophysical methods to design future experiments.

5. Conclusion

This research employed a self-managed pre- and post-intervention evaluation with fNIRS to investigate the neural mechanisms of *E-WAA* in relieving pain in CSS sufferers. The findings of the study revealed that *E-WAA* could trigger bottom-up alleviation of pain, which was seemingly reflected in the alteration of HbO concentration in the PF, particularly demonstrated by the differences in the hemodynamic responses in the PF and DLPFC regions that are associated with pain. The data confirm that *E-WAA* is likely to have a broad range of clinical uses and that a quantitative assessment of HbO levels may be capable of elucidating the underlying mechanisms of *E-WAA*.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of ChiRCT. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JD and PS designed the study. JD collected and analyzed the data and manuscript editing. FF and HY supervised the writing of the manuscript. All authors approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A systematic review and meta-analysis of voxel-based morphometric studies of fibromyalgia

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Objective: Although neuroimaging investigations have revealed significant changes in brain structure in fibromyalgia (FM) patients, these findings are inconsistent. The current study conducted a systematic review and meta-analysis of voxel-based morphometric studies in order to comprehend those alterations in brain structure in FM patients.

Methods: Voxel-based morphometric (VBM) studies published up to January 17, 2023 were searched in the Web of Science, PubMed, EMBASE, Cochrane Library (CENTRAL), China National Knowledge Infrastructure (CNKI), Chongqing VIP, Wanfang Database. Two independent researchers carried out study screening, quality assessment, clinical data and neuroimaging data extraction. The whole-brain voxel-based gray matter (GM) data of FM patients were collected from eligible studies, and meta-analyzed using anisotropic effect size-signed differential mapping (AES-SDM).

Results: Twelve researches were included in this study, including 289 FM patients (mean age: 47.36 years) and 272 HS (mean age: 47.34 years). According to the meta-analysis, FM patients had increased GM in the right postcentral gyrus and left angular gyrus, and decreased GM in the right cingulate gyrus, right paracingulate gyrus, left cerebellum, and left gyrus rectus.

Conclusion: Our study suggests that fibromyalgia patients have altered gray matter in several brain regions that are involved in affective, cognitive functions, and in motor adaptations to pain processing.

KEYWORDS

fibromyalgia, neuroimaging, meta-analysis, signed differential mapping, voxel-based morphometry

Introduction

Fibromyalgia (FM) is a chronic condition characterized by widespread musculoskeletal pain, along with fatigue, cognitive problems and sleep disturbances (Clauw, 2014; Winslow et al., 2023). FM affects 2 to 4% of the general population on average (Jones et al., 2015), with more female than male being diagnosed (Branco et al., 2010; Winslow et al., 2023). Fibromyalgia patients have high level of health care utilization and high costs associated

with medical visits and diagnostic test, which bring heavy economic burden to society and family (Boonen et al., 2005; Pinto et al., 2023). Fibromyalgia is underdiagnosed due to the uncertainty surrounding its etiology (Bair and Krebs, 2020; Gatta et al., 2021).

According to previous studies, FM is a disorder of pain regulation and central sensitization (O'Brien et al., 2018; Siracusa et al., 2021). FM patients showed alterations in gray matter, along with aberrant activity and functional connections in brain regions involving pain processing (Pomares et al., 2017; Aster et al., 2022). Voxel-based morphometric analysis showed that FM patients had increased gray matter in the angular gyrus, cuneus, postcentral gyrus, insula, and putamen (Ceko et al., 2013; Pomares et al., 2017), and decreased gray matter in the bilateral hippocampus, anterior insula, posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), precentral gyrus, and precuneus (Ceko et al., 2013; Pomares et al., 2017; Boehme et al., 2020). Because of the heterogeneous of the anomalies in gray matters, it is challenging to reconcile the findings of different researches. Although three meta-analyses have been published in 2016, the synthesized results were also heterogeneous (Dehghan et al., 2016; Lin et al., 2016; Shi et al., 2016).

Since 2016, a growing number of neuroimaging researches have helped us better understand the brain underpinnings of FM. Hence, the aim of the present study was to identify the most prominent and replicable GM regions that involved in FM patients from all the whole-brain VBM research published to date using the anisotropic effect size signed differential mapping (AES-SDM), which employs anisotropic kernel during the reconstruction of effect size maps to account for the anisotropy in the spatial covariance of the neuroimaging investigations (Radua et al., 2012a, 2014).

Methods and analysis

Search strategy

Systematic searches were conducted from origin to January 17, 2023 in seven electronic databases, including Web of Science, PubMed, EMBASE, Cochrane Library (CENTRAL), China National Knowledge Infrastructure (CNKI), Chongqing VIP, and Wanfang Database. The search terms in PubMed were "fibromyalgia" AND ("voxel-based morphometry" OR "VBM" OR "gray matter" OR "gray matter" OR "voxel wise" OR "voxel-wise"). This search strategy was modified to be suitable for the other six electronic databases. In addition, the review articles and references in the included publications were examined to identify any potential researches that might have been missed in the systematic searches.

Screening criteria

The article was included if: (1) the abnormalities of gray matter volume or density in adult fibromyalgia patients were investigated using VBM analysis; and (2) the control group were healthy subjects; and (3) the neuroimaging outcomes were reported in three-dimensional coordinates (x, y, z) in Montreal Neurological Institute (MNI) or Talairach space; and (4) magnet strength of the magnetic resonance imaging (MRI) scanner was at least 1.5 Tesla. The article was excluded if: (1) publications were not original article; or (2) the analysis was confined to regions of interests in brain; or (3) the number of participants in any group was fewer than 10.

If the data was ambiguous or confusing, the corresponding author of the research was contacted through email. If two or more researches used the same data source, only the article with the largest sample size and most thorough information was included. Only baseline data were included in longitudinal or intervention studies. The current study adhered to the PRISMA (preferred reporting items for systematic review and meta-analysis) guidelines (Figure 1).

Quality assessment

To evaluate the quality of the included researches, a specialized checklist based on those in prior neuroimaging meta-analyses was used in present study (Supplementary Table S1). The 12-point checklist covered diagnostic procedures, clinical and demographic characteristics, sample size, scanning parameters, analysis methods, and the caliber of the given outcomes. Each research was evaluated separately by two authors (MX, YQ). If there were any rating disputes, the papers were considered by the authors' group to get a decision on a final score.

Data extraction

The two authors (MX and YQ) independently extracted data from each study, using a predetermined data extraction form. Any discrepancies were discussed in the authors' group in order to be rectified. The authors' name, year of the publication, sample size, age and gender of the study population, disease duration, and the technical information about neuroimaging (MRI scanner, analysis software, full width at half maximum, thresholds, and significant gray matter alterations) were all extracted (Table 1). The peak coordinates in each research were collected following the standards of AES-SDM. In cases of significant results from both corrected and uncorrected thresholds in the VBM statistical analysis of one trial, only the corrected results were collected.

Standard meta-analyses of structural alterations

Alterations in brain structure were subjected to the whole-brain voxel-wise meta-analysis by AES-SDM (www.sdmproject.com/software) (Radua et al., 2012a,b). First, a Gaussian kernel was used to integrate the retrieved peak information to rebuild the effect-size and variance maps, which gave voxels closer to the peaks larger effect sizes. To prevent false-positive results, the assignment's full width at half maximum (FWHM) was fixed at 20 mm (Radua et al., 2012b). Study maps were computed voxel-wise to determining the random-effects mean while taking the sample size, intra-study variability, and

TABLE 1 Demographic and clinical characteristics of subjects in VBM studies included in the meta-analysis.

Study	Number (female)		Mean Age (y)		Durations (month)	MRI scanner	Software	FWHM	Threshold	Significant GM alterations		Quality score
	FM	HS	FM	HS	FM					Increase	Decrease	
Kuchinad et al. (2007)	10 (10)	10 (10)	52	45	109.2	1.5T	/	10	$p < 0.05$, corrected based on random field theory		↓	12
Schmidt-Wilcke et al. (2007)	20 (19)	22 (20)	53.6	50.7	173	1.5T	SPM2	10	$p < 0.05$, corrected	↑		11.5
Wood et al. (2009)	30 (30)	20 (20)	42.03	40.05	NA	1.5T	SPM2	12	$p < 0.0005$, uncorrected		↓	11
Hsu et al. (2009)	29 (29)	29 (29)	42.6	42.2	153.6	3T	SPM5	10	$p < 0.05$, Bonferroni corrected			12
Ceko et al. (2013)	14 (14)	15 (15)	42.4	43.1	105.6	3T	SPM8, VBM8	8	$p < 0.05$, RFT corrected	↑		12
	14 (14)	13 (13)	55.0	55.4	145.2	3T	SPM8, VBM8	8	$p < 0.05$, RFT corrected		↓	
Fallon et al. (2013)	16 (16)	15 (15)	38.5	39.4	109.2	3T	SPM8, VBM8	10	$p<0.05$, FWE corrected	↑	↓	12
Diaz-Piedra et al. (2016)	23 (23)	23 (23)	41.6	39.7	102.6	3T	SPM8	8	$p < 0.05$, AlphaSim corrected	↑	↓	12
Pomares et al. (2017)	26 (26)	25 (25)	61	61	NA	3T	SPM8, VBM8	7	$p < 0.05$, corrected based on random field theory	↑	↓	11
Sundermann et al. (2019)	27 (27)	22 (22)	52.6	52.24	189.12	3T	SPM12, CAT12	8	$p < 0.05$, FWE corrected			12
Boehme et al. (2020)	31 (31)	29 (29)	39.2	42.7	52.8	3T	SPM12, CAT12	NA	$p < 0.001$, uncorrected		↓	10
Müller et al. (2021)	32 (32)	32 (32)	50.7	52.5	NA	3T	SPM12	8	$p < 0.1$, FWE corrected			11
Baker et al. (2022)	17 (17)	17 (17)	48.12	48.42	NA	3T	SPM12	8	$p < 0.01$, uncorrected			11

FM, fibromyalgia patients; FWHM, full width at half maximum; HS, healthy subjects; NA, not available; SPM, statistical parametric mapping; T, tesla; VBM, voxel-based morphometry.

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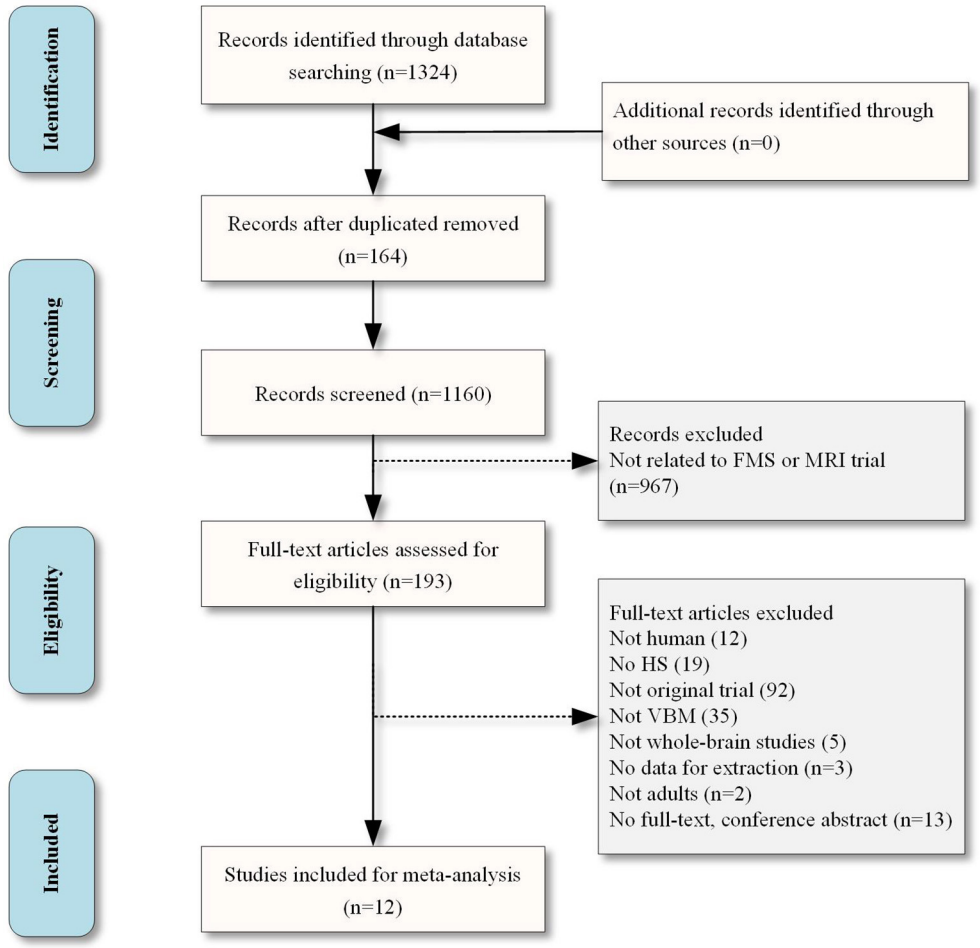

FIGURE 1
The flow diagram for VBM studies included in the present meta-analysis.

between-study heterogeneity into consideration. After determining the meta-analysis means, thresholds were applied using the default parameters (voxel threshold $p < 0.005$, peak height threshold $z > 1.00$, and cluster size threshold > 10 voxels) (Radua et al., 2012b). The meta-analysis effect-size map was then statistically assessed by comparison to a null distribution created using a permutation algorithm. The reproducibility of VBM research results was examined using a leave-one-out Jackknife sensitivity analysis, which did the mean analysis again after methodically removing each research. We furtherly performed a subgroup analysis to rule out any potential heterogeneity originating from different MRI scanning techniques (1.5T or 3.0T scanner). To see if the results could have been influenced by a few or tiny researches, funnel plots of the peaks of the main findings were conducted. Additionally, the Egger test was also conducted to look for any potential publication bias (Radua and Mataix-Cols, 2009).

Meta-regression analysis

An evaluation of relationships between changes in the brain and subject characteristics (age and duration of FM patients) was carried out using a meta-regression analysis, weighted by sample size and intra- and between-study variances, in order to look for any potential impacts (Radua et al., 2012b). The probability threshold was lowered to 0.005 to reduce the detection of false associations. Results for the slope and one of the regressor's extremes were considered, while results for regions that were not detected in the main analysis were discarded. Fits that were obviously driven by an insufficient number of studies were also discarded by examining the regression plot (Radua et al., 2012b).

Results

General information of the included studies

The search strategy resulted in 1,324 articles, and 12 articles were included in this meta-analysis (Figure 1) (Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007; Hsu et al., 2009; Wood et al., 2009; Ceko et al., 2013; Fallon et al., 2013; Diaz-Piedra et al., 2016; Pomares et al., 2017; Sundermann et al., 2019; Boehme et al., 2020; Müller et al., 2021; Baker et al., 2022). One study included two subgroups of fibromyalgia and did separate comparison analyses, so

TABLE 2 VBM brain regions showing GM differences between FM patients and HS.

Regions	MNI coordinates			SDM *z* score[a]	*P*-value[b]	Number of voxels[c]	Cluster breakdown (number of voxels)	Heterogeneity	Sensitivity
	x	y	z						
FM > HS									
R postcentral gyrus	38	−34	56	1.040	0.001	327	R postcentral gyrus, BA2, BA3, BA4, BA40 (256)	No	11/13
							R inferior parietal gyri, BA2, BA40 (30)		
							R precentral gyrus, BA4 (18)		
L angular gyrus	−40	−62	40	1.017	0.001	126	L angular gyrus, BA7, BA39 (57)	No	12/13
FM < HS									
R cingulate gyrus, R paracingulate gyrus	4	−22	40	−2.105	0.000	1,312	L cingulate / paracingulate gyri, BA23 (434)	No	12/13
							R cingulate / paracingulate gyri, BA23 (545)		
							R median network, cingulum (145)		
							L median network, cingulum (79)		
							L supplementary motor area (14)		
							L posterior cingulate gyrus, BA23 (14)		
							R supplementary motor area (10)		
L cerebellum, hemispheric lobule IV/V	−22	−30	−30	−1.486	0.001	195	L cerebellum, hemispheric lobule IV/V, BA30, BA37 (113)	No	11/13
							Middle cerebellar peduncles (25)		
L gyrus rectus	−2	42	−22	−1.300	0.004	13	L gyrus rectus, BA11 (12)	No	10/13

[a]Peak height threshold: $z > 1$.

[b]Voxel probability threshold: $p < 0.005$.

[c]Cluster extent threshold: regions with <10 voxels are not reported in the cluster breakdown. BA, Brodmann area; FM, fibromyalgia patients; GM, gray matter; HS, healthy subjects; L, left; MNI, Montreal neurological institute; R, right; SDM, signed differential mapping; VBM, voxel-based morphometry.

the study was considered separately into two studies for the meta-analysis (Ceko et al., 2013). As a result, the number of studies in meta-analysis was elevated to 13. Among these studies, 9 studies reported gray matter decrease or increase or both in FM patients (Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007; Wood et al., 2009; Ceko et al., 2013; Fallon et al., 2013; Diaz-Piedra et al., 2016; Pomares et al., 2017; Boehme et al., 2020), while 4 studies reported no abnormalities between FM patients and HS (Hsu et al., 2009; Sundermann et al., 2019; Müller et al., 2021; Baker et al., 2022). A total of 561 subjects were considered in this study, including 289 FM patients (mean age: 47.36 years) and 272 HS (mean age: 47.34 years). There was no significant difference in age or gender between the FM patients and HS ($p > 0.05$). The studies had a mean quality score of 11.5 out of a total possible score of 12, indicating that they were of high quality. Details of the literature search and criteria for article inclusion are shown in Figure 1. The clinical variables and technical details of the included studies were presented in Table 1.

Meta-analyses of GM alterations

The AES-SDM results showed that FM patients exhibited increased GM in the right postcentral gyrus ($p = 0.001$, $z = 1.040$), and left angular gyrus ($p = 0.001$, $z = 1.017$), and decreased GM in the right cingulate gyrus and right paracingulate gyrus ($p = 0.000$, $z = -2.105$), left cerebellum ($p = 0.001$, $z = -1.486$), and left

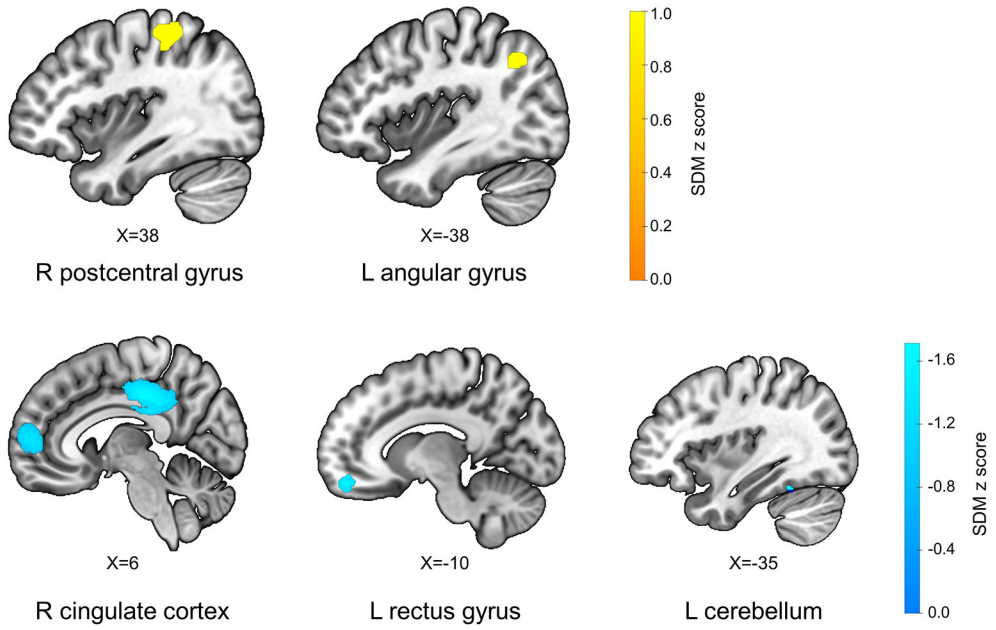

FIGURE 2
Differences in gray matter between fibromyalgia patients and healthy subjects. L, left; R, right; X, x-axis MNI coordinates of this section of the brain region.

gyrus rectus ($p = 0.004$, $z = -1.300$) compared with HS (Table 2; Figure 2).

Subgroup analysis

The subgroup analysis of VBM studies using 1.5 T scanners revealed structural abnormality in the right cingulate gyrus, right paracingulate gyrus ($p = 0.001$, z = −1.333), left cerebellum, hemispheric lobule IV / V ($p = 0.001$, z = −1.222) of FM patients (Table 3). The subgroup analysis of VBM studies using 3.0 T scanners revealed structural abnormality in the right postcentral gyrus ($p = 0.000$, $z = 1.162$), left angular gyrus ($p = 0.001$, $z = 1.016$), right cingulate gyrus and right paracingulate gyrus ($p = 0.000$, $z = -1.844$), and left gyrus rectus ($p = 0.002$, $z = -1.452$) of FM patients (Table 3).

Meta-regression

A meta-regression analysis was conducted to examine potential confounding variables (mean age, disease duration, and pain intensity). The mean age of FM patients was associated with changed GM in the left angular gyrus ($p = 0.001$, $z = 2.112$), and the right cingulate gyrus, right paracingulate gyrus ($p = 0.001$, $z = -2.696$) in VBM studies (Table 4). The disease duration was associated with altered GM in the left cerebellum ($p = 0.001$, $z = 2.401$) (Table 4). The mean pain intensity of FM patients was associated with abnormal GM in the right cingulate gyrus and right paracingulate gyrus ($p = 0.000$, $z = 2.054$) (Table 4).

Heterogeneity analysis, sensitivity analysis and publication bias

There was no significant heterogeneity among the VBM studies with GM alterations according to the heterogeneity analysis ($p > 0.005$, Table 2). The leave-one-out Jackknife sensitivity analysis indicated that the left angular gyrus and right cingulate gyrus, right paracingulate gyrus were preserved in 12 combinations (Supplementary Table S2). Publication bias were checked using the funnel plots and the Egger test. The funnel plots demonstrated that the main findings were driven by at least 10 VBM studies (Supplementary Figure S1). Analysis of publication bias revealed that the Egger tests were insignificant in the peaks of the altered brain regions in the VBM meta-analysis ($p = 0.591$).

Discussion

In order to evaluate the changes of gray matter in FM patients compared with HS, we performed an update meta-analysis using AES-SDM to pool VBM data. FM patients had increased GM in right postcentral gyrus and left angular gyrus, and decreased GM in right cingulate gyrus, right paracingulate gyrus, left cerebellum, and left gyrus rectus. These results remained consistent when each study was eliminated in the Jackknife sensitivity analysis.

Lin et al. included 6 voxel-wise VBM studies (156 FM patients vs. 147 HS), used activation likelihood estimation (ALE) to synthesize the altered gray matter of FM patients, and regional GM loss in left medial prefrontal cortex and right dorsal posterior cingulate cortex in FM patients was discovered (Lin et al., 2016). Shi et al. synthesized the abnormalities of 7 VBM studies (180 FM patients vs. 126 HS), and found GM decreases in the bilateral ACC,

TABLE 3 Regional differences of FM patients in VBM studies using 1.5 T and 3.0T scanner.

VBM studies using 1.5 T scanner							
Regions	MNI coordinates			SDM *z* score[a]	*P*-value[b]	Number of voxels[c]	Cluster breakdown (number of voxels)
	x	y	z				
FM < HS							
R cingulate gyrus, R paracingulate gyrus	6	−18	42	−1.333	0.001	92	R median cingulate / paracingulate gyri, BA23 (80)
L cerebellum, hemispheric lobule IV/V	−16	−42	−26	−1.222	0.001	444	L cerebellum, hemispheric lobule IV/V, BA30, BA37 (212)
							L fusiform gyrus, BA37 (71)
							L median network, cingulum (56)
							L parahippocampal gyrus, BA30 (25)
							L lingual gyrus, BA30 (17)
VBM studies using 3.0 T scanner							
FM > HS							
R postcentral gyrus	38	−34	56	1.162	0.000	534	R postcentral gyrus, BA2, BA3, BA4, BA40 (382)
							R precentral gyrus, BA4 (40)
							R inferior parietal gyri, BA2, BA40 (60)
							R superior parietal gyrus, BA2 (11)
L angular gyrus	−36	−64	40	1.016	0.001	200	L angular gyrus, BA7, BA39, BA40 (105)
							L inferior parietal gyri, BA40 (12)
FM < HS							
R cingulate gyrus, R paracingulate gyrus	4	−22	40	−1.844	0.000	943	R median cingulate / paracingulate gyri, BA23 (333)
							R median network, cingulum (122)
							L cingulate / paracingulate gyri, BA23 (346)
							L median network, cingulum (66)
							Corpus callosum (19)
L gyrus rectus	−2	42	−22	−1.452	0.002	125	Corpus callosum (50)
							L gyrus rectus, BA11 (47)

[a]Peak height threshold: $z > 1$.
[b]Voxel probability threshold: $p < 0.005$.
[c]Cluster extent threshold: Regions with <10 voxels are not reported in the cluster breakdown. BA, Brodmann area; FM, fibromyalgia patients; HS, healthy subjects; L, left; MNI, Montreal neurological institute; R, right; SDM, signed differential mapping; T, tesla; VBM, voxel-based morphometry.

MPFC, PCC, paracingulate cortex, and parahippocampal gyrus (Shi et al., 2016). Dehghan et al. synthesized the structural changes in 6 MRI studies, including 4 VBM studies (92 FM patients vs. 92 HS), 1 DTI study and 1 cortical thickness study, and showed variations in the left midcingulate gyrus (Dehghan et al., 2016). In the present study, 12 researches (289 FM patients vs. 272 HS) were analyzed using AES-SDM. Compared with Lin's study, five papers published recently have been added in present study, and the meta-analysis methods were different. The screening criteria used in Shi et al. SDM meta-analysis were inconsistent with our study. Dehghan's study included three kinds of structural MRI researches, and synthesized using ALE. There might be several reasons for the inconsistency of the results in these four meta-analyses. First, only whole-brain gray-matter VBM studies have been included in our study in order to reduce the heterogeneity, and the heterogeneity analysis demonstrated that the main results were robust. Second, the added five studies increased the proportion of 3.0T MRI scanner in present meta-analysis, which influence the results according to our subgroup analysis in studies using 1.5 T scanner and 3.0 T scanner. Third, the SDM and ALE, based on different algorithms, may have a non-negligible impact on the results.

The postcentral gyrus plays a critical role in the perception of pain, its gray matter was increased in people suffering from fibromyalgia (Lutz et al., 2008) and other chronic pain disorders (Ogino et al., 2005). The angular gyrus is involved in visual and sensorimotor information convergence (Prado et al., 2005).

TABLE 4 Meta-regression analysis for functional abnormalities in FM patients.

Regions	MNI coordinate			SDM *z* score[a]	*P*-value[b]	Number of voxels[c]
	x	y	z			
Effect of age						
L angular gyrus	−40	−62	38	2.112	0.000	84
R cingulate gyrus, R paracingulate gyrus	12	−36	34	−2.696	0.000	236
Effect of duration						
L cerebellum, hemispheric lobule IV / V	−22	−30	−34	2.401	0.001	61
Effect of pain intensity						
R cingulate gyrus, R paracingulate gyrus	8	−36	32	2.054	0.000	161

[a]Peak height threshold: $z > 1$.
[b]Voxel probability threshold: $p < 0.005$.
[c]Cluster extent threshold: Regions with <10 voxels are not reported in the cluster breakdown. L, left; MNI, Montreal neurological institute; R, right; SDM, signed differential mapping.

The increased gray matter in angular gyrus and postcentral gyrus, implicated in attention to the body and visuo-motor coordination (Macaluso and Maravita, 2010), might relate to increased attentional resources allocated in FM patients to nociceptive and other unpleasant sensory inputs (Schweinhardt et al., 2008). However, none of the three meta-analysis that were published in 2016 showed any increased modification in the gray matter of the postcentral gyrus or the angular gyrus (Dehghan et al., 2016; Lin et al., 2016; Shi et al., 2016), indicating that these alterations may result from the literatures published in recent years (Pomares et al., 2017). The subgroup analysis revealed that the structural MRI scanner (1.5T / 3.0T) had an impact on the increased GM in postcentral gyrus and angular gyrus in FM patients. Three researches using 1.5 T MRI scanners were published in 2007 (Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007) and 2009 (Wood et al., 2009), which had a high proportion of all included researches in the three meta-analysis of VBM studies in 2016 (Dehghan et al., 2016; Lin et al., 2016; Shi et al., 2016). It may also be the reason why there was no such outcome in the three VBM meta-analysis. Additionally, the meat-regression analysis revealed a relationship between age and the increase in gray matter of the angular gyrus in FM patients.

The statistically most robust gray matter declines were observed in the cingulate gyrus and paracingulate gyrus, which were consistent with Dehghan's (Dehghan et al., 2016) and Shi's meta-analysis (Shi et al., 2016). The altered gray matter in the cingulate gyrus was correlated with pain intensity. Cingulate cortex is involved in pain perception, pain modulation, selective attention, error awareness, working memory, and recognition (Kuchinad et al., 2007; Turriziani et al., 2008). Paracingulate gyrus was a significant anatomical marker in the medial prefrontal cortex, and when it is reduced, the ACC around them is increased in gray matter volume (Fornito et al., 2008).

Furthermore, it was noteworthy that gray matter loss in the gyrus rectus was similar to that seen in the cingulate cortex. The anterior cingulate was thought to extend into the frontal lobe through the gyrus rectus (Ballmaier et al., 2004), which may assist to explain why the gray matter abnormalities in both areas are identical. Approximately 30–60% of fibromyalgia patients have psychological comorbidities, which are often characterized by depression and anxiety (Hudson et al., 1985; Boissevain and McCain, 1991; Schmidt-Wilcke and Clauw, 2011). The cingulate cortex and gyrus rectus have also been previously identified as crucial regions implicated in pain catastrophizing and related psychiatric illnesses according to the structural neuroimaging researches conducted to date (Ballmaier et al., 2004; Diaz-Piedra et al., 2016).

In this context, it is also interesting to discuss our findings in the cerebellum. The cerebellum, which is now generally regarded as a cardinal area for pain processing, showed decreased gray matter in FM patients. Researches on both animals and humans has demonstrated that the cerebellum had a role in pain perception and regulation, in addition to motor adaptability, cognitive, and affective activities (Diano et al., 2016; Aster et al., 2022). The activation of cerebellum in FM patients was associated with catastrophizing scores (Gracely et al., 2004), indicating that the cerebellum was involved in pain expectancy and assessment (Schmidt-Wilcke and Clauw, 2011). Several studies have shown increased cerebellar gray matter (Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007), in agreement with the findings from Shi et al. (2016), while Boehme et al. found reduced gray matter density in the cerebellum (Boehme et al., 2020). Studies with larger sample sizes contributed more since the square root of each study's sample size was used to weight the mean map in the SDM analysis. Based on this, the reduction of gray matter in the cerebellum in current meta-analysis was partially influenced by the conclusion of Boehme et al.'s study (Boehme et al., 2020).

Limitations

There are several limitations that need to be considered when interpreting our results. FM is a chronic pain disorder and shows a wide range of symptoms and severity. The included articles in present study used several pain-related scales that couldn't be converted amongst one another, so the results of meta-regression analysis might not be robust. Besides, only 5 of 13 researches reported the medication used in the FM patients (Ceko et al., 2013; Diaz-Piedra et al., 2016; Boehme et al., 2020; Müller et al., 2021; Baker et al., 2022) and fewer researches

reported the emotion state of FM patients, so we can't perform meta-regression analysis to observe the effect of medication taken and emotion state on gray matter changes of FM patients. Furthermore, it is evident that the prevalence of FM in females is obviously higher than that in males (Jones et al., 2015). We are unable to conduct a gender subgroup analysis to compare the differences in gray matter changes between females and males because the majority of the participants in the current study are females.

Conclusion

In summary, our study suggests that FM patients have altered gray matter in several brain regions that are involved in affective, cognitive functions, and motor adaptations to pain processing. These results might reflect the alterations of chronic pain disorders.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

SC and MX contributed to the study conception and design, and conceived the data analysis strategy. MX and YQ acquired the data, collated and analyzed the data, and drafted the manuscript. SC, XP, and DZ discussed, read, and revised the manuscript. All authors approved the publication of this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1164145/full#supplementary-material

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OPRM1 A118G polymorphism modulating motor pathway for pain adaptability in women with primary dysmenorrhea

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Introduction: Primary dysmenorrhea (PDM) is a common condition among women of reproductive age, characterized by menstrual pain in the absence of any organic causes. Previous research has established a link between the A118G polymorphism in the mu-opioid receptor (*OPRM1*) gene and pain experience in PDM. Specifically, carriers of the G allele have been found to exhibit maladaptive functional connectivity between the descending pain modulatory system and the motor system in young women with PDM. This study aims to explore the potential relationship between the *OPRM1* A118G polymorphism and changes in white matter in young women with PDM.

Methods: The study enrolled 43 individuals with PDM, including 13 AA homozygotes and 30 G allele carriers. Diffusion tensor imaging (DTI) scans were performed during both the menstrual and peri-ovulatory phases, and tract-based spatial statistics (TBSS) and probabilistic tractography were used to explore variations in white matter microstructure related to the *OPRM1* A118G polymorphism. The short-form McGill Pain Questionnaire (MPQ) was used to access participants' pain experience during the MEN phase.

Results: Two-way ANOVA on TBSS analysis revealed a significant main effect of genotype, with no phase effect or phase-gene interaction detected. Planned contrast analysis showed that during the menstrual phase, G allele carriers had higher fractional anisotropy (FA) and lower radial diffusivity in the corpus callosum and the left corona radiata compared to AA homozygotes. Tractographic analysis indicated the involvement of the left internal capsule, left corticospinal tract, and bilateral medial motor cortex. Additionally, the mean FA of the corpus callosum and the corona radiata was negatively correlated with MPQ scales in AA homozygotes, but this correlation was not observed in G allele carriers. No significant genotype difference was found during the pain-free peri-ovulary phase.

Discussion: *OPRM1* A118G polymorphism may influence the connection between structural integrity and dysmenorrheic pain, where the G allele could impede the pain-regulating effects of the A allele. These novel findings shed light on the underlying mechanisms of both adaptive and maladaptive structural neuroplasticity in PDM, depending on the specific *OPRM1* polymorphism.

KEYWORDS

primary dysmenorrhea, *OPRM1* A118G polymorphism, white matter, diffusion tensor imaging, descending pain modulatory systems, motor pathway

1. Introduction

Primary dysmenorrhea (PDM) is a common gynecological disorder among young women characterized by menstrual pain in the absence of any observable pelvic abnormalities (Habibi et al., 2015; Iacovides et al., 2015). PDM is primarily caused by uterine myometrial hypercontractility and vasoconstriction, which can be attributed to various factors such as an increase in prostaglandin, cytokines, and vasopressin (Berkley, 2013; Ferries-Rowe et al., 2020). In addition, PDM can be linked to abnormal pain control mechanisms, as evidenced by structural and functional changes in pain processing networks (Berkley, 2013; Low et al., 2018). PDM is often associated with functional pain disorders and chronic pain conditions such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and lower back pain in adulthood (Altman et al., 2006; Berkley, 2013; Chung et al., 2014; Tu et al., 2020). It is suggested that maladaptive changes in the descending pain modulation system (DPMS) in young women with PDM may contribute to the high incidence of comorbidity with functional pain disorders in later life (Wei et al., 2016a).

During menstruation, individuals with PDM have been found to experience pelvic floor hypersensitivity (Iacovides et al., 2015; Lima et al., 2019). Pelvic muscle training, such as Kegel exercises, has demonstrated positive effects on managing pelvic pain of various types, including PDM (Ortiz et al., 2015; ElDeeb et al., 2019; Scott et al., 2020). It has been reported that the representation of the pelvic floor muscle in the motor cortex involves overlapping areas of the medial primary motor cortex (M1) and the supplementary motor area (SMA) (Yani et al., 2018). To define these regions of interest in our study, we referred to them as the medial motor cortex (MMC), which includes the medial M1 and pre-SMA/SMA regions. Recent research has suggested a possible link between dysmenorrhea and motor cortex dysfunction (Kutch and Tu, 2016). Our previous study has also revealed abnormal functional connectivity between the periaqueductal gray (PAG) and MMC in young women with PDM implicating possible dysregulation of the motor system and DPMS (Wei et al., 2016b). Therefore, it is crucial to investigate further the relationship between sensorimotor representation and pelvic pain processing in PDM.

The substitution of adenine with guanine at codon 118 (A118G) in the mu-opioid receptor (OPRM1) gene results a single nucleotide polymorphism (SNP) that has been associated with decreased OPRM1 expression (Zhang et al., 2005), heightened pain sensitivity (Yao et al., 2015), and increased analgesic use (Sia et al., 2008). OPRM1 is responsible for the pain-reducing effects of opioids within the central nervous system, and individuals carrying the G allele may be at a higher risk for developing chronic pain (Fields, 2004). According to our previous study using functional magnetic resonance imaging (fMRI), there is evidence to suggest that variations in pain perception and neural regulation in individuals may be attributed to differences in the *OPRM1* genotype, specifically affecting the functional connectivity between the sensorimotor and DPMS brain regions (Wei et al., 2017). The study found that active cortical modulation may be present during menstrual pain and that this may explain why AA homozygotes rated their pain experience lower than G allele carriers. Additionally, studies have suggested that white matter properties in the brain may predict pain chronification (Mansour et al., 2013). However, the current relationship between *OPRM1* A118G polymorphism and white matter changes in women with PDM is currently unknown.

Neuroimaging alterations during menstruation (painful state) were regarded as state changes, whereas alterations during the peri-ovulatory phase (pain-free state) were regarded as trait changes (Wei et al., 2016a). Specifically, our voxel-based morphometric study of gray matter volume found that PDM may be associated with cyclic state changes during the menstrual phase (MEN) in PDM subjects (Tu et al., 2013). Furthermore, our resting state fMRI-functional connectivity study revealed that only the G allele carriers of PDM subjects, compared to controls, may have hyperconnectivity in the PAG- MMC network during the MEN, implicating subclinical dysregulated pain modulation (Wei et al., 2017). This dysfunctional DPMS involving the MMC and PAG is a common factor in many chronic pelvic pain disorders (Kutch and Tu, 2016; Wei et al., 2017).

Our investigation aimed to assess the potential link between white matter alterations and the *OPRM1* A118G polymorphism in individuals with PDM, utilizing diffusion tensor imaging (DTI) (Le Bihan et al., 2001; Nucifora et al., 2007). We employed the tract-based spatial statistics (TBSS) method and probabilistic tractography (Behrens et al., 2003a) to analyze white matter connectivity. TBSS is a voxel-wise, data-driven approach that allows for the calculation of DTI metrics in white matter tracts. Our study specifically focused on investigating whether the *OPRM1* A118G polymorphism is associated with state or trait changes in white matter connectivity in individuals with PDM, with an emphasis on the connectivity between the motor cortex (particularly MMC) and DPMS.

2. Materials and methods

2.1. Subjects

The participants were selected based on the following criteria: (1) a menstrual cycle of approximately 27–32 days, (2) right-handedness as determined by the Edinburgh Handedness Inventory, and (3) a history of menstrual pain lasting more than 6 months, with an average pain score greater than 4 on a 0–10 verbal numerical scale (VNS) for the past 6 months under routine management for those with PDM. Subjects were excluded if they met any of the following conditions: (1) use of any medications, contraceptives, or hormone supplements in the 6 months prior to the study, (2) pituitary gland disease, (3) organic pelvic disease, (4) psychiatric or neurological disorders, (5) head injury with loss of consciousness, (6) pregnancy or plans to conceive, (7) history of childbirth, (8) metal implants, pacemakers, claustrophobia, or any contraindications to MRI. Participants were not allowed to take analgesics 24 h before the experiment. All subjects with PDM were diagnosed by a gynecologist and underwent a pelvic ultrasound to rule out organic pelvic diseases.

2.2. Experimental design

Blood samples were collected at the outset of the study for genetic analysis, but the participants' genotypes were kept unknown until the scanning session. The short-form McGill Pain Questionnaire (MPQ) (Melzack, 1987) was used to access participants' pain experience during the MEN phase. Two MRI scans, including T1 and DTI images, were performed at two time points during the menstrual cycle: during menstruation (days 1–3, MEN phase) and during the periovulatory phase (days 12–16, POV phase). For further information on the genetic analysis, please refer to our published article (Wei et al., 2016b).

2.3. Image acquisition

The imaging data for all participants was collected using a 3.0 T MRI scanner (Magnetom Trio Tim, Siemens, Erlangen, Germany), located at the National Yang-Ming University. Diffusion weight image (DWI) was acquired using 30 different directions and a *b*-value of 900 s/mm^2, in addition to a single *b*-value of 0 s/mm^2 image. The imaging parameters for DWI were set as TR/TE = 7,900 ms/79 ms, bandwidth = 1,346 Hz/Px, 70 slices with a thickness of 2 mm and no interslice gaps, a field of view of 256 × 256 mm^2, a matrix size of 128 × 128, and a voxel size of 2 × 2 × 2 mm^3, with 3 excitations and an acquisition time of 13 min and 4 s. High-resolution T1-weighted images (T1WI) were obtained with the imaging parameters set as TR/TE = 2,530 ms/3.03 ms, inversion time = 1,100 ms, bandwidth = 130 Hz/Px, 192 slices with a thickness of 1 mm, a field of view of 224 × 256 mm^2, a matrix size of 224 × 256, and a voxel size of 1 × 1 × 1 mm^3, a flip angle of 7 degrees and an acquisition time of 5 min and 23 s.

2.4. Image preprocessing

The DTI images were processed using FMRIB Software Library (FSL) v5.0[1] from the Oxford Center for Functional Brain MRI (Jenkinson et al., 2012). To perform the TBSS analysis, several steps were followed. First, the DTI images were corrected for eddy current distortion and movement, then registered to each participant's corresponding b0 image with affine registration using the FMRIB Diffusion Toolbox (Andersson et al., 2007). Participants with head motion greater than 3 mm were excluded. The DWI runs were then averaged to improve the signal-to-noise ratio of the image. A binary brain mask of each subject was created using the individual average, and non-brain tissue was removed using the brain extraction tool (BET) (Smith, 2002). The DTIFIT function in FDT was used to fit the DTIs using a linear least square algorithm, generating DTI maps that assessed white matter integrity by measuring DTI metrics, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). FA measures the difference between the largest eigenvalue and the other two and reflects the white matter microstructure. MD provides an average of all three eigenvalues and is sensitive to changes in cellularity, edema, and necrosis. An increase in RD, which is the average of the second and third eigenvalues, suggests demyelination in the white matter. AD, which only considers the first eigenvalue, tends to change with white matter pathology (Tromp and Scalars, 2016).

The standard TBSS procedure was then employed to analyze the results which included several steps (Smith et al., 2006). First, all subjects were aligned into a common space using a representative subject as the registration target. Non-linear alignment was performed on all FA images, and linear registration was performed on the MNI152 atlas template. The combined transformation was used to align all subjects' FA images into the MNI152 space, creating a study-specific mean FA atlas. A skeletonized mean FA image was created by thinning all aligned FA images with a threshold of >0.2. The FA map of each subject was projected onto the FA skeleton by searching perpendicular to the local skeleton structure. Then voxel-wise statistics analysis across subjects was performed on the skeleton-space FA data. The other DTI metrics, including MD, RD, and AD, were evaluated in a similar way to the FA analysis to gain a deeper understanding of the brain's microstructural integrity of subjects with PDM.

2.5. Statistical analyses and tractographic visualization

2.5.1. Demographic information and psychophysiological measurements

The data analysis was conducted using GraphPad Prism 9 (version 9.1.1). As some of the psychophysiological data did not adhere to a normal distribution, a non-parametric analysis was employed, and the findings were presented as median (range). Statistical significance was considered when the value of p was less than 0.05. The chi-square test was utilized to examine the

1 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation

Hardy–Weinberg equilibrium of the *OPRM1* genotype distribution. The Mann–Whitney U test was utilized to examine the impact of genotype on demographic factors such as the Edinburgh Handedness Inventory score and MPQ scores.

2.5.2. Image analysis and tractographic visualization

In the current study, a two-way ANOVA was used to examine the main effects and interactions of genotype and phase in the TBSS analysis of white matter microstructure. The FA skeleton map was analyzed using the FEAT function in FSL (Woolrich et al., 2004). Planned contrast methods were utilized to investigate genotype differences in each phase, with a two-sample *t*-test employed to detect subtle but potentially important findings (Wu and Slakter, 1990; Lee et al., 2018; Li et al., 2021). Non-parametric tests based on FSL permutation were used to compare the FA, with multiple comparisons corrected using the threshold-free cluster enhancement (TFCE) method at a significance level of $p < 0.05$ and a minimum cluster size of 30 voxels (Winkler et al., 2014). Additionally, the MD, RD, and AD metrics were also evaluated using TBSS procedure. The white matter label atlas of Johns Hopkins University-International Consortium for Brain Mapping (JHU-ICBM-DTI-81)[2] was used to identify significant differences in white matter tracts as regions of interest (ROI). To facilitate better visualization, the thresholded TBSS images were enhanced to have a thicker appearance.

To confirm the location of TBSS clusters within the motor system fiber tracts, the study employed probabilistic tractography using a composite mask composed solely of all significant FA seeds, as previously described (Szabó et al., 2012; Borich et al., 2013). FA was selected as the primary metric because it provides a comprehensive measure of diffusivity and directionality, and holistically captures microstructure changes (Alexander et al., 2007; Tromp and Scalars, 2016). Tractography was initiated using the composite mask as the starting point, without utilizing any restricted waypoint or termination masks. BEDPOSTX in FDT was utilized to estimate the diffusion parameter, with two probabilistic fiber directions burned 900 times for tractography (Behrens et al., 2003b). The DTIs were registered to T1 and transformed into standard space (MNI 152) through nonlinear registration with FDT registration (Andersson et al., 2007). The final tractographic analysis included tracing 5,000 probabilistic streamlines from each voxel within the TBSS seed, using a curvature threshold of 0.2 and a step length of 0.5. The study combined data from all subjects using FSLeyes[3] and applied a threshold of 5,000 for each subject, followed by a threshold of 300,000 streamlines for visualization.

2.5.3. Correlation analysis between DTI metrics and pain behavior

To explore the connection between white matter plasticity and pain experience, we performed a Spearman's correlation analysis on the FAs of the identified clusters. For each subject, we extracted the mean FA value from each ROI mask. The correlation between these values and MPQ scores was examined because the OPRM1 A118G polymorphism may affect the pain perception of individuals (Wei et al., 2017).

3. Results

3.1. Subjects

Participants were sourced through internet advertisements. Hundred and ten subjects with primary dysmenorrhea meet the inclusion criteria and were enrolled initially. Six participants were excluded from the study due to the presence of secondary dysmenorrhea, as detected by a pelvic ultrasound exam conducted by the gynecologist (HTC). Twelve subjects were excluded due to incidental abnormal brain findings identified in their MRI scans, and 35 subjects declined to participate. The final sample size consisted of 57 PDM patients who completed the two-phase study that involved behavioral assessments and neuroimaging scans.

Of these, 14 subjects with PDM were excluded further due to a high probability of premenstrual dysphoric disorder and disruption of daily life, poor data quality, or head motion greater than 3 mm during the scan. Finally, the study included 43 PDM patients (13 with AA genotype, 25 with AG genotype, and 5 with GG genotype, with a mean age of 23 [10] years) (Figure 1).

3.2. Genetic data and clinical characteristics

The distribution of the A118G gene in the PDM subjects ($p = 0.38$) did not deviate from the Hardy–Weinberg equilibrium. The AG heterozygotes and GG homozygotes were combined as G allele carriers, based on their similar clinical characteristics (Sia et al., 2008). There were no significant differences in demographic variables such as age, gynecological age, menstrual cycle, education, body mass index (BMI), or Edinburgh Handedness Inventory scores among the different genotypes (Table 1).

The subjects in the study had a long history of menstrual pain, with a median duration of 9 years (range 14 years), and pain lasting approximately 2 days per menstrual cycle (median [range] = 2 [4.9]). Over half of the subjects with PDM (55.8%) reported missing school or work due to their menstrual pain, and 44.18% of them required analgesics. However, there were no significant differences in the history of menstrual pain, duration of pain per cycle, or scores on the McGill Pain Questionnaire among the different genotypes (Table 1).

3.3. Differences in tract diffusion measurements

A two-way ANOVA on TBSS analysis revealed a significant effect of genotype without any phase-gene interaction in PDM. Planned contrast analysis did not find any significant genotype differences (trait changes) during the POV phase. Compared to AA homozygotes, PDM individuals with the G allele displayed a state change during the MEN phase

2 https://identifiers.org/neurovault.image:1401

3 https://git.fmrib.ox.ac.uk/fsl/fsleyes/fsleyes

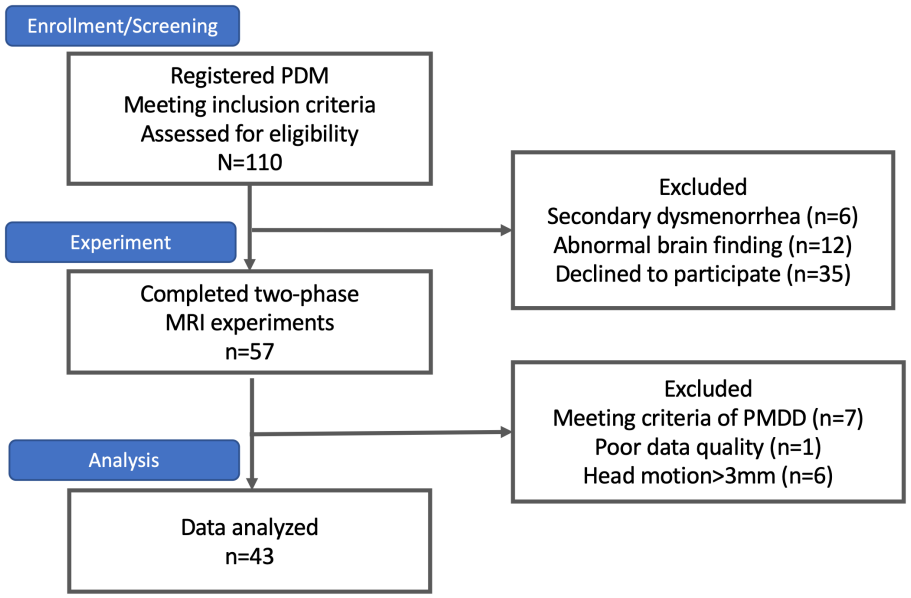

FIGURE 1
The subject flowchart. At the outset, 110 subjects with primary dysmenorrhea were enrolled, as indicated in the flowchart. However, six subjects were excluded due to secondary dysmenorrhea, 12 were excluded due to abnormal brain findings, and 35 declined to participate. Only 57 subjects successfully completed the two-phase study. Among them, seven subjects were excluded due to premenstrual dysphoric disorder (PMDD), one due to poor data quality, and six due to excessive head motion (>3mm) during the scan. Consequently, the final sample size was 43 subjects.

TABLE 1 Demographic data and baseline information.

	AA homozygotes (*n*=13)	G allele carriers (*n*=30)	Value of *p*
Calendar age (year)	23.0 (9.0)	23.0 (8.0)	0.27
Gynecological age (year)	12.0 (10.0)	10.0 (12.0)	0.07
Menstrual cycle (day)	29.5 (5.5)	29.0 (5.5)	0.69
Education (year)	16.0 (3.0)	16.0 (4.0)	0.27
BMI	20.6 (12.0)	20.5 (11.8)	0.20
Edinburg handedness	90.0 (60.0)	90.0 (60.0)	0.82
McGill pain (PRI_total)	32.0 (37.0)	34.0 (54.0)	0.87
PRI_sensory	16.0 (25.0)	18.0 (28.0)	0.55
PRI_affective	4.0 (10.0)	4.5 (11.0)	0.89
PRI_evaluation	5.0 (4.0)	5.0 (4.0)	0.56
PRI_miscellaneous	9.0 (12.0)	9.0 (15.0)	0.61
Present pain	3.0 (3.0)	3.0 (4.0)	0.82

Data are presented as median (range). The non-parametric Mann–Whitney *U* (two-tail) test was conducted for between-group comparisons. BMI, body mass index; PRI, pain rating index.

(planned contrast), characterized by increased FA and decreased RD in the corpus callosum (primarily in the body region and adjacent splenium) as well as the corona radiata (specifically the left superior and left posterior regions). All these regions are known to have projection fibers to the motor cortex (Hofer and Frahm, 2006; Park et al., 2008; Jang, 2009; Moeller et al., 2015). In addition, G allele carriers demonstrated decreased regional white matter RD in the left superior longitudinal fasciculus, which is thought to contain projection fibers to the motor cortex (Janelle et al., 2022), compared to AA homozygotes (Table 2 and Figure 2). Probabilistic tractography analysis (FA seeds only) revealed the involvement of the left internal capsule, left corticospinal tract, and bilateral MMC (*cf.* Hofer and Frahm, 2006; Figure 3).

3.4. Correlation analysis

Table 3 illustrates that among AA homozygotes, the study discovered a negative correlation between the mean FA of the body of corpus callosum and the pain rating index (affective), as well as a negative correlation between the mean FA of the left posterior corona radiata and the pain rating index (sensory) of McGill Pain Questionnaire. Moreover, the study observed a positive correlation between the mean RD of the body of corpus callosum and the pain rating index (affective) in AA homozygotes. However, no significant correlation was found between DTI metrics and MPQ scales in G allele carriers.

TABLE 2 Between genotype differences in TBSS analysis.

Cluster location		*x*	*y*	*z*	Value of *p*	Cluster size (voxel)
MEN phase, G allele carriers >AA homozygotes						
Body of corpus callosum	FA	−17	−9	36	0.044	312
Splenium of corpus callosum	FA	−13	−36	26	0.046	35
Left superior corona radiata	FA	−17	−9	37	0.044	85
Left posterior corona radiata	FA	−22	−32	30	0.046	79
MEN phase, AA homozygotes > G allele carriers						
Body of corpus callosum	RD	7	19	18	0.048	175
Splenium of corpus callosum	RD	−13	−36	26	0.048	45
Left superior corona radiata	RD	−18	−20	36	0.048	65
Left posterior corona radiata	RD	−19	−40	36	0.046	101
Left superior longitudinal fasciculus	RD	−43	−42	3	0.048	51
POV phase, G allele carriers >AA homozygotes						
NS						
POV phase, AA homozygotes > G allele carriers						
NS						

TBSS, tract-based spatial statistics; OPRM1, mu opioid receptor; POV, periovulatory phase; MEN, menstrual phase; FA, fractional anisotropy; RD, radial diffusivity. All clusters are significant at FWE-corrected $p < 0.05$, cluster voxel > 30.

4. Discussion

Our study depicts that the *OPRM1* A118G polymorphism subtly influences the white matter microstructure during the painful MEN phase, but not during the pain-free POV phase. Specifically, AA homozygotes and G carriers exhibit different state changes. The current findings are consistent with our previous study which found that individuals with PDM who carry the G allele have a maladaptive motor cortex and descending pain modulatory systems (Wei et al., 2017). The present study further demonstrated that G allele carriers with PDM have higher FA and lower RD in the corpus callosum and the left corona radiata during the menstrual phase, as compared to AA homozygotes. TBSS-tractography analysis showed that these differences involved the left internal capsule, left corticospinal tract, and bilateral MMC. However, in AA homozygotes, the mean FA of the corpus callosum and the corona radiata was negatively correlated with pain-related scales, which was not present in the G allele carriers. These results suggest that the *OPRM1* A118G polymorphism may play a critical role in modulating dysmenorrheic pain and that the neuromodulatory capacity of the A allele may be reduced in the G allele group. Such menstrual phase related rapid structural alterations is corroborated by our previous voxel-based morphometric study of gray matter volume in PDM (Tu et al., 2013).

The corpus callosum is involved in selective attention (Banich, 2003) and pain perception (Stein et al., 1989). Damage to the corpus callosum can result in somatosensory processing disorders, disrupted emotional regulation, and decreased working memory capacity (Luerding et al., 2008; Short et al., 2013; Kim et al., 2014; Fang et al., 2017). Numerous chronic pain conditions, such as pelvic pain (Woodworth et al., 2015), irritable bowel syndrome (Ellingson et al., 2013; Fang et al., 2017), low back pain (Kregel et al., 2015), temporomandibular disorder (Moayedi et al., 2012), migraine (Yuan et al., 2012; Coppola et al., 2020), and fibromyalgia (Kim et al., 2014), are associated with corpus callosum white matter abnormalities. Agenesis of the corpus callosum has been associated with changes in sensory processing, such as a higher pain tolerance and threshold for pain perception (Demopoulos et al., 2015). Moreover, the corpus callosum's enhanced interhemispheric connectivity can modulate attentional capacity, enabling individuals to concentrate on a specific task while disregarding others (e.g., hypnotic analgesia) (Horton et al., 2004). The corpus callosum consists of transcallosal fibers that connect the bilateral sensorimotor and superior frontal cortices, with a larger proportion of these fibers targeting the premotor, supplementary motor, and primary motor areas (Paul et al., 2007). The motor cortex has been pinpointed as playing a crucial role in modulating pain processes in PDM according to our previous functional MRI study (Wei et al., 2016a). In our current tractographic analysis of the PDM group, we found that the left corona radiata extends to the MMC, which corresponds to the motor representation of the pelvic floor muscle (Yani et al., 2018). Dysfunction in these regions has been linked to chronic pelvic pain (Kutch and Tu, 2016), and persistent pelvic pain has been suggested to cause axonal reorganization of the corticospinal tract in this region (Huang et al., 2016). These findings collectively suggest that G allele carriers exhibit maladaptive changes in the corticospinal tract of the corona radiata.

The corona radiata is a projection of fibers to the internal capsule and corticospinal tract, which contains motor neurons responsible for voluntary fine muscle movements and posture. The observed negative correlation between pain experience and FA of the corona radiata in the AA homozygous group may be attributed to learned motor responses that aim to adapt or alleviate pelvic pain physically (Huang et al., 2016). White matter integrity changes in the corona radiata, internal capsule, or corticospinal tract have been observed in many chronic pain conditions (Moayedi et al., 2012; Ellingson et al., 2013; Moana-Filho et al., 2013). This corticospinal tract is responsible for descending pain modulation and mediates inhibitory and facilitatory

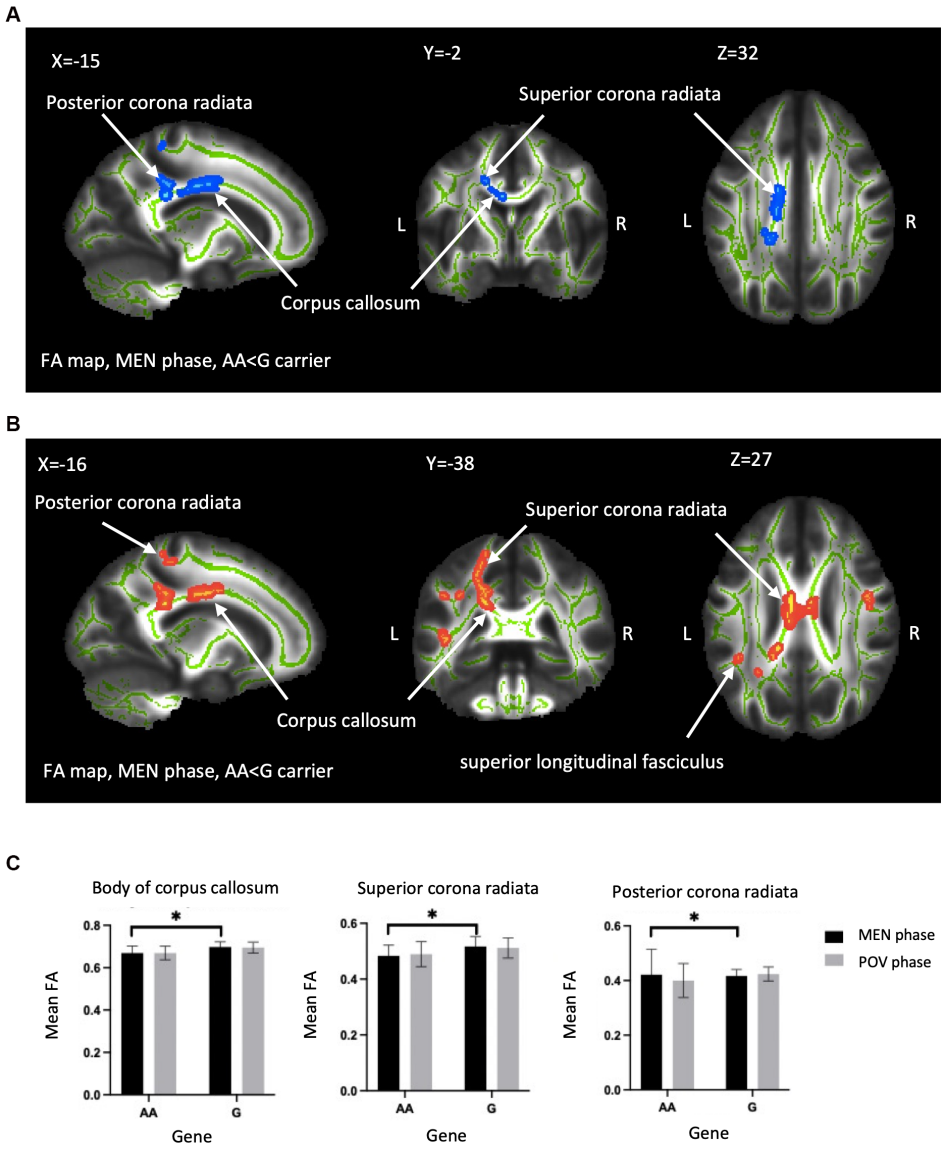

FIGURE 2
Between-genotype differences of DTI metrics. TBSS analyses showed group difference in FA and RD in the *OPRM1* A118G polymorphism during the MEN phase. **(A)** Blue regions indicate areas showing significantly lower FA in AA homozygotes compared to G carriers. **(B)** Red regions indicate significantly higher RD in AA homozygotes. The labeled clusters (white arrows) are significant at TFCE/FWE-corrected $p<0.05$, cluster voxel >30, thickened for better visualization, and overlaid on the white matter skeleton (shown in green). The group differences are observed in the body of the corpus callosum, superior corona radiata, and posterior corona radiata. **(C)** The FA value (mean±SD) of significant regions extracted from **(A,B)** for visualization. FA, fractional anisotropy; RD, radial diffusivity; MEN, menstrual; TFCE, threshold-free cluster enhancement; FWE, family-wise error; SD, standard deviation; TBSS, tract-based spatial statistics; L, left; R, right; Asterisks (*) indicate significant difference by TBSS procedure.

influences on spinal nociceptive transmission (Fishman et al., 2009). Several animal studies indicate that therapeutic motor stimulation, including stimulation of the sensorimotor cortex, can modulate the nociceptive response by activating the C fiber of the dorsal horn (Rojas-Piloni et al., 2010). Clinical studies that use repetitive motor cortex stimulation techniques, including transcranial magnetic stimulation (TMS), motor cortex stimulation (MCS), and transcranial direct current stimulation (tDCS), for treating neuropathic pain also suggest that top-down modulation of the thalamus, basal ganglia, and PAG in the brainstem leads to descending inhibition of the spinal cord (Garcia-Larrea and Peyron, 2007). Studies have shown that elevated FA in the corona radiata is not only present in individuals with PDM but also in those with other chronic pelvic pain conditions (Kilpatrick et al., 2014; Farmer et al., 2015; Kutch et al., 2015; Huang et al., 2016). It has been suggested that corticospinal excitability is reduced in response to acute muscle pain as a protective mechanism against further injury (Burns et al., 2016).

Our research revealed that the *OPRM1* A118G polymorphism is associated with genetic differences in FA and RD in certain white matter tracts, suggesting that it may affect axonal structure and myelination. Alterations in white matter integrity can occur through changes in axonal structure, myelination, fiber organization, and branching (Basser and Jones, 2002; Song et al., 2002; Bammer, 2003; Apkarian et al., 2005). For instance, FA may reflect myelination in

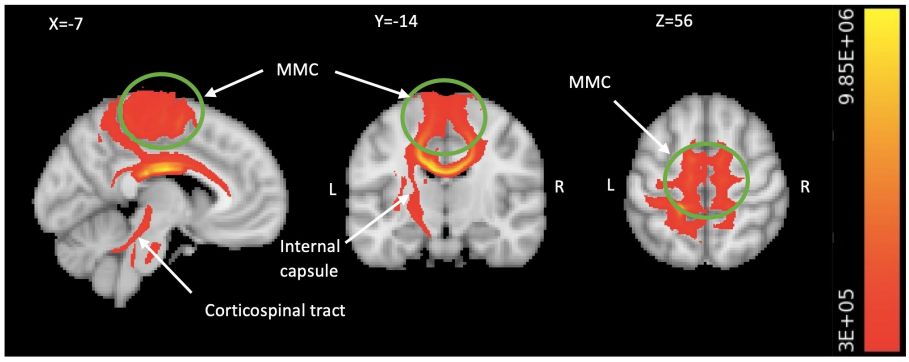

FIGURE 3
Motor system engagement revealed by TBSS-based tractography. The TBSS analysis generated probabilistic tractography (comprising all significant FA seeds in Table 2), which illustrates the connectivity between the bilateral MMC including medial M1 and pre-SMA/SMA (in green circle), all the way to the spinal cord *via* the corpus callosum, left internal capsule, and left corticospinal fiber pathways (in red/yellow). We visualize the result by aggregating data from all subjects and setting a threshold of 300,000 streamlines. The color bar indicates the number of streamlines traversing a voxel. TBSS, tract-based spatial statistics; FA, fractional anisotropy; MMC, medial motor cortex; M1, primary motor area; SMA, supplementary motor area; L, left; R, right.

TABLE 3 Correlation between the TBSS results and the MPQ scores.

	White matter tract	Behavior data	Value of *p*	*r*
MEN phase, white matter regions of G allele carriers> AA homozygotes (mean FA)				
AA homozygotes	Body of corpus callosum	PRI_affective	0.0103	−0.7503
	Left posterior corona radiata	PRI_sensory	0.04	−0.6328
G-allele carriers	NS	NS	NS	NS
MEN phase, white matter regions of AA homozygotes >G allele carrier (mean RD)				
AA homozygotes	Body of corpus callosum	PRI_affective	0.0221	0.6930
G-allele carriers	NS	NS	NS	NS

TBSS, tract-based spatial statistics; MPQ, McGill Pain Questionnaire; MEN, menstrual phase; FA, fractional anisotropy; RD, radial diffusivity; PRI, pain rating index of MPQ; NS, non-significant.

specific regions of interest, while RD may indicate changes in membrane permeability and myelination (Tromp and Scalars, 2016). Decreased FA and increased RD have been linked to several chronic pain conditions, indicating changes in axonal structure, branching, or fiber crossing (Ellingson et al., 2013; Farmer et al., 2015; Kregel et al., 2015). On the contrary, one study has reported that women with PDM have higher FA in the corpus callosum and corticospinal tract, which correlates with the duration of pain (Liu et al., 2016). Our findings indicate that G allele carriers have higher FA and lower RD compared to AA carriers in the corpus callosum and corona radiata in MEN phase. However, there were no significant differences in MD and AD between the gene groups, suggesting that neuro edema, necrosis, and prominent white matter pathology (Tromp and Scalars, 2016) are not involved in the structural modulation of the brain in PDM by the *OPRM1* A118G polymorphism. While G carriers have higher FA in the corona radiata, the strong correlation observed between MPQ scores and the FA of the corona radiata (as well as the RDs of other white matter tracts) in the AA homozygous group is diminished in the group of individuals carrying the G allele (Table 3), indicative of dysregulated pain modulation of white matter tract during the stressful pain in G allele carrier PDM subjects. The discrepancy in the aforementioned studies of chronic pain disorders and PDM (acute cyclic pain in nature) pinpoints that the genotype-informed brain imaging approach is important in elucidating mechanisms and clarifying the discrepancies in the neuroimaging study of different types of clinical pain.

Although opioid receptors are absent in the primary motor area, other brain regions such as the primary somatosensory area, basal ganglia, and brain stem (particularly the PAG) contain abundant opioidergic neurons (Peckys and Landwehrmeyer, 1999; Kibaly et al., 2019; Sjöstedt et al., 2020). The primary somatosensory area is responsible for pain intensity recognition and perception (Vierck et al., 2013), while the basal ganglia, traditionally known as a motor hub, also have an important role in pain processing due to the significant overlap between the basal ganglion network and the sensorimotor network (Figley et al., 2017). In addition, the PAG, a key component of the descending pain modulatory system, also contains opioidergic neurons (Linnman et al., 2012). It is plausible that the *OPRM1* polymorphism may directly or indirectly influence these hub regions involved in motor cortex-actuated descending pain modulation, leading to variations in pain experiences among individuals.

The exact cause of the observed left lateralized expression in the corona radiata and corticospinal tract in our study remains unknown. However, one possible contributing factor could be asymmetric opioid availability. Previous studies have suggested that mu-opioid receptors are more abundant in the right hemisphere (Kantonen et al., 2020), while the OPRM1 gene has greater

expression in the left ventral horn of the spinal cord (Kononenko et al., 2017). Nonetheless, the lateralization of clinical pain processing is a multifactorial phenomenon that involves various factors (Roza and Martinez-Padilla, 2021). Therefore, the asymmetrical gene distributions and expressions identified in previous studies may only partly explain the lateralized findings in our research. To gain a more comprehensive understanding of this topic, further investigation is necessary.

The study has some limitations that need to be considered. Firstly, the sample size, particularly in the AA group, was relatively small, but the distribution was in accordance with the Hardy–Weinberg equilibrium. Secondly, the use of 30 diffusion-direction tensor images without correction for top-down eddy current artifacts could affect the precision of the results. Further research with larger sample sizes and incorporating up-to-date techniques to correct for these pitfalls would be valuable to validate these findings.

To sum up, our study sheds light on the significance of the *OPRM1* A118G polymorphism for modulating structural integrity and dysmenorrheic pain in subjects with PDM. Individuals with AA homozygosity demonstrate better pain adaptability within the motor cortex-related pain modulation system, whereas those carrying the G allele display maladaptive changes. These genetic differences in white matter structure may contribute to variations in pain susceptibility and potentially lead to the chronic pain later in life. Our results provide insight into the neuroplasticity of the central nervous system in PDM and underscore the need for personalized pain management approaches. These findings highlight the impact of the *OPRM1* A118G polymorphism on the microstructure of white matter in individuals with PDM and suggest potential avenues for future research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Taipei Veterans General Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

P-SH: conceptualization, investigation, formal analysis, validation, methodology, data curation, writing – original draft, and visualization. C-MC: formal analysis and validation. H-TC: investigation and resources. M-WL: methodology and resources. W-CL: investigation and data curation. L-CL: investigation and validation. C-HL: investigation and validation. L-FC: conceptualization, methodology, resources, and funding acquisition. J-CH: conceptualization, methodology, resources, funding acquisition, project administration supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Electrophysiological correlates of semantic pain processing in the affective priming

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Introduction: Pain plays a fundamental role in the well-being of the individual, and its semantic content may have specific properties compared to other negative domains (i.e., fear and anger) which allows the cognitive system to detect it with priority. Considering the influence of the affective context in which stimuli (targets) are evaluated, it is possible that their valence could be differentially processed if preceded by negative stimuli (primes) associated with pain than negative stimuli not associated with pain. Thus, the present study aims to investigate the electrophysiological correlates of the implicit processing of words with pain content by using an affective priming paradigm.

Methods: Event-related potentials (ERPs) were recorded while participants were presented with positive and negative word targets (not associated with pain) that were preceded by positive, negative (not associated with pain), and pain word primes. Participants were asked to judge the valence of the target word.

Results: Results showed faster reaction times (RTs) in congruent conditions, especially when the negative target was preceded by a pain prime rather than a positive one. ERPs analyses showed no effect of pain at an early-stage processing (N400), but a larger waveform when the pain prime preceded the positive prime on the LPP.

Discussion: These results reaffirm the importance that valence has in establishing the priority with which stimuli are encoded in the environment and highlight the role that pain has in the processing of stimuli, supporting the hypothesis according to which the valence and the semantics of a stimulus interact with each other generating a specific response for each type of emotion.

KEYWORDS

affective priming, pain, words, event-related potentials, N400, LPP, semantics

1. Introduction

Given the large number of sensory inputs constantly competing for the individuals' limited processing resources, the attentional system seems to be able to automatically encode the stimuli present in the environment in terms of priority established based on their affective content, i.e., their evaluation in terms of positive or negative valence (Fazio et al., 1986). For this reason, positive and negative stimuli are processed with priority over neutral stimuli (Johansson et al., 2004; Gross and Schwarzer, 2010), and negative stimuli with priority over positive ones (Wentura, 2000; Rhudy and Williams, 2005), consistently with the importance of detecting negative stimuli for the survival of

the individual (*negativity bias*; Ito et al., 1998; Dahl, 2001). This effect has been observed also for stimuli whose valence is not innate but culturally acquired as words (Kanske and Kotz, 2007; Kousta et al., 2009; Yap and Seow, 2014; Goh et al., 2016).

Beyond the affective content of a stimulus, also its semantic content, i.e., the conveyed information or meaning, has a role in modulating the attentional system. Affective and semantic contents refer to different and independent dimensions of stimuli and while the role of the former in modulating cognitive responses is well established, only recently it has been proposed that also the latter may play a part (Witherell et al., 2012; Kveraga et al., 2015; Lindquist et al., 2016; Brooks et al., 2017; Borelli et al., 2018).

Stimuli semantically associated to pain, like words conveying pain or faces expressing pain, usually hold a negative affective content. Yet, a semantic content associated to pain is more salient compared to other negative semantic contents. This is likely because of its relevance for the well-being and survival of the individual (Kveraga et al., 2015; Brooks et al., 2017; Aguado et al., 2018; Yao et al., 2019), which makes the stimulus processing more urgent compared to other negative stimuli with different, less salient, semantic contents. Although pain is usually not considered an emotion, it can be defined as an unpleasant emotional and sensory experience (Raja et al., 2020), which gives it an extremely negative valence (Borelli et al., 2018, 2021). This can be true in the case of real pain as well as potential pain or pain threat. Regardless, pain threat may represent a signal that individuals have to move away to protect themselves and to promote their own survival. By virtue of its evolutionary function, it must be detected by the cognitive system with priority with respect to other stimuli (Yamada and Decety, 2009).

In this context, attention would be biased by a threatening stimulus both in terms of engagement and disengagement (Van Damme et al., 2008a). Attentional engagement and disengagement toward a threatening stimulus refer to the processes by which attention is facilitated in redirecting to and inhibited in withdrawing from the location in which a stimulus perceived as threatening is detected, modulating the response times or accuracy in processing a subsequent stimulus. Distraction, i.e., the shift of attention from the painful stimulus, has often been claimed as an effective strategy to reduce attentional engagement and disengagement; however, a high threatening value of the pain stimulus appears to be a powerful enough feature to disrupt such efficacy by reducing engagement in the distraction task (Van Damme et al., 2008b). These attentional effects are modulated by a number of variables, like task difficulty, as per the attentional-capacity models, or the individual relevance attributed to the stimulus, as per the attention-bias models (Vuong et al., 2018).

However, pain also holds a pro-social value when it implies an approach response toward someone else in pain (Yamada and Decety, 2009). A review by Betti and Aglioti (2016) reported numerous studies in agreement that observing individuals expressing or experiencing pain activates the same brain areas involved in the physical experience of pain itself, generating a sensory, perceptive, and behavioral simulation as a first-hand pain experience (Borelli et al., 2018).

Not only the attention but also the behavioral response to the stimulus seems to be guided by valence (Mouras and Lelard, 2021). Based on the motivational priming theory (Lang, 1995; Davidson and Irwin, 1999; LeDoux, 2000), emotions prime two motivational systems which guide behaviors: the aversive system, which facilitates avoidance/withdrawal responses towards negative stimuli, and the appetitive system, which promotes approaching responses towards positive stimuli (Lang et al., 2000, 2005; Bradley et al., 2001; Lang and Bradley, 2007; Horslen and Carpenter, 2011). The activation of these two motivational systems seems to produce subjective responses to emotions; on the contrary, their impairment may result in emotional deficits. On one hand, valence defines which of the two systems activates; on the other hand, the arousal seems to determine the intensity of activation (Rhudy and Williams, 2005). In this regard, the affective context in which a stimulus is embedded plays a critical role in its processing. When the aversive system is pre-activated by negative emotional stimuli present in the environment, it can indeed be facilitated in the generation of avoidance behaviors; on the contrary, it can be inhibited if pre-activated by positive ones (Meagher et al., 2001).

In literature, an experimental paradigm massively used to investigate how the affective context affects the evaluation of the stimulus in terms of positivity or negativity is the affective priming (Gibbons et al., 2018; Hu and Liu, 2019). Affective priming refers to the influence of emotionally charged stimuli on subsequent evaluations or reactions. According to this paradigm, the elaboration of a first stimulus (prime) may facilitate or inhibit the subsequent behavioral response to a second stimulus (target) if the two stimuli are congruent or incongruent, respectively, in terms of valence (e.g., prime HOLIDAY - target TRIUMPH vs. prime JOYFUL - target STINK).

In agreement with the spreading activation theory (Fazio et al., 1986; Murphy and Zajonc, 1993), the priming effect is due to the fact that the valence of the prime pre-activates the network of concepts associated with it, facilitating the subsequent processing of the target if its affective meaning is represented in this network of concepts, through a mechanism similar to one underlying the semantic priming (Neely, 1991). This agrees with the motivational priming theory: when the aversive system is pre-activated by negative stimuli, the individual will be facilitated in implementing avoidance behaviors. On the contrary, this avoidance response will be inhibited when the appetitive system is pre-activated by positive stimuli (an incongruent condition between prime and target).

Although the affective congruency effect, named priming effect, seems to be consistent for positive valence stimuli (Aguado et al., 2013; Contreras-Huerta et al., 2013; Gibbons et al., 2014), results are not much coherent as regarding negative stimuli. It is not clear whether the negative valence information facilitates (Paulmann and Pell, 2010; Meng et al., 2013) or inhibits (Song et al., 2019; Wu et al., 2021) the processing of subsequent negative stimuli.

Because attention determines what information we focus on and process in the environment by allocating cognitive resources, it might play a significant role in influencing the magnitude of the affective priming effect, modulating the extent to which primes and targets are processed (Seib-Pfeifer et al., 2020). Prime valence is processed automatically under defined conditions, for example when it has a highly motivational relevance for the individual (Codispoti et al., 2007), or when the evaluative dimension is goal-relevant (Spruyt et al., 2018; Rohr and Wentura, 2022). Regardless, it is likely that an increased affective prime processing will boost the priming effect. Conversely, a decreased affective prime processing will likely dampen the priming effect, decreasing the chances of an affective misattribution (Spruyt et al., 2018). Similarly, an increased target processing will likely result in a target evaluation based on its properties rather than solely on the valence of the preceding prime, reducing the priming effect, while a decreased target processing will likely result in a target evaluation more affected by the valence of the preceding primes, minimizing the priming effect (Spruyt et al., 2018). Attention to the target may be reduced in the case of a relevant affective and semantic meaning of the prime.

Even the neural dynamics of this interaction are not clearly understood (Herring et al., 2011; Eder et al., 2012; Comesaña et al., 2013; Hietanen and Astikainen, 2013; Diéguez-Risco et al., 2015; Hartigan and Richards, 2016; Aguado et al., 2018; Song et al., 2019). Event-related potentials (ERPs) indeed represent an online measure of such an effect with a temporal resolution within millisecond range. In literature, several studies on affective priming showed that the incongruency of valence between two stimuli can be indexed by ERPs components as the N400 (Zhang et al., 2006, 2010; Steinbeis and Koelsch, 2011; Eder et al., 2012; Hietanen and Astikainen, 2013), which is a negative-ongoing wave peaking around 400 ms after stimulus onset typically associated with the violation of semantic content (Kutas and Hillyard, 1984). Despite most of the studies found this effect, some reported a null effect (Herring et al., 2011), or even a reverse priming effect with a greater amplitude of the N400 in affective congruent conditions (Paulmann and Pell, 2010; Aguado et al., 2013; Wang and Zhang, 2016). In addition, another ERP component often modulated by the affective incongruency is the late positive potential (LPP) can appear in a window between 400 and 700 ms after stimulus onset and is sensitive to the evaluation of properties of stimuli and to the inconsistency of valence (Herring et al., 2011; Aguado et al., 2013; Comesaña et al., 2013; Hietanen and Astikainen, 2013; Hartigan and Richards, 2016). As for the N400, results are still inconsistent with some studies reporting no effect (Wu et al., 2021) or even a reverse priming effect (Eder et al., 2012; Hartigan and Richards, 2016) due to several overlapping components that appear in that time window. In particular, few studies pointed out how an earlier phase of the LPP (400–600 ms) may indicate the automatic allocation of attention to salient stimuli, while a later phase (post 600 ms) is affected by the top-down influence explicitly interpret the stimulus (Olofsson et al., 2008) or by contextual factors (Foti and Hajcak, 2008). The inconsistency of these results may lie in the fact that the negative valence is generally treated as a single semantic domain when, on the contrary, it embraces a heterogenous group of semantic categories (Rossell and Nobre, 2004). For this reason, it is possible to speculate that when the cognitive system needs to determine the priority of a stimulus, the negative valence of the stimuli interacts with their semantic content generating specific responses for each type of emotion (Fazio et al., 1986). Thus, pain may represent an appropriate model to understand if the specificity of the semantic content of a stimulus present in the environment can interact with the valence to the point of influencing the subsequent elaboration of positive and negative information.

So far, only a few studies demonstrated that the semantics of pain embedded in pictures (Meng et al., 2013; Cameron et al., 2017), faces (Burton et al., 2005; Chiesa et al., 2015, 2017), and words (Yamada and Decety, 2009; Grynberg and Maurage, 2014; Richter et al., 2014; Swannell et al., 2016; Meconi et al., 2018) can be processed in an automatic and early way to the point of influencing the response to subsequent pain stimuli. According to the motivational priming theory, the negative emotional information contained in a stimulus can pre-activate the aversive system and enhance both the physiological and behavioral response to a following pain stimulus (Yamada and Decety, 2009; Meng et al., 2013; Grynberg and Maurage, 2014; Richter et al., 2014; Swannell et al., 2016; Cameron et al., 2017; Meconi et al., 2018). This means that the individual previously exposed to negative information will be more likely to rapidly respond to a pain stimulus by its aversive nature (Yamada and Decety, 2009). In addition, a study recently conducted in our laboratory (Gilioli et al., 2023), increasingly corroborated these results showing that the semantics of pain content in the prime can also facilitate the processing of a negative target not associated with pain. Nevertheless, there is little evidence that showed a reverse effect reporting that the processing of a negative prime might also inhibit the subsequent elaboration of a pain stimulus (Burton et al., 2005; Song et al., 2019). Almost no studies have investigated the neural dynamics of this effect on pain and outcomes are still unclear (Sessa et al., 2014; Swannell et al., 2016; Meconi et al., 2018; Song et al., 2019).

In light of this, the present research aimed at investigating the time course of the implicit processing of pain words, analyzing the ERPs correlates of this effect. For this purpose, we replicated our previous behavioral experiments (Gilioli et al., 2023) using the EEG technique. In Gilioli et al. (2023), we adopted an affective priming paradigm and presented healthy participants with prime words with positive and negative valence (associated and not-associated with pain) and target words with positive and negative valence (not-associated with pain). Participants had to evaluate the valence of the target (valence judgment task) by pressing one of two buttons.

In the present study, we recruited a different sample of participants and asked them to perform the same task on the same stimuli while recording their electrophysiological activity as well as their reaction times (RTs).

Our first goal was to confirm the behavioral findings of our prior work, i.e., a priming effect for pairs of negative words only if the prime had pain-related semantics, as shown by faster reaction times and better accuracy scores. This would support the idea that the processing of a stimulus semantically associated to pain can possibly enable the individual to respond more quickly to upcoming negative information in the environment by allocating the appropriate number of resources for generating a response.

Our second goal was to study the electrophysiological correlates of this effect by focusing on two main ERPs components, the N400 and LPP. To the best of our knowledge, this is the first study to apply ERP component analysis to an affective priming paradigm involving word stimuli associated with pain. We hypothesized that if pain-related semantics elicit a distinct response, then these components would capture it to a greater extent at an electrophysiological level. However, due to the limited and inconclusive nature of previous research, it remains unclear whether this effect is present and in what direction. Therefore, it is reasonable to consider the possibility that the priming effect may also occur in other ERP time windows.

2. Methods

2.1. Ethics statement

This study was carried out in accordance with the recommendations of the "Italian Association of Psychology" (AIP) Ethical Guidelines (Codice Etico),[1] and was approved by the local Ethical Committee of the University of Modena and Reggio Emilia. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

1 www.aipass.org/node/11560

TABLE 1 Descriptive statistics of familiarity, length in letters, valence, and arousal for the three word categories (i.e., positive, negative, and pain stimuli).

		Familiarity M (SD)	Valence M (SD)	Arousal M (SD)	Length M (SD)
Prime	Positive words	5.05 (±0.46)	5.99 (±0.32)	4.85 (±0.63)	7.44 (±2.11)
	Negative words	4.71 (±0.74)	1.83 (±0.24)	5.06 (±0.50)	8.34 (±1.7)
	Pain words	4.71 (±1.13)	1.67 (±0.39)	5.25 (±0.7)	8.44 (±2.37)
Target	Positive words	5.05 (±0.58)	5.97 (±0.30)	5.06 (±0.45)	7.47 (±1.97)
	Negative words	4.76 (± 0.6)	1.85 (±0.23)	4.82 (±0.60)	7.77 (±1.72)

2.2. Participants

Thirty-seven students at the University of Modena and Reggio Emilia, all females (age range: 19–51 years.; mean age = 25.16; SD = 7.49) participated in the experiment for course credit. All participants were right-handed (L.Q. = 91.7) as assessed by the Italian version of the Edinburgh Handedness Inventory (Oldfield, 1971), and they had normal or corrected-to-normal visual acuity, no history of neurological or mental disorders, and they were Italian native speakers.

Three participants were excluded from the analyses: the first due to a recording error of the experimenter, the second started to perform the task before the recording was initiated, and the last needed to be excluded since the experiment was interrupted by an external issue. Therefore, the statistical analyses were performed on 34 female subjects (age range:19–51 years; mean age = 24.65; SD = 7.21). The sample size was established based on heuristic evaluations of the literature on affective priming, which reports numerous studies with samples of 22–33 subjects (Yamada and Decety, 2009; Wu et al., 2021). We also conducted *a posteriori* sensitivity power analysis (Lakens, 2022) using G*Power 3.1 (Faul et al., 2007) according to which given $N = 34$, $\alpha = 0.05$ and a power = 80% a minimum partial equal to $\eta^2 = 0.1968$ was found, consistent with the literature on this topic.

The choice of selecting an entire sample of female participants was based on our previous study (Gilioli et al., 2023) in which we found gender differences in the priming effect: indeed, females reported a significant priming effect when asked to evaluate a positive target preceded by a positive prime rather than a pain prime. This effect was not found in males.

2.3. Stimuli

Overall, 256 Italian words (both adjectives and nouns) were adopted for this study, among which 32 negative words associated with pain (henceforth, pain words; e.g., *ferita*, injury), 96 negative words not associated to pain (henceforth, negative words; e.g., *vandalo*, vandal), and 128 positive words (e.g., *vita*, life; for the complete word list and English translation, see Supplementary Table S1). Positive and negative words were selected from the Italian version of the ANEW database (Affective Norms for English Words; Montefinese et al., 2014), while pain words were selected from the WOP database (Words of Pain, WOP; Borelli et al., 2018). Pain words were chosen based on their pain-relatedness scores (Borelli et al., 2018), which had to be in the range between 6 and 7 on a rating scale from 1 (not at all associated with pain) to 7 (extremely associated with pain). The three categories of words were controlled for the main psycholinguistic and affective variables that are known to affect the time it takes to process a word, namely familiarity, length in letters, valence, and arousal (see Table 1 for descriptive statistics). Each prime-target pair was also controlled for semantic relatedness (Pedersen et al., 2004).

The 256 words were divided into 128 prime stimuli and 128 target stimuli. Prime stimuli included 32 negative words/prime, 32 pain words/prime, and 64 positive words/prime, whereas target stimuli comprised the remaining 64 negative words/target and the remaining 64 positive words/target. Both prime words and target words were presented 4 times during the entire experiment in 4 blocks and paired to form 512 prime - target pairs (Figure 1). Thereby, we obtained 256 congruent pairs (128 positive prime - positive target; 64 pain prime – negative target; 64 negative prime – negative target), and 256 incongruent pairs (128 positive prime - negative target; 64 negative prime - positive target; 64 pain prime - positive target).

Participants performed four blocks. Within each block, a list of 128 out of 512 prime-target pairs was presented each in a separate trial in a randomized order. The lists were randomized among participants.

2.4. Procedure

The experiment was implemented in E-prime software (Version 3; Psychology Software Tools, Pittsburgh, PA) and was presented as a study on how people categorize stimuli based on their positive or negative valence. All stimuli were presented in the center of a 17 CRT monitor synchronous with the screen refresh [Philips 107B; refresh rate = 60 Hz (16.67 ms)] that was positioned at eye level approximately 70 cm in front of the participant, such that each stimulus subtended 1.2–4.1° of horizontal visual angle and 0.5° of vertical visual angle. As shown in Figure 1, each trial began with a fixation cross (+) presented in the middle of the screen and stayed there until participants pressed a button to start the trial. Then a black screen (blank) was displayed for 500 ms and replaced by a prime stimulus lasting 150 ms, followed by another blank lasting 100 ms. Once the blank disappeared, a target stimulus appeared and remained on the screen until the participant's response. The primes and the targets were presented in the center of the screen in white lowercase letters for the former and in uppercase letters for the latter (20-point Calibri bold font) on a black background. The interstimulus interval was set up at 1000 ms after the participant's response. Participants were instructed to evaluate, as quickly and accurately as possible, whether the target was a positive or negative word (valence judgment task) and to respond by pressing one of two buttons, which were counterbalanced (left and right) across

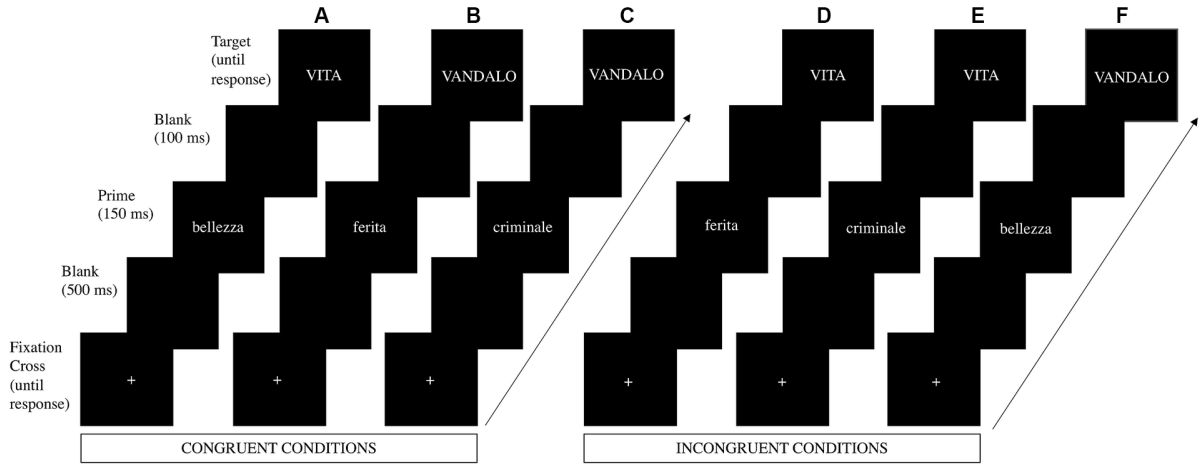

FIGURE 1
Time sequence of events during an illustrative **(A)** positive prime – positive target trial, **(B)** pain prime – negative target trial, **(C)** negative prime – negative target trial, **(D)** pain prime – positive target trial, **(E)** negative prime – positive target trial, and **(F)** positive prime – negative target trial. The illustrative trials a, b, and c represent the congruent condition, and the illustrative trials d, e, and f represent the incongruent condition. Briefly, a fixation cross (+) was displayed on the screen. Once participants pressed the start button, they were presented in this order with a blank for 500ms, the prime stimulus for 150ms, another blank for 100ms, and the target stimulus, which remained on the screen until the participants' response. Participants were instructed to evaluate the valence of the target stimulus and to press a button if positive or another button if negative. Adapted with permission from Gilioli et al. (2023).

participants. Participants performed a practice session consisting of 16 trials (half congruent pairs and half incongruent pairs) prior to study onset to ensure that they understood the task. Stimuli in the practice session were different from the experimental ones. The experiment lasted approximately 35 min.

2.5. Questionnaires

To assess for individual differences in pain processing, we administered three questionnaires at the end of each experimental procedure: the Italian version of Behavioral Approach/Inhibition System Scale (BIS/BAS scale; Leone et al., 2002) which evaluates the activation and inhibition system; the Italian version of Pain Catastrophizing Scale (PCS-I, Monticone et al., 2012) which measures the individual disposition in pain anxiety and catastrophizing; and the Italian version of the Interpersonal Reactivity Index (IRI, Albiero et al., 2006) which is a measure the dispositional response empathy by integrating affective and cognitive components (e.g., perspective taking, personal distress).

2.6. EEG recording and analysis

The EEG data is recorded continuously *via* 64 active electrodes (ActiCap Slim, BrainProducts) placed on the scalp according to the International 10–10. Electrical activity was amplified and sampled at 1000 Hz by a 24-bit ActiCHamp Plus System (BrainProducts) and recorded with BrainVision recorder software (BrainProducts, version 1.25.0101) running on a Windows 10 computer. All electrodes were recorded with the online reference located at FCz. Two electrodes were placed over the left and right mastoids to serve as an offline reference, two were placed at the external ocular canthi of both eyes to monitor horizontal eye movements (HEOG) and one was placed under the left eye to monitor blinks (VEOG). Electrical impedances were kept below 20 kΩ.

Brain Vision Analyzer 2 (Brain Products, Gilching, Germany) was used to perform off-line signal processing analyses. The EEG signal was bandpass filtered between 0.1 and 80 Hz and referenced offline to the average activity of the two mastoids. Artifact activity was rejected using a semiautomated procedure, with artifacts identified by the following criteria: Gradient, with 75 μV maximal allowed voltage step; Max–Min with 200 ms maximal allowed absolute difference; Low activity, with 0.5 μV/100 ms lowest allowed activity. Data with excessive blinks were adaptively corrected using ICA. 1,000-ms epochs containing the ERP elicited by the target word were extracted. A 200 ms pre-stimulus baseline was used in all analyses. Segments including artifacts due to activity exceeding ±100 μV in amplitude were rejected.

The data has been filtered at 30 Hz with the sole purpose of better graphic visualization. The statistical analyses were conducted on the data initially filtered at 0.1–80 Hz. Based on visual inspection of grand average ERP waveforms and in line with previous literature, the following components were identified for target onset at frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) scalp sites: N400 from 300 to 500 ms after target onset; LPP from 500 to 700 ms after target onset. For each ERP component amplitude was measured as mean activity within the respective time window.

2.7. Statistical analysis

Statistical analyses were performed using JASP software (JASP Team, 2022 Version 0.16.3).

The analysis of accuracy scores was initially performed. RTs and ERP analyses were then carried out on trials with correct responses. Individual RTs exceeding ±2 standard deviations (SD) were excluded from the analysis.

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To control for potential confounding effects of primes and targets familiarity, length in letters, valence, arousal, and semantic relatedness we added them as covariates in four analyses of covariance on stimuli RTs and accuracy, one with prime valence and one with prime semantics as a factor.

At the behavioral level, to investigate the role of the prime valence, we performed repeated-measures 2 × 2 ANOVAs on the accuracy rates and the mean RTs with prime valence and target valence as within-subject factors. To investigate the role of the semantic content of prime, we performed repeated-measures 3 × 2 ANOVAs on the accuracy rates and the mean RTs with prime semantics and target valence as within-subject factors. To examine significant interactions, we performed planned paired samples t-tests based on *a-priori* hypotheses. In the 3 × 2 ANOVAs on prime semantics, 64 positive words were compared to negative words, of which 32 were unrelated to pain and 32 were related to pain. For this reason, this analysis resulted in not having the same power as the 2 × 2 ANOVA on prime valence and some effects detected in the latter might appear to weaken in the former. For this reason, both ANOVAs are meaningful to the aim of the study.

At the ERP level, ERP effects time-locked to the onset of the target were evaluated considering 6 clusters of electrodes representing the mean amplitude of three electrodes in close position: Anterior (F3, Fz, F4), Central (C3, Cz, C4), Posterior (P3, Pz, P4), Left (F3, C3, P3), Midline (Fz, Cz, Pz), Right (F4, C4, P4).

A repeated-measures 2×2x3x3 ANOVA was conducted on mean ERP amplitudes with prime valence (positive, negative), target valence (positive, negative), longitude (anterior, central, posterior), and latitude (left, midline, right) as within-subject factors. Secondly, to consider the effect of the semantic content associated to the negative prime, a repeated-measures 3x2x3x3 ANOVA was performed on ERP amplitudes with prime semantics (positive, negative, pain-related), target valence (positive, negative), longitude (anterior, central, posterior), and latitude (left, midline, right) as within-subject factors. To further understand the nature of the interactions, both analyses were followed by separate ANOVAs which were run on the positive and negative target valence. Additionally, *post-hoc* mean comparisons were employed to further examine significant interactions.

In addition, we analyzed the influence of individual differences in pain processing measured by the above-mentioned questionnaires on the behavioral and ERP effects. For each subscale of the questionnaires, the correlation with accuracy scores and RTs Δ congruent-incongruent conditions was measured by the Spearman coefficient for non-parametric measures. As well the correlation with ERP amplitudes of all electrodes Δ congruent-incongruent conditions was measured by the Spearman coefficient for non-parametric measures. This was calculated for both time windows (300–500 and 500–700 ms).

To account for violations of sphericity, the Greenhouse–Geisser procedure was used to correct degrees of freedom: only corrected significance levels are reported. The level of significance for all statistical analyses was set to $p < 0.05$. Holm correction was applied for multiple comparisons and only corrected *p*-values are reported. The main effects of prime valence and target valence in the omnibus ANOVAs were not central to the questions under study. Therefore, they are reported but not discussed. Here, we discussed only the interaction between prime valence and target valence which was of interest to the study. In the separate ANOVAs for the target valence, the main effect of the prime valence was crucial to the analyses: for this reason, it has been discussed.

3. Results

3.1. Behavioral results

Results from the two ANCOVAs on stimuli accuracy did not reveal any confounding effect of prime and target familiarity, length, valence, arousal, semantic relatedness neither with prime valence nor with prime semantics as a factor. Results from the two ANCOVAs on stimuli RTs did reveal a possible confounding effect of target length ($p < 0.001$) when prime valence was a factor and a possible confounding effect of target length ($p < 0.001$) and target arousal ($p = 0.008$) when prime semantics was a factor. Because the overall results with and without these potentially confounding variables were the same, they have not been included in the analyses on participants' RTs and accuracy and will not be further discussed.

Overall, 6.6% of trials were excluded from the analyses because the RTs exceeded ±2 SD.

In order to investigate the role of the prime valence, we performed repeated-measures 2×2 ANOVAs on the accuracy rates and the mean RTs. The analysis on the accuracy scores showed a significant main effect of target valence [$F(1,33) = 6.13$, $p = 0.019$, $\eta_p^2 = 0.16$] so that responses to the negative target ($\mu = 0.96$, $SE = 0.0008$) were more accurate than to the positive one ($\mu = 0.94$, $SE = 0.009$).

The analysis on RTs showed a significant main effect of prime valence [$F(1,33) = 8.56$, $p = 0.006$, $\eta_p^2 = 0.21$] so that the positive prime ($\mu = 695.86$, $SE = 8.48$) was elaborated faster than the negative one ($\mu = 702.71$, $SE = 8{,}43$), and a significant prime valence × target valence interaction [$F(1,33) = 12.289$, $p = 0.001$, $\eta_p^2 = 0.271$]. Paired sample t-tests showed significantly faster RTs when the positive target was preceded by a positive prime ($\mu = 687.38$, $SE = 14.74$) rather than a negative prime ($\mu = 711.14$, $SE = 14.85$) [$t(33) = -4.4$, $p = 0.002$ $p \leq 0.001$, Cohen's $d = -0.75$]; and significant faster RTs when the negative target ($\mu = 694.27$, $SE = 13.94$) was preceded by a negative prime rather than a positive one ($\mu = 704.34$, $SE = 13.57$) [$t(33) = -1.89$, $p = 0.034$, Cohen's $d = -0.32$], as shown in Figure 2.

To investigate the role of the prime semantics, we performed repeated-measures 3×2 ANOVAs on the accuracy rates and the mean RTs. The analysis on accuracy rates showed a significant main effect of target valence [$F(1,33) = 5.58$, $p = 0.024$, $\eta_p^2 = 0.15$] so that responses to the negative target ($\mu = 0.96$, $SE = 0.001$) were more accurate than to the positive one ($\mu = 0.94$, $SE = 0.007$). The analysis on RTs showed a significant main effect of prime semantics [$F(1.8,\ 60.9) = 3.15$, $p = 0.05$, $\eta_p^2 = 0.09$] so that the positive prime ($\mu = 695.86$, $SE = 8.48$) was elaborated faster than the negative ($\mu = 702.3$, $SE = 5.73$) and the pain one ($\mu = 702.86$, $SE = 11.06$); and a significant prime semantics x target valence interaction [$F(1.5,\ 49.85) = 10.35$, $p \leq 0.001$, $\eta_p^2 = 0.24$]. Paired samples t-tests showed significantly faster RTs when the positive target was preceded by a positive prime ($\mu = 687.38$, $SE = 14.74$) rather than a pain prime ($\mu = 713.92$, $SE = 14.49$) [t (33) = −4.4, $p = 0.003$, Cohen's $d = -0.75$] or a negative prime ($\mu = 708.03$,

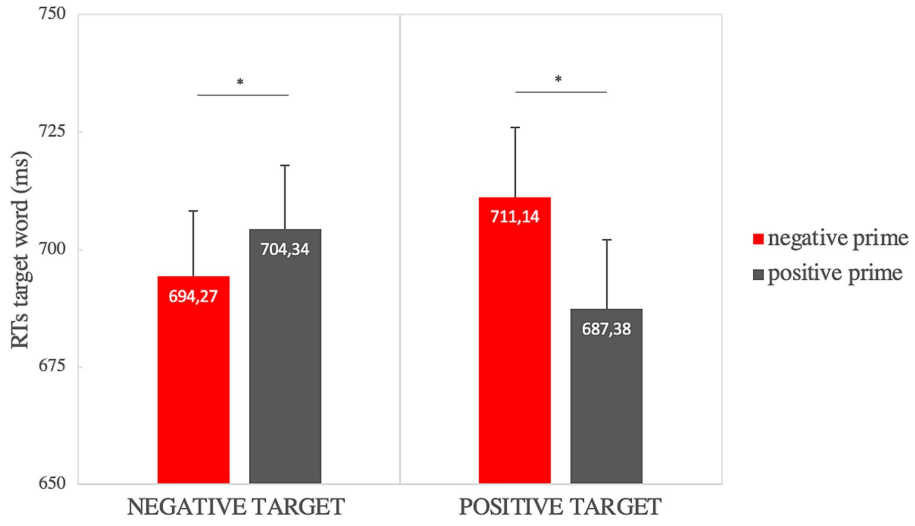

FIGURE 2
Affective priming effect on RTs for the "valence" factor (in the graph significant comparisons are indicated with *: this highlights the priming effect for positive and negative targets). Error bars represent standard errors of the mean.

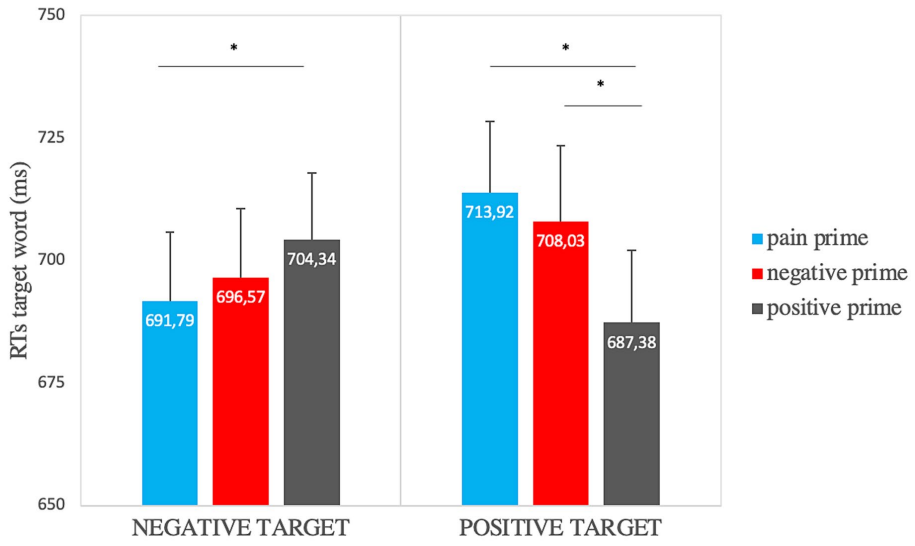

FIGURE 3
Affective priming effect on RTs for the "semantic" factor (in the graph significant comparisons are indicated with *: this highlights the priming effect for positive and negative targets). Error bars represent standard errors of the mean.

$SE = 15.50$) [t (33) = −3.59, $p = 0.003$, Cohen's $d = -0.62$] and significantly faster RTs when the negative target was preceded by a pain prime ($\mu = 691.79$, $SE = 14.07$) rather than a positive one ($\mu = 704.34$, $SE = 13.57$) [t (33) = −2.21, $p = 0.017$, Cohen's $d = -0.38$] (Figure 3).

3.2. ERP results

Grand-averaged ERPs elicited by the different experimental conditions are represented in Figure 4 and their topographical maps in Figure 5.

3.2.1. N400

To investigate the role of prime valence, we performed repeated-measures 2x2x3x3 ANOVAs on ERPs amplitudes which showed a marginally significant main effect of prime valence [$F(1,33) = 3.63$; $p = 0.066$; $\eta_p^2 = 0.1$] so that the negative prime elicited larger negative waveforms ($\mu V = 1.05$, $SE = 0.32$) rather than the positive one ($\mu V = 1.21$, $SE = 0.32$). The analysis also showed the following significant interactions: target valence x longitude [$F(1.41, 46.66) = 7.22$; $p = 0.005$; $\eta p^2 = 0.18$]; latitude x prime valence x target valence [$F(1.82, 60.16) = 4.32$; $p = 0.02$; $\eta_p^2 = 0.12$]; longitude x prime valence x target valence [$F(1.33, 43.8) = 11.99$; $p \leq 0.001$; $\eta_p^2 = 0.27$]. To further explore these interactions, the ERPs amplitudes of positive

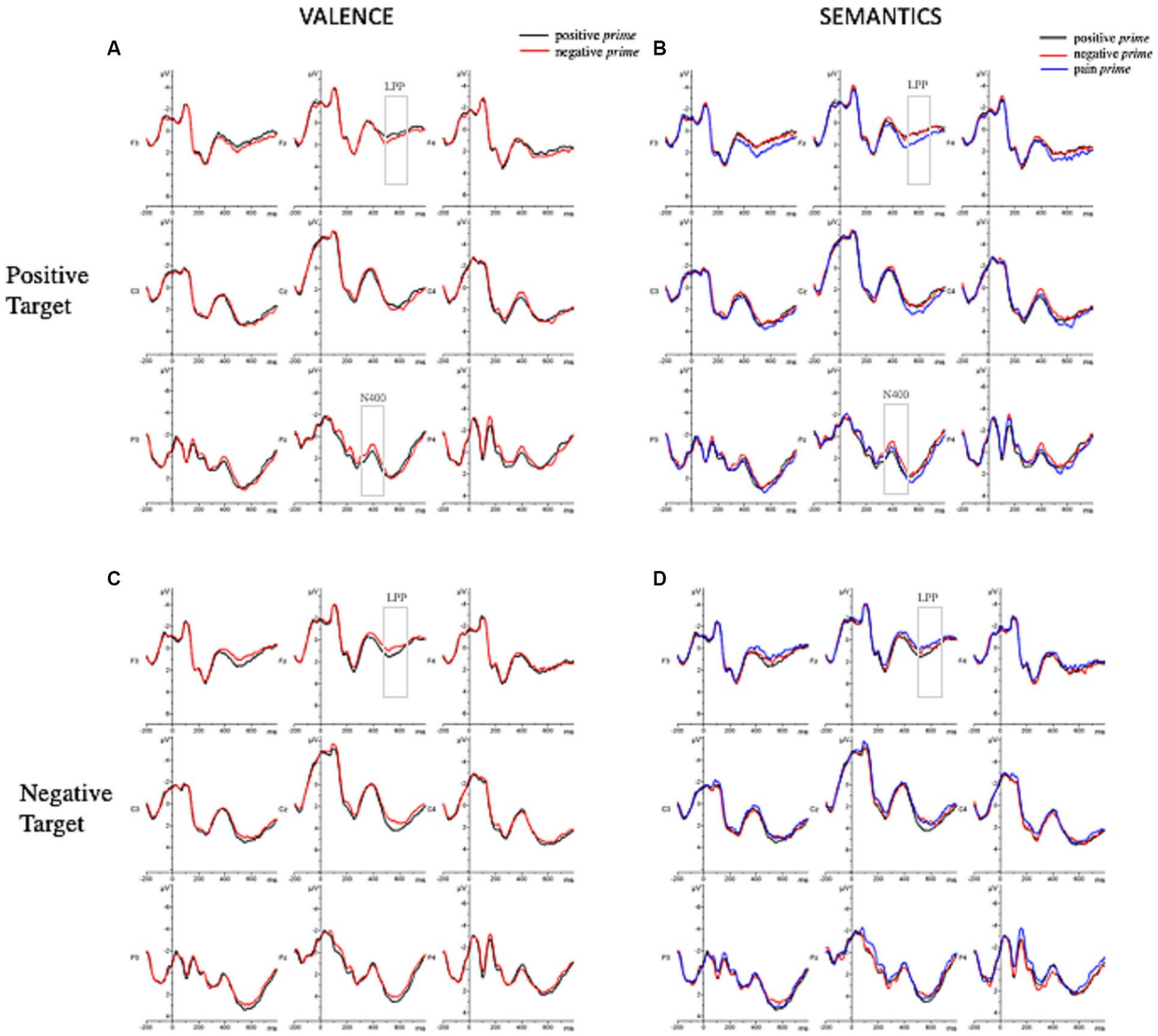

FIGURE 4
Grand-averaged ERP waveforms elicited by positive and negative target words for the valence manipulation condition **(A,C)** and the semantic manipulation condition **(B,D)** as a function of prime type.

target and negative target were analyzed separately. The 2 × 3 × 3 ANOVA on the positive targets showed a significant longitude x prime valence interaction [$F(1.28, 42.34) = 10.37$; $p = 0.001$; $\eta_p^2 = 0.24$]. *Post-hoc* analyses revealed a larger negative waveform when the positive target is preceded by a negative prime ($\mu V = 0.99$, $SE = 0.43$) rather than a positive prime ($\mu V = 1.46$, $SE = 0.43$) at posterior positions.

Considering the negative target, the 2 × 3 × 3 ANOVA on the negative targets showed the subsequent significant interactions: latitude x prime valence [$F(1.87, 61.65) = 6.02$; $p = 0.005$; $\eta_p^2 = 0.15$]; longitude x prime valence [$F(1.41, 46.59) = 4.09$; $p = 0.036$; $\eta_p^2 = 0.11$]. No effects in the *post-hoc* analyses resulted significant.

To investigate the role of the prime semantics, a further 3 × 2 × 3 × 3 ANOVA showed the following significant interactions: prime semantics x target valence [$F(1.67, 55.06) = 5.38$; $p = 0.011$; $\eta_p^2 = 0.14$], longitude x target valence [$F(1.45, 47.81) = 13.86$; $p \leq 0.001$; $\eta p^2 = 0.3$], longitude x prime semantics x target valence [$F(2.5, 82.6) = 4.52$; $p = 0.009$; $\eta_p^2 = 0.12$]; and a marginally significant latitude × longitude x prime semantics × target valence [$F(4.7, 155.45) = 2.1$; $p = 0.074$; $\eta_p^2 = 0.06$]. To further explore these interactions, the ERPs amplitudes of positive and negative targets were analyzed separately. The 3 × 3 × 3 ANOVA on the positive targets showed a significant main effect of prime semantics [$F(1.92, 63.35) = 5.48$; $p = 0.007$; $\eta_p^2 = 0.14$] so that the positive target elicited larger negative waveforms when preceded by a negative prime ($\mu V = 0.91$, $SE = 0.35$) rather than a pain one ($\mu V = 1.31$, $SE = 0.35$), and when it was preceded by a negative prime rather than a positive one ($\mu V = 1.29$, $SE = 0.35$). The analysis also showed a significant longitude x prime semantics interaction [$F(2.44, 80.64) = 3.71$; $p = 0.021$; $\eta_p^2 = 0.1$]. *Post-hoc* analyses revealed a larger negative waveform when the positive target is preceded by a negative prime ($\mu V = 0.8$, $SE = 0.43$) rather than a positive one ($\mu V = 1.46$, $SE = 0.43$) at posterior positions.

The 3x3x3 ANOVA on the negative targets showed a marginally significant latitude x longitude x prime semantics interaction [$F(5.62,185.55) = 2.17$; $p = 0.052$; $\eta_p^2 = 0.06$]. No significant *post-hoc* analyses resulted significant.

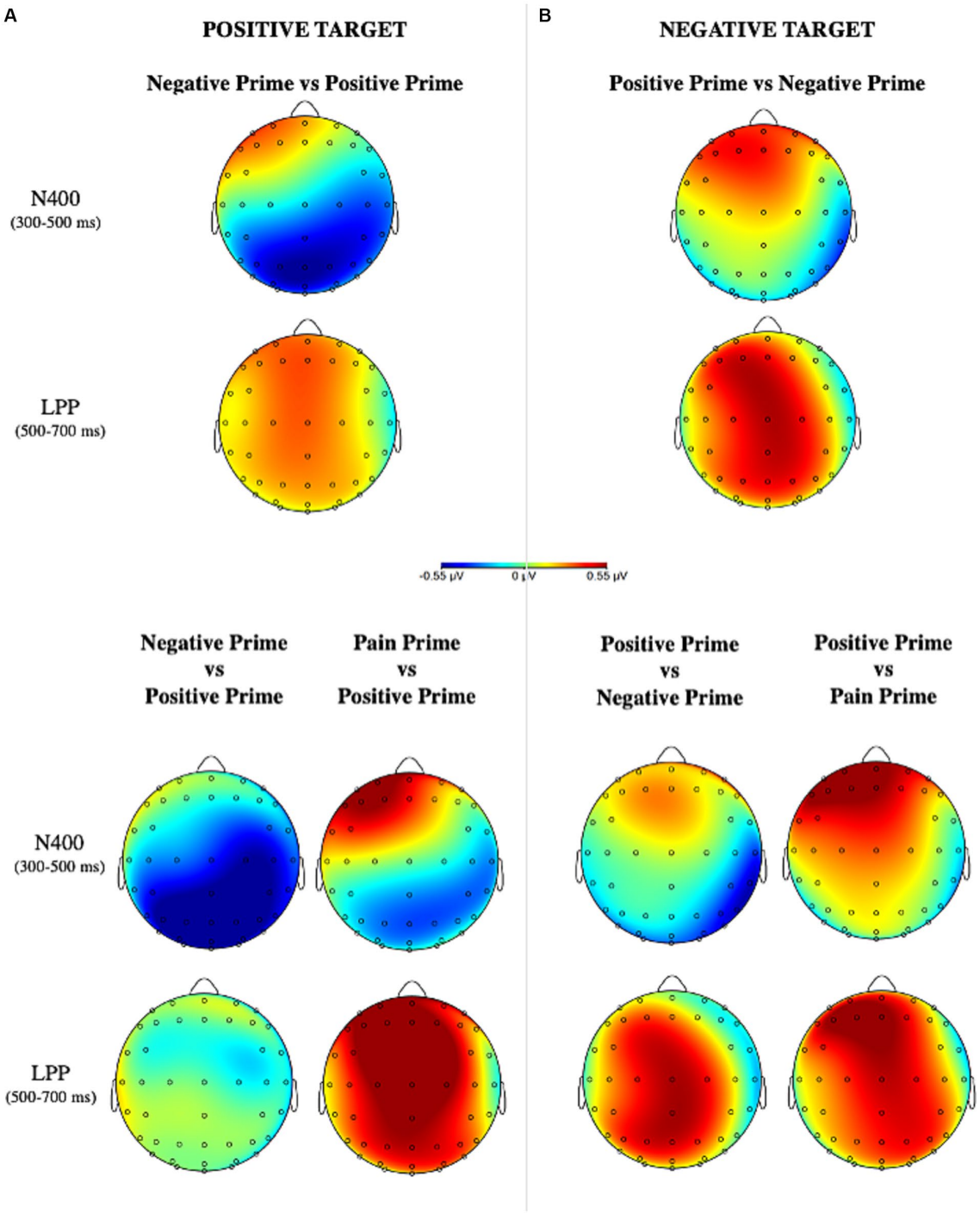

FIGURE 5
Topographical scalp distribution for positive and negative targets for the valence manipulation conditions **(A)** and for the semantic manipulation condition **(B)** in the two critical time windows, created by subtracting incongruent conditions and congruent conditions.

3.2.2. LPP

To investigate the role of prime valence, we performed repeated-measures 2x2x3x3 ANOVA on ERPs amplitudes which showed the following significant interactions: prime valence x target valence [$F(1, 33) = 7.38$; $p = 0.010$; $\eta_p^2 = 0.18$], longitude x target valence [$F(1.44, 47.54) = 11.95$; $p \leq 0.010$; $\eta p^2 = 0.27$], and a marginally significant latitude x prime valence x target valence interaction [$F(1.7, 56.08) = 3.20$; $p = 0.056$; $\eta_p^2 = 0.09$]. To further explore these interactions, the ERPs amplitudes of positive target and negative target were analyzed separately. The $2 \times 3 \times 3$ ANOVA on the positive targets showed a significant main effect of the prime valence [$F(1, 33) = 4.21$; $p = 0.048$; $\eta_p^2 = 0.11$] in which the positive target elicited larger positive waveforms when preceded by a negative prime ($\mu V = 2.33$, $SE = 0.46$) rather than a positive prime ($\mu V = 2.07$, $SE = 0.46$). The 2x3x3 ANOVA on the negative targets showed a significant main effect of prime valence [$F(1, 33) = 6.13$;

$p = 0.019$; $\eta_p^2 = 0.16$] in which the negative target elicited larger positive waveforms when preceded by a positive prime ($\mu V = 2.58$, $SE = 0.41$) rather than a negative one ($\mu V = 2.23$, $SE = 0.41$). In addition, the analysis also showed a significant latitude x prime valence interaction [$F(1.82, 60.11) = 4.83$; $p = 0.014$; $\eta_p^2 = 0.13$]. *Post-hoc* analyses revealed larger positive waveforms when the negative target is preceded by a positive prime ($\mu V = 2.92$, $SE = 0.43$) rather than a negative ($\mu V = 2.44$, $SE = 0.43$) one at midline positions.

Thereafter, to investigate the role of the prime semantics, a further 3x2x3x3 ANOVA was performed which showed the following significant interactions: prime semantics x target valence [$F(1.83, 60.22) = 8.40$; $p \leq 0.001$; $\eta_p^2 = 0.2$], longitude x target valence [$F(1.44, 47.44) = 11.44$; $p \leq 0.001$; $\eta p^2 = 0.26$], and a marginally significant latitude × longitude × prime semantics × target valence interaction [$F(4.78, 157.45) = 2.21$; $p = 0.059$; $\eta_p^2 = 0.06$]. To further explore these interactions, the ERPs amplitudes of positive target and negative target were analyzed separately. The 2x3x3 ANOVA on the positive targets showed a significant main effect of prime valence [$F(1.95, 64.45) = 8.99$; $p \leq 0.001$; $\eta_p^2 = 0.21$] with larger positive waveforms when preceded by a pain prime ($\mu V = 2.6$, $SE = 0.46$) rather than a negative one ($\mu V = 2.06$, $SE = 0.46$) and a positive one ($\mu V = 2.06$, $SE = 0.46$). The $2 \times 3 \times 3$ ANOVA on the negative targets showed a marginally significant main effect of prime semantics [$F(1.98, 65.48) = 3.08$; $p = 0.053$; $\eta_p^2 = 0.085$] so that the negative target elicited larger positive waveforms when preceded by a positive prime ($\mu V = 258$, $SE = 0.41$) rather than a pain prime ($\mu V = 2.18$, $SE = 0.41$). Moreover, the analysis also showed a significant latitude × prime semantics interaction [$F(3.59, 118.41) = 2.83$; $p = 0.032$; $\eta_p^2 = 0.08$] and only a marginally significant latitude × longitude × prime semantics interaction [$F(5.17, 170.69) = 2.00$; $p = 0.079$; $\eta p^2 = 0.06$]. No effects in the *post-hoc* analyses resulted significant.

3.3. Correlations

To test the influence of individual differences in pain processing on the accuracy and RT effects, we performed the correlation between the scores in the questionnaires' subscales and the behavioral effects both for prime valence and prime semantics. In the analysis on prime valence, the correlation between the questionnaire's subscales and the difference in accuracy scores Δ between congruent and-incongruent conditions showed that both the priming effects associated with the negative target and the positive target were positively correlated to the subscale Magnification of the PCS questionnaire (respectively Spearman's rho = 0.42, $p = 0.00137$; Spearman's rho = 0.350, $p = 0.042$).

In the analysis on prime semantics, the correlation analysis on accuracy scores showed a negative correlation between the priming effect associated with the negative target (pain prime-negative target vs. positive prime-negative target) and the subscales of the Empathic Concern (Spearman's rho = −0.33, $p = 0.027$) and the Perspective Taking (Spearman's rho = −0.37, $p = 0.03115$) of the IRI questionnaire. An additional negative correlation was detected between the priming effect associated with the negative target (negative prime-negative target vs. positive prime-negative target) and the Magnification subscales of the PCS questionnaire (Spearman's rho = −0.38, $p = 0.02914$). The correlational analyses on RTs did not show any significant results.

As well we analyzed the individual differences in pain processing on the ERP effect. In the analysis on prime valence for both the ERP components, the correlation analysis between questionnaires' subscales and the difference in mean amplitudes for all electrode sites Δ between congruent and-incongruent conditions did not show any significant results. In the analysis on the prime semantics, the correlation analyses on N400 mean amplitudes showed that the priming effects associated with the positive target (positive prime-positive target vs. negative prime-positive target) correlated with both the BIS scale (Spearman's rho = 0.43, $p = 0.012$), the Personal Distress subscale of the IRI questionnaire (Spearman's rho = 0.40, $p = 0.019$), and the Rumination subscale of the PCS questionnaire (Spearman's rho = 0.354, $p = 0.04$). The correlation analyses on LPP mean amplitudes showed that the priming effects associated with the negative target (pain prime-negative target vs. negative prime-negative target) correlated with both the Fantasy subscale of the IRI questionnaire (Spearman's rho = 0.35, $p = 0.04$), and the Rumination subscale of the PCS questionnaire (Spearman's rho = 0.38, $p = 0.029$).

4. Discussion

In the present experiment, we explored the time course of the implicit processing of pain words, particularly whether the processing of a stimulus semantically associated to pain can help the individual to respond to an upcoming negative information in the environment. To our knowledge, our study represents the first to adopt the well-known affective priming paradigm combined with EEG recordings to investigate the neural correlates of the elaboration of pain words.

At the behavioral level, results confirmed what we have already found in our previous study using the same paradigm (Gilioli et al., 2023). They showed an affective priming, that is the participant responded faster to the target when this was preceded by a prime of the same valence. The affective priming effect for positive congruent conditions confirmed the effect already described in the literature (Aguado et al., 2013; Contreras-Huerta et al., 2013; Gibbons et al., 2014), whereas the affective priming for negative congruent conditions supports the hypothesis according to which a negative prime may facilitate the response to a negative target (Meagher et al., 2001). A subsequent analysis considering separately negative prime and pain prime revealed that the affective priming effect described above emerged only in the condition in which the negative target was preceded by a pain prime but not by a negative prime. Thus, the semantics of pain embodied in the prime would therefore appear to have facilitated the processing of the negative target.

ERPs findings allowed a deeper understanding of the underlying mechanism of this effect. At an earlier stage of stimulus processing, our data showed a significant effect on the N400 for the positive target with larger negativity when it is preceded by a negative prime (affective incongruency) rather than a positive one (affective congruency), in accordance to what had already been found in the literature (Zhang et al., 2006, 2010; Eder et al., 2012). Against our expectation, no effect has been detected for the negative target. Once the semantic of pain was entered in the analyses, it is interesting to see how the N400 component had larger amplitude when the positive target was preceded by a negative prime at posterior scalp positions rather than a positive prime or a pain prime. Again, no effect was found for the negative target. At first glance, at an early time window (300–500 ms) the semantic of pain is not playing any role in guiding the processing

of upcoming information. Indeed, on the positive target, the N400 which primarily reads the semantic incongruency between stimuli is mainly elicited by a negative prime and not by a pain prime. Moreover, this effect was detected at the posterior scalp locations (Figures 4,5) restating previous findings of affective priming on words stimuli (Kissler et al., 2009; Zhang et al., 2010). This may also have depended by the visual modality of the stimuli (Zhang et al., 2006; Kutas and Federmeier, 2011; Eder et al., 2012) and, in particular, by the involvement of posterior areas during the perceptual analysis of word strings (Ponz et al., 2014).

At a later stage of stimulus elaboration, the affective incongruent conditions elicited a greater positivity on the LPP component for both positive and negative targets in agreement with previous studies on affective priming. Additionally, considering the semantic of pain it emerged that for the positive target, this effect was entirely driven by the pain prime: in fact, a positive waveform was elicited when a positive target was preceded by a pain prime but not by a negative prime. As well, a greater LPP was detected when the negative target was preceded by a positive prime rather than a pain prime. It is possible to speculate that the semantics of pain needs the allocation of more attentional resources to be elaborated, thus, influencing the subsequent response to a target information. It is well-known that a greater LPP is usually elicited by the inconsistency of valence due to the increased attentional resources (Kissler et al., 2009; Zhang et al., 2010). This component is indeed involved in tasks of attention, evaluation, and memory encoding (Kissler et al., 2009).

Considering that our study was the first to investigate the neural correlates of pain words using this paradigm, our findings need to be further interpreted. At an earlier stage (N400) of processing, the majority of ERPs studies on affective priming usually reported larger negativity in affectively incongruent conditions highlighting the sensitivity of the N400 to the semantic relatedness and congruency between the prime and the target (Zhang et al., 2006, 2010; Steinbeis and Koelsch, 2011; Eder et al., 2012). This might be read in the context of the spreading activation within the semantic network (Fazio et al., 1986; Murphy and Zajonc, 1993). Nevertheless, there is also additional evidence showing no effects (Herring et al., 2011; Kissler and Koessler, 2011) or even a reverse N400 effect (Paulmann and Pell, 2010; Aguado et al., 2013; Wang and Zhang, 2016) with a larger negativity for affectively congruent trials.

According to the literature, the N400 has also a role in the processing of integrating a target stimulus into the preceding context given by the prime. Embedding the target into the context may entangle two levels of affective evaluation: the first regards the elaboration of the valence, and the second regards the elaboration of the semantics of the stimulus (Aguado et al., 2013). The result of this dual evaluation turns out to differ for positive and negative emotional stimuli. For instance, a study by Aguado et al. (2013) showed how a positive facial expression may be representative of several positive emotions so that it can be easily embedded within a large variety of positive target words. On the contrary, the integration of a target into a negative context (e.g., anger) requires the individual to distinguish among a broad range of emotional contents activated by negative valence stimuli. The high demands of this task may require the individual more time to be able to discriminate among the negative affective domain (Aguado et al., 2013). This may account for the inconsistency of results found in the literature regarding the affective priming for negative stimuli: the heterogeneity of the semantics embraced in the negative valence could have limited the emergence of the affective priming for the negative target (Rossell and Nobre, 2004). Nevertheless, it is worth pointing out that the semantics of pain needs more time to be elaborated on due to the necessity of additional attentional resources as a result of the specificity of the affective content that characterized it (Kissler et al., 2009; Zhang et al., 2010). This reaffirms the great sensitivity of the N400 discriminating the semantic content of the stimuli rather than just their valence.

However, at a later stage (LPP) of stimulus processing, the cognitive system is prepared to elaborate the evaluative properties of the stimuli generating peculiar effects according to the affective value of the stimulus (Herring et al., 2011). At this time, both positive and negative stimuli showed greater positive waveforms in the affectively incongruent conditions. Importantly, it is worth highlighting that these effects were entirely guided by the semantic of pain embedded in the prime: indeed, as soon as we considered it in the analyses, the LPP component resulted larger only when the positive target was preceded by a pain prime and not by a negative one. As well it is larger when the negative target was preceded by a positive prime rather than a pain one, and no significant effect was detected instead when the negative target was preceded by a positive prime rather than a negative one. These findings confirmed the involvement of the LPP during the processing of emotionally salient stimuli showing its role in generating a specific response to each type of emotion, in particular, it is clear how the effect on this component is due to the semantics of pain. Thus, if on one hand individuals are engaged in resolving the conflict between the semantics and the valence of a stimulus in the time window between 300 and 500 ms, then in the interval between 500 and 700 ms they are engaged in producing affective responses peculiar to each emotional content.

Besides positive and negative stimuli are differently processed in the brain, potentially due to the involvement of different brain areas (Comesaña et al., 2013), the relevance of considering the extreme heterogeneity of semantic contents among negative stimuli has largely been discussed in other previous studies on affective priming (Rossell and Nobre, 2004; Aguado et al., 2018; Gilioli et al., 2023). Indeed, pairs of words belonging to "fear" category generate a modest priming effect on negative targets (Rossell and Nobre, 2004). Conversely, pairs of words belonging to the "sadness" category produced an inhibiting effect on the processing of pain targets (Song et al., 2019). It follows that affective categories within negative valence should be considered separately, which is why results are so inconsistent (Paulmann and Pell, 2010; Herring et al., 2011; Eder et al., 2012; Aguado et al., 2013).

Although the affective priming research has been mainly focused on the role of the prime in influencing the response to the target, it has been stated that also the target can intervene in this effect (Chan et al., 2006). Results from the study showed an affective priming effect for low frequency target words and a reverse priming effect for high frequency target words. Despite in our study the familiarity of the targets, a good estimate of the frequency (Leroy and Kauchak, 2014), did not significantly covariate with the affective priming effect, the arousal and the length of the target words did significantly covariate. Nevertheless, they have not interfered with the interaction between the prime and the target which was the main focus of our analysis.

Eventually, a parameter that may have played a role in these results is the stimulus onset asynchrony (SOA) which is the interval between the prime and the target onset. Indeed, a previous study by Paulmann and Pell (2010) found a greater N400 for affective incongruent trials at 400 ms SOA and a reverse N400 effect for congruent trials at 200 ms

SOA. It is reasonable to think that in our study using a SOA of 300 ms may have contributed to generating this complex pattern of results. Future studies should take this variable into account.

In addition, another limitation of our experiment was the recruitment of a sample composed only by females. Indeed, other studies reported gender differences using this particular paradigm, with stronger effects in female than male participants (Hermans et al., 1998; Schirmer et al., 2005). Moreover, gender differences have been extensively covered by studies on pain processing (Rhudy and Williams, 2005). Much research has shown that females reported more intense reactions to pain stimuli (Rhudy and Williams, 2005), and even a different perception of risk than males (Charness and Gneezy, 2012). Based on these differences and our previous study using the same paradigm (Gilioli et al., 2023), we initially preferred to focus on females to maximize a possible effect, but for generalizability of the results, there is the need to extend the study to males.

To sum up, the ERPs components analysis gave an interesting insight on the time course of the implicit processing of pain. It turned out that the time window between 300 and 500 ms is crucial to studying the interaction between the semantics and the valence of a stimulus. Even more, it restated the importance of considering the semantics of negative stimuli. In fact, at this time, the semantics of pain of the prime required the allocation of more cognitive resources to be elaborated among the heterogeneous groups of emotional contents of negative stimuli. The more the stimulus processing progresses in time, the more the cognitive system is able to recognize the adaptive value of the pain content pre-activating the individual to respond as quickly as possible to un upcoming negative information, as behavioral findings showed. Indeed, the time window between 500 and 700 ms turns out to be extremely sensitive to generate specific responses to each affective and emotional information. As already stated by Herring et al. (2011), we can speculate that the N400 is more sensitive to the evaluation of the semantics of stimuli and the LPP to their affective evaluation.

Ultimately, it is possible that the double nature of pain itself may have contributed to generating this complex pattern of results. According to the motivational priming theory (Lang, 1995; Davidson and Irwin, 1999; LeDoux, 2000), pain has specific properties, and its elaboration may promote the survival of the individual both by facilitating the individual to respond faster to aversive signals, both by supporting approach responses to others' pain.

However, individual differences in pain processing may account for the effect as showed by correlation analyses. In particular, on behavioral results, the correlation of the affective priming and the Magnification subscale of the PCS suggested that the individual tendency to amplify the severity of negative stimuli may have influenced the response to the target. In particular, the correlation between the negative priming associated to pain prime and the Perspective Taking subscale of IRI proposes a relation with the capacity of feeling compassion for others. On ERP results, the N400 elicited by the negative prime on the positive target might have been influenced by the tendency of an individual to respond to threat signals (BIS scale) and to feel personal distress (IRI Personal Distress subscale).

On the other side, the LPP on the negative target correlated with the tendency of the individual to get involved in vivid and imaginative fantasies (IRI Fantasy subscale). Both the N400 and the LPP seemed to be impacted by the tendency of an individual to ruminate about negative thought (Rumination subscale of PCS). The individual influences on the affective priming related to pain prime especially on the LPP restated that the role of the component in the elaboration of emotionally salient stimuli can be top-down modulated by the subjective interpretation of the stimuli (Hartigan and Richards, 2016).

In the present study, the category of negative, pain-unrelated words included words belonging to different semantic contents. In future studies, it would be of interest to compare pain-related words to other defined semantic categories, like other negative emotions, as they may represent more appropriate comparisons. However, not all words may be unambiguously categorized into a discrete emotion or a specific semantic content, raising concerns about statistical power (Witherell et al., 2012; Kveraga et al., 2015). Defining an appropriate paradigm, experimental design, normative data, and statistical analysis are crucial aspects that researchers should carefully consider avoiding this potential problem. For instance, a paradigm that includes contextual information to aid the disambiguation of semantic content may be useful for better accuracy. Collecting normative data may also help categorize the semantic content of each stimulus and prevent extraneous sources of variation.

In conclusion, although some ERPs results do not survive correction for multiple comparisons and we are aware that cautious interpretations are needed, this study represents the first data on the topic. It provides a small contribution to studying the process of sensorimotor resonance between oneself and others, also called empathy, that allows understanding the other through the vicarious sharing of their emotional experiences and beliefs (Betti and Aglioti, 2016).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethical Committee of the University of Modena and Reggio Emilia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AG, EB, LS, and FP conceptualized the research study and design, interpreted the results and wrote the manuscript. FP and AG programmed the experiment and performed the analysis. AG and EB coordinated participants' recruitment and data collection. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1201581/full#supplementary-material

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Words hurt: common and distinct neural substrates underlying nociceptive and semantic pain

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Introduction: Recent studies have shown that processing semantic pain, such as words associated with physical pain, modulates pain perception and enhances activity in regions of the pain matrix. A direct comparison between activations due to noxious stimulation and processing of words conveying physical pain may clarify whether and to what extent the neural substrates of nociceptive pain are shared by semantic pain. Pain is triggered also by experiences of social exclusion, rejection or loss of significant others (the so-called social pain), therefore words expressing social pain may modulate pain perception similarly to what happens with words associated with physical pain. This event-related fMRI study aims to compare the brain activity related to perceiving nociceptive pain and that emerging from processing semantic pain, i.e., words related to either physical or social pain, in order to identify common and distinct neural substrates.

Methods: Thirty-four healthy women underwent two fMRI sessions each. In the Semantic session, participants were presented with positive words, negative pain-unrelated words, physical pain-related words, and social pain-related words. In the Nociceptive session, participants received cutaneous mechanical stimulations that could be either painful or not. During both sessions, participants were asked to rate the unpleasantness of each stimulus. Linguistic stimuli were also rated in terms of valence, arousal, pain relatedness, and pain intensity, immediately after the Semantic session.

Results: In the Nociceptive session, the 'nociceptive stimuli' vs. 'non-nociceptive stimuli' contrast revealed extensive activations in SI, SII, insula, cingulate cortex, thalamus, and dorsolateral prefrontal cortex. In the Semantic session, words associated with social pain, compared to negative pain-unrelated words, showed increased activity in most of the same areas, whereas words associated with physical pain, compared to negative pain-unrelated words, only activated the left supramarginal gyrus and partly the postcentral gyrus.

Discussion: Our results confirm that semantic pain partly shares the neural substrates of nociceptive pain. Specifically, social pain-related words activate a wide network of regions, mostly overlapping with those pertaining to the affective-motivational aspects of nociception, whereas physical pain-related words overlap with a small cluster including regions related to the sensory-discriminative aspects of nociception. However, most regions of overlap are differentially activated in different conditions.

KEYWORDS

pain, semantics, language, words, social pain-related words, physical pain-related words, nociception, fMRI

1. Introduction

Translating the experience of pain into words is a challenge, as attested by scientific evidence, literary sources, and personal experience. Nonetheless, language remains the main medium for conveying our own experience of pain to others, including health professionals (Galli et al., 2019). The International Association for the Study of Pain (IASP) recently revised the definition of pain to "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." In an accompanying note, it is mentioned that "a person's report of an experience as pain should be respected," referring to the fact that the subjective nature of pain should not be interpreted as less valid or reliable (Raja et al., 2020). Pain is defined and ultimately evaluated by subjective reports: as Gracely (2016) put it, "Much can be inferred from objective measures of anatomy, physiology, and behavior, but verbal report remains the standard by which all other measures are compared." This led to the use, in medical research, of questionnaires that should capture different aspects of the pain experience by asking patients to translate their pain into standardized pain descriptors (e.g., McGill Pain Questionnaire—MPQ; Melzack, 1975; Main, 2016).

Since pain communication significantly relies on language, it is important to establish how the mind and the brain treat the complex relationships between words and pain. Accumulating evidence suggests that actual physical pain (nociceptive pain) and the pain conveyed by words (semantic pain) influence each other at behavioral and neural levels (e.g., Knost et al., 1997; Dillmann et al., 2000; de Wied and Verbaten, 2001; Pincus and Morley, 2001; Weiss et al., 2003; Sitges et al., 2007; Wang et al., 2008; Chooi et al., 2011; Meng et al., 2012; Ott et al., 2012; Schoth et al., 2012; Crombez et al., 2013; Ritter et al., 2016; Schoth and Liossi, 2016; Swannell et al., 2016; Reuter et al., 2017; Brodhun et al., 2021; Borelli et al., 2021b). This evidence clearly shows that the experience of physical pain affects the way in which we process pain-related words, and that the presentation of pain-related words impacts on the experience of physical pain; therefore, we can consider language as part of the broad set of endogenous modulators (Koban et al., 2017; Seymour, 2019) which ultimately modulate the processing and perception of pain. However, despite an increasing number of studies, the neural architecture underlying the bi-directional relationships between language and pain is not yet fully understood.

The brain response to a nociceptive stimulus consists in the activation of a complex network of cortical and subcortical structures (Fauchon et al., 2020; Xu et al., 2020), commonly referred to as "pain matrix" (Ingvar, 1999; Singer et al., 2004; Tracey, 2005; Jääskeläinen and Kosonogov, 2023; Kumari et al., 2023). The pain matrix is thought to play a key role in elaborating two important aspects of the nociceptive experience: the sensory-discriminative aspect and the affective-motivational aspect (Melzack and Casey, 1968; for overviews, see Price, 2000; Auvray et al., 2010). The sensory-discriminative aspect is processed by the primary and secondary somatosensory cortices (SI and SII, respectively), and posterior insula, which are sometimes referred to as the "lateral component" of the pain matrix (because it projects through specific lateral thalamic nuclei; Treede et al., 1999); the affective-motivational aspect is processed by the anterior insula (AI) and the anterior mid-cingulate cortex (aMCC), in turn, sometimes referred to as the "medial component" of the pain matrix (because it projects through specific medial thalamic nuclei; Melzack and Casey, 1968; Treede et al., 1999; Kulkarni et al., 2005; Vogt, 2016). The thalamus is therefore involved in both the sensory-discriminative and the affective-motivational components, with prominent functions played by different nuclei in one or the other (Ab Aziz and Ahmad, 2006).

A handful of neuroimaging studies on healthy participants has shown that, in the absence of any noxious stimuli, the brain areas engaged in processing pain-related words partly overlap with those thought to be involved in experiencing physical pain, both the affective-motivational component of the pain matrix (Osaka et al., 2004; Kelly et al., 2007; Ritter et al., 2016), and also the sensory-discriminative one (Gu and Han, 2007; Richter et al., 2010).

Across many different languages, the words that describe physical pain are often used also to convey the so-called social pain, namely, the painful feelings associated with actual or potential social rejection, exclusion, or loss (e.g., betrayal can be described as a stab, a divorce as a scar, a defeat as being painful; Eisenberger and Lieberman, 2005; MacDonald and Leary, 2005).

These ways of referring to social pain are not simple metaphorical extensions borrowed from otherwise unrelated experiences of physical pain: according to the literature, physical and social pain are more neurally intertwined than it was initially thought (for an overview, see Eisenberger, 2015). This is not surprising, since social bonds are fundamental for survival in mammalians, and their interruptions represent a threat potentially as relevant as a noxious stimulus (MacDonald and Leary, 2005; Eisenberger, 2012). Lesion and neuroimaging studies have shown that physical and social pain partly share the same neural substrates, predominantly in the affective-motivational part of the pain matrix (e.g., Eisenberger et al., 2003, 2007; Cacioppo et al., 2013; Cristofori et al., 2013). In these studies, social pain was predominantly elicited through the participant's exclusion in a virtual-ball game, the Cyberball game (Williams et al., 2000). In the Cyberball game, participants are led to believe that they are playing online with other real people, whereas they are actually playing against the computer. The game consists of throwing the ball at each other. The computer is programmed to initially include the participant in the game and then increase the ball exchanges between the other simulated players to exclude the participant. Exclusion in the Cyberball game is considered a form of ostracism, involving being ignored or excluded by others. It is considered a reliable paradigm to induce negative feelings of distress, decreased satisfaction of the need to belong, and other psychological responses associated with social exclusion. Since the affective-motivational pain component is crucial for signaling an aversive state and for motivating behaviors aimed to reduce or escape pain, the activation of this component was interpreted as a hallmark of the neural overlap of physical and social pain. Some studies on social pain also reported activation of sensory-related brain regions, especially when the neural underpinnings of physical and social pain were tested within the same individuals (Novembre et al., 2015) and/or with tasks and stimuli eliciting social pain more powerfully than with the standard version of the Cyberball game (e.g., by having participants, who recently experienced an unwanted break-up, viewing a photo of the ex-partner; Kross et al., 2011).

However, whether, and the extent to which, social pain operates on the same neural pain matrix as nociceptive inputs is still a matter of discussion (Somerville et al., 2006; Cacioppo et al., 2013; Perini et al., 2018; Mwilambwe-Tshilobo and Spreng, 2021; for an overview, see Rotge et al., 2015; but see also Eisenberger, 2015).

Notwithstanding the fact that social pain may also be conveyed by words (Zhang et al., 2019), it has predominantly been studied using either the Cyberball game or non-verbal stimuli reminiscent of socially painful experiences (Kross et al., 2007, 2011; Takahashi et al., 2009; Wager et al., 2009; Fisher et al., 2010; Eisenberger, 2012). Therefore, it is still an open question whether social pain-related words indeed are as powerful as visual images or virtual games in eliciting brain responses in the pain matrix.

The aim of the present study is threefold: (i) to compare the brain areas involved in experiencing nociceptive pain and in processing semantic pain conveyed by physical and social pain-related words in the same individuals; (ii) to clarify whether the processing of semantic pain as conveyed by either physical pain-related words or social pain-related words recruits common or different brain regions; and (iii) to define whether semantic pain activations only concern the affective-motivational dimension of pain or also the sensory-discriminative dimension. Finding involvement also of the sensory-discriminative dimension of pain would support the view that pain-related words resonate with past pain experiences, reactivating their memory, be they associated to physical or social events.

2. Materials and methods

2.1. Participants

Because of the well-documented gender differences on pain perception (Dai et al., 2018) and social exclusion perception (Benenson et al., 2013; Tomova et al., 2014; Morese et al., 2019), an all-female sample was preferred over a gender-mixed sample (Novembre et al., 2015; Benuzzi et al., 2018). Thirty-seven right-handed healthy females participated in the fMRI experiment after informed consent. Two were excluded because they did not accept to undergo the second fMRI session, and one was excluded because of a minor abnormal finding that emerged during the first structural scan. Therefore, the final sample was composed of 34 female participants (age range: 18–34 years, mean age: 22.6 years, SD = 3), which is considered an adequate sample size for fMRI analysis according to Friston (2012). Handedness was assessed by means of the Edinburgh Inventory (Oldfield, 1971). Inclusion criteria were to be Italian native speakers, with no history of psychiatric or neurological illness, no current or past condition of chronic pain, and no current use of any psychoactive medications. Participants were rewarded for their participation. The study was conducted according to the 2013 version of the Declaration of Helsinki and was approved by the Ethics Committee of Modena.

2.2. Personality assessment

In order to correlate the functional MR results with individual personality characteristics, participants were also presented with the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS; Carver and White, 1994; Italian version: Leone et al., 2002) and the Interpersonal Reactivity Index (IRI, formed by four subscales: Empathic Concern, Perspective Taking, Fantasy, Personal Distress; Davis, 1980; Italian version: Albiero et al., 2006). The activation and inhibition systems measured by the BIS/BAS are thought to play an important role in pain processing in both healthy individuals and chronic pain patients (Jensen et al., 2015; Serrano-Ibáñez et al., 2018). IRI was administered because of the several studies attesting the role of empathy in elaborating pain-related information (for an overview, see Xiang et al., 2018).

2.3. Stimuli

2.3.1. Linguistic stimuli

Participants were visually presented with 102 Italian singular nouns belonging to the following categories: 51 positively-valenced nouns (henceforth, PosW; e.g., dono, present) and 51 negatively-valenced nouns, of which 17 not related to pain (henceforth, NegNoPW; e.g., immondizia, rubbish), 17 related to physical pain (henceforth, PhysPW; e.g., cefalea, cephalalgy), and 17 related to social pain (henceforth, SocPW; e.g., abbandono, abandonment). PhysPW and SocPW were selected from the Words Of Pain database, a normed collection of Italian pain words (WOP; Borelli et al., 2018), which also reports quantitative data on how much each word refers to a type of pain rather than the other, allowing us to avoid ambiguity in the selection process; PosW and NegNoPW were selected from the Italian version of the Affective Norms for English Words database (Italian ANEW; Montefinese et al., 2014). PosW were used as fillers to avoid a negativity bias potentially induced by an all-negative word experiment and were not discussed, while NegNoPW were used as a control condition (Richter et al., 2010), being pain defined as an unpleasant experience, i.e., associated to negative affect (Raja et al., 2020).

We chose the words in the different conditions so that they were balanced for the main psycholinguistic, distributional, affective, and pain-related variables that are known to influence comprehension processes, based on WOP and Italian ANEW scores. Specifically, PosW and the negatively-valenced words (i.e., NegNoPW, PhysPW, and SocPW all together) had, as expected, a significantly different valence (Mann–Whitney test; $U = 0$, $p < 0.001$) but were balanced for frequency (Mann–Whitney test; $U = 1363.5$, $p = 0.68$), length in letters (Mann–Whitney test; $U = 1319.5$, $p = 0.9$), familiarity (Student t-test; $t = -0.220$, $p = 0.83$), age of acquisition (Student t-test; $t = 1.389$; $p = 0.17$), imageability (Student t-test; $t = 0.243$; $p = 0.81$), concreteness (Mann–Whitney test; $U = 1{,}461$; $p = 0.28$), context availability (Student t-test; $t = 1.793$; $p = 0.08$), and arousal (Student t-test; $t = 1.425$; $p = 0.16$). NegNoPW, PhysPW, and SocPW were balanced for frequency ($F = 0.588$, $p = 0.56$), length in letters ($F = 0.254$, $p = 0.78$), familiarity ($F = 1.399$, $p = 0.26$), age of acquisition ($F = 2.316$, $p = 0.11$), imageability ($F = 3.043$, $p = 0.06$), context availability ($F = 0.573$, $p = 0.57$), valence ($F = 0.566$, $p = 0.57$), and arousal ($F = 0.483$, $p = 0.62$), but not for concreteness ($F = 12.325$, $p < 0.001$), with PhysPW significantly more concrete than both NegNoPW and SocPW ($p = 0.007$ and $p < 0.001$, respectively). PhysPW and SocPW were also balanced for pain intensity (Student t-test; $t = 0.439$, $p = 0.66$) and pain unpleasantness (Mann-Whitnet test; $U = 123$, $p = 0.47$), but SocPW were more pain-related (Student t-test; $t = 2.597$, $p = 0.014$). For the variables that are more strictly relevant for our research, i.e., valence, arousal, pain-relatedness, intensity, and unpleasantness, the words were balanced considering only the databases' ratings obtained by females. Considering the inherent subjectivity in ratings, we also asked participants to rate each word for variables most relevant for the study (see section 2.4). The list of words is available as Supplementary Table 1.

2.3.2. Mechanical stimuli

As in a prior study (Benuzzi et al., 2018), participants were administered cutaneous mechanical stimuli consisting of touching the skin with a sharp end (21 nociceptive stimulations, NocS) or with a rubber end (21 non-nociceptive stimulations, NonNocS; control condition) by means of a mechanical stimulator. The mechanical stimulator was custom-built in our laboratory and included four aluminum hollow cylinders, each one containing a sliding brass weight of 12, 25, 51, and 75 g, respectively. Each sliding brass weight ended with a plastic tip, on which a disposable stainless-steel wire (0.2 mm section) was mounted for nociceptive stimulation. A fifth aluminum hollow cylinder containing a sliding brass weight of less than 5 g ending with a foam-rubber tip (approximate diameter 2 mm) was mounted for tactile, non-nociceptive stimulation. The hollow cylinders had a lower-end opening that allowed the plastic tip and stainless-steel wire to protrude from the cylinder itself when it was maintained in a vertical orientation. The experimenter held the hollow cylinder vertically and perpendicular to the participant's hand, with the stainless-steel wire positioned approximately 1 cm away from the skin. During each stimulation, triggered at pre-defined moments signaled by an LED, the experimenter gently lowered the hollow cylinder onto the hand. This action caused the tip to make contact with the skin and led the brass weight to slide up inside the hollow cylinder, transferring its weight onto the stainless-steel wire (see Supplementary Figure 1).

2.4. Procedures

All participants underwent two fMRI sessions (see Figure 1). In one session, they were visually presented with the linguistic stimuli (henceforth, Semantic session) and in the other session they received cutaneous mechanical stimulations (henceforth, Nociceptive session). The order of the Semantic and Nociceptive sessions was pseudo-randomized across participants. The interval between the two sessions ranged from a minimum of 2 days to a maximum of 2 weeks for each participant.

The Semantic session comprised four runs, each one lasting approximately 11 min. Within each run, 25 or 26 words were visually presented each in a separate trial in pseudo-random order (no more than three consecutive words belonging to the same category), so that all 102 words (see section 2.3.1) were presented once to each participant. Each trial began with a blue flash (300 ms) on the screen to capture the participant's attention, followed by a lowercase word remaining at the center of the screen for 1.2 s. Participants were instructed to read the stimulus and wait for a Visual Analog Scale (VAS), which appeared on the screen after 10.5 s, and then rate the unpleasantness of the pain conveyed by each word by rotating a control knob previously fixed under their right hand. The extremes of the VAS scale were labeled as "Not unpleasant at all" and "Extremely unpleasant." The VAS scale remained on the screen for 5 s. Once it disappeared, participants returned the knob to the initial position. In case of a rating equal to zero, participants were told to rapidly rotate the knob back and forth, in order to register a motor response also for words rated as not unpleasant at all. Finally, a gray screen followed for 10 s, and then the next trial started. The overall duration of each trial was 27 s.

Before the experiment started, the participants performed a few practice trials inside the scanner, which lasted approximately 2 min in total. Thus, the Semantic session including the practice trials lasted about 46 min. Stimulus presentation and response collection were carried out using an in-house built software developed in Visual Basic 6.[1] The VAS ratings were converted into a 0–100 scale.

Once the Semantic session was concluded, participants were asked to rate, for each word: valence (on a Likert scale ranging from −3 to +3), arousal (on a Likert scale ranging from 1 to 7), pain-relatedness (on a Likert scale ranging from 1 to 7), and pain intensity (on a VAS scale ranging from "Not at all intense" to "The maximum imaginable intensity," then converted into a 0–100 scale). These ratings were used to classify the words for the subsequent analysis and to carry out parametric analyses with functional data (see paragraph 2.6.2 fMRI data analyses).

The Nociceptive session comprised three runs, each lasting approximately 8 min. Within each run, 7 tactile stimuli and 7 painful stimuli were administered in a pseudo-random order (no more than three consecutive stimulations belonging to the same category). Tactile and painful stimuli were delivered to the dorsum of the left hand by means of a mechanical stimulator (see section 2.3.2). After each stimulation, participants were instructed to rate tactile and painful stimuli unpleasantness through the same procedure already described for the Semantic session. The overall duration of each trial was 27 s.

Before the experiment started, each participant's pain threshold was set by means of a few tests, which lasted approximately 10 min in total. Thus, the Nociceptive session including the pain threshold measurement lasted about 34 min. As a result, brass weights were individually selected for each volunteer, so that the tip would induce a medium pain sensation (value of ~30–40 on the VAS scale) for painful stimuli and a pure tactile sensation (value of 0 on the VAS scale) for tactile stimuli. VAS ratings collection and transformation into 0–100 values were performed using the same in-house built software and procedure used for the Semantic session.

The in-house built software enabled experimenters to monitor both the precise stimulus timing and participants' responses in both sessions in real-time from the control room; this ensured that there were no signs of fatigue, e.g., missing responses or decrease in accuracy.

2.5. MRI data acquisition and pre-processing

Functional MRI data were acquired by means of a Philips Achieva MRI system at 3 T and a BOLD (Blood Oxygenation Level Dependent)-sensitive gradient-echo echo-planar sequence [repetition time (TR): 2,000 ms; echo time (TE): 30 ms; field of view: 240 mm; 80 × 80 matrix; 35 transverse slices, 3 mm each with a 1 mm gap]. Each subject underwent four runs (348 or 361 volumes each, depending if 25 or 26 stimuli were presented in the run) for the Semantic session, and three runs (218 volumes each) for the Nociceptive session. A high-resolution T1-weighted anatomical image was also acquired for each participant to allow anatomical localization and spatial standardization (TR: 9.9 ms; TE: 4.6 ms; 170 sagittal slices; voxel size: 1 mm × 1 mm × 1 mm).

Processing of the functional images and statistical analyses were performed using Matlab 8.1.0.604 (The MathWorks Inc., Natick, MA, United States) and SPM12 softwares (Wellcome Department of

1 http://web.tiscali.it/MarcoSerafini/stimoli_video/

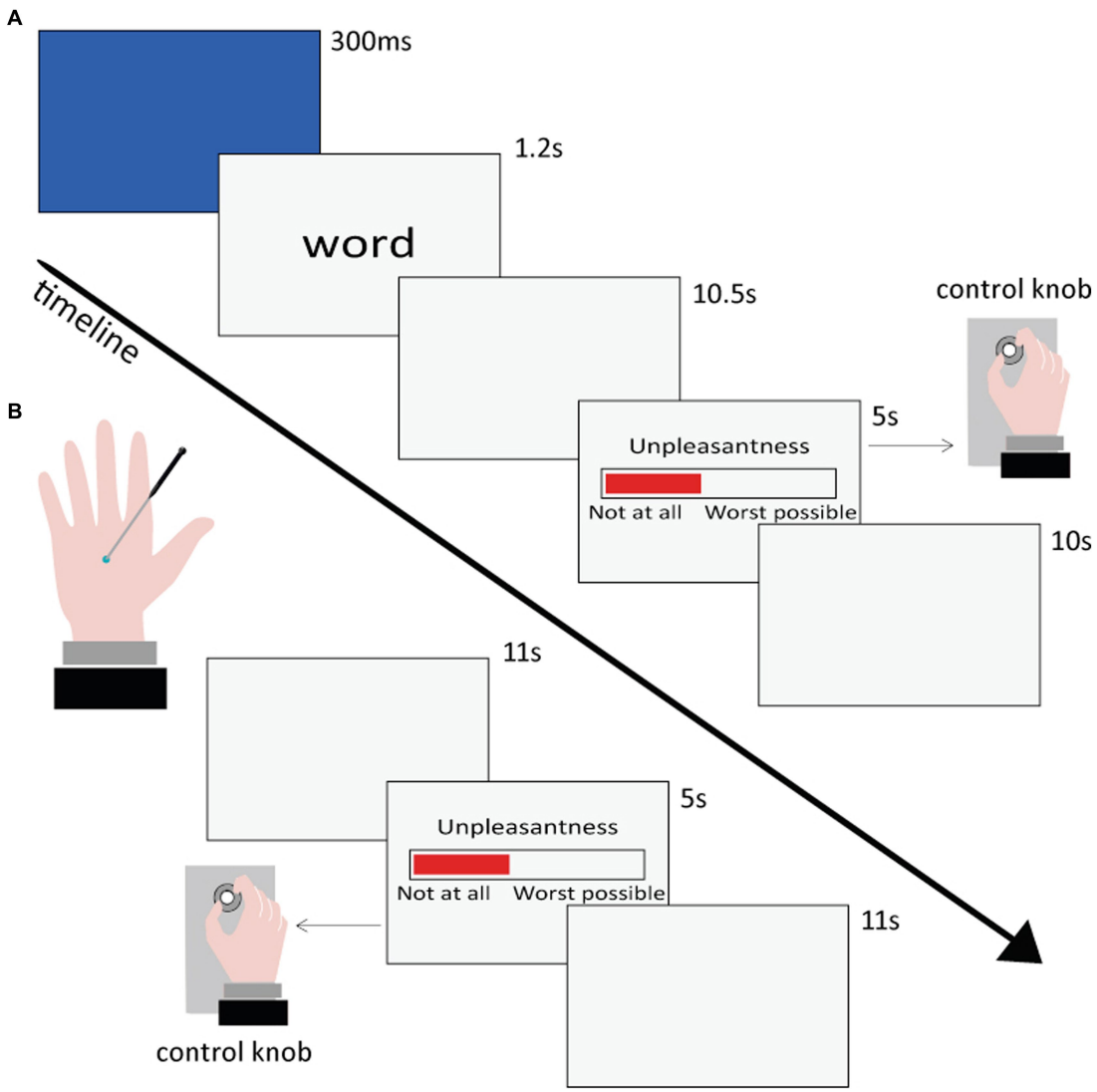

FIGURE 1
Time sequence of the presentation and rating of the stimuli in the Semantic **(A)** and Nociceptive **(B)** sessions.

Imaging Neuroscience, London, United Kingdom, https://www.fil.ion.ucl.ac.uk/spm/). Functional volumes of each participant were corrected for slice-time acquisition differences, realigned to the first volume acquired, normalized to the MNI (Montreal Neurologic Institute) template implemented in SPM12, and smoothed with a 9 × 9 × 12 mm FWHM Gaussian kernel.

2.6. Statistical analysis

2.6.1. Behavioral data analyses

Descriptive (mean, standard deviation) and inferential statistics (ANOVAs and post-hoc tests for significant interactions) were computed on valence, arousal, pain-relatedness, and intensity ratings given by participants after the Semantic session and on the unpleasantness ratings given by participants during the Semantic session, for each category of semantic stimuli (PosW, NegNoPW, PhysPW, SocPW).

Descriptive statistics (mean, standard deviation) were also performed on scores of the BIS/BAS and IRI scales.

2.6.2. fMRI data analyses

Eleven out of the 136 overall runs (8.1%) from the Semantic sessions and 3 out of the 102 overall runs (2.9%) from the Nociceptive sessions were discarded because of excessive movements during scanning.

Two different analyses were performed for each subject, one for the Semantic session and one for the Nociceptive session. The conditions of the Semantic session (NegNoPW, PhysPW, SocPW as conditions of interest, plus the PosW) and the two conditions of the Nociceptive session (NocS, NonNocS) were modeled by convolving the respective stimulus timing vectors with the standard hemodynamic response function. Condition effects were estimated using a general linear model framework, and region-specific effects were investigated with linear contrasts comparing the three conditions of interest of the Semantic session and the two experimental conditions of the Nociceptive session. For each volunteer, stimuli in the Semantic session were classified according to the valence ratings that the subject provided during the post-scanning session, whereas stimuli in the Nociceptive session were classified according to the unpleasantness ratings provided during scanning. The words that each participant rated as zero in valence were

included in a "Neutral words" category (on average 15 words per participant), the words that were missed or unknown to the participant were included in an "Other words" category (on average 2 words per participant); these two categories were included in the analysis matrix, but were not further considered. The classification of words based on participants' ratings differed by one word on average compared to the classification based on the WOP and ANEW databases, therefore this procedure did not cause a significant unbalance between the stimuli categories. Group random-effects analyses were performed by entering the individual contrast images corresponding to the effects of interest into separate one-sample t-tests.

In order to verify whether the areas involved in experiencing nociceptive pain mediate also the comprehension of physical and social pain-related words, the functional results of the NocS > NonNocS contrast were used as "spatial localizer" for the results of the Semantic session, and both qualitative and quantitative analyses were performed. Qualitatively, the two fMRI sessions were compared overlaying the functional blobs of the NocS > NonNocS, PhysPW > NegNoPW, and SocPW > NegNoPW contrasts on the standard T1 weighted brain template implemented in SPM12. A quantitative analysis was conducted using the thresholded image of the NocS > NonNocS contrast, to mask inclusively the results of the PhysPW > NegNoPW, and SocPW > NegNoPW contrasts.

Moreover, our results were compared with a recent meta-analysis (Jensen et al., 2016). Specifically, we verified which coordinates associated with noxious stimulation in healthy subjects were encompassed within, or in the immediate vicinity of (i.e., no more than 10 mm from) one of the regions we identified by means of the masking procedures. These coordinates were used for an additional Regions of Interest (ROI) analysis. With this method, we identified 12 ROIs (xyz coordinates are expressed in MNI throughout the paper): the anterior (xyz = 2, 36, 18) and middle cingulate cortex (xyz = 4, 12, 38), the right and left AI (xyz = 40, 14, 2 and xyz = −38, 10, 4, respectively), the right and left thalamus (xyz = 14, −14, 6 and xyz = −12, −12, 4, respectively), right putamen (xyz = 20, 10, −4), left parahippocampal gyrus (xyz = −26, 2, −14), the right and left cerebellum (xyz = 28, −64, −30, xyz = −36, −58, −34 and xyz = −34, −70, −22), and the postcentral gyrus (xyz = −58, −22, 18). The latter only was found within the masking of the PhysPW > NegNoPW contrast. It is to be noted that for most of the ROIs we followed the nomenclature proposed by Jensen et al. (2016), however, one of the foci (xyz = 4, 12, 38) these authors called simply cingulate actually falls within the aMCC according to the topography suggested by Vogt, 2016 (aMCC; see Figure 1B in Vogt, 2016, for coordinates of anterior cingulate cortex (ACC)-aMCC borders); therefore, although Jensen et al., 2016 never mention aMCC, we named this focus accordingly. ROIs were built as 6-mm radius spheres by means of the MarsBar function of SPM12.[2] The beta values were extracted from each ROI and for each contrast of interest (NocS > NonNocS, PhysPW > NegNoPW, SocPW > NegNoPW); 12 different one-way repeated-measure ANOVAs were run, one for each ROI.

Finally, regression analyses were performed on participants' BIS/BAS and IRI scores, whereas participants' ratings of valence, arousal, pain-relatedness, intensity, and unpleasantness were used for parametric analyses.

A family-wise error (FWE) correction or a double statistical threshold (single-voxel statistics and spatial extent) were used; the latter allows to achieve a combined experiment-wise (i.e., corrected for multiple comparisons) significance level of $\alpha < 0.05$, using the 3dClustSim AFNI routine,[3] with the "-acf" option.

3. Results

3.1. Behavioral results

Descriptive statistics of the word ratings of valence, arousal, intensity, and pain-relatedness given by participants after the Semantic session, and of the word ratings of unpleasantness given by participants during the Semantic session, are reported in Supplementary Table 2 and plotted in Figure 2 for each category of words. Descriptive statistics of the BIS/BAS and IRI scores are reported in Supplementary Table 3.

As expected based on our experimental paradigm and stimulus selection, ANOVAs on participants' word ratings of affective and pain-related variables revealed a significant difference between PosW, NegNoPW, PhysPW, and SocPW for valence ($F_{Brown\text{-}Forsythe} = 467.648$, $p < 0.001$), with PosW significantly more positive than NegNoPW, PhysPW, and SocPW (all $p < 0.001$); for pain relatedness ($F_{Brown\text{-}Forsythe} = 199.353$, $p < 0.001$), with PosW significantly less pain related than NegNoPW, PhysPW, and SocPW (all $p < 0.001$) and NegNoPW significantly less pain related than both PhysPW and SocPW (all $p < 0.001$); for intensity ($F_{Brown\text{-}Forsythe} = 137.152$, $p < 0.001$), with PosW conveying a significantly less intense pain than NegNoPW, PhysPW, and SocPW (all $p < 0.001$) and NegNoPW conveying a significantly less intense pain than PhysPW and SocPW (all $p < 0.001$); and for unpleasantness ($F_{Brown\text{-}Forsythe} = 252.416$, $p < 0.001$), with PosW conveying a significantly less unpleasant pain than NegNoPW, PhysPW, and SocPW (all $p < 0.001$) and NegNoPW conveying a significantly less unpleasant pain than PhysPW and SocPW ($p = 0.003$ and $p < 0.001$, respectively).

However, ANOVAs on participants' word ratings of affective and pain related variables also revealed some unexpected differences. Specifically, they revealed a significant difference between PosW, NegNoPW, PhysPW, and SocPW for valence ($F_{Brown\text{-}Forsythe} = 467.648$, $p < 0.001$), with SocPW significantly more negative than NegNoPW ($p = 0.011$); for arousal ($F_{Brown\text{-}Forsythe} = 5.084$, $p = 0.003$), with SocPW significantly more arousing than PosW ($p = 0.007$); and for intensity ($F_{Brown\text{-}Forsythe} = 137.152$, $p < 0.001$) and unpleasantness ($F_{Brown\text{-}Forsythe} = 252.416$, $p < 0.001$), with SocPW conveying a significantly more intense and unpleasant pain than PhysPW ($p = 0.006$ and $p = 0.048$, respectively).

3.2. fMRI results

3.2.1. Nociceptive session

At the whole-brain level, in the contrast NocS > NonNocS we observed clusters of activation in the right SI and left SII, in the

2 http://marsbar.sourceforge.net/

3 https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html

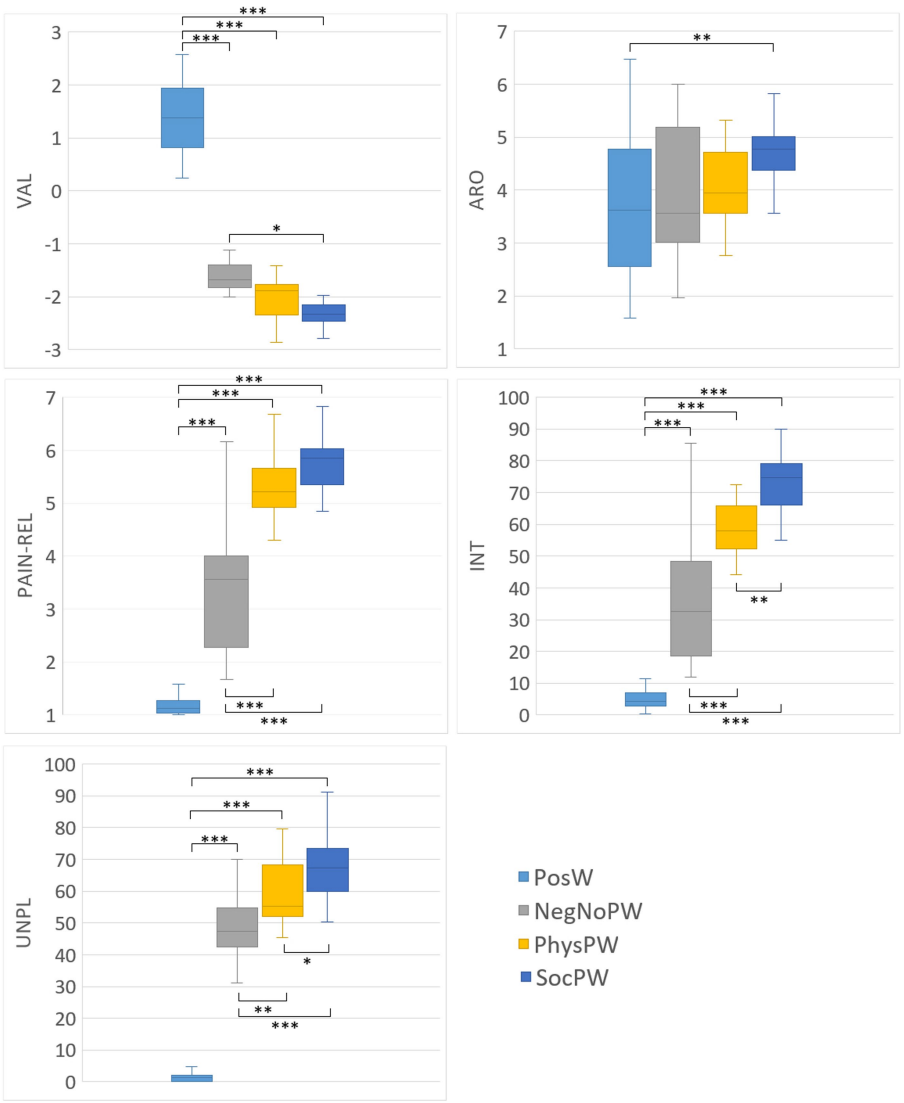

FIGURE 2
Box-and-whisker plots of the word ratings for valence, arousal, pain-relatedness, and intensity given by participants after the Semantic session, and of the word ratings for unpleasantness given by participants during the Semantic session, for each category of words (PosW, NegNoPW, PhysPW, and SocPW). Lower and upper lines represent 10th and 90th percentiles, respectively. Line inside the box represents the median. Lines connecting box-plots indicate significant differences with *p*-values of * < 0.05, ** < 0.01, and *** < 0.001. PosW, positive words; NegNoPainW, negative pain unrelated words; PhysPW, physical pain words; SocPW, social pain words; VAL, valence; ARO, arousal; PAIN-REL, pain relatedness; INT, intensity; UNPL, unpleasantness.

aMCC, in the insula bilaterally, in the inferior frontal gyrus bilaterally, in the left supplementary motor area, and in subcortical structures such as the periaqueductal gray (PAG), thalamus, and basal ganglia (see Figure 3; Table 1). The opposite contrast, NonNocS > NocS, did not reveal any clusters meeting the adopted statistical threshold.

3.2.2. Semantic session

3.2.2.1. Physical pain-related words vs. negative non pain-related words

At the whole-brain level, in the contrast PhysPW > NegNoPainW we observed a single cluster of activation encompassing the left supramarginal gyrus, extending to the postcentral gyrus and the superior temporal gyrus (see Figure 4; Table 2). The opposite contrast, NegNoPainW > PhysPW, did not show any clusters meeting the adopted statistical threshold.

3.2.2.2. Social pain-related words vs. negative non pain-related words

At the whole-brain level, in the contrast SocPW > NegNoPW we observed clusters of activation bilaterally in the prefrontal cortex, posterior and ACC, insula, precuneus, thalamus, angular gyrus, supramarginal gyrus, caudate nucleus, middle temporal gyrus, hippocampus, and cerebellum. In the left hemisphere, the activations encompassed the inferior and superior parietal lobules, cuneus and basal ganglia. In addition, we observed activity in the right superior temporal gyrus (see Figure 5; Table 3). The opposite contrast, NegNoPW > SocPW, did not reveal any significant clusters.

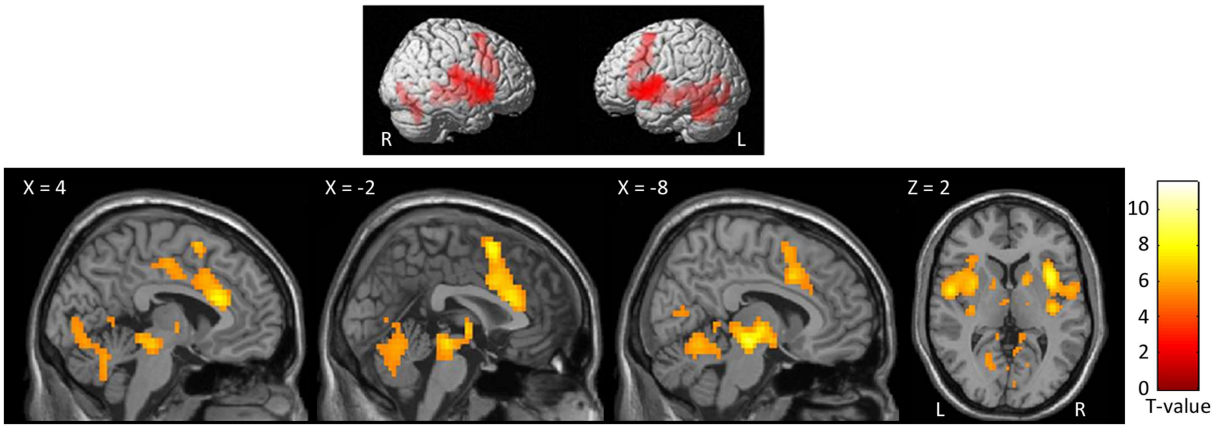

FIGURE 3
Second level group analyses. Brain areas activation associated with the contrast NocS > NonNocS. Activations are overlaid on the SPM12 canonical template. Xyz coordinates are expressed in MNI. FWE corrected. Color bar represents T-values. NocS, nociceptive stimulation; NonNocS, non-nociceptive stimulation; L, left; R, right.

TABLE 1 Regions of increased signal for the contrast NocS > NonNocS.

Brain areas	Side	*k*	*Z*	MNI coordinates		
				x	*y*	*z*
Insula, superior temporal gyrus, inferior frontal gyrus, parietal operculum	R	537	7.25	36	−16	14
			6.47	36	11	2
			5.54	57	11	−6
Midbrain (PAG), parahippocampal gyrus, cerebellum, lingual gyrus, thalamus, hippocampus, right basal ganglia	L/R	1,108	6.27	12	−19	−6
			6.25	−12	−22	−10
			5.85	6	−34	−6
Insula, inferior frontal gyrus, superior temporal gyrus	L	432	6.14	−42	14	−2
			5.84	−54	−1	6
			5.70	−33	5	10
aMCC, left supplementary motor area, superior frontal gyrus	L/R	321	5.96	−3	8	58
			5.91	0	23	22
			5.52	−6	11	38
Posterior insula	L	87	5.91	−36	−19	18
Cerebellum	R	27	5.04	33	−58	−30
	R	52	4.86	6	−13	46
Basal ganglia	L	15	4.71	−15	8	2
Supramarginal gyrus	R	9	4.68	63	−22	22
Primary motor cortex, SI	R	12	4.65	36	−25	62
	R	20	4.64	15	−67	10
	R	8	4.55	6	−55	6
SII	L	2	4.45	−54	−16	14

FWE corrected. The 'MNI coordinates' column reports coordinates of statistically significant peaks in each cluster, with the highest statistical significances given first. The 'Brain areas' column reports all activated areas in the same cluster. L, left; R, right.

3.2.3. Comparison between physical and semantic pain

3.2.3.1. Qualitative and quantitative whole brain comparisons

Both qualitative and quantitative analyses performed using the functional map of the NocS > NonNocS contrast as a "spatial localizer" for the semantic pain contrast revealed areas of overlap. Specifically, the PhysPW > NegNoPW map overlaps with NocS > NonNocS in a left-lateralized cluster including the postcentral gyrus and the supramarginal gyrus (Figure 6, top and bottom-left; Table 4A). Instead, several shared regions between the NocS > NonNocS and the SocPW > NegNoPW contrasts were found: anterior, middle and posterior cingulate cortex, right inferior frontal and superior temporal gyri, precuneus, AI, thalamus, and cerebellum, bilaterally (Figure 6, top and bottom-right; Table 4B).

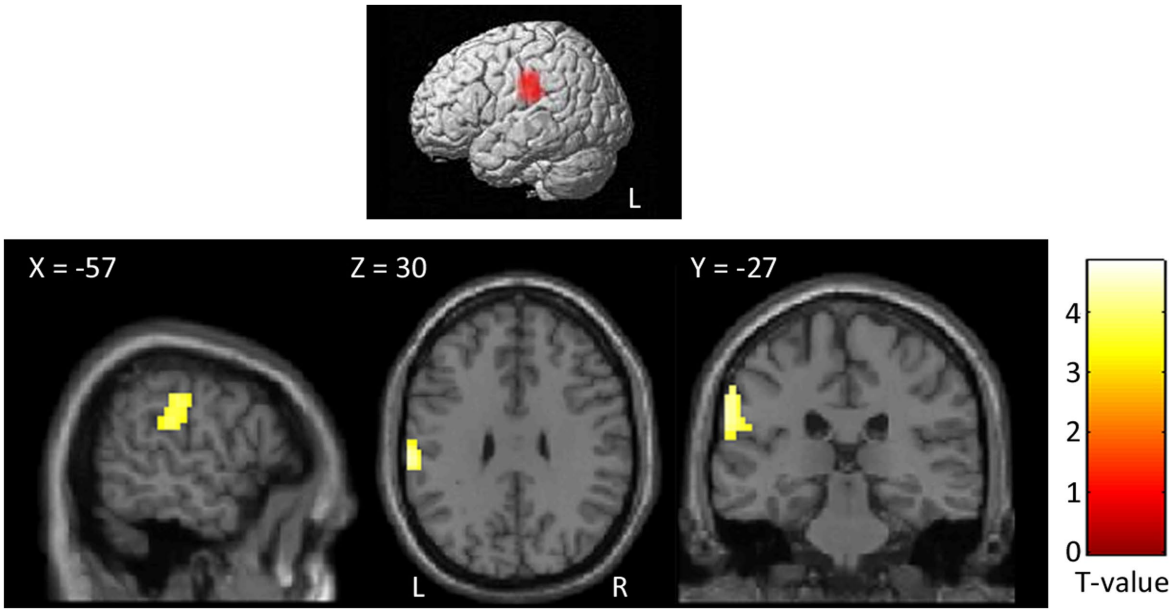

FIGURE 4
Second level group analyses. Brain areas activation associated with the contrast PhysPW > NegNoPainW. Activations are overlaid on the SPM12 canonical template. Xyz coordinates are expressed in MNI. Double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 47, combined $\alpha < 0.05$. Color bar represents T-values. PhysPW, physical pain-related words; NegNoPW, negative pain-unrelated words; L, left; R, right.

TABLE 2 **Regions of increased signal for the contrast PhysPW > NegNoPainW.**

Brain areas	Side	*k*	*Z*	MNI coordinates		
				x	*y*	*z*
Supramarginal gyrus, SI, superior temporal gyrus	L	98	4.18	−63	−22	34

Double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 47, combined $\alpha < 0.05$. The 'MNI coordinates' column reports coordinates of statistically significant peaks in each cluster, with the highest statistical significances given first. The 'Brain areas' column reports all activated areas in the same cluster. L, left.

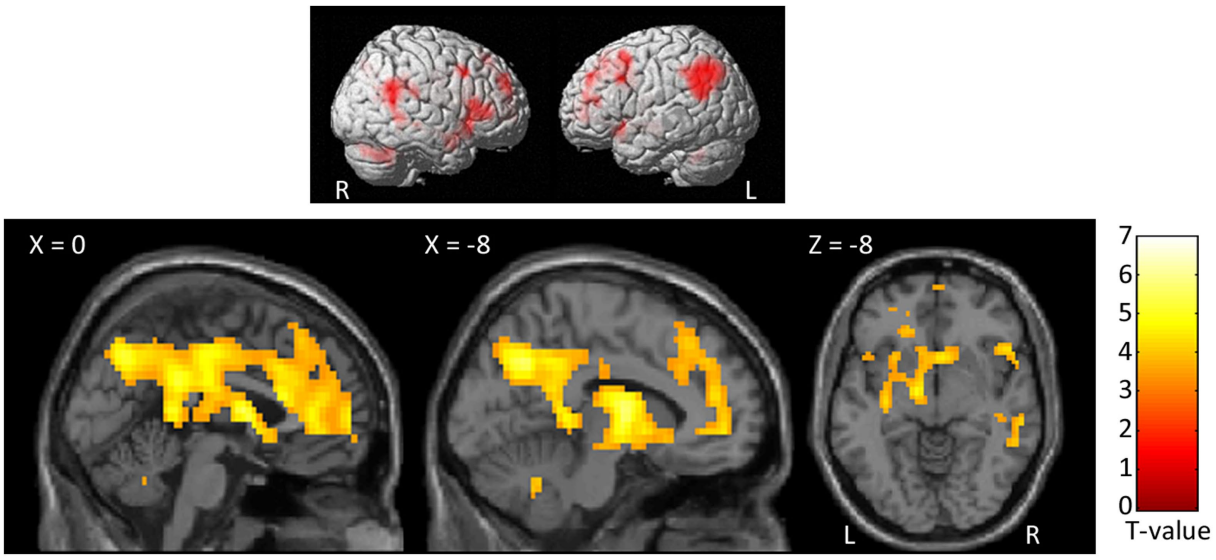

FIGURE 5
Second level group analyses. Brain areas activation associated with the contrast SocPW > NegNoPW. Activations are overlaid on the SPM12 canonical template. Xyz coordinates are expressed in MNI. Double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 63, combined $\alpha < 0.05$. Color bar represents T-values. SocPW, social pain-related words; NegNoPW, negative pain-unrelated words; L, left; R, right.

TABLE 3 Regions of increased signal for the contrast SocPW > NegNoPW.

Brain areas	Side	*k*	*Z*	MNI coordinates		
				x	*y*	*z*
Angular gyrus, inferior parietal gyrus, superior temporal gyrus, middle temporal gyrus, supramarginal gyrus, precuneus	L	566	5.42	−42	−64	46
			4.66	−36	−58	30
			4.51	−48	−52	42
Medial frontal gyrus, superior frontal gyrus, ACC, MCC and posterior cingulate cortex, precuneus, basal ganglia, thalamus, insula, inferior frontal gyrus (pars orbitalis), left hippocampus, left cuneus	L/R	3,808	4.78	12	−7	14
			4.71	−9	−7	10
			4.70	−6	−64	38
Superior temporal gyrus, middle temporal gyrus, inferior parietal lobule, angular gyrus, supramarginal gyrus	R	340	4.53	60	−52	22
			4.16	48	−46	18
			4.03	42	−49	10
Inferior frontal gyrus (pars triangularis and orbitalis), middle temporal gyrus, superior temporal gyrus, insula, hippocampus	R	316	4.25	54	23	10
			3.92	51	38	2
			3.83	48	20	−10
Superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus (pars triangularis and pars opercularis)	L	267	4.24	−39	11	46
			3.91	−27	14	58
			3.89	−30	8	30
Cerebellum	R	315	4.17	27	−52	−34
			4.06	42	−58	−38
			3.88	12	−55	−34
Cerebellum	L	81	3.97	−24	−52	−34
			3.50	−9	−55	−30

Double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 63, combined $\alpha < 0.05$. The 'MNI coordinates' column reports coordinates of statistically significant peaks in each cluster, with the highest statistical significances given first. The 'Brain areas' column reports all activated areas in the same cluster. L, left; R, right.

3.2.3.2. ROI analyses

The beta analysis we performed on the ROIs obtained by comparing our results with those by Jensen et al. (2016) (see section 2.6.2) revealed (Figure 7): (a) no significant differences between the word categories NocS (contrast NocS > NonNocS), PhysPW (contrast PhysPW > NegNoPW), and SocPW (contrast SocPW > NegNoPW) in one of the two ROIs identified in the left cerebellum ($F = 1.886$, $p = 0.16$), and a significant difference in the ACC ($F_{Greenhouse\text{-}Geisser} = 3.487$, $p = 0.047$), but with none of the subsequent *post hoc* tests reaching the threshold $\alpha = 0.05$; (b) NocS significantly more activated than SocPW, but no difference with PhysPW, in the left postcentral gyrus ($F = 5.219$, $p = 0.008$); (c) NocS significantly more activated than both PhysPW and SocPW in the right and left AI ($F = 10.858$, $p < 0.001$ and $F = 9.041$, $p > 0.001$, respectively); (d) NocS and SocPW significantly more activated than PhysPW in the right putamen ($F = 9.407$, $p > 0.001$) and in the right and left cerebellum ($F = 8.603$, $p < 0.001$ and $F = 7.189$, $p = 0.002$, respectively); (e) NocS significantly more activated than PhysPW, but no significant differences with SocPW, in the MCC ($F = 7.048$, $p = 0.002$), right and left thalamus ($F = 8.597$, $p < 0.001$ and $F_{Greenhouse\text{-}Geisser} = 5.44$, $p = 0.12$, respectively), and left parahippocampal gyrus ($F = 4.013$, $p = 0.023$).

3.2.4. Regression and parametric analyses

The regression analyses on the brain activity considering each individual participant's BIS/BAS and IRI scores did not reveal any significant results.

The parametric analysis on brain activity considering participants' ratings of arousal for each word as parameter of interest in the analysis of PhysPW revealed two significant right-lateralized clusters including the superior and middle temporal gyri, the supramarginal gyrus and the precentral gyrus (Figure 8; Table 5). No significant results were found for other parametric analyses, neither for arousal in other categories of words, nor for participants' ratings of valence, pain relatedness, intensity, and unpleasantness in any category of words.

4. Discussion

The aims of the present study were: (i) to compare the brain areas involved in experiencing nociceptive pain and in processing semantic pain conveyed by physical and social pain-related words in the same individuals; (ii) to clarify whether the processing of semantic pain as conveyed by either physical pain-related words or social pain-related words recruits common or different brain regions; and (iii) to define whether semantic pain activations are linked only to the affective-motivational dimension of pain or also to the sensory-discriminative dimension.

A strength of this study is that, to the best of our knowledge, it is the first one comparing the processing of nociceptive and semantic pain in the same individuals using both words associated with physical and social pain. Overall, the results of this study highlight the presence of an extensive overlap in the areas involved in

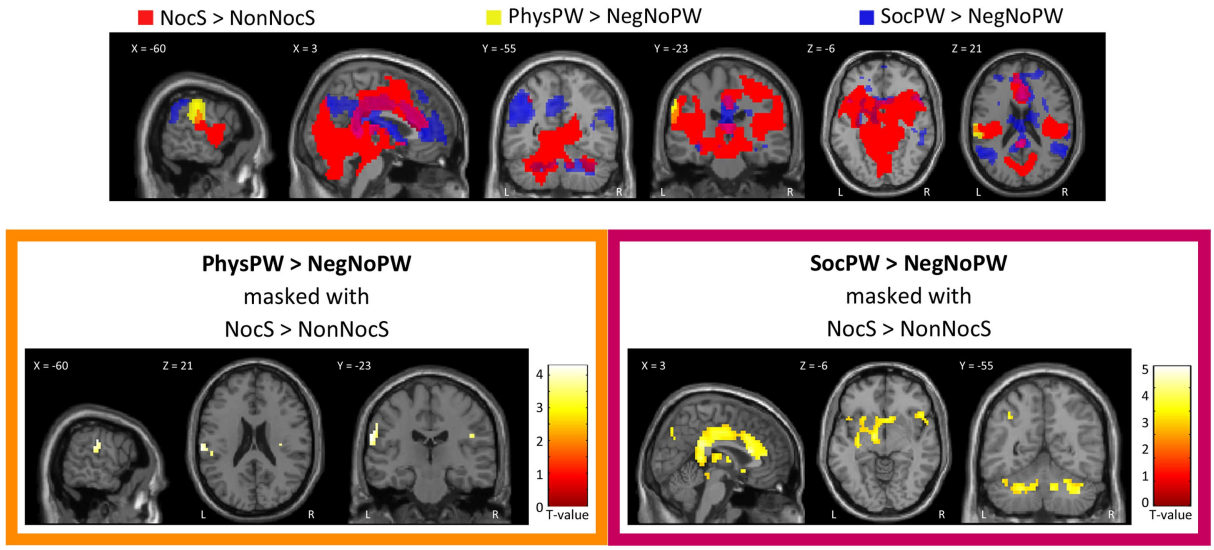

FIGURE 6
Qualitative (top) and quantitative (bottom) comparison between Nociceptive and Semantic sessions. Top: Suprathreshold clusters for the contrasts NocS > NonNocS (red), PhysPW > NegNoPW (yellow), and SocPW > NegNoPW (blue) are shown; the intersection of NocS > NonNocS and PhysPW > NegNoPW is depicted in orange; the intersection of NocS > NonNocS and SocPW > NegNoPW is depicted in violet. Bottom: Results of the contrasts PhysPW > NegNoPW (left) and SocPW > NegNoPW (right) masked inclusively with the contrast NocS > NonNocS ($p < 0.001$, uncorrected for multiple comparisons). Activations are overlaid on the SPM12 canonical template. Xyz coordinates are expressed in MNI. Color bars represent T-values. NocS, nociceptive stimulation; NonNocS, non-nociceptive stimulation; PhysPW, physical pain-related words; SocPW, social pain-related words; NegNoPW, negative pain-unrelated words; L, left; R, right.

TABLE 4 Regions of increased signal for the contrasts (A) PhysPW > NegNoPW (double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 47, combined $\alpha < 0.05$) and (B) SocPW > NegNoPW (double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 63, combined $\alpha < 0.05$), each masked inclusively with the NocS > NonNocS contrast ($p < 0.001$, uncorrected for multiple comparisons).

Brain areas	Side	k	*Z*	MNI coordinates		
				x	*y*	*z*
(A) PhysPW > NegNoPW masked with NocS > NonNocS						
Supramarginal gyrus, postcentral gyrus	L	20	4.19	−63	−25	22
(B) SocPW > NegNoPW masked with NocS > NonNocS						
ACC, MCC, and posterior cingulate cortex, medial thalamus, AI, basal ganglia	L/R	1,371	5.11	−9	−7	10
			4.46	3	20	18
			4.44	12	−7	10
Precuneus	L/R	120	5.03	−9	−64	38
			4.29	−3	−73	42
			4.07	6	−73	42
Inferior frontal gyrus (pars triangularis), superior temporal gyrus	R	77	4.17	54	23	2
			4.23	48	20	−10
			4.07	57	8	−14
Cerebellum	R	141	4.17	27	−52	−34
			4.05	39	−55	−38
			4.28	12	−55	−34
AI	R	28	4.39	27	17	−14
Cerebellum	L	79	4.37	−24	−52	−34
			3.50	−9	−55	−30
Cerebellum	L	25	4.07	−45	−61	−30

Only clusters with k >20 are reported. The 'MNI coordinates' column reports coordinates of statistically significant peaks in each cluster, with the highest statistical significances given first. The 'Brain areas' column reports all activated areas in the same cluster. L, left; R, right.

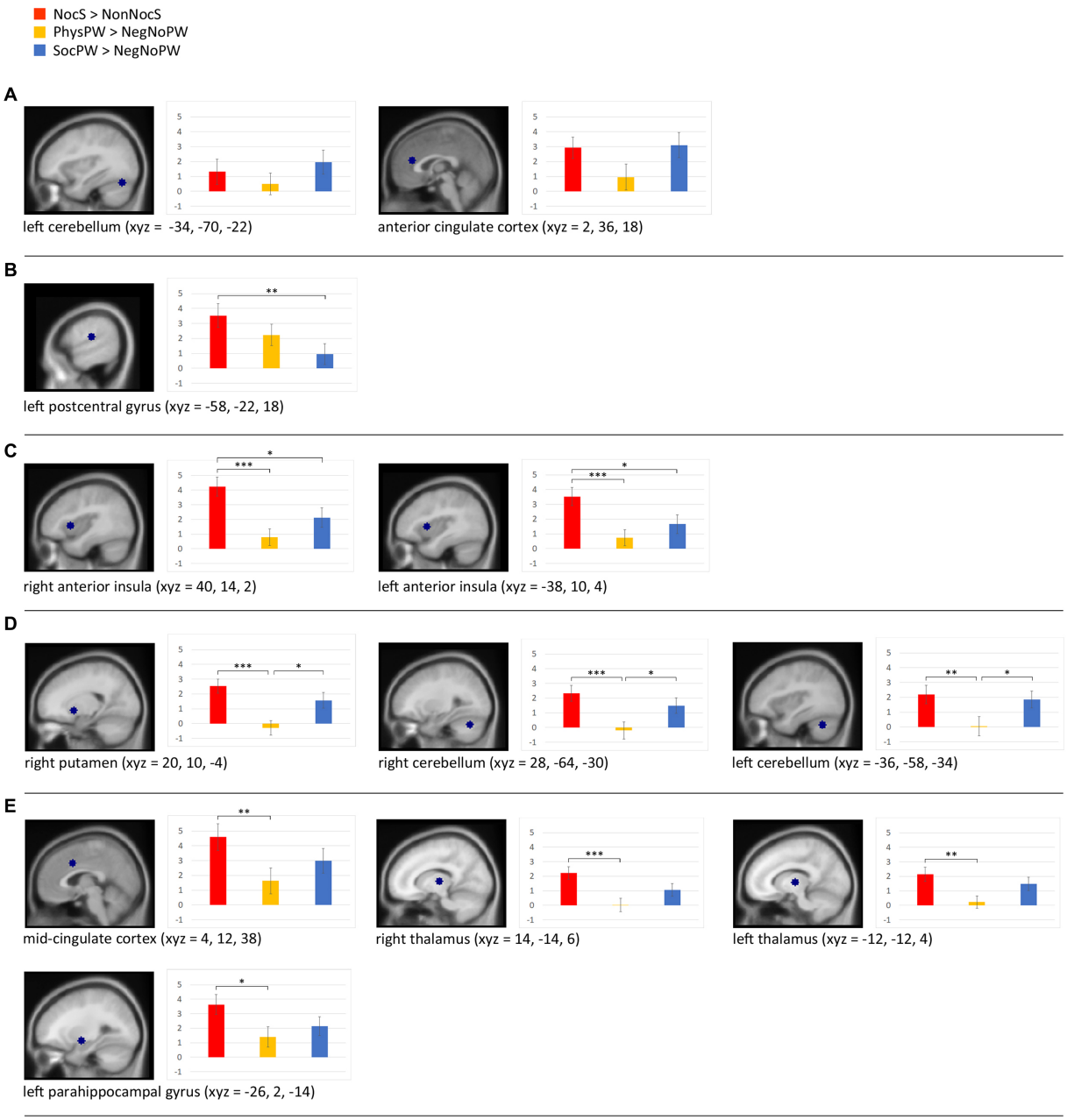

FIGURE 7
Beta analyses with sagittal section views of the twelve regions of interest (ROIs) and histograms illustrating the beta value means for the stimuli categories NocS (contrast of interest: NocS > NonNocS), PhysPW (contrast of interest: PhysPW > NegNoPW), and SocPW (contrast of interest: SocPW > NegNoPW) and the statistically significant differences: **(A)** brain regions exhibiting no significant differences between word categories; **(B)** brain regions where NocS elicits significantly more activation than SocPW; **(C)** regions where NocS triggers significantly more activation than both PhysPW and SocPW; **(D)** regions where both NocS and SocPW induce significantly higher activation than PhysPW; **(E)** regions where NocS elicits significantly higher activation than PhysPW. Xyz coordinates are expressed in MNI. Error bars represent standard errors. Lines connecting boxplots indicate significant differences with p-values of *<0.05, **<0.01, and ***<0.001. NocS, nociceptive stimulation; NonNocS, non-nociceptive stimulation; PhysPW, physical pain-related words; SocPW, social pain-related words; NegNoPW, negative pain-unrelated words.

processing nociceptive and semantic pain. Interestingly, PhysPW and SocPW elicited very different activations: processing SocPW triggered a complex network of neural activity, where the overlap with the nociceptive pain network included activations of the cingulate cortex, anterior insula, medial thalamus, basal ganglia, precuneus, and cerebellum. In contrast, processing PhysPW led to the activation of a much more restricted network where the areas of overlap with the nociceptive pain network included the left supramarginal and postcentral gyrus. In sum, our findings suggest that only the words related to physical pain resonate with areas involved in the sensory-discriminative dimension of pain, whereas words related to social pain resonate with areas involved in the affective-motivational dimension of pain. However, our results also suggest some caution when assigning each area to one dimension or the other of pain processing, as is the case for instance of primary somatosensory cortex (see sections 4.1 and 4.2).

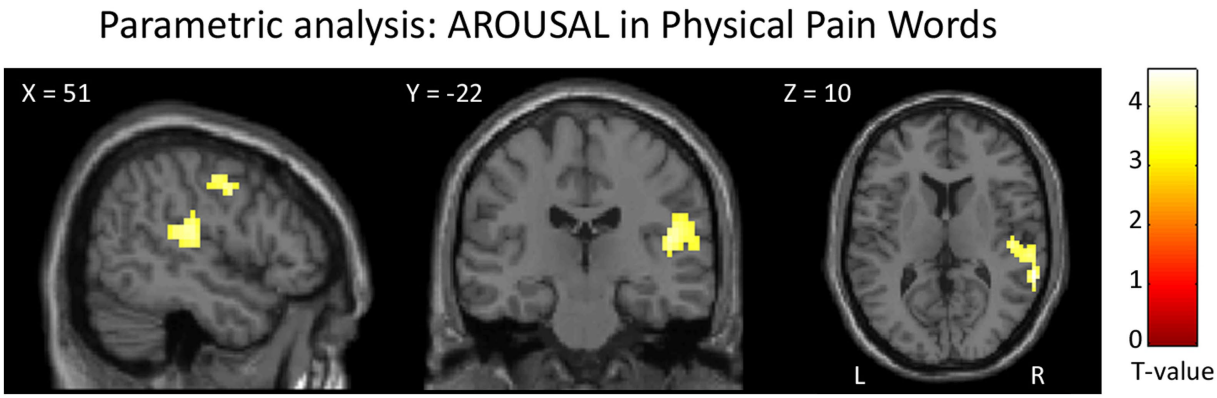

FIGURE 8
Results of the parametric analysis on the brain activity considering participants' ratings of arousal as parameters of interest in the analysis of PhysPW. Activations are overlaid on the SPM12 canonical template. Xyz coordinates are expressed in MNI. Double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 44, combined $\alpha < 0.05$. Color bar represents T-values. PhysPW, physical pain-related words; L, left; R, right.

TABLE 5 Results of the parametric analysis on the brain activity considering participants' ratings of arousal as parameters of interest in the analysis of PhysPW.

Brain areas	Side	k	*Z*	MNI coordinates		
				x	*y*	*z*
Middle and superior temporal gyrus, supramarginal gyrus, postcentral gyrus, parietal operculum	R	142	4.01	63	−40	10
Pre- and post-central gyrus			4	60	−31	14
			3.70	48	−22	14
	R	47	3.80	54	−10	46
			3.59	48	−4	42

Double statistical threshold to correct for multiple comparisons: single-voxel statistics $p < 0.001$ and spatial extent > 44, combined $\alpha < 0.05$. The 'MNI coordinates' column reports coordinates of statistically significant peaks in each cluster, with the highest statistical significances given first. The 'Brain areas' column reports all activated areas in the same cluster. R, right.

The neural network of pain semantics found in this study is consistent with the brain-based componential semantic representation model of Binder et al. (2016), who identify "Somatic-Pain" (associated with pain or physical discomfort) and "Emotion-Harm" (associated with someone or something that could cause harm) as dimensions of experience that are fundamental for the neural coding of concrete and abstract concepts. A speculative interpretation suggests that the neural activation in pain matrix regions during pain word processing might align with Hebbs' neural network model (Hebbs, 1949). This model suggests that repeated experiences create a neural memory network. This network strengthens connections and enhances efficacy whenever exposed to similar experiences. In the case of pain, our findings and others' suggest that the neural activation in pain matrix regions may resonate with prior pain experiences, triggering the associative semantic memory traces of nociceptive pains whenever we face tangible or potential painful stimuli, or stimuli conveying harm or threat (Ritter et al., 2019; Brodhun et al., 2021). Additionally, our results may suggest that the strength of this associative memory network is higher for social pain words than for physical pain words.

4.1. Behavioral data and parametric analysis

The words used as experimental stimuli were chosen to be carefully balanced for the main psycholinguistic, distributional, affective, and pain-related variables that are known to affect comprehension processes. To this aim, we used two normative databases (Italian ANEW; Montefinese et al., 2014; WOP; Borelli et al., 2018) which involve large numbers of participants (1,084 and 1,020, respectively). The participants in the present study provided ratings which in part differed from those of the much larger and heterogeneous set of participants tested in the two databases. This was not unexpected, as the sample involved in a normative word corpus development is usually much larger and more heterogeneous compared to the sample involved in a cognitive neuroscience study. In choosing stimuli, whether linguistic or not, researchers have the option of using normative words from databases or collecting them directly from study participants. While normative databases offer standardized measures, ensuring consistency and comparability across studies, they might not capture the nuances of the target population or context. Conversely, collecting normative data directly from study participants is extremely time-consuming yet grants insight into stimuli perception, enhancing their relevance and representativeness of the experimental conditions being studied. Therefore, having integrated norms from word databases with participant's ratings represents a further strength of our study.

As already mentioned in Methods (section 2.6.2), the stimuli reallocation due to valence differences between our participants' and normative corpora' ratings was minimal. Yet, we found that SocPW were significantly more intense and unpleasant than PhysPW. This was not an unexpected result. Although it is undeniable that the two types of pain share common features, their psychological characteristics

diverge in many respects. For instance, while feelings of social pain can be re-experienced even years after the painful event (Meyer et al., 2015), the sensory feelings of physical pain cannot be relived after the painful episode. Beyond ours, other studies have found that social pain words are considered to convey more intense and unpleasant painful experiences than physical pain words by both healthy participants and advanced cancer patients (Borelli et al., 2018, 2021a). However, a possible confounding effect of differences in intensity and unpleasantness ratings was ruled out by performing parametric analyses which did not show any significant results for these variables. In fact, the parametric analyses returned only one positive correlation between PhysPW and arousal, in a single cluster including pre- and post-central cortex, superior and middle temporal gyri, and supramarginal gyrus, on the right. The postcentral gyrus, i.e., the somatosensory cortex, is known to respond for actual nociceptive stimulation (Apkarian et al., 2005; Lui et al., 2008; Jensen et al., 2016), although not depending on different pain intensities (Favilla et al., 2014). Yet, the increased activation we found in the postcentral gyrus for the arousal induced by PhysPW suggests that this region may be involved not only in the sensory-discriminative dimension of pain but also in its affective-motivational dimension.

As to the right supramarginal gyrus, together with the adjacent angular gyrus it is part of the inferior parietal lobule, a high level associative brain region which is anatomically and functionally composite. Different authors use different labels to indicate the same areas, or areas which partly overlap with one another, with often ill-defined borders, within this region, e.g., inferior parietal lobule, angular and supramarginal gyri, parietal operculum (e.g., Jensen et al., 2016; Xu et al., 2020). Activation of this complex region is often observed in studies on nociceptive pain, but its specific relevance is not always fully discussed (Jensen et al., 2016). On the other hand, the BOLD signal in the right supramarginal gyrus has been correlated also with different empathic characteristics (Flasbeck et al., 2019; Zhao et al., 2021; Giacomucci et al., 2023) and with emotional regulation competencies (Wadden et al., 2018; Imai et al., 2023), both in healthy and pathological populations. A recent meta-analysis on pain and empathy (Fallon et al., 2020) specifically addressed the possible double involvement of the inferior parietal cortex, identifying a specific role of the more ventral regions of this complex ("parietal operculum") in sensory functions, whereas the supramarginal gyrus proper, bilaterally, appears involved both in empathy and in pain perception, although with a prevalence for empathy. Our results only partly confirm what was observed by Fallon and colleagues since both the supramarginal gyrus and the parietal operculum were encompassed in our cluster that correlates with arousal in processing PhysPW. These results suggest that both regions may be involved not only in the sensory-discriminative dimension of pain.

Based on our initial stimuli classification through normative databases, we found that PhysPW were significantly more concrete than SocPW, as already found in a previous psycholinguistic study. It has been suggested that abstract concepts are more affectively-laden than concrete concepts (Lenci et al., 2018). The recruitment of the affective-motivational component of pain we have found during the processing of SocPW and not PhysPW may reflect the closer connection of SocPW with abstract concepts. In other words, the different brain activations found for PhysPW and SocPW would mirror the difference between concrete words, more grounded in sensory-motor experiences, and abstract words, primarily grounded in the inner emotional states (Kousta et al., 2011; Meteyard et al., 2012; Vigliocco et al., 2013). However, recent data suggest that the concept of emotional grounding only applies to a limited number of abstract concepts, and that when the measurement of concreteness/abstractness does not rely on concreteness ratings, concrete concepts tend to be rated as more emotional than abstract concepts (Winter, 2023). Therefore, since the concept of the greater emotionality of abstract words is controversial, further testing is needed to investigate whether our results can be explained by this hypothesis.

4.2. Overlap between nociceptive pain and each category of pain words

In summary, as expected according to the literature on nociceptive pain (Treede et al., 1999; Apkarian et al., 2005; Lui et al., 2008; Moulton et al., 2010; Xu et al., 2020), in our study NocS enhanced activation in several cortical regions and subcortical structures, involving both the sensory-discriminative and the affective-motivational components of the pain matrix. Reading PhysPW increased the BOLD signal in a cluster encompassing the primary somatosensory cortex and supramarginal gyrus on the left, and this cluster overlaps with the nociceptive pain map. On the other hand, processing SocPW activated both regions that are involved in the processing of pain (Jensen et al., 2016), such as AI, cingulate cortex, medial thalamus, basal ganglia, precuneus, cerebellum, and several other areas that were not identified by the overlap with our spatial localizer (namely: bilateral prefrontal cortex, bilateral supramarginal and angular gyri, bilateral superior and middle temporal gyri, left cuneus and right superior temporal gyrus).

The ROI beta analysis gives us an interesting additional perspective, in that it provides an insight into the different involvement of each brain region in perceiving and discriminating nociceptive pain and the two types of semantic pain presented in this study. Most of these ROIs show the highest signal for nociceptive pain, which is not surprising, considering that the ROIs were selected using the nociceptive pain map as a localizer. However, some interesting differences are apparent.

First of all, the ROI in ACC did not show any significant difference among NocS, PhysPW, and SocPW; this is consistent with a prominent role of this region not just in the sensory dimension of pain, but in the integration of sensory functions and negative affect. Although previous meta-analyses and reviews have often emphasized the role of the ACC in pain perception (Peyron et al., 2000; Apkarian et al., 2005; Lanz et al., 2011; Duerden and Albanese, 2013; Jensen et al., 2016), it is worth noting that what is called ACC or dorsal ACC, often coincide with MCC or aMCC (see specific discussion on this ambiguity in nomenclature, for instance, in Peyron et al., 2000;Vogt, 2016; Rolls, 2019). It is especially interesting to point out that the ROI that falls within aMCC shows a different beta pattern from the ROI in ACC, namely, significantly lower activity for PhysPW, but not for SocPW, as compared to NocS. Our results are consistent with previous studies showing that the aMCC contributes to emotions and/or avoidance behavior (Vogt, 2016; Rolls, 2019) and to the integration of negative affect, pain, and cognitive control (Etkin et al., 2011; Shackman et al., 2011; Spunt et al., 2012), also, with the observation of pain in others (Singer et al., 2004; Vogt, 2016). However, Kragel et al. (2018) found a specialization in aMCC for pain and not for negative affect (including social rejection); nevertheless, we should point out that none of the cited studies used words as stimuli.

The anterior insula bilaterally is the only region which, although being activated by all three categories of stimuli presented in this study, exhibits a significant preference for nociceptive pain over both categories of semantic pain. Therefore, our results point to a notable differentiation between cingulate cortex and anterior insula, the two regions which are often referred to together as involved in the elaboration of the affective dimension of pain, in that the insula appears as more connected to the presence of an actual physical stimulus.

Since the seminal work of Eisenberger et al. (2003; for an overview, see Eisenberger (2015)), many studies reported the activation of part of the affective-motivational component of the pain matrix (i.e., AI and aMCC) when participants experienced or were reminiscent of social pain (Peyron et al., 2000; Eisenberger and Lieberman, 2005; Masten et al., 2012; Cacioppo et al., 2013; Novembre et al., 2015; Rotge et al., 2015). These regions are those most frequently involved in nociceptive pain elaboration (e.g., Lui et al., 2008; for an overview, see Xu et al., 2020), including the codification of pain intensity (Favilla et al., 2014), but also in conditions that include pain modulation, observation of painful stimuli, placebo and nocebo, and empathy (Zaki et al., 2016; Zunhammer et al., 2021; Tu et al., 2022).

In general, AI is involved in the neural processing of negative affect and of self- and other-directed aversive experiences (Lamm and Singer, 2010; Eisenberger, 2012; Čeko et al., 2022). Interestingly, Morese et al. (2019) found that receiving emotional support such as a gentle touch during an experience of social exclusion, compared to informational support like an explanation text, led to a reduction of activity in the right AI. More recently, a comprehensive model of the neural basis of comforting touch has been proposed, including not only comfort from distress and discomfort, but also from pain (Shamay-Tsoory and Eisenberger, 2021).

The left postcentral gyrus is the only ROI among the ones we identified where nociceptive pain induces significantly higher activity than SocPW, but no significant difference with PhysPW. Previous studies using pain-related words (Gu and Han, 2007; Richter et al., 2010; Ritter et al., 2016) showed a rather inconsistent pattern of activations, variably including different portions of the insular and cingulate cortex, secondary somatosensory cortex and other regions, but they never reported enhanced signal in primary somatosensory cortex. This discrepancy may reflect methodological differences among studies: first of all, our experimental sample was much more numerous than in any one of the above-mentioned studies, and it was also homogeneous for the gender of the participants. Furthermore, we only selected unambiguous physical pain words in that none of the PhysPW could be used to denote social pain. In addition, while we only used nouns, other studies used verbs, which necessarily imply actions (Gu and Han, 2007), or adjectives (Richter et al., 2010; Ritter et al., 2016), which, by definition, are modifiers with a semantically large and unspecified content when presented without the nouns they refer to (Palazova et al., 2011). Finally, these previous studies required participants to actively imagine situations connected to the proposed pain-related words, probably eliciting a more vivid emotional representation of the stimuli. It is worth noting that our findings suggest a multifaceted role for the postcentral gyrus, capable of responding not only to the sensory characteristics of nociceptive pain but also to various stimuli semantically related to pain; by the same token, the results of the parametric analysis reveal a correspondence with the arousal induced by pain-related words (see section 4.1); however, it appears that a physical aspect is critical for the response, as words conveying social pain are significantly less effective to this end. The active cluster obtained also included the left supramarginal gyrus. Again, what we pointed out above (see section 4.1) about the somewhat troublesome definition of the inferior parietal lobe, equally applies in the case of the left hemisphere, given the difficulties in precisely defining the anatomical regions and in establishing their functional role. In addition to what has been said above about the right hemisphere, the left inferior parietal lobule is involved in processing pain words (Richter et al., 2010). This region in the left hemisphere is one of the main nodes of the semantic system (Binder et al., 2009; Stoeckel et al., 2009; Huth et al., 2016). We contrasted PhysPW with NegNoPW, therefore the involvement of purely semantic areas should have been ruled out; however, we might hypothesize that the greater engagement of this region was due to a deeper elaboration of words with a greater emotional and/or semantic resonance, compared to more neutral ones.

Several other regions, specifically, aMCC, as already mentioned above, furthermore, right and left thalamus, parahippocampal gyrus, putamen, and cerebellum, bilaterally, had significantly higher signals for NocS than for PhysPW, with the last two showing also significantly higher signals for SocPW than for PhysPW. The involvement of the medial thalamus for the processing of both NocS and SocPW may be due to the involvement of this subcortical region in ascending-to-activate as well as in descending-to-modulate pain pathways (Wang et al., 2016). Since the thalamus is also associated with negative emotions, apprehension, and regulation (Panksepp, 2003; Woo et al., 2014), one possible explanation for the absence of thalamic activation for PhysPW is that they have lower negativity and arousal levels. Traditionally, the cerebellum is associated with motor processing, but several studies reported its involvement in pain (Peyron et al., 2000; Apkarian et al., 2005; Borsook et al., 2008; Moulton et al., 2010) as well as in cognitive process, emotion, and hypnosis (Adamaszek et al., 2017; Santarcangelo and Manzoni, 2021). Although the exact role of this structure in processing pain still is poorly understood, it has been proposed that the cerebellum may integrate affective processing, pain modulation, and sensorimotor processing (Moulton et al., 2010) associated, for instance, to aversive motor responses. Interestingly, our results showed that also SocPW can trigger cerebellar activations as if participants indeed had mentally simulated an aversive response to the words they considered to be the most negative, unpleasant, and arousing.

4.3. Limitation and future directions

A possible limitation of this study is that, given the observed gender differences in the perception of physical pain (Dai et al., 2018) and social pain (Benenson et al., 2013; Tomova et al., 2014; Morese et al., 2019), we used an all-female sample (as already done in other studies, e.g., Novembre et al., 2015; Benuzzi et al., 2018) with a narrow age range; however, this choice was made intentionally to identify homogeneous strategies and therefore to increase statistical power. As a future direction, including a more diverse sample in terms of gender and age would provide a more comprehensive understanding of the phenomena under investigation and allow for better generalizability and characterization of the population. Furthermore, since the lack of significant results in the regressions with BIS/BAS and IRI could be due to an inadequate sample size to identify inter-individual differences, future studies should plan a larger sample size and include more scales assessing other personal attitudes toward physical pain and social pain.

Although it could be argued that our acquisition parameters might not be optimal for effectively detecting activation in smaller structures, they were chosen as a compromise between research demands and technical limitations posed by the equipment. Specifically, the decision to employ a voxel size of 3 × 3 × 3 with a 1 mm gap and to include 35 slices was driven by the goal of encompassing the whole brain and the cerebellum; the gap had the additional aim of preventing interference among adjacent slices. The 2-s repetition time (TR) was chosen to accommodate the acquisition of 35 slices. Additionally, the application of a 9x9x12 FWHM Gaussian kernel smoothing was intended to increase the signal-to-noise ratio (e.g., Molloy et al., 2014; Caparelli et al., 2019) and to take into account individual anatomical variations during group analyses.

4.4. Conclusion

In summary, we have revealed that, even though the areas involved in experiencing nociceptive pain and processing semantic pain overlap to a great extent, the degree of activity in the various overlapping areas depends on the type of pain conveyed by words. Whereas processing words conveying physical pain appears to activate the postcentral gyrus, a sensory-discriminative area, processing words conveying social pain seems to activate areas associated with the affective-motivational component of pain processing. In most of the regions we analyzed, the signal increase during the processing of words associated with social pain words is not significantly different from that caused by nociceptive stimuli: only in the AIs, activity is significantly higher during nociceptive pain than in both categories of semantic pain.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Modena. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EBo, CC, and CAP conceptualized the study. EBo, FB, CC, CAP, and FL designed the experiment. EBo, FB, DB, and FL collected the data. EBo, FB, and DB analyzed the data. EBo, FB, DB, CC, and FL contributed to the interpretation of the results and draft the manuscript. EBo, FB, DB, EBa, ML, CC, CAP, and FL provided critical feedback on the manuscript and contributed to the revisions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Alteration of static and dynamic intrinsic brain activity induced by short-term spinal cord stimulation in postherpetic neuralgia patients

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Introduction: Short-term spinal cord stimulation (stSCS) is an effective treatment for postherpetic neuralgia (PHN). However, how exactly stSCS affects time-dynamic intrinsic brain activity in PHN patients is not clear. The purpose of this study was to examine the static and dynamic variability of neural activity in PHN patients after stSCS.

Methods: In this study, 10 patients with PHN underwent resting-state functional magnetic resonance imaging (rs-fMRI) at baseline and after SCS. The amplitude of low-frequency fluctuations (ALFF) and dynamic ALFF (dALFF) were used to investigate the static and dynamic variability of neural activity in PHN patients after stSCS. We additionally examined the associations between clinical parameters and functional changes in the brain.

Results: There was a significant increase in dALFF in the left precuneus and right superior parietal gyrus, and a decrease in dALFF in the left inferior temporal gyrus, right gyrus rectus, left superior temporal gyrus, right orbitofrontal cortex, and left orbitofrontal cortex. There was significantly increased ALFF in the right inferior temporal gyrus, and decreased ALFF in the right lingual gyrus, left superior parietal gyrus, right superior parietal gyrus, and left precuneus. Furthermore, Pittsburgh sleep quality index scores were positively associated with dALFF changes in the left superior temporal gyrus and left orbitofrontal cortex. Hospital anxiety and depression scale scores and continuous pain scores exhibited significant negative correlation with dALFF changes in the right superior parietal gyrus.

Conclusion: This study indicated that stSCS is able to cause dALFF changes in PHN patients, thus stSCS might alter brain functions to relieve pain, sleep, and mood symptoms. The findings provide new insights into the mechanisms of stSCS efficacy in the treatment of patients with PHN.

KEYWORDS

fMRI, amplitude of low-frequency fluctuation, dynamic amplitude of low-frequency fluctuation, spinal cord stimulation, postherpetic neuralgia

1. Introduction

Herpes zoster (HZ) is caused by the reactivation of varicella-zoster virus and typically presents as a painful blister-like rash (Altena et al., 2010). The annual incidence of HZ is about 3.4/1000, rising sharply from the age of 50 to about 11/1000 by the ninth decade of life (Argaman et al., 2020). Postherpetic neuralgia (PHN) is the most common chronic complication of HZ, with pain appearing or persisting for around 1 to 3 months after the onset of the rash (Briggs et al., 2020). After 50 years of age, about 20% of patients with HZ will develop PHN (Brisson et al., 2001). PHN remains an important public health problem that leads to suffering and a reduced quality of life, and raises the cost of individual and societal health care (Buckner et al., 2008).

Because of the complexity of its pathogenesis, traditional pharmacological therapy is not always effective in relieving pain and may lead to a variety of drug-related complications (Borsook, 2012). stSCS whose electrodes are placed percutaneously to the spinal epidural for 2 weeks, and stSCS is known to be a clinically effective treatment option for these PHN patients. Since the introduction of spinal cord stimulation (SCS) as a therapeutic option for PHN, the mechanism of pain relief by SCS has been investigated. Multiple spinal segmental and supraspinal structures may play roles in the pain-alleviating effects of SCS (Drolet et al., 2010; Borsook, 2012; Deogaonkar et al., 2016). However, the potential functional alterations occurring in the brain as a result of SCS are less clear. Functional magnetic resonance imaging (fMRI) is a powerful noninvasive tool for understanding and mapping brain areas associated with pain perception and modulation (Deogaonkar et al., 2016). Moreover, the amplitude of low-frequency fluctuations (ALFF) can effectively reflect spontaneous brain activity and thus has been examined in PHN-related research. For example, Gu et al. (2019) observed a prominent decrease in ALFF in the right prefrontal cortex and increased ALFF in the bilateral brainstem and cerebellum anterior lobe in PHN patients. However, when HZ developed into PHN, neural activity was significantly increased in large areas of the cerebellum and frontal lobe but significantly decreased in the occipital lobe and limbic system (Cao et al., 2018). Only a few studies have used neuroimaging methods to explore the changes in brain activity after pain relief (Cao et al., 2018).

Based on resting-state functional MRI (rs-fMRI) evidence, ALFF was shown to reflect the average intrinsic activity of the brain over the entire scan. Although a previous study found abnormal ALFF in PHN patients, the neural activity of the brain is highly dynamic (Wen et al., 2021). ALFF only is not sufficient to describe the dynamic variability of spontaneous brain activity. Most previous studies have focused on static changes to neural activity in PHN patients (Cao et al., 2018; Gu et al., 2019; Zhang et al., 2020), and it is not sufficient to focus only on static changes in brain connectivity (Chang and Glover, 2010). Dynamic ALFF (dALFF) captures the temporal variability of the spontaneous neural activity of the brain with a sliding window that reflects changes in the information over the temporal dimension (Liao et al., 2019). Currently, changes in dynamic spontaneous brain activity occurring after SCS therapy in patients with PHN have not been evaluated. We hypothesized that, after stSCS, patients with PHN may present static and dynamic brain activity changes in some brain regions. We thus examined whether there are associations between clinical data and functional brain mapping changes in PHN patients after stSCS.

2. Materials and methods

2.1. Participants

We recruited 19 right-handed PHN patients from our pain department between January and October 2021 whose pain was not relieved by conventional medication alone and, therefore, were treated with stSCS at the First Affiliated Hospital of Zhengzhou University. All participants signed a written informed consent prior to participation in this study. Nine patients withdrew their consent or had poor quality MRI images; therefore, the final valid data from our study were obtained from 10 patients.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Reference: 2020-KY-0299-001). The trial registration number and web address are ChiCTR2000040239.[1]

2.2. Research protocol

In this prospective cohort study, patients were enrolled pre-stSCS implantation and followed for 14 days after receiving stSCS. During admission, clinical scales were assessed prior to MRI, which took 30 min, and patients were asked to complete questions relating to the pain numerical rating scale (NRS), the short-form McGill pain questionnaire version-2 (SF-MPQ-2), the Pittsburgh sleep quality index (PSQI), and the hospital anxiety and depression scale (HADS). The SF-MPQ-2 involves four subscale scores (continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors). Electrodes were removed 14 days after SCS implantation, and all patients underwent neuroimaging with an fMRI-protocol before (baseline) and 14 days after SCS implantation.

All patients received SCS at the cervicothoracic level for PHN. For the detailed methodology of SCS used in the study, please refer to the previous study by Fan et al. (2022). Neurostimulation test electrodes (Model 3,873, US) were implanted under dynamic monitoring with DSA imaging, then connected to an extension cable (Model 355,531, Medtronic, US) and external neurostimulator (Model 37,022, Medtronic, US). The physician adjusted the parameters to determine the effective contact, and the patient was free to change the amplitude in 0.1 mV increments to provide adequate pain relief. The stimulation parameters were as follows: voltage 0–10.5 V, pulse width 210–480 μs, frequency 30–60 Hz. Spinal electrical stimulation was applied for 14 consecutive days.

2.3. MRI image acquisition

All MRI images were acquired with a 3-T Siemens MR scanner (Magnetom Prisma, Siemens, Germany) at the magnetic resonance

1 http://www.chictr.org.cn/listbycreater.aspx

department of the First Affiliated Hospital of Zhengzhou University. During the scans, all subjects were asked to close their eyes and try not to think about anything else. Foam pads were applied to control the subjects' head movements, and earmuffs were fixed on both ears to reduce the noise made by the scanner. At the end of the scan, patients were asked whether they had fallen asleep during the scan. All patients reported that they had been awake at all times. The rs-fMRI was acquired using an echo-planar imaging sequence, and the scanning parameters were as follows: repetition time (TR) = 1,000 ms, echo time (TE) = 30 ms, flip angle = 70°, slice number = 52, field of view = 220 × 220 mm^2, matrix = 110 × 110, slice thickness = 2.2 mm, 400 volumes, scan time = 412 s.

2.4. MRI data processing

The Data Processing Assistant for rs-fMRI Analysis Toolbox (DPARSF, http://rest.Restfmri.Net/forum/DPARSF; Chao-Gan and Yu-Feng, 2010; Song et al., 2011) and SPM8 software (Wellcome Department, University College of London, UK) based on MATLAB R2012a (MathWorks, USA) were used to preprocess the rs-fMRI data. The main steps were as follows: (1) removal of initial 10 volumes to ensure signal stability; (2) slice timing and realignment; (3) spatial normalization to the standard Montreal Neurological Institute (MNI) space and resampling with a resolution of 3 × 3 × 3 mm^3; (4) detrending: multiple linear regression analysis was used to regress several spurious variances, including global mean signals, white matter signals, cerebrospinal fluid signals, and Friston-24 head motion parameters; (5) scrubbing of the image volumes with frame-wise displacement, (FD) > 0.5 mm, using spline interpolation to reduce the influence of head motion; (6) spatial smoothing of functional images with a full-width Gaussian kernel at half-maximum of 6 mm; (7) removal of high-frequency physiological noise and frequency drift lower than 0.01 Hz using band-pass filtering (0.01–0.08 Hz; Greicius et al., 2003).

2.5. Imaging analysis

The dALFF analysis data were analyzed using the Dynamic Brain Connectome toolbox (Liao et al., 2014; v2.0, http://restfmri.net/forum/DynamicBC). A sliding window approach was applied to characterize the temporal dynamic modes. Window length is an important parameter in the calculation of resting state dynamics, and the range of window lengths should be small enough to detect potential transients but large enough to analyze small fluctuations of interest in ALFF (Sakoglu et al., 2010; Zheng et al., 2021). A previous study (Leonardi and Van De Ville, 2015) showed that, to avoid introducing false fluctuations, a frequency interval of [0–1/w] Hz should be targeted, and the minimum window length should be 1/fmin. Therefore, we chose a window size of 30 TRs (30s) and a window overlap of 80% to calculate the dALFF of each subject. In addition, we calculated the results with other window sizes and overlaps and included them in the validation analyses. To explore the correlations between abnormal intrinsic timescales and clinical outcomes, we extracted the average intrinsic timescale values of all voxels within each cluster from the corrected statistical plots.

2.6. Validation analysis

To validate our main results, we tested the differences between the results and those obtained using other window lengths (50 TRs, 0.8 overlap, 80 TRs, 0.8 overlap) and different overlap rates.

2.7. Statistical analysis

To explore changes in the dynamic variability of dALFF, paired *t*-tests were performed on dALFF data between baseline and after stSCS with SPM8 in a whole-brain voxel-wise manner. Gaussian random field (GRF) was used to correct all results. The significance levels of the voxel and cluster were set at $p < 0.005$ and $p < 0.05$, respectively, and the minimum cluster size was 30 voxels. When significant differences in dALFF were observed in any regions of the brain, we extracted the mean dALFF values of the region of interest for each dALFF using the toolkit rs-fMRI analysis (http://www.restfmri.net/forum/REST; Song et al., 2011). The relationships between the mean values (dALFF variability) and clinical variables (NRS, SF-MQP-2, PSQI, HADS score) were then further assessed using the non-parametric Spearman correlation test. The threshold for all correlation analyses was $p < 0.05/108$ (Bonferroni corrected), which was statistically significant.

3. Results

3.1. Patient characteristics

Ten patients with PHN (five females and five males) with a median age of 70 years were included in our study. The demographics and clinical features of the patients are summarized in Table 1.

3.2. Clinical results

There were significantly reduced total scores for SF-MPQ-2($Z = -2.694$, $p = 0.007$), PSQI ($Z = -2.675$, $p = 0.007$), HADS ($Z = -2.668$, $p = 0.008$), and NRS ($Z = -2.694$, $p = 0.007$) after stSCS compared with the baseline (Figures 1–4). When examining continuous pain, intermittent pain, neuropathic pain, and affective descriptors of SF-MPQ-2, we found that the scores significantly decreased after stSCS ($Z = -2.371$, $p = 0.018$; $Z = -2.207$, $p = 0.027$; $Z = -2.527$, $p = 0.012$; and $Z = -2.524$, $p = 0.012$, respectively), as displayed in Figure 1. Concerning the anxiety and depression aspects of HADS, we found a significant decrease in HADS-A and HADS-D scores after stSCS ($Z = -2.677$, $p = 0.007$; and $Z = -2.673$, $p = 0.008$, respectively), as presented in Figure 3.

3.3. fMRI results

3.3.1. dALFF and ALFF results

The main results of the study were based on dALFF analysis using 30 TRs and 80% overlap and are displayed in Table 2 and Figure 5. Compared to baseline, dALFF was significantly increased in the left precuneus and right superior parietal gyrus, but decreased in the left

TABLE 1 Individual characteristics of patients included in this study (n = 10).

Patients ID	Sex(F/M)	Age (years)	Pain side	Pain duration (month)	Duration of SCS (days)
1	F	62	Left	6	14
2	F	79	Left	3	14
3	F	70	Right	2	14
4	F	68	Left	4	14
5	F	87	Right	1.5	14
6	M	39	Right	6	14
7	M	60	Right	7	14
8	M	70	Left	1	14
9	M	77	Left	1	14
10	M	83	Left	1	14

M: male, F: female, SCS: spinal cord stimulation.

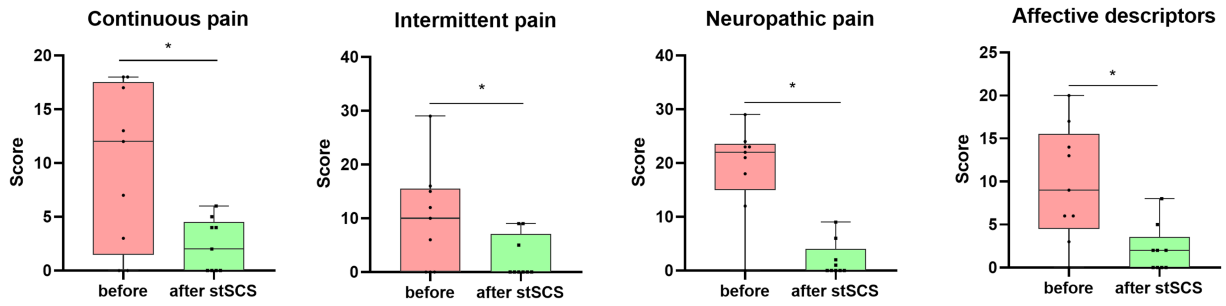

FIGURE 1
Boxplots showing the clinical SF-MPQ-2 scores of all patients at baseline (in pink) and after stSCS (in green). The four boxplots represent the four subscale scores of the SF-MPQ-2 (continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors). SCS, spinal cord stimulation.

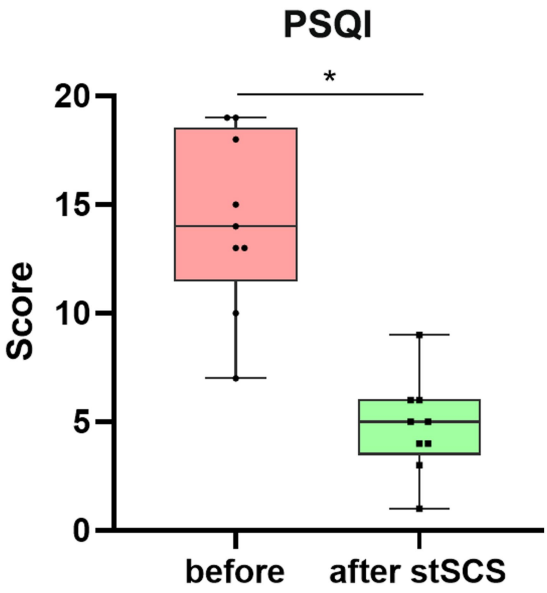

FIGURE 2
Boxplot showing the clinical PSQI scores of patients at baseline (in pink) and after stSCS (in green). PSQI, Pittsburgh sleep quality index; SCS, spinal cord stimulation.

inferior temporal gyrus, right gyrus rectus, left superior temporal gyrus, right orbitofrontal cortex, and left orbitofrontal cortex (GRF corrected $p_{voxel} < 0.005$, $p_{cluster} < 0.05$).

The differences between ALFF at baseline and after stSCS of static ALFF patterns are shown in Table 3 and Figure 6. There was significantly elevated ALFF in the right inferior temporal gyrus; and a decrease in ALFF in the right lingual gyrus, left superior parietal gyrus, right superior parietal gyrus, and left precuneus (GRF corrected $p_{voxel} < 0.005$, $p_{cluster} < 0.05$).

3.3.2. Correlation analyses

The PSQI score was positively associated with the dALFF values in the right gyrus rectus, the left superior temporal gyrus, and the left orbitofrontal cortex ($r = 0.746$, $p = 0.021$; $r = 0.729$, $p = 0.026$; $r = 0.678$, $p = 0.045$, respectively). The HADS-D score and continuous pain score were significantly negatively correlated with dALFF changes in the right superior parietal gyrus ($r = -0.700$, $p = 0.036$; $r = -0.689$, $p = 0.040$, respectively). The HADS-A score was positively associated with ALFF values in the right lingual gyrus ($r = 0.820$, $p = 0.007$). Neuropathic pain and affective descriptors were significantly positively correlated with ALFF changes in the right superior parietal gyrus and the left precuneus ($r = 0.866$, $p = 0.003$; $r = 0.845$, $p = 0.004$; $r = 0.765$, $p = 0.016$; $r = 0.820$, $p = 0.007$; respectively). However, this difference in

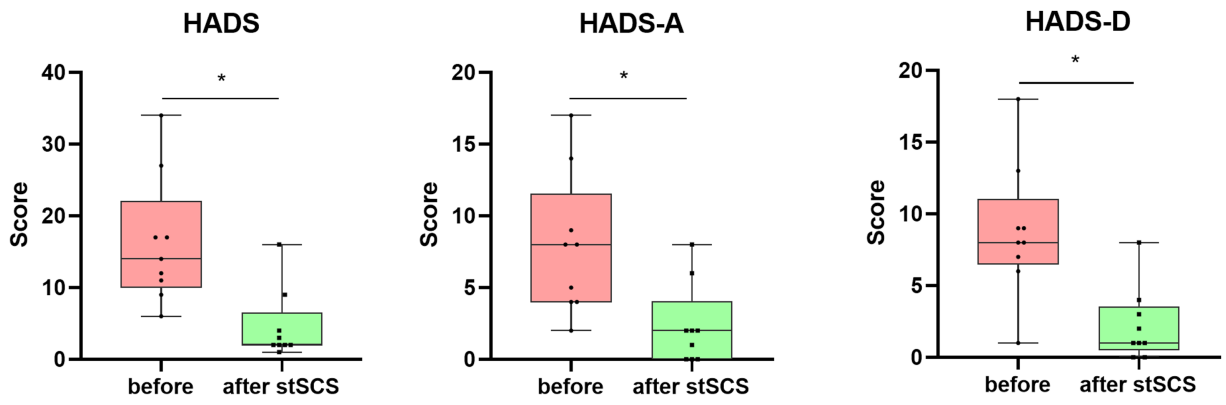

FIGURE 3
Boxplots showing the clinical HADS scores of patients at baseline (in pink) and after stSCS (in green). The second and third boxplots represent the two subscale scores for the HADS (HADS-A and HADS-D, respectively). HADS, hospital anxiety and depression scale; HADS-A: hospital anxiety and depression scale-anxiety: HADS-D: hospital anxiety and depression scale-depression; SCS: spinal cord stimulation.

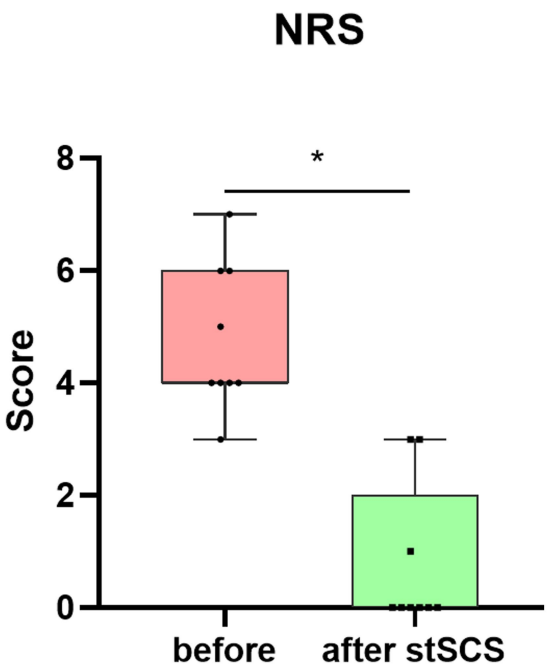

FIGURE 4
Boxplot showing the clinical NRS scores of patients at baseline (in pink) and after stSCS (in green). NRS, numerical rating scale; SCS, spinal cord stimulation.

significance level was cancelled out after Bonferroni calibration ($p < 0.05/108 = 0.000463$).

3.3.3. Validation analyses

In our study, the different sliding window lengths and different overlap rates were applied to validate our results. The results of different overlap (30 TRs, 0.6 overlap) and the other two window lengths (50 TRs, 0.8 overlap; 80 TRs, 0.8 overlap) are presented in Supplementary Tables 1–3. Supplementary Figures 1–3. These results were generally consistent with our main results.

4. Discussion

Researchers have found that dALFF can provide evidence for the dynamic variability of spontaneous brain activity in the brain, and it has provided us with a new way to explore fluctuations in spontaneous brain activity in PHN patients after stSCS. In our research, we studied changes in the dALFF and ALFF values of brain regions associated with pain relief after stSCS in PHN patients. The dALFF and ALFF analyses verified that the improvement of symptoms was, to some extent, associated with altered regional brain functions. Our study also assessed the relationship between changes in brain function and clinical variables, and our findings suggest that stSCS alters the statics and dynamics of local neural activity to relieve pain, sleep, and mood disorders.

In the present study, stSCS can rapidly and effectively relieve pain in PHN patients, which is consistent with previous results (Dong et al., 2017; Feng and Ye, 2021; Sheng et al., 2022). Moreover, stSCS can effectively improve sleep quality and emotion in patients (Feng and Ye, 2021; Liu et al., 2021). In addition, we found that, after stSCS treatment, PHN patients had functional alterations in several brain regions that may be associated with pain relief.

In this study, we observed changes in several brain functions associated with sleep quality after stSCS treatment of PHN patients. The main clinical features of patients with neuropathic pain are the symptoms of mood disorders, such as anxiety, depression, and insomnia (Inoue et al., 2017). Previous studies have suggested that neuropathic pain and affective disorders may share a common pathogenesis (Aloisi et al., 2016). PHN patients in our study also experienced varying degrees of depression and poor sleep quality, but experienced a mood boost and improved sleep after stSCS. Our study found that dALFF decreased after treatment in the left orbitofrontal cortex, right orbitofrontal cortex, and right gyrus rectus. In addition, we also found that changes in dALFF in the left orbitofrontal cortex and right gyrus rectus were positively correlated with PSQI. The orbitofrontal cortex (OFC) is mainly involved in sensory integration and monitoring the responses of internal organs and the internal state of the body, as well as evaluating sensory responses and regulating autonomic responses (Kringelbach, 2005; Vandenberghe et al., 2007).

TABLE 2 Different dALFF values between baseline and after stSCS.

Regions	MNI coordinate			Peak *T* value	Voxels
	x	y	z		
dALFF increase					
Left precuneus	−15	−60	66	25.1361	82
Right superior parietal gyrus	33	−57	63	9.741	42
dALFF decreased					
Left inferior temporal gyrus	−48	0	−42	−6.3794	37
Right gyrus rectus	9	33	−21	−8.1885	65
Left superior temporal gyrus	−45	12	−21	−14.0498	40
Right orbitofrontal cortex	6	63	−3	−8.7597	42
Left orbitofrontal cortex	−12	60	−12	−6.99	66

dALFF, dynamic amplitude of low-frequency fluctuation; MNI, Montreal Neurological Institute.

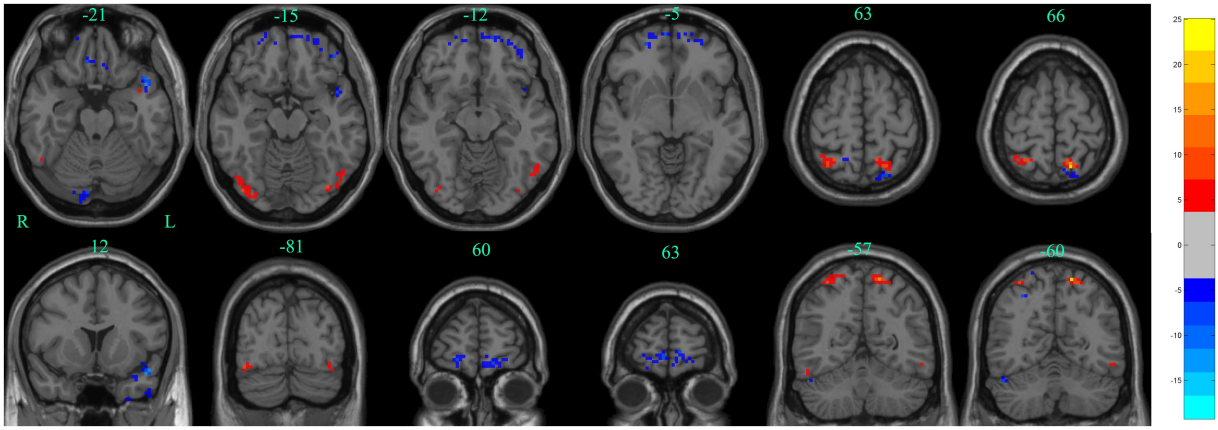

FIGURE 5
Significant differences in dALFF between baseline and after stSCS in axial and coronal slices (30 TRs, 80% overlap). Warm colors indicate higher dALFF values, while cooler colors indicate lower dALFF values at baseline and after stSCS. The statistical significance level was set at $p_{voxel} < 0.005$, $p_{cluster} < 0.05$ (GRF corrected).

In addition, the orbitofrontal cortex is an important region known to be involved in pain processing at multiple levels, influencing bidding behavior and decision-making, and mediating pain inhibition (Mouraux et al., 2011; Winston et al., 2014). A study showed back and leg pain patients to have increased ALFF in their bilateral OFC (Zhou et al., 2018). Therefore, we concluded that decreased intrinsic activity in the OFC may reduce pain in PHN patients. The OFC also plays an important role in sleep. Park et al. (2021) reported that reduced cerebral blood flow in the orbitofrontal and insular cortices was associated with poor sleep quality. We reasoned that one of the mechanisms behind the improvement in sleep may be related to changes in the OFC.

In this study, we identified the superior parietal gyrus as being related to pain intensity and HADS-D after the treatment of PHN with stSCS. The parietal gyrus is involved in the processing of emotional, sensory, and cognitive functions of the brain (Lai, 2019). Some studies have found that the onset of anxiety is associated with reduced cerebral blood flow in the parietal gyrus (Fredrikson et al., 1997). Dai et al. (2020) demonstrated that PHN patients had increased fALFF in the left cerebellum posterior gyrus, left orbital gyrus, and right superior parietal gyrus. Yue and Du (2020) found increased cerebral blood flow (CBF) in the bilateral superior parietal gyri in patients with chronic neck pain, which might be a compensatory manifestation. In our study, we found decreased ALFF values in the bilateral superior parietal gyri after stSCS, and there was a positive correlation between ALFF values, neuropathic pain, and affective descriptors. The superior parietal gyrus is believed to be associated with visuospatial attention (Wu et al., 2016). Furthermore, it has been shown that the stronger the spontaneous activity in the superior parietal gyrus, the higher the level of pain experienced by the patient (Li et al., 2021).

We discovered that the precuneus is associated with the modulation of pain intensity. We noticed a decrease in ALFF values in the left precuneus after stSCS compared to baseline. Significant correlations were also found between changes in ALFF in the left precuneus and changes in neuropathic pain and affective descriptors. The precuneus is responsible for collecting information about somatosensory sensations and is therefore primarily responsible for identifying pain sensations (Nagamachi et al., 2006). The precuneus is also involved in a range of highly integrated tasks, mainly including self-processing operations, visuospatial image processing, the processing of conscious

TABLE 3 Different ALFF values between baseline and after stSCS.

Regions	MNI coordinate			Peak *T* value	Voxels
	x	y	z		
ALFF increase					
Right inferior temporal gyrus	51	−72	−12	8.6165	32
ALFF decreased					
Right lingual gyrus	15	−90	−12	−11.1194	70
Left superior parietal gyrus	−27	−72	57	−7.5537	45
Right superior parietal gyrus	18	−54	69	−10.1811	53
Left precuneus	−15	−57	63	−16.5591	45

ALFF, amplitude of low-frequency fluctuation; MNI, Montreal Neurological Institute.

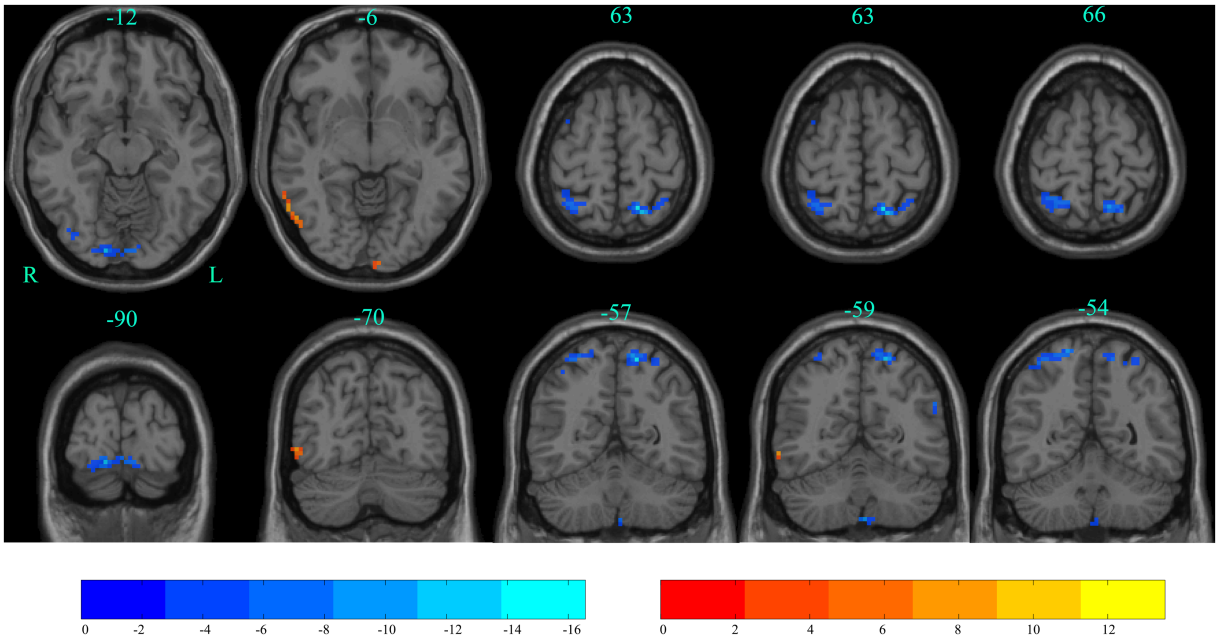

FIGURE 6
Significant differences in ALFF between baseline and after stSCS in axial and coronal slices. Warm colors indicate higher ALFF values, while cooler colors indicate lower ALFF values at baseline and after stSCS. The statistical significance level was set at $p_{voxel} < 0.005$, $p_{cluster} < 0.05$ (GRF corrected).

information, pain perception, and the modulation of endogenous pain (Cavanna and Trimble, 2006; Greicius et al., 2009). De Groote et al. (2020) suggested that the precuneus could be used as a monitoring tool for the therapeutic effects of SCS. dALFF reflects the dynamic changes occurring in local spontaneous brain activity over time (Fu et al., 2018), and the greater the dALFF value, the more unstable the local spontaneous brain activity. In our study, we also observed an increase in dALFF values in the left precuneus, which may confirm the important role of the precuneus in pain reduction, and the precuneus showed fluctuations in regional spontaneous brain activity. The precuneus is the main center of the brain and one of the core regions of the default mode network (DMN). The DMN is the resting-state network of the brain and is mainly composed of the precuneus, the medial frontal gyrus, the posterior cingulate cortex, the posterior parietal cortex, and the lateral temporal cortex (Raichle et al., 2001). The DMN is responsible not only for emotional processing, self-introspection, and the extraction of awareness and scenario memory (Buckner et al., 2008) but also for associated pain inhibition (Argaman et al., 2020). In addition, DMN is a brain network and functional connection hub (Tomasi and Volkow, 2011). Patients with chronic pain show abnormalities in their resting DMN, suggesting that this chronic state affects areas beyond pain perception (Tagliazucchi et al., 2010; Otti et al., 2013; Zhang et al., 2014).

We observed decreased ALFF values in the right lingual gyrus after stSCS. The lingual gyrus is a part of the occipital lobe, and previous research has demonstrated that the lingual gyrus is also involved in activities related to visual memory processing and is strongly associated with the progression of major depressive disorder (Palejwala et al., 2021). A previous study also found that the right lingual gyrus is a sign of depression relief (Yang et al., 2018). Correlation analysis in our study showed that ALFF values in the right lingual gyrus were positively correlated with HADS and HADS-A scores. Therefore, we hypothesized that stSCS acts on the lingual gyrus to relieve depression and thus pain.

The main limitation of this study was the relatively small sampling size. This study was conducted over a long period of time, and it was difficult to collect cases due to the study design's focus on treatment effects. In the future, a multi-center study will be conducted to collect more cases and obtain more reliable results. Furthermore, we investigated changes in brain function in patients who experienced pain relief after stSCS treatment; future studies will include a sham group to make the results more credible.

5. Conclusion

The findings of study suggest that stSCS may alter the local neural activity of ALFF and dALFF in key brain regions to alleviate pain, sleep, and emotional disorder in PHN patients. This study has provided further evidence of the neural mechanisms of stSCS in the treatment of PHN patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Reference: 2020-KY-0299-001). The trial registration number and web address are ChiCTR2000040239 (http://www.chictr.org.cn/listbycreater.aspx). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CB: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Methodology, Software. HR: Data curation, Writing – review & editing, Formal analysis, Methodology. QL: Formal analysis, Investigation, Software, Writing – original draft. HB: Conceptualization, Data curation, Investigation, Writing – review & editing. XG: Conceptualization, Investigation, Software, Writing – review & editing. RZ: Conceptualization, Investigation, Software, Writing – review & editing. HH: Conceptualization, Investigation, Software, Writing – review & editing. WW: Formal analysis, Project administration, Validation, Writing – review & editing. YW: Supervision, Validation, Writing – review & editing. JC: Project administration, Validation, Writing – review & editing. YZ: Formal analysis, Project administration, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1254514/full#supplementary-material

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Interplay between noxious heat sensitivity and temporal summation magnitude in patients with fibromyalgia and long-term opioid use

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Introduction: In chronic pain conditions such as fibromyalgia (FM), pain amplification within the central nervous system, or "central sensitization," may contribute to the development and maintenance of chronic pain. Chronic pain treatments include opioid therapy, and opioid therapy may maladaptively increase central sensitization, particularly in patients who take opioids long-term. However, it has remained unknown how central sensitization is impacted in patients who use opioids long-term.

Methods: To investigate how long-term opioid therapy affects central sensitization, we used the validated measure of temporal summation. The temporal summation measurement consists of applying a series of noxious stimuli to a patient's skin and then calculating changes in the patient's pain rating to each stimulus. Using this measurement, we evaluated temporal summation in study participants with fibromyalgia who take opioids long-term (i.e., greater than 90 days duration; n =24, opioid-FM). We compared opioid-FM responses to 2 control groups: participants with fibromyalgia who do not take opioids (n =33, non-opioid FM), and healthy controls (n =31). For the temporal summation measurement, we applied a series of 10 noxious heat stimuli (sensitivity-adjusted temperatures) to the ventral forearm (2s duration of each stimulus, applied once every 3s). Additionally, we collected responses to standard pain and cognitive-affective questionnaires to assess pain severity and other factors.

Results and discussion: Group differences in sensitivity-adjusted stimulus temperatures were observed, with only the non-opioid FM group requiring significantly lower stimulus temperatures (The opioid-FM group also required lower temperatures, but not significantly different from the control group). However, all 3 groups exhibited similar magnitudes of temporal summation. Across combined FM groups, temporal summation negatively correlated with pain severity (r =−0.31, p =0.021). Within the opioid-FM group, higher pain sensitivity to heat (i.e., lower sensitivity-adjusted temperatures) showed a trend relationship with higher opioid dosage (r =−0.45, p =0.036), potentially reflective of opioid-related hyperalgesia. Our findings also indicated that heightened pain severity may skew sensitivity-adjusted temporal summation, thereby limiting its utility for measuring central sensitization. Overall, in participants taking opioids, temporal summation may be influenced by hypersensitivity to heat pain, which appeared to vary with opioid dosage.

KEYWORDS

temporal summation, sensitivity-adjusted temperature, opioids, fibromyalgia, chronic pain, opioid-related hyperalgesia, pain severity, central sensitization

1. Introduction

While acute pain acts as a protective mechanism against tissue damage, progression to chronic pain can be debilitating. Characterized by plasticity of nociceptive pathways, chronic pain entails abnormal sensitization of the central nervous system (CNS) (i.e., central sensitization) and impaired pain modulatory systems, which together increase pain sensitivity (Ji et al., 2018).

Fibromyalgia (FM) is a chronic pain condition that involves increased sensitivity and pain widespread across the body (Clauw, 2014). Individuals with fibromyalgia demonstrate enhanced pain response to noxious and innocuous stimuli, altered pain circuits, and evidence of central sensitization (Gomez-Arguelles et al., 2018). Central sensitization can be reduced by administration of exogenous opioids, in line with opioids' analgesic and hypoalgesic effects (Busse et al., 2018). However, in clinical trials, opioids often fail to reduce pain in individuals with fibromyalgia (Ngian et al., 2011; Goldenberg et al., 2016). Nonetheless, many patients with chronic pain continue to use opioids long-term. It remains an open question how long-term opioid use alters pain processing – specifically in terms of how opioids alter pain sensitivity and central sensitization.

Temporal summation is a validated procedure to evaluate the degree of central sensitization in humans based on physiological responses to repeated stimuli. It uses a series of repetitive noxious stimuli to calculate changes in pain response across the stimuli series (McMahon et al., 1993; Arendt-Nielsen et al., 1997). Repetitive heat stimuli at rates ≥0.33 Hz activate primary afferent nociceptors; the excessive input from these afferent fibers progressively increases perceived pain intensity (Vierck et al., 1997). Compared with healthy pain-free individuals, those with fibromyalgia demonstrate enhanced temporal summation (i.e., greater peak pain levels and lower pain thresholds) (Staud et al., 2001).

Chronic pain conditions are typically associated with enhanced magnitude of temporal summation. However, the impact of opioids on temporal summation is less clear. When acutely administered, opioids reduce temporal summation in both preclinical models of chronic pain (Lomas and Picker, 2005) and in clinical neuropathic pain patients (Suzan et al., 2016). Meanwhile, as shown in patients with fibromyalgia, temporal summation reductions occur with both placebo and acute treatments (Price et al., 2002). Thus, temporal summation diminution could result from drug administration or expectations.

Conversely, prolonged opioid use can lead to opioid-induced hyperalgesia (OIH), an increased sensitivity to painful stimuli (Lee et al., 2011). For example, after chronic pain patients receive 3 months of opioid therapy, heat pain thresholds decrease while temporal summation increases (Chen et al., 2009). Further, among patients with chronic back/neck pain who regularly use opioids, endogenous pain modulatory systems appear compromised (Martel et al., 2019). However, no published studies have tested temporal summation in individuals with fibromyalgia who take opioids long-term. Here, our objective in studying the degree of temporal summation was to clarify the impact of chronic opioid use on central sensitization. We further sought to determine the extent to which pain symptoms are influenced by duration, timing, and amount of opioid use.

In this study, we calculated temporal summation in participants with fibromyalgia who were taking opioids long-term (opioid-FM). We compared their temporal summation responses to healthy controls and to participants with fibromyalgia who were not taking opioids (non-opioid FM). In line with prior evidence of enhanced central sensitization in fibromyalgia, we expected that temporal summation would be increased in non-opioid FM compared to healthy controls. We hypothesized that opioid-FM participants would demonstrate the greatest temporal summation (i.e., enhanced central sensitization due to OIH-related symptoms). Lastly, because individuals with fibromyalgia also experience non-pain-related symptoms such as changes in affect/mood, we predicted that increased temporal summation in participants with fibromyalgia would correlate with greater cognitive-affective and clinical symptoms (e.g., anxiety, depression, pain severity, and negative affect).

2. Methods

2.1. Participants

Participants were recruited from the Durham, NC area. All data were collected from July 15, 2019 until May 1, 2022. The study included only female participants due to the greater prevalence of fibromyalgia in females and the need for sex-matched participant groups. All participants with fibromyalgia met the inclusion criteria of pain reported in 4 out of 5 body regions and self-reported average pain score of at least 4 out of 10 over the prior month. Additionally, all fibromyalgia participants met the 2016 revised American College of Rheumatology (ACR) criteria for fibromyalgia: widespread pain index [WPI] score ≥ 7 and symptom severity scale [SSS] score ≥ 5 or WPI score of 4–6 and SSS score ≥ 9; similar symptoms for at least 3 months; and pain attributable solely to fibromyalgia and no other disorder (Wolfe et al., 2016). Healthy controls were included only if they did not have chronic pain, take any pain or mood-altering medications, or experience any anxiety or depression at the time of the study. Participants were ineligible if they had any MRI contraindications.

All individuals with fibromyalgia and healthy controls signed a written informed consent indicating that they were willing to participate in the study, understood all study procedures, and could withdraw at any time. All study procedures were conducted in accordance with the Declaration of Helsinki, and approved by the Duke University Institutional Review Board.

2.2. Study procedures

2.2.1. Sample size

We collected data from 97 participants: 36 participants with fibromyalgia who do not take opioids (non-opioid FM), 27 participants with fibromyalgia who take opioids (opioid-FM), and 34 healthy controls. Nine participants were excluded from the analysis: 4 were excluded due to their intolerance of the heat stimuli required for the temporal summation paradigm (non-opioid FM, $n = 2$; opioid-FM, $n = 2$), 4 were excluded due to a lack of pain response to the heat stimuli (healthy controls, $n = 3$; opioid-FM, $n = 1$), and 1 was excluded due to a misunderstanding of the pain rating instructions (non-opioid FM, $n = 1$). Thus, the final dataset used for analysis contained data for 88 participants, which included 33 non-opioid FM, 24 opioid-FM, and 31 healthy controls (Figure 1).

Prior to the analysis, and as part of a preregistered analysis plan, we ran a power analysis, using G*Power 3.1 software, on a sample size

of 66 participants (22 per group). The power analysis showed that a one-way ANOVA to evaluate temporal summation in participants with fibromyalgia and healthy controls could detect a Cohen's *F* effect size of 0.39 with ≥0.80 power at an alpha level of 0.05. Similarly, post-hoc Bonferroni *t*-tests could detect a Cohen's *D* effect size of 1.01 with ≥0.80 power at an alpha level of 0.017. Given that prior literature reports an effect size of 1.47 for a 2-group comparison (Staud et al., 2001), our dataset was adequately powered to compare patients vs. healthy controls.

2.2.2. Thermal pain threshold measurement

We conducted all quantitative sensory tests at Duke University in a private behavioral testing room at the Duke University Hospital. Similar to prior temporal summation protocols (Potvin et al., 2012; Staud et al., 2021), prior to the temporal summation test, we measured thermal pain thresholds. We administered thermal stimuli using a computer-connected Q-Sense thermode (Peltier-based device; 30 × 30-mm thermode surface area; Medoc Inc., Ramat Yishay, Israel). We placed the thermode on the right ventral forearm of each participant to test pain sensitivity. Then, we informed the participant that the temperature of the thermode would slowly change to higher temperatures. We asked participants to immediately report their pain level after each stimulus by using a visual analogue scale (VAS). The VAS is a validated scale for measuring experimental pain evoked by noxious heat stimuli (Price et al., 1983). The VAS used in our study was a double-sided slider. The side facing the participant had verbal anchors from "No pain at all" (0) to "Most painful sensation imaginable" (10), while the side facing the experimenter displayed a numeric scale of 0–10. For the thermal thresholding test, we increased the thermode temperature from 40°C to 47°C in 1-°C increments at a rate of 2°C/s. Using the participant's pain ratings for each temperature, we determined the temperature that would evoke a pain rating of 5 on the VAS for each participant.

If a participant did not report a VAS rating of 5 during the first threshold test, we ran a second thresholding test on a slightly different part of the right forearm. For this second thresholding test, we increased the thermode's temperature in smaller 0.2-°C increments, and tested temperatures between the 2 temperatures from the first threshold test that evoked pain ratings just below and above a rating of 5 on the VAS. Using pain ratings from the second thresholding test, we then chose the stimulus temperature that evoked a rating of 5, or closest to 5, on the VAS for the temporal summation paradigm.

2.2.3. Experimental heat stimuli and temporal summation measurement

As described to participants, a "thermal tapping test" was then performed to measure temporal summation by using repeated "taps" of the thermode to the participant's forearm. The thermode was preheated to each participant's VAS = 5 temperature; the temperature remained constant throughout the test. Prior to the actual test

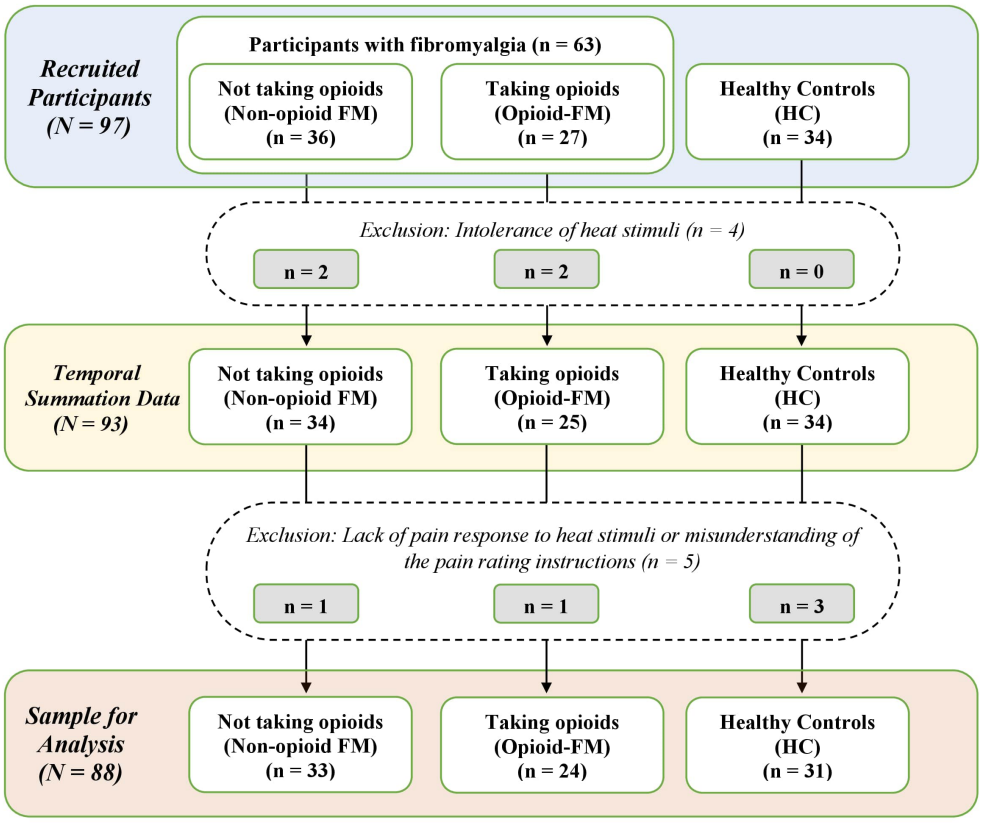

FIGURE 1
Flow chart of participant exclusions. Counts of participant datasets are shown for the stages of recruitment, data collection, and final sample used in the analysis. Non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids; HC, healthy controls.

procedure, 2 practice taps were used to show the participants the speed of the test, and how to rate their pain. As previous studies have not found consistent differences in heat pain sensitivity due to handedness (Long, 1994; Coghill et al., 2001; Sarlani et al., 2003) and to avoid habituation to heat stimuli during thresholding, the temporal summation protocol involved a thermal stimulus tap on the left ventral forearm every 3 s (2 s with the thermode touching the skin, 1 s with the thermode above the skin) for a total of 10 stimulus taps (Bosma et al., 2018). After each thermode tap, participants rated their pain on a case report form with 10 pre-drawn 10-cm lines. The case report form was designed as a paper version of the VAS, unnumbered, and with the number of centimeters indicating pain ratings on a 0–10 scale. After the testing session, the recorded pain ratings were measured with a ruler in centimeters and converted to a 1–100 scale from a 0–10 scale by multiplying by 10 (e.g., 0 ➔ 1, 0.1 ➔ 1, 1.1 ➔ 11). Conversion to this 1–100 scale allowed us to quantify temporal summation with both a difference and percentage calculation (see below). The converted data were then manually recorded onto electronic spreadsheets and double-checked for accuracy. We calibrated the temperature of the thermode before each test, using a built-in Medoc pre-test. The same Medoc Q-Sense thermode was used for all participants. Moreover, to limit the impact of expectation bias on pain ratings, we did not inform participants that the temperature would remain constant, or provide any indication that we expected summation to occur during the test.

For this study, we defined temporal summation as the calculated difference between the peak pain rating and baseline/initial pain rating (Staud et al., 2001). Others have used a percentage calculation of temporal summation to provide a relative measure of summation (Bosma et al., 2018). As the percentage calculation accounts for baseline pain rating variation, this calculation may potentially better portray the degree to which pain ratings change over time. As such, we also calculated temporal summation as the percent change from the baseline to peak pain rating (see Supplementary material).

2.3. Medication usage

Per our eligibility criteria, we required non-opioid FM participants to have <30 days of opioid use within their lifetimes, no opioid use within the 90 days prior to start of the study, and no opioid use for pain treatment during the study. We required opioid-FM participants to have taken opioid medications continuously for the 90 days prior to start of the study and for the duration of the study. Beyond these requirements, participants continued their normal use of medications during study participation.

As recorded during the study visits, opioid-FM participants were taking codeine (n = 1), hydrocodone (n = 2), hydrocodone/acetaminophen (n = 7), hydromorphone (n = 1), methadone (n = 1), morphine (n = 2), oxycodone (n = 1), oxycodone/acetaminophen (n = 1), tapentadol (n = 2), or tramadol (n = 9). Participants in both fibromyalgia groups were taking an assortment of other medications including nonsteroidal anti-inflammatory drugs (NSAIDs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, other anxiolytics, antiepileptic drugs, and gamma-aminobutyric acid (GABA) analogues. Two FM participants took cannabidiol products, which have known analgesic effects (Mlost et al., 2020), 3 days before their respective study visits. In a post-hoc analysis, the exclusion of the data from these 2 participants did not significantly alter the group results, so their data were retained in the final analysis.

All healthy control participants had no history of chronic pain and were not taking any regularly prescribed medications at the time of the study. At the study visit, most of the healthy controls (n = 31) reported not taking any pain or mood-altering medications. Three healthy controls reported taking pain and/or mood-altering medications: one reported taking naproxen (~ 500–1,000 mg) for menstrual cramps on the day of the study visit, one reported taking ibuprofen one day prior to the study visit, and one reported taking zolpidem (5 mg) four days prior to the study visit. In a post-hoc analysis, the exclusion of the data from these participants did not significantly impact group results, so their data were retained in the final analysis.

2.4. Questionnaires

In addition to general demographic and medication questionnaires, all participants completed the following questionnaires: Beck Depression Inventory (BDI) (Beck et al., 1988), Behavioral Inhibition System/Behavioral Approach System (BIS/BAS) (Carver and White, 1994), Brief Pain Inventory (BPI) (Keller et al., 2004), Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983), Fibromyalgia Assessment Status (FAS) (Salaffi et al., 2009), Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue (Cella et al., 2010), Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), Profile of Mood States (POMS) (McNair et al., 1971), and State–Trait Anxiety Inventory (STAI-State, STAI-Trait) (Spielberger et al., 1970). Questionnaire data were collected and stored using a secure REDCap database. We used the data from the STAI-Trait, BDI, BPI, and PANAS questionnaires in analyses to test *a priori* hypotheses. We used data from the other questionnaires in our exploratory analyses.

2.5. Statistical analysis

A power analysis, study hypotheses, and all planned analyses were pre-registered on the Open Science Framework.[1] The analyses were performed using R 4.1.3.

We used an omnibus one-way ANOVA across the 3 groups to analyze general characteristics of heat pain response, which included VAS = 5 temperatures, initial and peak stimulus ratings, and differences in temporal summation. Upon significant ANOVA results ($p < 0.05$), we performed additional post-hoc t-tests between groups (i.e., non-opioid FM vs. opioid-FM, healthy controls vs. non-opioid FM, and healthy controls vs. opioid-FM). We evaluated the ANOVA results at a Bonferroni-corrected threshold of $p < 0.0167$ to account for 3 comparisons of interest. Due to the potential impact of age, we ran an additional ANCOVA that adjusted for participant age while comparing initial pain ratings, peak pain ratings, and temporal summation.

1 OSF, https://doi.org/10.17605/OSF.IO/AQ6TS.

TABLE 1 Participant demographics.

		HC	Non-opioid FM	Opioid-FM
Total number of participants		31	33	24
Right-handed		29	31	20
Hispanic or Latinx ethnicity		1	2	3
Self-identified race	Asian	3	1	0
	African American	2	5	2
	Caucasian	25	26	20
	American Indian/Alaskan/Pacific Islander	1	0	0
	Other	0	1	1
Employment status	Part-time employed	4	6	4
	Full-time employed	18	19	5
	Unemployed	4	5	6
	Retired	5	0	0
	Disabled	0	2	9
	Other	0	1	0
Education level	High school	0	1	2
	College/University	19	27	18
	Advanced degree	12	5	4

Two controls, two non-opioid FM participants, and four opioid-FM participants were left-handed. Two participants reported their race category as "other," which refers to race other than all of the listed categories. One opioid-FM participant did not indicate race or ethnicity. "Part-time employed" and "unemployed" criteria included full-time students who worked part-time or were not employed. For education level, "High school" refers to "up to or through high school"; "College/University" refers to "up to or through college/university"; and "Advanced degree" refers to "any amount of education post college/university." HC, healthy controls; non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids.

Prior investigations have established a relationship between chronic pain and trait anxiety (Ruscheweyh et al., 2017), depressive symptoms (Grinberg et al., 2018; Overstreet et al., 2021), pain severity (Røsland et al., 2015), and negative affect (Staud et al., 2003). Therefore, we ran Spearman correlations to assess the relationships of temporal summation with our clinical/affective measures of trait anxiety (STAI-Trait), depression (BDI), average 24-h pain severity (BPI), and negative affect (PANAS, NAS subscale). Correlations between our selected clinical/affective measures resulted in 2 independent measures: (1) STAI-Trait, BDI, and NAS ($p < 0.001$) and (2) BPI pain severity (not correlated with other *a priori* variables). Thus, the correlations of temporal summation with clinical/affective measures were corrected for 2 independent comparisons, and determined to be statistically significant at $p < 0.025$.

2.6. Exploratory analyses of opioid use

We evaluated relationships of opioid use behaviors with pain sensitivity (as derived from the sensitivity-adjusted temperatures of each participant) and with temporal summation. For opioid use behaviors, we included opioid dosage (calculated in morphine milligram equivalents [MME]), duration of opioid use, and timing of last opioid dose (prior to the start of the study visit). We ran Spearman correlations using each of the 3 opioid use behavior variables vs. the 2 pain variables of VAS = 5 temperature and temporal summation. By testing correlations between the 3 opioid use behavior variables, we identified 2 independent measures: (1) duration of opioid use (not correlated with any other behavior variable) and (2) opioid dosage and timing of last opioid dose ($p = 0.030$; negative correlation). Therefore, we evaluated significance at a corrected threshold of $p < 0.0125$, correcting for 4 independent comparisons. Additionally, we ran exploratory analyses to identify potential effects of phase of opioid use (i.e., based on timing of opioid dose prior to study visit), other medication use, and other variables' effects on temporal summation (see Supplementary material).

3. Results

3.1. Participants

The final analysis included data from 31 healthy controls, 33 non-opioid FM participants, and 24 opioid-FM participants. Most of the participants were right-handed (healthy controls: 94%; non-opioid FM: 94%; opioid-FM: 83%), white (healthy controls: 81%; non-opioid FM: 79%; opioid-FM: 83%), and had earned a college/university degree (healthy controls: 61%; non-opioid FM: 82%; opioid-FM: 75%). Most of the healthy controls and non-opioid FM participants were employed full-time (healthy controls: 58%; non-opioid FM: 58%); however, the opioid-FM group had a smaller percentage employed full-time (opioid-FM: 21%). Complete demographics are shown in Table 1.

3.2. Opioid usage

Participants were asked to self-report their medication use on paper case report forms with assistance from the study experimenter. In the opioid-FM participant group, the median morphine milligram equivalent (MME) dosage per day was 15.53 mg, while the median duration of opioid use was 5 years. The distribution of opioid MME dosage per day was right-skewed, with all participants taking 5–40 mg/day except for 2 participants who were taking 85 mg/day and 90 mg/day, respectively. The distribution for opioid use duration was slightly less right-skewed, with opioid use ranging from 7 months to 10 years, with one outlier at 15 years opioid use duration. Across all participants with fibromyalgia ($n = 57$), 16 (28%) were taking NSAIDs, 19 (33%) were taking SNRIs, 10 (18%) were taking benzodiazepines, and 14 (25%) were taking GABA analogues. Further information about medication use for each group is presented in Table 2.

3.3. Clinical and psychological measures

Questionnaire data revealed significant differences between the healthy controls and fibromyalgia groups. Compared to healthy controls, the fibromyalgia groups demonstrated more pain areas, greater fatigue, higher negative affect, worse mood, and higher anxiety

(Table 3). Despite our efforts to recruit similar age ranges among the groups, we identified a significant interaction between age and group [$F_{(2, 85)} = 5.965$, $p = 0.004$]. Post-hoc *t*-tests revealed that the non-opioid FM cohort (37.70 ± 13.32 years) was significantly younger than the opioid-FM cohort (48.96 ± 9.70 years).

As shown by post-hoc *t*-tests, the questionnaire responses were not significantly different between the 2 fibromyalgia groups. Both fibromyalgia groups reported similar number of pain areas (FAS), similar level of pain severity, and similar level of pain interference (BPI). Participants in the non-opioid FM group reported 5 to 19 (maximum) body areas with pain, average 24-h pain severity (5.3/10), and average pain interference (6.7/10). Likewise, opioid-FM participants reported 4 to 19 body areas with pain, average 24-h pain severity (5.8/10), and average pain interference (6.3/10). Thus, as validated by these reported pain variables, our sample of participants with fibromyalgia had widespread distribution and daily significance of pain.

3.4. Temporal summation characteristics across groups

In order to reduce variability due to individual differences in thermal sensitivity, we calibrated the stimulus temperature for each individual that evoked a pain rating of 5 on the VAS. The average individually calibrated stimulus temperature for each group was 46.8 ± 1.5°C for healthy controls, 45.4 ± 2.2°C for non-opioid FM, and 45.7 ± 2.0°C for opioid-FM [$F_{(2, 85)} = 4.505$, $p = 0.014$]. Although the participants in both fibromyalgia groups required lower temperatures to evoke a pain rating of 5 on the VAS, post-hoc tests identified significant group differences in the VAS = 5 temperature between only the healthy controls and non-opioid FM group ($p = 0.005$). Temperatures required to evoke a VAS of 5 were not significantly different for the healthy controls vs. opioid-FM group ($p = 0.039$) nor the non-opioid FM group vs. opioid-FM group ($p = 0.333$).

Across the 10 stimuli of the temporal summation test, pain ratings increased from 34.21 ± 23.30 to 63.39 ± 20.24 in the non-opioid FM group, from 24.13 ± 19.98 to 49.25 ± 25.12 in the opioid-FM group, and from 21.81 ± 16.16 to 48.61 ± 21.51 in healthy controls (Figure 2). Overall, within each group, peak pain ratings were significantly higher than initial pain ratings [healthy controls: $t_{(30)} = 8.84$, $p < 0.001$; non-opioid FM: $t_{(32)} = 10.578$, $p < 0.001$; opioid-FM: $t_{(23)} = 6.124$, $p < 0.001$]. This indicated an overall increase in pain across repetitive heat stimuli, as expected with temporal summation.

Across the 3 groups, significantly different responses were observed for both initial and peak pain ratings [initial: $F_{(2, 85)} = 3.399$, $p = 0.038$; peak: $F_{(2, 85)} = 4.448$, $p = 0.015$]. As indicated by post-hoc two-sample *t*-tests (Bonferroni corrected *p*-value, $p < 0.0167$), initial and peak pain ratings were significantly higher in the non-opioid FM group compared to the healthy controls [initial: $t_{(62)} = 2.464$, $p = 0.016$; peak: $t_{(62)} = 2.832$, $p = 0.009$] (Figure 3). However, initial and peak pain ratings were not significantly different in the opioid-FM group compared to the healthy controls (initial: $p = 0.333$; peak: $p = 0.333$) nor compared to the non-opioid FM group (initial: $p = 0.065$; peak: $p = 0.019$). Furthermore, as indicated by the ANCOVA with age as a covariate, initial and peak pain ratings were significantly different across groups [initial: $F_{(2, 85)} = 3.456$, $p = 0.036$; peak: $F_{(2, 85)} = 4.613$, $p = 0.013$].

Temporal summation was not significantly different across all 3 groups [$F_{(2, 85)} = 0.390$, $p = 0.678$] (Figure 4). A post-hoc ANCOVA with age as a covariate confirmed no significant difference in temporal summation across all 3 groups [$F_{(2, 85)} = 0.388$, $p = 0.680$]. Finally, an additional post-hoc analysis that excluded participants who did not exhibit temporal summation to repeated stimuli (one healthy control,

TABLE 2 Medication usage.

	HC ($n = 31$)	Non-opioid FM ($n = 33$)	Opioid-FM ($n = 24$)
Opioids	0	0	24
Codeine			1
Hydrocodone			2
Hydrocodone/acetaminophen (e.g., *Norco*)			7
Hydromorphone			1
Methadone			1
Morphine ER			2
Oxycodone			1
Oxycodone/acetaminophen (e.g., *Percocet*)			1
Tapentadol (e.g., *Nucynta*)			2
Tramadol			9
NSAID (e.g., ibuprofen)	0*	8	8
Acetaminophen	0	5	4
SNRI (e.g., duloxetine)	0	10	9
SSRI (e.g., fluoxetine)	0	6	3
Tricyclic Antidepressant (e.g., amitriptyline)	0	1	1
Other Anxiolytic (e.g., buspirone)	0	1	6
Antiepileptic (e.g., topiramate)	0	4	7
Triptans (e.g., sumatriptan)	0	5	2
SARI (e.g., trazodone)	0	2	5
NDRI (e.g., methylphenidate, bupropion)	0	5	3
Benzodiazepine (e.g., clonazepam)	0	7	3
Benzodiazepine-like (e.g., eszopiclone)	0*	1	3
Muscle Relaxant (e.g., cyclobenzaprine)	0	8	12
GABA Analogue (e.g., gabapentin)	0	5	9
CBD (e.g., oil, tincture)	0	1	2
Taking no medications	31	3	0

The number of healthy controls, non-opioid FM, and opioid-FM who were taking each class of medication is shown. *See exceptions in section 2.3 of text. HC, healthy controls; non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; GABA, gamma-aminobutyric acid; CBD, cannabidiol.

TABLE 3 Clinical, psychological, and behavioral variables.

	HC (n = 31)		Non-opioid FM (n = 33)		Opioid-FM (n = 24)		ANOVA	FM t-test
	n	Mean ± sd	n	Mean ± sd	n	Mean ± sd	p-Value	p-Value
Age	31	44.1 ± 13.1	33	37.7 ± 13.3	24	49.0 ± 9.7	0.004	0.003*
Depression (BDI)	30	2.4 ± 3.6	33	18.4 ± 9.6	24	17.6 ± 10.5	< 0.001	0.942
Behavioral inhibition system (BIS)	31	19.7 ± 3.2	33	21.1 ± 3.7	24	21 ± 4.7	0.302	0.999
Behavioral approach system (BAS)	31	39.7 ± 4.8	33	37.9 ± 5.6	24	38.7 ± 5.5	0.400	0.844
Pain severity (BPI)	–	–	31	5.3 ± 1.2	24	5.8 ± 1.3	–	0.197
Pain interference (BPI)	–	–	31	6.7 ± 2.0	24	6.3 ± 2.5	–	0.502
Global severity index (BSI)	30	2.5 ± 2.9	33	19.6 ± 10.3	24	16.3 ± 13.6	< 0.001	0.404
Total pain areas (FAS)	30	0.5 ± 0.9	33	13.1 ± 3.4	24	12.7 ± 4.1	< 0.001	0.864
Cognitive (FAS)	30	1.3 ± 2	33	9.7 ± 1.3	24	8.9 ± 1.9	< 0.001	0.252
Comorbid (FAS)	30	0.2 ± 0.5	33	2.2 ± 0.9	24	2.1 ± 0.9	< 0.001	0.891
Fatigue (PROMIS)	30	43.1 ± 6.8	33	67.1 ± 6.3	24	65.3 ± 8.0	< 0.001	0.597
Positive affect (PANAS)	30	36.3 ± 6.1	33	23.7 ± 7.2	24	26 ± 7.6	< 0.001	0.412
Negative affect (PANAS)	20	13.9 ± 3.9	33	21.2 ± 6.1	24	19.5 ± 7.5	< 0.001	0.540
Tension (POMS)	30	1.1 ± 1.4	33	4.4 ± 3.9	24	4.3 ± 4.5	< 0.001	0.981
Depression (POMS)	30	0.5 ± 1.2	33	2.9 ± 3.8	24	3.2 ± 5.0	0.008	0.970
Anger (POMS)	30	0.4 ± 0.9	33	2.2 ± 3.6	24	2 ± 3.3	0.024	0.973
Fatigue (POMS)	30	1.8 ± 1.6	33	10.4 ± 4.3	24	11.3 ± 4.8	< 0.001	0.648
Confusion (POMS)	30	2.5 ± 1.1	33	4.5 ± 3.1	24	5.0 ± 3.4	0.003	0.768
Vigor (POMS)	30	8.6 ± 4.2	33	3 ± 3.2	24	2.5 ± 2.1	< 0.001	0.818
Total mood disturbance (POMS)	30	−2.1 ± 6.1	33	21.5 ± 15.6	24	23.3 ± 19.4	< 0.001	0.884
State anxiety (STAI)	29	28.8 ± 6.9	32	39.8 ± 9.4	24	39.9 ± 12.4	< 0.001	0.999
Trait anxiety (STAI)	30	30.8 ± 7.2	32	44.4 ± 10	21	42.9 ± 10.2	< 0.001	0.811

Participant counts (n) for each measure may differ from the total number of participants because some participants did not complete all questionnaires. Healthy controls, for example, did not complete the BPI questionnaire to assess pain severity and impact on daily function, due to their eligibility requirement for no history of chronic pain. HC, healthy controls; non-opioid FM, fibromyalgia participants who were not taking opioids; opioid-FM, fibromyalgia participants who were taking opioids; BDI, beck depression inventory; BIS/BAS, behavioral inhibition system/behavioral approach system; BPI, brief pain inventory; BSI, brief symptom inventory; FAS, fibromyalgia assessment status; PROMIS, patient-reported outcomes measurement information system; PANAS, positive and negative affect schedule; POMS, profile of mood states; STAI, state–trait anxiety inventory; sd, standard deviation. p-values for the one-way analysis of variances (ANOVA) across the 3 groups are reported for significance of group effect. *Post-hoc* t-test p-values are reported for comparison between the non-opioid FM and opioid-FM groups; significance was evaluated at a value of $p < 0.0125$, corrected for multiple comparisons. *$p < 0.0125$.

one non-opioid FM, and one opioid-FM) also showed no significant differences in temporal summation [$F_{(2, 82)} = 0.369$, $p = 0.692$].

3.5. Explored clinical and psychological variables with temporal summation

Measured across all participants, STAI-trait anxiety ($r = 0.06$, $p = 0.606$, $n = 83$), BDI depression ($r = 0.17$, $p = 0.110$, $n = 87$), and PANAS negative affect ($r = 0.04$, $p = 0.692$, $n = 87$) were not significantly correlated with temporal summation (Table 4).

Measured across fibromyalgia groups (non-opioid FM and opioid-FM), average 24-h pain severity (BPI) was significantly negatively correlated with temporal summation ($r = -0.31$, $p = 0.021$, $n = 55$) (Figure 5). Pain severity was correlated with initial pain ratings, but did not survive Bonferroni correction ($r = 0.23$, $p = 0.043$, $n = 55$). We also evaluated the relationship between temporal summation and other variables (i.e., age, race, state anxiety, positive affect, total mood disturbance, average pain interference, total pain areas, fatigue, and global severity index) across all participants (see Supplementary material).

3.6. Explored relationships between opioid use and temporal summation

Within the opioid-FM group, after excluding one participant who did not demonstrate temporal summation ($n = 23$), temporal summation was not significantly correlated with opioid MME dosage, duration of opioid use, or timing of last opioid dose (dosage: $r = 0.19$, $p = 0.391$, $n = 22$; duration of use: $r = 0.26$, $p = 0.251$, $n = 21$; timing: $r = -0.14$, $p = 0.533$, $n = 21$). Opioid dosage was related to sensitivity-adjusted (VAS = 5) temperature. Specifically, higher opioid dosage correlated with increased sensitivity to heat stimuli ($r = -0.45$, $p = 0.036$, $n = 22$); however, this relationship did not survive Bonferroni correction at a value of $p < 0.0125$. All correlation results are shown in Table 5. We also compared temporal summation and each opioid variable within 2 subgroups: early- and late-phase opioid-FM participants (see Supplementary material).

4. Discussion

This was the first study to assess the experience of temporal summation in individuals with fibromyalgia who take long-term opioids. Temporal summation was evoked by administering repetitive stimuli at sensitivity-calibrated temperatures. As indicated by predetermined sensitivity-adjusted temperatures, the non-opioid FM group exhibited greater pain sensitivity compared to healthy controls. Meanwhile, healthy control and opioid-FM groups demonstrated comparable pain sensitivity. Notably, all groups demonstrated similar temporal summation magnitude. Thus, our hypotheses that non-opioid FM and opioid-FM participants would demonstrate greater heat pain sensitivity and temporal summation than healthy controls were not confirmed.

Importantly, from our correlation analyses across fibromyalgia groups, we identified a trend toward lower temporal summation in participants who reported higher pain severity (Of note, this finding was contrary to our hypothesized positive correlation between pain severity and temporal summation). Further, suggestive of opioid-related hyperalgesia, in the opioid-FM group, higher pain sensitivity was related to higher opioid dosage. As indicated by our results, chronic pain severity modulates sensitivity-adjusted measurement of temporal summation. Additionally, chronic opioid dosage may affect the extent to which chronic opioid use modifies central sensitization.

4.1. Abnormal pain processing in participants with fibromyalgia

Compared to opioid-FM and healthy control groups, the non-opioid FM group demonstrated higher initial pain ratings and higher peak pain ratings. Notably, the higher pain ratings occurred in the non-opioid FM group despite significantly lower sensitivity-adjusted stimulus temperatures.

All groups exhibited similar magnitudes of temporal summation. Consistently, with across-group comparisons using a percentage calculation for temporal summation, all groups still exhibited similar temporal summation magnitudes (see Supplementary Results 2.1). While we expected to identify greater temporal summation in our FM groups, our results mirror prior evidence for similar pain responses among healthy controls and individuals with fibromyalgia (Potvin et al., 2012; Bosma et al., 2016; Staud et al., 2021). Notably, these studies used repeated heat stimuli at sensitivity-adjusted temperatures, similar to the procedures we used in this study.

The opioid-FM group demonstrated VAS = 5 temperatures and temporal summation that were analogous to healthy controls. Pain characteristics of the opioid-FM group provide some support for potential analgesic effects of opioid agonists (Stein, 2016). Indeed, these findings parallel prior findings of reduced temporal summation in individuals with chronic pain who take clinically administered morphine sulfate (Price et al., 1983) or oxycodone (Suzan et al., 2013). These earlier studies, together with our findings in FM patients with chronic opioid use, suggest that opioid use may reduce some aspects of pain response in individuals with fibromyalgia.

Our opioid-FM and non-opioid FM groups had similar VAS = 5 temperatures and temporal summation. Compared to opioid-FM participants, we observed only a trend toward higher peak pain ratings among non-opioid FM. Thus, while not modulating pain sensitivity (i.e., individually sensitivity-determined temperatures), opioid use may modulate the upper bounds of central sensitization (i.e., peak pain ratings).

Distinct mechanisms may contribute to processing afferent pain signals at classically defined innocuous temperatures (i.e., < 45°C) vs. classically defined noxious temperatures (≥ 45°C). Prior studies of FM

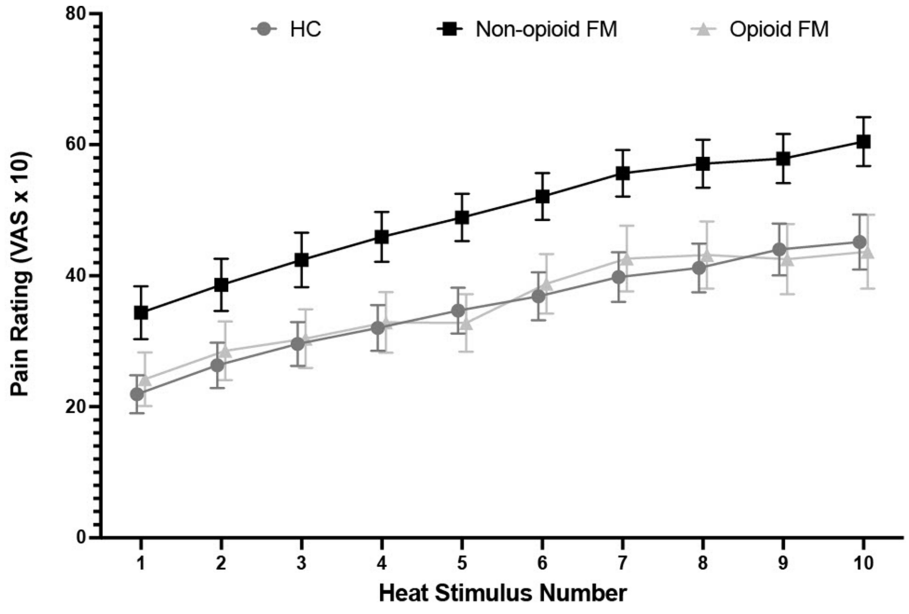

FIGURE 2
Pain rating distribution across 10 repeated heat stimuli by group. For the temporal summation test, participants received a stimulus tap for 2 s at a frequency of 0.33 Hz with an interstimulus interval of 1 s, and provided pain ratings after each stimulus. Stimulus temperature was calibrated to a VAS = 5 temperature that was determined for each individual participant before the experiment began. Error bars indicate standard error. HC, healthy controls; non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids.

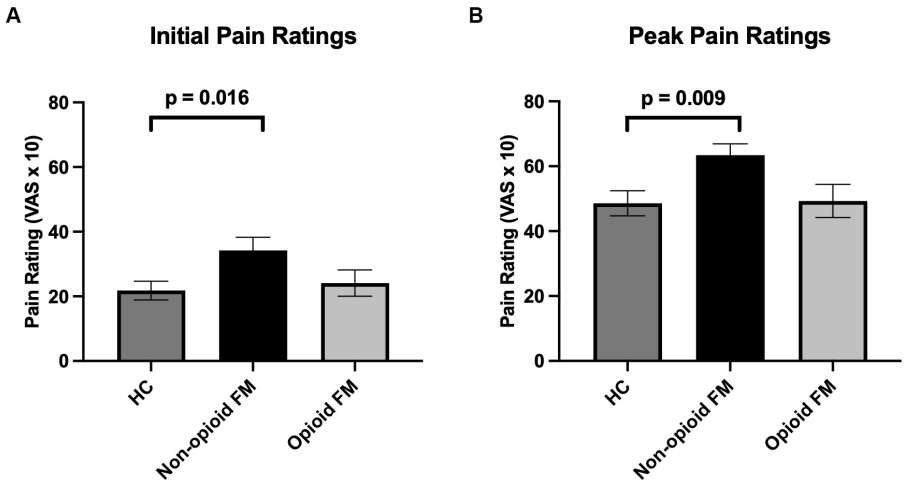

FIGURE 3
Mean initial and peak pain ratings across all participant groups. Pain ratings were analyzed separately for initial pain ratings (i.e., the pain rating after the first stimulus in the temporal summation stimulus series) and peak pain ratings (i.e., the highest reported pain rating to any stimulus from the 2nd to 10th stimulus in the temporal summation stimulus series). **(A)** Initial pain ratings were significantly different across groups, and post-hoc testing revealed that this difference was primarily due to significantly higher initial pain ratings in the non-opioid FM group compared to healthy controls. **(B)** For peak pain ratings, non-opioid FM participants exhibited significantly higher peak pain ratings compared to healthy controls. Error bars indicate standard error. HC, healthy controls; non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids.

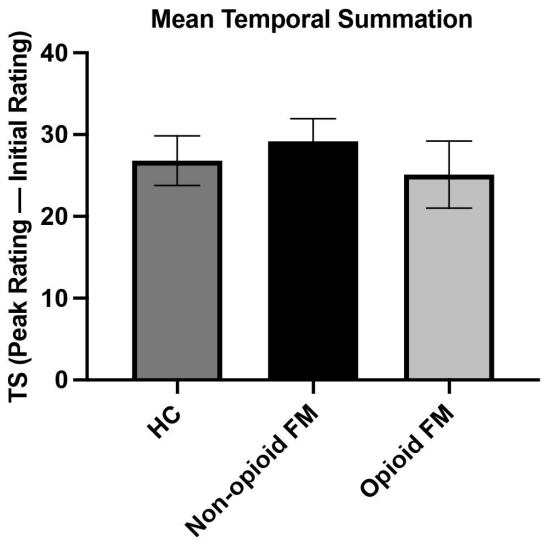

FIGURE 4
Mean temporal summation across all participant groups. For each participant group, temporal summation was calculated as the difference between peak and initial pain ratings. The average temporal summation of each group was as follows: healthy controls 26.81±16.89; non-opioid FM 29.18±15.85; and opioid-FM 25.13±20.10. One participant in each group did not experience summation (i.e., these 3 participants did not report increasing pain responses as the series of 10 stimuli progressed). Temporal summation did not differ significantly between the participant groups. Error bars indicate standard error. HC, healthy controls; non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids; TS, temporal summation.

have identified greater temporal summation at fixed temperatures of 49.5–52°C (Staud et al., 2001; Price et al., 2002). Therefore, in our supplementary analyses, we divided all participants into subgroups based on VAS = 5 temperature. After excluding participants with sensitivity-adjusted temperatures below 45°C, we still identified no group differences in temporal summation (see Supplementary material). The conflicting results may be due to the lower intensity stimuli used in our study.

Finally, because the stimulus number that evoked a "peak" pain rating varied by participant, it was challenging to accurately compare summation rates using the 1st, 5th, and 10th stimuli (see Supplementary material). Nonetheless, pain-rating fluctuations across repeatedly administered stimuli provide rich datasets of information. Future efforts should take advantage of these stochastic data to better quantify temporal summation using computational modeling.

4.2. Clinical and demographic factors associated with temporal summation

In contrast with our initial hypothesis and prior findings (Castelo-Branco et al., 2022), we observed a negative relationship between temporal summation and pain severity among both our non-opioid FM and opioid-FM groups. While this correlation only reached significance across combined FM groups, similar trends were evident in each FM group, with the opioid-FM group driving the relationship. Thus, regardless of opioid use, patients with the highest reported pain severity exhibited the least temporal summation. Due to the nature of VAS ratings, peak pain ratings may have been influenced by a ceiling effect, thereby decreasing calculated summation in individuals who reported higher pain ratings to the stimuli. Thus, even though we attempted to use personalized (i.e., sensitivity-adjusted) temperatures to measure temporal summation, temporal summation may be methodologically limited in patients who report high pain severity.

Of note, although we calibrated the stimulus temperature for each participant based on her VAS = 5 rating, many FM participants rated their pain to the initial temporal summation stimulus as VAS > 5. Pain ratings can be increased by psychological states such as expectation

TABLE 4 Clinical and psychological associations with temporal summation.

Variable	TS – All Participants (N = 88)		TS – FM (n = 57)		TS – Non-opioid FM (n = 33)		TS – Opioid-FM (n = 24)	
	Rho	*P*-Value	Rho	*P*-Value	Rho	*P*-Value	Rho	*P*-Value
Trait anxiety (STAI)	0.06	0.606	0.06	0.675	−0.04	0.816	0.12	0.605
Depression (BDI)	0.17	0.110	0.16	0.243	0.13	0.473	0.16	0.470
Pain severity (BPI)	–	–	−0.31*	0.021	−0.20	0.280	−0.45	0.029
Negative affect (PANAS)	0.04	0.692	−0.10	0.470	−0.12	0.512	−0.25	0.239

Spearman correlations across all participants compared clinical, psychological, and behavioral variables with temporal summation. Correlations were also assessed within each fibromyalgia subgroup (non-opioid FM and opioid-FM participants). Comparisons differed in the number of data values (± 5), due to some incomplete questionnaire forms during the study visit. A significant correlation between pain severity and reduced temporal summation was observed within the combined fibromyalgia cohort. Healthy controls did not complete the BPI questionnaire. Significance was observed at a Bonferroni-corrected p-value <0.025. *p < 0.025. FM, combined fibromyalgia cohort; TS, temporal summation; non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids.

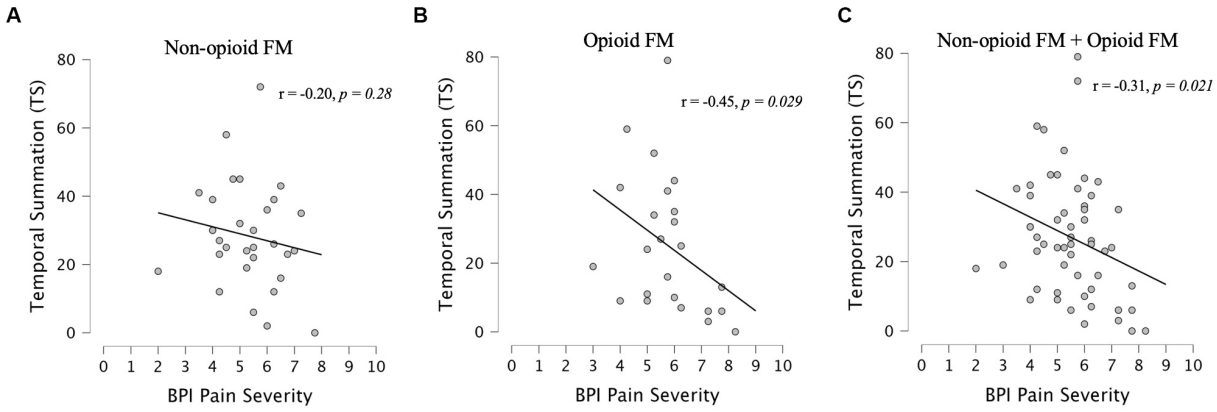

FIGURE 5
Correlations between pain severity and temporal summation. Spearman correlations between BPI pain severity and temporal summation were assessed within each fibromyalgia group [non-opioid FM **(A)** and opioid-FM **(B)**] and within the combined cohort of participants with fibromyalgia **(C)**. Healthy controls did not complete the BPI questionnaire. At a Bonferroni-corrected value of p <0.025, a significant negative correlation between BPI pain severity and temporal summation was observed in the combined cohort of fibromyalgia participants (r = −0.31, p = 0.021) – this indicated less temporal summation among participants with higher pain severity. Similar trends were observed in each fibromyalgia subgroup, but did not reach significance. Non-opioid FM, participants with fibromyalgia who were not taking opioids; opioid-FM, participants with fibromyalgia who were taking opioids.

TABLE 5 Opioid use characteristics and pain response.

Opioid variable	VAS = 5 Temperature			Temporal summation		
	n	Rho	*P*-value	n	Rho	*P*-value
Opioid dosage	22	−0.45	0.036	22	0.19	0.391
Duration of opioid use	21	0.01	0.966	21	0.26	0.251
Timing of last dose	21	−0.003	0.989	21	−0.14	0.533

Patterns of opioid use were evaluated against the experimental VAS = 5 temperature and temporal summation across all opioid-FM participants. One participant did not exhibit temporal summation; one participant did not report daily dosage; 2 participants did not report duration of use; and one participant did not report timing of last dose. Spearman correlations were assessed for significance at a Bonferroni-corrected threshold of p < 0.0125.

(Koyama et al., 2005), depression (Gorczyca et al., 2013), and state anxiety (Lacourt et al., 2014). While we did not assess expectations prior to the temporal summation test, neither depression nor state anxiety significantly correlated with temporal summation among our participant cohort. By including pain-free control groups with depression and/or elevated levels of state anxiety, future investigations may better differentiate influences of cognitive and affective states on pain sensitivity and temporal summation. Moreover, while our thresholding procedures (to determine VAS = 5 temperatures) were similar to those used by others (Chen et al., 2009; Staud et al., 2014; Bosma et al., 2016), increased initial ratings to VAS = 5 temperatures during temporal summation testing may have resulted from procedural differences between thresholding (i.e., 5 s stimulus duration) vs. the temporal summation test (i.e., 2 s stimulus duration).

4.3. Pain rating patterns potentially reflect opioid-related hyperalgesia

When receiving long-term opioid therapy, chronic pain patients show enhanced temporal summation and exacerbated hyperalgesia (Chen et al., 2009; Compton et al., 2020). While we did not identify enhanced temporal summation in our opioid-FM group, opioid dosage

was negatively correlated with timing of the last opioid dose (i.e., higher dosage correlated with more recent last opioid dose). This correlation potentially reflects greater susceptibility to pain during withdrawal, which may relate to more frequent opioid use. We noted trend relationships of (1) greater heat pain sensitivity (i.e., lower VAS = 5 temperature) with higher opioid dosage, and (2) greater temporal summation (when evaluated as a percentage change) with less recent last opioid dose (see Supplementary material). As suggested by these findings, pain hypersensitivity and development of opioid-related hyperalgesia may be most relevant at more frequent and higher opioid dosage.

4.4. Limitations

Our results should be considered with some limitations. First, all opioid-FM participants were taking multiple (i.e., opioid and non-opioid) medications and a variety of opioid formulations (i.e., immediate-release and/or extended-release). Such use of other medications with distinct analgesic and psychoactive profiles could differentially contribute to temporal summation changes; however, we were underpowered to analyze the effects of unique medications and/or different combinations of medications (see Supplementary material). Second, for our assessments of temporal summation, our ability to accurately identify sensitivity-calibrated temperatures could have been impacted by heightened pain anticipation and motivational deficits that occur in fibromyalgia. Among individuals with chronic pain, differences in pain anticipation and expectations can alter pain experience (Brown et al., 2014; Lindheimer et al., 2019). Individuals with fibromyalgia exhibit altered reward systems and motivation response (Loggia et al., 2014; Martucci et al., 2018). Therefore, future investigations of temporal summation should assess expectations and motivation directly. Third, due to the greater prevalence of fibromyalgia in females, our comparison focused on comparing temporal summation and heat pain sensitivity among females only. It is possible that sex-based pain perception and sensitivity differences could impact temporal summation in fibromyalgia (Ruschak et al., 2023). Lastly, while 3 different female experimenters collected data for the present study, they were trained together using the same instructional scripts and protocol; we did not detect significant differences in temporal summation between datasets collected by each experimenter (see Supplementary material).

5. Conclusion

Our study presents the first evaluation of temporal summation in individuals with fibromyalgia on long-term opioids. While we had expected individuals on opioids to exhibit enhanced temporal summation, instead, we observed similar temporal summation among all groups. In patients, temporal summation was influenced by chronic pain severity (i.e., ceiling effect) despite our use of sensitivity-adjusted temperatures. Additionally, even though higher pain sensitivity (i.e., lower sensitivity-adjusted temperature) occurred in non-opioid FM, pain sensitivity was similar between healthy controls and opioid-FM, suggesting at least partial thermal opioid analgesia in the opioid-FM group. Meanwhile, within the opioid-FM group, greater thermal pain sensitivity occurred with higher opioid dosage. Thus, as suggested by our results, individuals with fibromyalgia who take opioids do not demonstrate enhanced temporal summation, but they do demonstrate modest thermal analgesia. Further, such individuals on opioid therapy exhibit greater thermal pain sensitivity when taking higher opioid dosages. For the measurement of central sensitization in patients who take opioids, temporal summation relies on complex interactions between chronic pain severity, thermal pain sensitivity, and opioid dosage. Based on our results, future chronic pain research is needed to empirically investigate how opioid use impacts pain sensitivity and central sensitization.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Duke University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JB: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. MR: Formal analysis, Methodology, Software, Writing – review & editing. SP: Validation, Writing – review & editing. AB: Validation, Writing – review & editing. KM: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1275921/full#supplementary-material

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Response to experimental cold-induced pain discloses a resistant category among endurance athletes, with a distinct profile of pain-related behavior and GABAergic EEG markers: a case–control preliminary study

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Pain is a major public health problem worldwide, with a high rate of treatment failure. Among promising non-pharmacological therapies, physical exercise is an attractive, cheap, accessible and innocuous method; beyond other health benefits. However, its highly variable therapeutic effect and incompletely understood underlying mechanisms (plausibly involving the GABAergic neurotransmission) require further research. This case–control study aimed to investigate the impact of long-lasting intensive endurance sport practice (≥7 h/week for the last 6 months at the time of the experiment) on the response to experimental cold-induced pain (as a suitable chronic pain model), assuming that highly trained individual would better resist to pain, develop advantageous pain-copying strategies and enhance their GABAergic signaling. For this purpose, clinical pain-related data, response to a cold-pressor test and high-density EEG high (Hβ) and low beta (Lβ) oscillations were documented. Among 27 athletes and 27 age-adjusted non-trained controls (right-handed males), a category of highly pain-resistant participants (mostly athletes, 48.1%) was identified, displaying lower fear of pain, compared to non-resistant non-athletes. Furthermore, they tolerated longer cold-water immersion and perceived lower maximal sensory pain. However, while having similar Hβ and Lβ powers at baseline, they exhibited a reduction between cold and pain perceptions and between pain threshold and tolerance (respectively −60% and − 6.6%; −179.5% and − 5.9%; normalized differences), in contrast to the increase noticed in non-resistant non-athletes (+21% and + 14%; +23.3% and + 13.6% respectively). Our results suggest a beneficial effect of long-lasting physical exercise on resistance to pain and pain-related behaviors, and a modification in brain GABAergic signaling. In light of the current knowledge, we propose that the GABAergic neurotransmission could display multifaceted changes to be differently interpreted, depending on the training profile and on the homeostatic setting (e.g., in pain-free versus chronic pain conditions). Despite limitations related to the sample size and to absence of direct observations under acute physical exercise, this precursory study brings into light the unique profile of resistant individuals (probably favored by training)

allowing highly informative observation on physical exercise-induced analgesia and paving the way for future clinical translation. Further characterizing pain-resistant individuals would open avenues for a targeted and physiologically informed pain management.

KEYWORDS

physical exercise, endurance training, pain, cold pressure test, electroencephalogram, GABA, pain resistance, exercise-induced hypoalgesia

1 Introduction

Pain, especially chronic pain (CP), constitutes a major public health issue worldwide, affecting millions of individuals (Treede et al., 2015). Despite remarkable progress made in the development of analgesic drugs, about one third of pain-affected people do not experience satisfactory pain relief (Todd, 2017; Finnerup et al., 2018). This failure to obtain efficient pharmacological analgesia has brought interest and focus to numerous non-pharmacological methods such as mindfulness, hypnosis, physical therapy, etc. Among them, physical exercise (PE) is attractive, owing to its low cost, high accessibility and multiple beneficial effects on health, well beyond analgesia, e.g., in cardiovascular (Adams and Linke, 2019) and mental diseases (Schuch and Vancampfort, 2021), and in dementia (Jia et al., 2019 etc).

However, as for a number of other non-pharmacological methods, mechanisms counteracting pain in PE are not fully elucidated (Lesnak and Sluka, 2020). On the other hand, CP syndromes are usually not studied and/or managed according to their underlying pathological mechanisms (Vargas-Schaffer, 2010; Raffaeli et al., 2021). In fact, this mechanism-based approach of both CP syndromes and of analgesic therapies could be used as a strategy to improve pain management (Gallagher, 2006; Vardeh et al., 2016; Teixeira et al., 2021). Furthermore, by selecting the most responsive patients to therapies targeting a given pain mechanism, this "mechanism-targeted analgesia" would plausibly also reduce the variability of the therapeutic response.

Nevertheless, an appropriate study of mechanisms subtending the analgesic effect of PE in CP patients is subject to several challenges mainly related to patients' reluctance to move and in particular to perform physical activities, as a consequence of aberrant behavioral changes (e.g., fear-avoidance, pain catastrophizing) developed toward pain and, in several of them, toward movement (Vlaeyen and Linton, 2000; Crombez et al., 2012; Zale and Ditre, 2015). On the other side, acute exercise is known to consistently reduce experimental pain in healthy individuals, although this effect remains brief and highly variable (Naugle et al., 2012; Koltyn et al., 2014; Vaegter and Jones, 2020). Regular exercise practiced over a long period, in turn, modifies the ability of pain-free individuals to cope with experimentally induced pain, which results, for example, in higher pain tolerance (Ellingson et al., 2012; Sluka et al., 2018; Vaegter and Jones, 2020). Furthermore, the so-called exercise-induced hypoalgesia (EIH) is more consistent in healthy individuals than in CP patients (Ellingson et al., 2016; Rice et al., 2019; Vaegter and Jones, 2020) under experimental pain conditions. For all these reasons, studying how PE modifies experimental pain response in pain-free populations could be an interesting alternative method to better understand physiological mechanisms subtending the analgesic effect of PE.

The current literature suggests that the analgesic effect of PE goes beyond purely psychological aspects (Lima et al., 2017; Sluka et al., 2018). The Gamma-Aminobutyric Acid (GABA)ergic signaling is impaired in neuropathic pain animal models (Senba and Kami, 2020). Upon PE, glutamate acid decarboxylase (GAD), the GABA-synthetizing enzyme, is upregulated, which results not only in GABAergic restoration, but also in reduced experimental nociception (Kami et al., 2016). Moreover, it seems that regular PE would counteract CP also by promoting balance between excitatory and inhibitory neurotransmission through improved GABAergic neurotransmission (Fitzgerald and Carter, 2011), possibly through enhancement of descending inhibitory pathways (Zheng et al., 2021).

In addition to the above-mentioned direct effect, regular PE is suggested to counteract central sensitization (Nijs et al., 2014; Tan et al., 2022). The latter represents originally a physiological adaptive process protective against (acute) pain (Latremoliere and Woolf, 2009), consisting in lowered activation threshold and facilitated response to painful stimuli of nociceptive pathway components in the central nervous system. However, as pain persists, central sensitization may become maladaptive and participate to the transition from acute pain to CP (Latremoliere and Woolf, 2009; Lluch et al., 2014; Nijs et al., 2016; Ji et al., 2018; Guler et al., 2020). Clinically, pathological central sensitization manifests as allodynia and hyperalgesia, while pain-related behaviors lose their protective benefit and become aberrant, now contributing to perpetuate pain (Latremoliere and Woolf, 2009; Jensen and Finnerup, 2014). Mechanistically, there is an increased excitability and facilitation (resulting from the imbalance between excitatory and inhibitory neurotransmission) that reasonably allows hypothesizing on, among other mechanisms, a deficit in GABAergic neurotransmission (Curatolo et al., 2006; Latremoliere and Woolf, 2009; Li et al., 2019a; Comitato and Bardoni, 2021; Wang et al., 2021).

Overall, the potential (direct or indirect) involvement of the GABAergic neurotransmission in exercise-induced analgesia is interesting and even physiologically meaningful in many regards, notably given the key role played by GABA in nociception, pain regulation and modulation (Enna and McCarson, 2006; Barr et al., 2013; Du et al., 2017; Li et al., 2019b; Wang et al., 2021; Benke, 2022), but also taking into account the GABAergic reduction documented in CP patients (Barr et al., 2013; Teixeira et al., 2021; Makowka et al., 2023). Thus, the GABAergic system could be a suitable target in the mechanistic approach of EIH. However, little is known about the GABAergic correlates of exercise-induced modifications of experimental pain response in humans. Also, behavioral modifications

leading to the observed improvement in pain-copying strategies (i.e., higher tolerance; see above) are poorly documented.

This study aimed at investigating experimental pain response and its GABAergic correlates in pain-free individuals with different PE regimes, as an interesting strategy to study mechanisms underlying the analgesic effect of PE out of CP context (see above). The experimental cold-induced pain was preferred as the closest and most reliable experimental model mimicking clinical CP, owing to its tonic nature and engaged physiological mechanisms (Rainville et al., 1992; Gram et al., 2015; Hansen et al., 2017; Terrighena et al., 2017).

Despite controversial reports on the effect of intensive physical training (Monda et al., 2017; El-Sayes et al., 2020; Nicolini et al., 2021; Hendy et al., 2022), we expected an increase in the GABAergic input, based on the results obtained in EIH settings (Gramkow et al., 2020) (see above). Furthermore, we assumed that individuals with more intensive PE (e.g., endurance sports) would have a better response to cold-induced pain. We also made the assumption that some premorbid differences in indicators of central sensitization and other CP-related aberrant behaviors, could be associated to differences in pain response between the two training groups (Lentini et al., 2021). These differences would possibly feature responsiveness to exercise-induced analgesia or susceptibility to develop CP. Moreover, we assumed that these differences would be more prominent between highly trained and non-trained individuals.

2 Materials and methods

2.1 Study type and ethics

This monocentric case–control study submitted healthy highly trained athletes and age-adjusted non-trained controls to experimental pain induced by cold stimulation. The study fulfilled all the requirements of the Declaration of Helsinki and was approved by the Ethical Committee of Vaud under the reference 2019-00442. Each participant signed an informed consent prior to any investigation and received a financial compensation thereafter as requested by the Ethical Committee.

2.2 Participants

Participants were recruited mainly through public advertisements, social networks and clubs dedicated to endurance sports in the Canton of Fribourg (Switzerland). The primary eligibility criteria consisted in adult age (≥18 years), right-handed reported manual laterality (because of potential lateralization in pain-related brain function; Teixeira et al., 2021) and male sex (to mitigate potential data variability due to sex-based differences in pain perception; Fillingim, 2000; Kowalczyk et al., 2006). The decision to exclude women was therefore neither arbitrary nor discriminatory in this exploratory study aiming to detect group differences with the least bias as possible. The group of athletes was defined by ≥7 h of training per week in endurance sports (e.g., triathlon, running, or cycling) during the last 6 months before recruitment, whereas controls were engaged in PE or sports (to be distinguished from physical activity; Nicolini et al., 2021) for <2.5 h per week during the last 6 months before the experiments. Exclusion criteria were the presence of any type of pain, known or documented neurological dysfunction or lesions, severe sleep disorders (that could interfere with EEG results), significant cognitive or psychiatric disorders (which could prevent from appropriate evaluation), and limb ischemia, diabetes, respiratory and cardiovascular disease, Raynaud's phenomenon, or musculoskeletal lesions or diseases (in order to avoid symptom aggravation or complications due to cold stimulation; Pienimäki, 2002).

2.3 Data collection

2.3.1 General data

All recruited participants were individually submitted to a formal questionnaire to collect their personal and medical information, as well as details regarding their physical (sport) activity and sleep habits. The Insomnia Severity Index (ISI) (Omachi, 2011) was compiled to assess sleep difficulties, while the Hospital Anxiety and Depression (HAD) (Zigmond and Snaith, 1983) scale evaluated mood disorders (anxiety and depression more specifically).

2.3.2 The cold pressure test

The cold pressor test (CPT) was the procedure used to induce pain and determine pain threshold and tolerance. It was conducted at room temperature (at ~20°C) using two different Plexiglas trays (36 cm×23.5 cm×26 cm) further isolated with an external 3 cm-thick layer of ROOFMAT polystyrene to maintain a stable temperature as long as possible. The first tray was half-filled with warm water (water volume estimated to 8 L) from the tap (~32°C). The second tray was also half-filled, but with cold water from the tap (~4 L) and with crushed ice from a small container (~4 L volume). This procedure was efficient enough to maintain the cold-water temperature around the desired level of ~4°C, as shown through continuous monitoring (mean ± SD: 4.18 ± 0.49°C) using an electronic immersible thermometer (Traceble Excursion-trac Datalogging Thermometer). That way, we could avoid a variation of ≥2°C that could affect experimental results (Mitchell et al., 2004).

Prior to the experiment, the participant was allowed to briefly immerse his non-dominant (left) hand in the iced-cold water to feel the experimental temperature and avoid unwanted anxiety that could affect his response. Right before and after the CPT, the participant immersed his right-hand in warm water at 32°C (mean ± SD: 31.8 ± 0.92°C) during 2 min for procedure standardization before cold-induced pain and for his comfort during recovery (see below).

The CPT procedure (illustrated in Figure 1) properly started as the participant immersed his right hand in cold water up to his wrist. His hand had to be positioned horizontally and relaxed in water without touching the bottom of the tray. To avoid water warming up around the hand, the participant had to gently and slowly move his hand while keeping it in a horizontal position. He was instructed to inform the investigator as soon as he began to experience pain. At that moment, he had to verbally rate the intensity and the unpleasantness level of the perceived pain, giving two separate numbers out of 10 on a scale from 0 to 10 using the numeric rating scale (NRS) displayed in front of him on the wall. This exact experimental step (i.e., the switch from cold to pain perception) represented the participant's pain threshold (THR). As the experiment evolved, pain level increased, and the participant was required to remove his hand from the cold water when pain

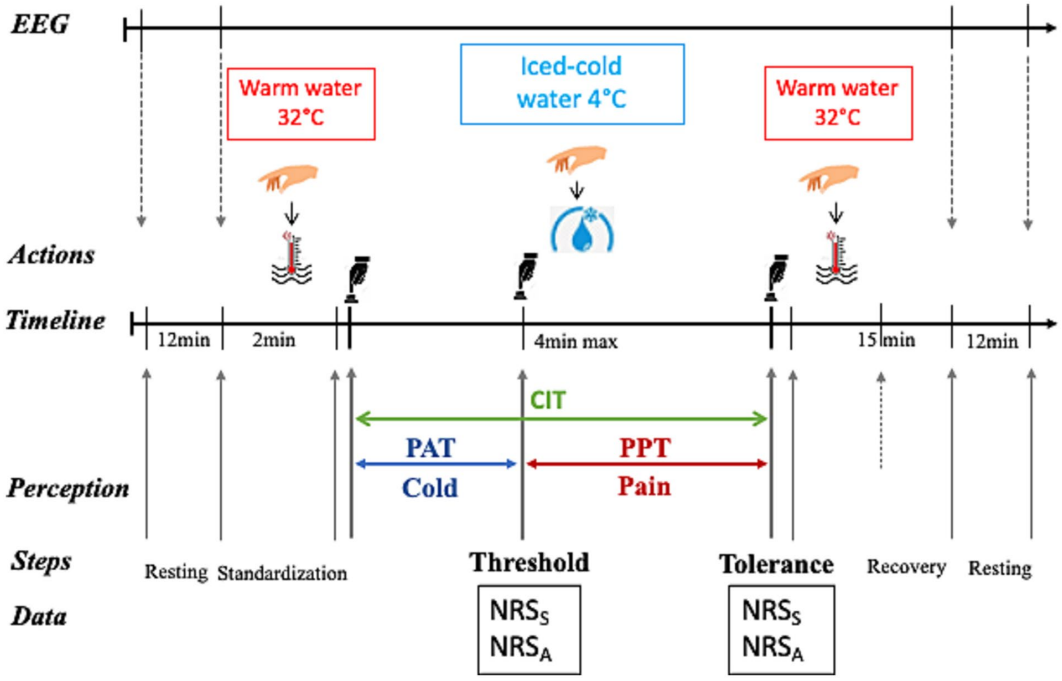

FIGURE 1
The cold pressure test (CPT) procedure. A continuous EEG recording was performed during the whole procedure (black right-oriented arrow on top of the figure), as well as an additional resting-state recording before and after the CPT. After 2 min of warm water immersion at 32°C (red thermometer in water), the participant immersed his right hand in iced cold-water at 4°C (blue water drop with ice) for a maximal duration of 4 min and thereafter again in warm water to recover for 15 min. The time elapsed between cold water immersion and the appearance of pain (pain threshold, THR) corresponded to the pain appearance time (PAT, blue horizontal line with double arrow), whereas the time between pain appearance and the maximal pain (pain tolerance, TOL; when the participant was required to remove his hand from the cold water) represented the pain perception time (PPT, blue horizontal double arrowed line). The cold immersion time (CIT, green double arrow) was the sum of PAT and PPT. The respective levels of pain intensity (indicating the sensory pain, S) and unpleasantness (assessing the affective pain, A) were separately measured using the numerical rating scale (NRS) at THR and at TOL. Key experimental step timing was recorded using E-Prime 3.0-generated triggers initiated by the investigator (black hand above the button) upon the participant's indications. The illustrating cartoons (Right hand, Hot water, Cold water and Black hand pushing the button) were dowloaded as freely available images from the web links in September 2021.

became "unbearable." After cold-water removal, he immersed his hand in warm water for his comfort and to recover from pain sensation. This maximal pain time-point represented the participant's pain tolerance (TOL). Again, as for the THR, the participant was required to quantify his pain intensity and unpleasantness levels at that moment. The maximal cold-immersion time allowed was 4 min, in order to prevent and limit the risk of tissue damage (MacLachlan et al., 2016). However, the participant was left blind to this predetermined maximal duration to avoid targeting. Each experimental step (start, cold-water hand immersion, pain appearance, hand removal time from cold water, end) was precisely recorded using the E-Prime 3.0 program (Psychology Tools, Inc., Pittsburgh, PA, USA) though triggers controlled by the investigator upon the participant's indications.

Response to pain stimulation was documented and interpreted as following. The level of pain intensity and unpleasantness (separately quantified using the NRS, see above) assessed, respectively, the participant's sensory and affective dimensions of pain. The latter represents the emotional experience associated to- and in response to pain (Melzack, 1975, 1987). The THR was indicated by pain intensity and unpleasantness at the moment when cold perception switched to pain perception, as well as by the time elapsed between cold-water immersion and appearance of pain (referred to as pain appearance time). Pain intensity and unpleasantness at THR and pain appearance time were considered as indicators of the sensitivity to pain stimulation (or pain sensitivity). The pain perception time was defined as the time duration between pain onset and hand removal from cold water and represented an estimate of resistance to pain (or pain resistance). The sum of pain appearance time and pain perception time represented the cold immersion time.

2.3.3 Pain-related behavioral data

Although this study exclusively investigated pain-free persons, we were interested, as stated above, in detecting some premorbid traits in indicators of pain-related behaviors, which would expectedly influence response to experimental pain. Conceptually, they would constitute premises of- or indicate some susceptibility to develop maladaptive behaviors toward pain in CP contexts. In addition to central sensitization (largely discussed above), catastrophizing beliefs and fear of pain were targeted, knowing also that they can affect experimental pain experience (Sullivan et al., 2001; George et al., 2006), especially in highly trained individuals (Lentini et al., 2021). In absence of validated tools to assess these behavioral features in pain-free populations, we used, respectively, the Central Sensitization Index (CSI) (Neblett et al., 2013), the Pain Catastrophizing Scale (PCS) (Sullivan et al., 2001; Lentini et al., 2021) and the Fear of Pain Questionnaire (FPQ-9) (McNeil et al., 2018). Participants were submitted to these

standard questionnaires on the experimental day, prior to the CPT procedure.

2.3.4 Electroencephalographic recordings

Brain GABAergic activity can be reliably measured by electroencephalography (EEG) (Barr et al., 2013), through fast oscillations (β (13–30 Hz) and ɤ (30–100 Hz) waves); the latter being mainly driven by inhibitory interneurons (Gaetz et al., 2011; Christian et al., 2015; Baumgarten et al., 2016). In this study, we analyzed β EEG activity, which is more reliably measured by scalp EEG than deeply generated ɤ activity (Teixeira et al., 2021) and is related to GABA levels in the somatosensory cortex (Baumgarten et al., 2016; Teixeira et al., 2021).

Thus, a continuous high-density (64 electrodes) resting-state EEG recording (BIOSEMI Active Two recording system) was conducted at baseline before and after the whole experiment in three randomized conditions lasting 3 min each: seated with eyes open, seated with eyes closed and standing with eyes closed (see Figure 1). In addition, the EEG recording took place throughout the experiment, without other tasks than instructions given to participants (e.g., hand immersion, hand removal, etc). The EEG recording was performed at a sampling rate of 1,024 Hz, referenced to the common mode sense-driven right leg (CMSDRL) ground placed on each side of the POz electrode.

2.4 Data analysis

2.4.1 Electroencephalography preprocessing and spectral analysis

Automated EEG data preprocessing was performed offline, using a customized MATLAB toolbox (EEGpalCS), including functions from the EEGLab Toolbox (Delorme et al., 2011). First, raw EEG data were bandpass filtered by a high pass of 1 Hz and a low pass of 60 Hz using Finite Impulse Response (FIR) filters (Winkler et al., 2015). Automated artefacts rejection algorithms (EEGlab plugin) were applied to remove sinusoidal noise stemming from alternating current powerline fluctuation [CleanLine (Mullen, 2012)][1] or high amplitude eye movements, muscle artefacts, and electrode drifts (ASR; Mullen et al., 2015; Chang et al., 2018). Bad EEG channels were excluded by visual inspection using the Cartool software (Brunet et al., 2011) for data visualization (limited to a maximum of seven rejected electrodes). Then, selected channels were interpolated using spherical splines (Perrin et al., 1989) [median (IQR) = 3.1 (24.7) % interpolated electrodes]. Obtained preprocessed data were re-referenced to the average of all electrodes and segmented in 1-s epochs using EEGpalCS. All epochs containing one channel or more above the threshold were automatically rejected from the final analysis to eliminate remaining artefacts. This study set the artefactual signals threshold to 100 μV according to our laboratory standard.

Finally, retained epochs were recomputed into the frequency domains using the Fast Fourier Transform (FFT) with a frequency resolution of 1 Hz. The β frequency domain (13–30 Hz) constituted the main focus of interest in this investigation (see above). In addition, in this exploratory study, we also analyzed the δ (2–4 Hz) and α (7–12 Hz) frequency ranges to increase the specificity of our observations regarding GABAergic markers (Pinheiro et al., 2016; Mussigmann et al., 2022). The spectral power of each frequency was divided by the average power of all epochs for that given frequency to remove 1/f noise. Frequency bands were obtained by averaging all frequency bins within, respectively, each frequency range. The global power spectrum (GPS, i.e., the frequency power within the band averaged across all electrodes) constituted the quantitative measure of the power for a given frequency band.

The β frequency domain was previously shown to have two power peaks in chronic neuropathic pain patients (Teixeira et al., 2021), yielding two sub-bands; namely the high (20–30 Hz) and the low (13–20 Hz) β ranges (respectively abbreviated as Hβ and Lβ). Because this study was conducted in relation with CP and using the same analysis paradigm, we similarly discriminated the two β sub-bands in our analyses.

In order to evaluate the individual GPS corresponding to different sensory perceptions (i.e., warm, cold or pain) during the experiment, the GPS of each participant was averaged, respectively, over the total duration of each perception in each frequency domain. For each frequency domain, the participant's GPS at threshold was computed as the mean value within the time interval between 2 s before and 2 s after the threshold, considering that there could be a small error between the real pain appearance time and when the participant indicated pain appearance to the experimenter. At TOL, because the movement of hand removal from the cold water induced an important EEG artefact, we considered the mean GPS during the 4 s of clean recording closest to the hand removal time.

2.4.2 Statistical analyses and power estimation

Statistical analyses were conducted using the Jamovi Statistical Software (version 2.2.5; Sydney, Australia) and RStudio [Version 2023.06.1 + 524 (2023.06.1 + 524)]. Clinical data were all quantified as mean ± SD and analyzed with parametric statistical tests for easiness of interpretation, although some of them were not normally distributed. In contrast, the CPT-related psychophysical data and all EEG data displayed non-normal distribution and were thus presented as median (IQR) and analyzed using non-parametric tests.

The significance threshold was set at $p < 0.05$ (two-tailed; 95% CI). Differences in clinical data between groups were assessed by an independent sample *t*-test (simple comparison between groups) or multivariate analysis of variance (ANOVA; when comparison between groups implied more than one condition). Differences in CPT psychophysical data were assessed using the Welch's t-test, while differences within and between groups in EEG data were assessed using repeated measures multivariate ANOVA. The Tukey post-hoc analysis corrected for multiple comparisons. In this exploratory study, in order to complete data interpretation beyond statistical significance, the effect size was further computed in most comparative analyses using the Cohen's *d* [small effect if $d \sim 0.2$, moderate effect if $d \sim 0.5$ and large effect if $d \geq 0.8$; (Lakens, 2013)]. In order to refine the analysis of EEG data, we also computed differences between different perceptions (normalized as % to the value at pain perception) and between THR and TOL values (normalized as % to the TOL value). Correlations were assessed employing the Spearman Rho (r_s) correlation coefficient (two-tailed) and correction for multiple testing performed by the Benjamin Holm (BH) procedure, while the effect size was evaluated as

1 https://www.nitrc.org/projects/cleanline

follows: small correlation if $-0.5 < r_s \leq 0$ or $0 \leq r_s < 0.5$, large correlation if $-1.0 < r_s \leq -0.5$ or $0.5 \leq r_s < 1.0$ (Akoglu, 2018).

When significance vanished upon multiple testing corrections in above-mentioned inferential analyses, only results with large size effect were mentioned, and considered for further discussion in coherence with persistently significant data.

It was challenging to precisely perform an *a priori* sample size estimation in such an exploratory study investigating both clinical and EEG data. Indeed, while one pain study with similar design (between and within comparisons, correlations), assessing clinical and psychophysical parameters (e.g., pain intensity and unpleasantness) related to exercise-induced hypoalgesia, calculated a total sample size of 26 (13 per group) for moderate to high power (Cohen's *d* of 0.5, two-tailed alpha of 0.05 and a power of 0.8) (Peterson et al., 2019), a longitudinal study of electrophysiological indicators of exercise-induced cortical excitability yielded a sample of 22 participants for statistical similar power (Lulic et al., 2017; El-Sayes et al., 2020).

3 Results

3.1 General demographic, clinical and EEG characteristics

In total, 55 participants were screened and enrolled, among which one athlete was secondarily excluded as found to be ambidextrous (Figure 2). The primary analysis was thus performed on 27 athletes and 27 non-athletes (mean ± SD age 35.4 ± 8.43 years and 41.6 ± 10.2 respectively). Further specific comparative analyses were conducted between two sub-groups of 13 and 19 participants (see below for more information).

An overview of general demographic and clinical characteristics of the participants can be found in Table 1 (top part). Athletes devoted nearly ten times more hours per week to their training compared to non-athletes ($p < 0.001$, large effect size), were significantly older ($p = 0.019$, moderate effect size) and had a lower body mass index (BMI) ($p < 0.001$, large effect size). The HAD_A and HAD_D subscales and ISI scores were not significantly different between the two groups and remained within normal ranges. Pain-related behavior scores (CS, FPQ-9 and PCS) were all lower in athletes, but only the FPQ-9 reached statistically significant difference ($p = 0.006$, large effect size).

Four participants were excluded from EEG analyses because of poor data quality during the pre-processing step (Figure 2). The remaining 26 athletes and 24 non-athletes were comparatively analyzed, focusing on data collected in standing position with eyes closed at baseline (i.e., before hand immersion) and during warm, cold and pain perceptions. Our analysis indicates no significant difference between the two groups at any frequency, at baseline and during all perceptions (data not shown). In contrast, a significant interaction was noticed in the Lβ frequency band ($p = 0.026$, small effect size) between cold and pain perceptions when comparing the two groups, with non-significant post-hoc Lβ and Hβ GPS *decrease*, *unchanged* δ GPS, but a significant α GPS *increase* ($p = 0.038$, small effect size) between perceptions in athletes. In non-athletes, there was a power *increase* at all frequencies, reaching statistical significance within the Lβ ($p = 0.030$, small effect size) and the *α* ($p = 0.022$, moderate effect size) ranges (Figure 3).

3.2 The unique profile of resistant athletes

During the CPT, a category of participants did not experience unbearable pain within the maximal limit of immersion time (4 min). They were qualified as "resistant" for this reason and were requested to remove their hands from the cold water before experiencing maximal pain for safety reasons, according to the protocol (see methods). Interestingly, they were more commonly represented among athletes (48.1%; $n = 13$) than among non-athletes (18.5%; $n = 5$). Because the number of "resistant" non-athletes was too small, they were excluded in the remainder analyses. In order to take into consideration the potential ability of resistant athletes (RA) to exceed the artificially settled maximal immersion time (which probably introduced a biasing "ceiling effect"), we considered their clinical and EEG data separately from those of non-resistant athletes (NRA) and of non-resistant non-athletes (NRNA) (Figure 2).

According to primary analyses, the most significant differences were noticed between RA and NRNA, which oriented the focus of subsequent analyses on them (data from NRA are shown in the Supplementary material).

3.3 Comparative analysis of RA and NRNA profiles

The new comparative analysis between RA ($n = 13$) and NRNA ($n = 22$) found similar trends as for the general comparison between athletes and non-athletes (see above) regarding all clinical parameters, except age (which, despite similar results, was now non-significantly different) (Table 1, bottom part).

At baseline, there was again no statistically significant differences in EEG markers (eyes closed, standing position) at all perceptions between RA and NRNA (see Supplementary Table 1). However, significant interactions were found for Hβ ($p = 0.031$, small effect size) and Lβ ($p = 0.026$, small effect size) GPS, when comparing the two groups during cold and pain perceptions (Table 2, top part), with no significant post-hoc *decrease* in RA and *increase* in NRNA Hβ GPS, but significant *increase* in Lβ GPS for NRNA ($p = 0.030$, small effect size) and non-significant *decrease* for RA (Figure 4). An interaction was also noticed in the δ domain (non-significant post-hoc differences), but not in the α band (where, though, a significant *increase* was observed in RA between cold and pain perception; $p = 0.045$, moderate effect size) (Figure 4). It should be finally noted that there existed a "within" effect related to the experimental step (i.e., from cold to pain perception) in the α frequency range (Table 2, top part).

The same types of analyses were conducted between the transition from cold to pain perception (THR) and the subsequent maximal pain level (TOL) in NRNA, or the safety limit of 4 min in RA (Table 2, bottom part). At THR, NRS intensity and unpleasantness were rated at the same level in both NRNA and RA (3.0/10 and 4.0/10, respectively; Table 3). Likewise, at TOL, NRS unpleasantness level was equal (8.0/10) in both groups, while RA experienced slightly but significantly *lower* NRS intensity than NRNA ($p = 0.023$, moderate to large effect size) (Table 3). Finally, pain appearance time and pain perception time were both much *longer* in RA, the difference reaching significance however only for pain perception time ($p < 0.001$, large effect size). Comparison of EEG markers between THR and TOL in RA and NRNA showed

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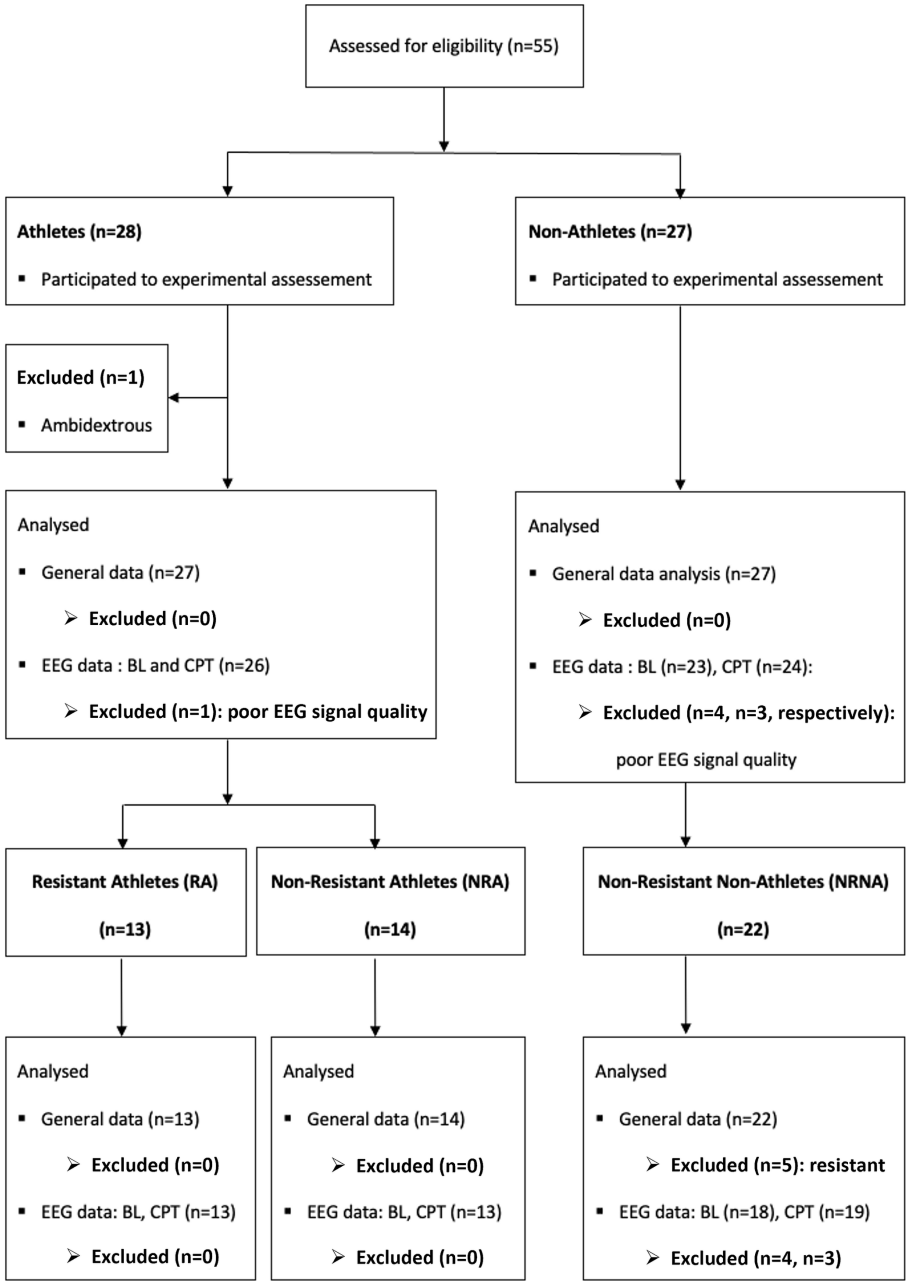

FIGURE 2
Overview of the selection procedure for participants and data at different analysis steps. In total 55 participants were screened (28 athletes and 27 non-athletes). One athlete was secondarily excluded from the primarily analysis because he was ambidextrous. In addition, 4 participants (1 athlete and 3 non-athletes) were excluded from the EEG analysis and one more non-athletes from the EEG analysis at baseline (BL) because of the poor quality their recordings. For the specific analysis of the three categories related to pain resistance (RA, NRA and NRNA), 5 resistant non-athletes were excluded because of the small sample and the same participants excluded from the EEG data analysis belonged, respectively, to the non-resistant athlete (NRA, $n = 1$) and to the non-athletes [NA, baseline (BL): $n = 4$, cold pressure test (CPT): $n = 3$] groups.

similar trends as between cold and pain perceptions (Figure 4). Accordingly, there was an interaction for Lβ ($p = 0.015$, moderate effect size) and Hβ ($p = 0.014$, moderate effect size) GPS (Table 2, bottom part), with this time a significant *decrease* of Hβ GPS in RA ($p = 0.039$, large effect size), but still non-significant slight decrease of Lβ GPS, upon post-hoc analysis. Despite absence of interaction in other frequency ranges, a significant *increase* of α GPS ($p = 0.037$, moderate effect size) was noticed in NRNA (Figure 5). The within effect was again present in the *α* band (Table 2, bottom part).

3.4 Associations between clinical indicators and EEG markers of RA and NRNA

It was interesting to comparatively test if and how clinical indicators (especially pain-related behavioral and CPT response indicators) were correlated between them and with EEG markers (especially GABAergic biomarkers) in RA and NRNA (Figure 6). Although there was a large set of significant correlations noticed in the two groups, only some of them persisted after correction for multiple testing (BH method, see the

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TABLE 1 Participants' demographic and general characteristics.

	A (n = 27)	NA (n = 27)	p	Cohen's d
Age [years]	35.4 (8.43) (20–53)	41.6 (10.2) (23–58)	0.019	0.658
BMI [kg/m^2]	22.7 (2.43) (17.9–27.1)	26.4 (3.44) (20.6–37.5)	<0.001	1.258
Hours of training [h/week]	11.4 (0.94) (8.0–20.0)	1.34 (3.21) (0.0–2.5)	<0.001	4.231
HAD_A [/21]	6.00 (2.66) (0–11)	6.41 (3.59) (1–18)	0.637	0.129
HAD_D [/21]	2.22 (1.83) (0–6)	2.89 (2.59) (0–9)	0.280	0.297
ISI [/28]	7.59 (5.23) (0–18)	7.04 (5.35) (0–18)	0.701	0.105
Sleep duration [h/night]	7.97 (0.95) (6.0–9.50)	7.69 (0.66) (6.0–9.0)	0.203	0.350
CSI [/100]	19.9 (8.74) (1–35)	22.0 (11.3) (3–49)	0.446	0.209
FPQ-9 [9 to 45]	18.6 (3.86) (10–27)	22.4 (5.60) (9.0–34)	0.006	0.785
PCS [/52]	9.56 (4.71) (2–19)	11.6 (8.67) (1–28)	0.280	0.297

	RA (n = 13)	NRNA (n = 22)	p	Cohen's d
Age [Years]	35.2 (9.54) (20–53)	41.4 (10.8) (23–58)	0.099	0.595
BMI [kg/m^2]	22.5 (2.03) (19.6–26.8)	26.1 (2.84) (20.6–33.2)	<0.001	1.401
Hours of training [h/week]	11.8 (2.67) (8–15)	1.26 (1.5) (0–2.5)	<0.001	5.970
HAD_A [/21]	5.85 (2.82) (2–11)	6.64 (3.62) (2–18)	0.505	0.236
HAD_D [/21]	2.15 (1.68) (0–6)	3.27 (2.68) (0–9)	0.185	0.474
ISI [/28]	6.54 (4.91) (0–16)	7.14 (5.24) (0–18)	0.741	0.117
CSI [/100]	19.0 (7.43) (6–31)	23.1 (11.5) (3–49)	0.261	0.400
FPQ-9 [9 to 45]	18.8 (2.51) (13–23)	22.8 (5.97) (9–34)	0.030	0.795
PCS [/52]	9.54 (4.59) (2–18)	12.7 (8.58) (1–28)	0.226	0.432

Data are shown as mean (SD) and values below represent data range (min - max). The p values result from an Independent Sample Students' t-test and displays differences between Athletes (A) and Non-Athletes (NA) (upper part), as well as between Resistant-Athletes (RA) and Non-Resistant Non-Athletes (NRNA) (lower part). Numbers in bold display statistical significance ($p < 0.05$, 95% CI). The effect size was evaluated with the Cohen's d as following: small effect ($d \sim 0.2$), moderate effect ($d \sim 0.5$) and large effect ($d > 0.8$). BMI, Body Mass Index; HAD, Hospital Anxiety and Depression scale for anxiety (HAD_A) and for depression (HAD_D); ISI, Insomnia Severity Index; CSI, Central Sensitization Index; FPQ-9, Fear of Pain Questionnaire (9 Items); PCS, Pain Catastrophizing Scale.

Methods section). Residual significant correlations showed all a large effect size and a $p < 0.001$. We primarily concentrated on them (unless otherwise specified, the effect size and the significance level will be the above-mentioned ones). RA displayed a *negative* correlation between pain appearance time and pain perception time ($r_s = -1.0$) and between Lβ GPS at THR and NRS intensity at TOL ($r_s = -0.780$, $p = 0.002$). NRNA group showed significant *positive* correlations between CSI and HAD_A ($r_s = 0.740$), CSI and HAD_D ($r_s = 0.658$), and between HAD_A and HAD_D ($r_s = 0.599$, $p = 0.003$). In addition, a *positive* correlation existed between cold immersion time and pain perception time ($r_s = 0.887$); and between NRS intensity and unpleasantness at THR ($r_s = 0.732$) and at TOL ($r_s = 0.723$).

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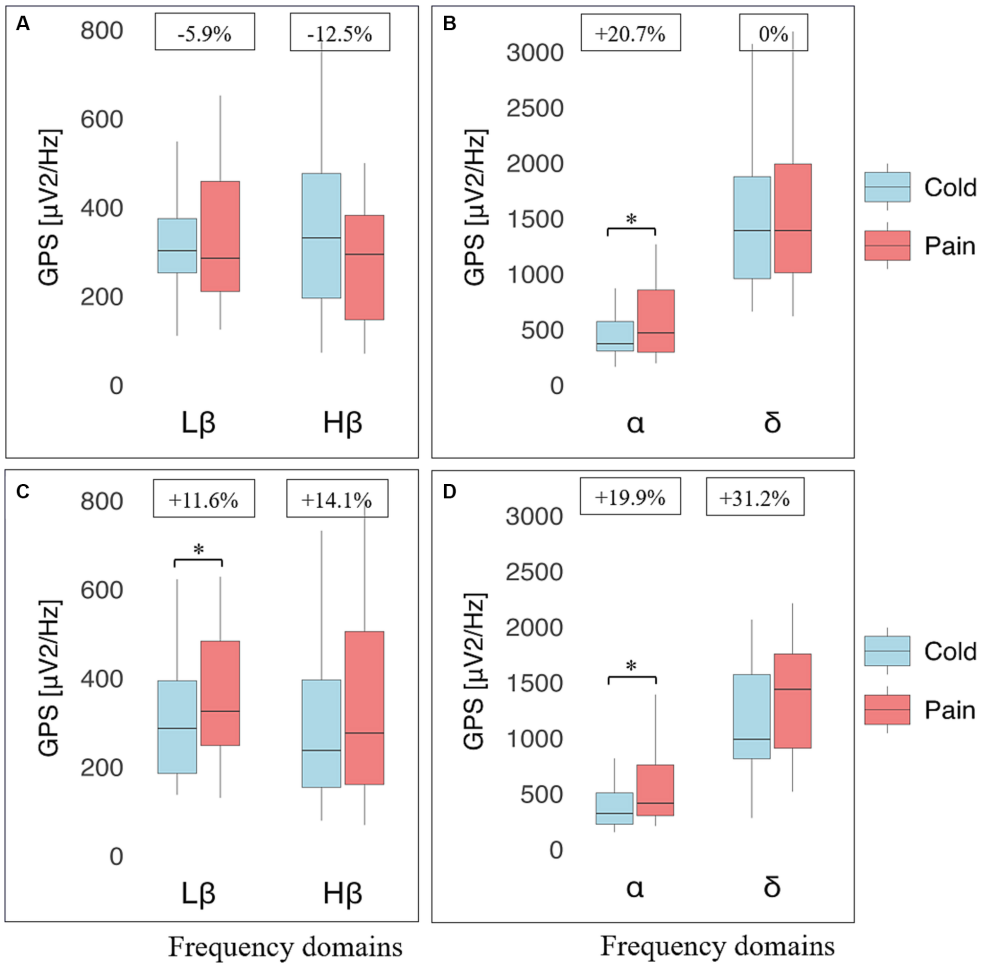

FIGURE 3
Electroencephalographic (EEG) global power spectra (GPS) according to frequency bands during cold and pain perceptions in athletes and non-athletes. GPS (in $\mu V^2/Hz$) are presented on the y-axis as median (horizontal black line) and interquartile range (IQR, upper and lower edges of the box), while grey whiskers indicate minimum and maximum values. GPS during cold and pain perceptions are, respectively, shown in light blue and light red colors. Different frequency bands are represented on the *x*-axis: Low Beta (Lβ; 13-20 Hz) and High Beta (Hβ; 20–30 Hz) in A and C graphs; Alpha (α; 8–12 Hz) and Delta (δ; 2–4 Hz) in B and D graphs. The numbers at the top indicate GPS decrease (–) or increase (+) between cold and pain in percentage (%) normalized to the value during pain perception. Athletes (top panels) showed a decrease in GABAergic markers **(A)**; respectively from 302 (122) to 285 (248) $\mu V^2/Hz$ (Lβ, $p = 1.0$) and from 331 (281) to 294 (235) $\mu V^2/Hz$ (Hβ, $p = 0.318$). In contrast, an increase was observed in the α band (from 371 (266) to 468 (560) $\mu V^2/Hz$; $p = 0.018$) whereas δ GPS remained unchanged (from 1390 (918) to 1,390 (979); $p = 0.912$) **(B)**. Non-athletes (bottom panels) displayed a systematic increase in all frequency bands: Lβ (from 287 (209) to 325 (235) $\mu V^2/Hz$; $p = 0.014$) and Hβ (from 237 (242) to 276 (344) $\mu V^2/Hz$; $p = 0.903$) **(C)**; α (from 317 (281) to 396 (335) $\mu V^2/Hz$; $p = 0.010$) and δ (from 989 (756) to 1,438 (847); $p = 0.059$) **(D)**. *Indicates significant results ($p < 0.05$, 95% CI) from a repeated ANOVA and a Tukey tested for post-hoc differences, while at the same time correcting for multiple testing.

In order to allow a broader discussion in such an exploratory study, statistically significant correlations with large effect size, that lost significance after BH correction for multiple testing, were secondarily taken into consideration (Figure 6). In this respect, in the RA group, the PCS was *negatively* correlated with the weekly training duration and HAD_A, while the latter exhibited a *positive* correlation with ISI. During the CPT, a *negative* correlation was observed between pain appearance time and NRS unpleasantness level and a positive correlation between pain perception time and NRS unpleasantness, both at TOL. A *negative* correlation was found between Lβ GPS at THR and PCS; between Lβ GPS and NRS intensity, both at TOL; as well as between Hβ GPS at THR and both PCS and NRS intensity at TOL. Conversely, a *positive* correlation was observed between α GPS during cold perception and NRS unpleasantness at THR, and between δ GPS during pain perception and PCS. In the NRNA group, a *negative* correlation existed between pain perception time and HAD_A, while pain appearance time *positively* correlated with NRS unpleasantness at THR. In addition, a *positive* correlation was observed between Hβ GPS at THR and FPQ-9, as well as between α GPS during cold perception and ISI; and between α GPS at THR and ISI. Additionally, a *positive* correlation was detected between α GPS during pain perception and at TOL, and the self-reported sleep duration per night.

Overall, the correlational analysis showed a negative set of correlations in RA, in contrast to positive correlations noticed in NRNA. Here, it is interesting to note that significant correlations persisting after correction for multiple testing were coherent with

TABLE 2 Results from repeated ANOVA between RA and NRNA across frequency ranges.

Dependent measures	COLD VS PAIN PERCEPTIONS
Hß GPS	PERCEPTION$_{(1,30)}$ = 0.894; p = 0.352
	GROUP$_{(1,30)}$ = 0.245; p = 0.624
	PERCEPTION × GROUP$_{(1,30)}$ = 5.097; p = 0.031
Lß GPS	PERCEPTION$_{(1,30)}$ = 2.87; p = 0.101
	GROUP$_{(1,30)}$ = 0.354; p = 0.556
	PERCEPTION × GROUP$_{(1,30)}$ = 5.45; p = 0.026
α GPS	**PERCEPTION$_{(1,30)}$ = 14.116; p < 0.001**
	GROUP$_{(1,30)}$ = 0.683; p = 0.415
	PERCEPTION × GROUP$_{(1,30)}$ = 0.257; p = 0.616
δ GPS	PERCEPTION$_{(1,30)}$ = 1.25; p = 0.273
	GROUP$_{(1,30)}$ = 0.00583; p = 0.940
	PERCEPTION × GROUP$_{(1,30)}$ = 5.19; p = 0.030

Dependent measures	THRESHOLD VS TOLERANCE TIME POINTS
Hß GPS	TIME POINTS$_{(1,30)}$ = 3.07; p = 0.09
	GROUP$_{(1,30)}$ = 1.05; p = 0.314
	TIME POINTS × GROUP$_{(1,30)}$ = 6.84; p = 0.014
Lß GPS	TIME POINTS $_{(1,30)}$ = 0.605; p = 0.443
	GROUP$_{(1,30)}$ = 0.765; p = 0.389
	TIME POINTS × GROUP$_{(1,30)}$ = 6.621; p = 0.015
α GPS	**TIME POINTS $_{(1,30)}$ = 5.94; p = 0.021**
	GROUP$_{(1,30)}$ = 0.421; p = 0.522
	TIME POINTS x GROUP$_{(1,30)}$ = 1.44; p = 0.239
δ GPS	TIME POINTS $_{(1,30)}$ = 2.66; p = 0.113
	GROUP$_{(1,30)}$ = 0.250; p = 0.621
	TIME POINTS x GROUP$_{(1,30)}$ = 0.0229; p = 0.881

Resistant athletes (RA) and non-resistant non-athletes (NRNA) are compared according to cold and pain perceptions (upper part); and between threshold (THR) and tolerance (TOL) time points (lower part). The correction for multiple comparison was performed by a Tukey post-hoc analysis (the statistical significance of post-hoc differences is presented in Figures 4, 5 in the main manuscript). Values in bold represent significant results ($p < 0.05$, 95% CI). GPS, global power spectrum; Hβ, high beta (20–30 Hz); Lβ, low beta (13–20 Hz); *α*, alpha (8–12 Hz); *δ*, delta (2-4 Hz).

those with large effect size of which significance vanished after BH correction (Figure 6), both in the RA and in the NRNA groups.

4 Discussion

4.1 General considerations and main findings

This study aimed to explore mechanisms underlying the analgesic effect of PE in pain-free individuals, with a special interest on the GABAergic neurotransmission (potentially involved in EIH and owing to its implication in pain regulation and documented CP-associated modifications). For this purpose, we compared intensively trained endurance athletes with age-adjusted non-trained controls during exposure to a CPT (an appropriate CP experimental procedure). No participant suffered from specific pain disturbance. Additionally, we investigated their pain-related behaviors (central sensitization, fear of pain and catastrophizing features). We made the general hypothesis that the highly trained group would better resist to cold-induced pain and would exhibit an increase in brain GABAergic neurotransmission in addition to more favorable pain-related behavioral profiles.

As stated in the methods, in addition to correlations that remained statistically significant after corrections for multiple testing, only initially significant correlations were mentioned in the result section, and they all displayed a large effect size. Interestingly, most of them were coherent with significant results, suggesting that BH corrections might have been too conservative in this small preliminary study. Therefore, we also discuss them below, but solely in relation with the main results.

The most important finding of this study was the identification of a group of individuals mostly represented in the athlete group (resistant athletes, RA), who, compared to non-resistant non-athletes (NRNA), displayed potentially interesting distinctive characteristics: not only they showed significantly lower fear of pain level, but they better resisted to cold-induced pain, all this in accordance with our working hypotheses. Surprisingly however, RA showed *decreasing*

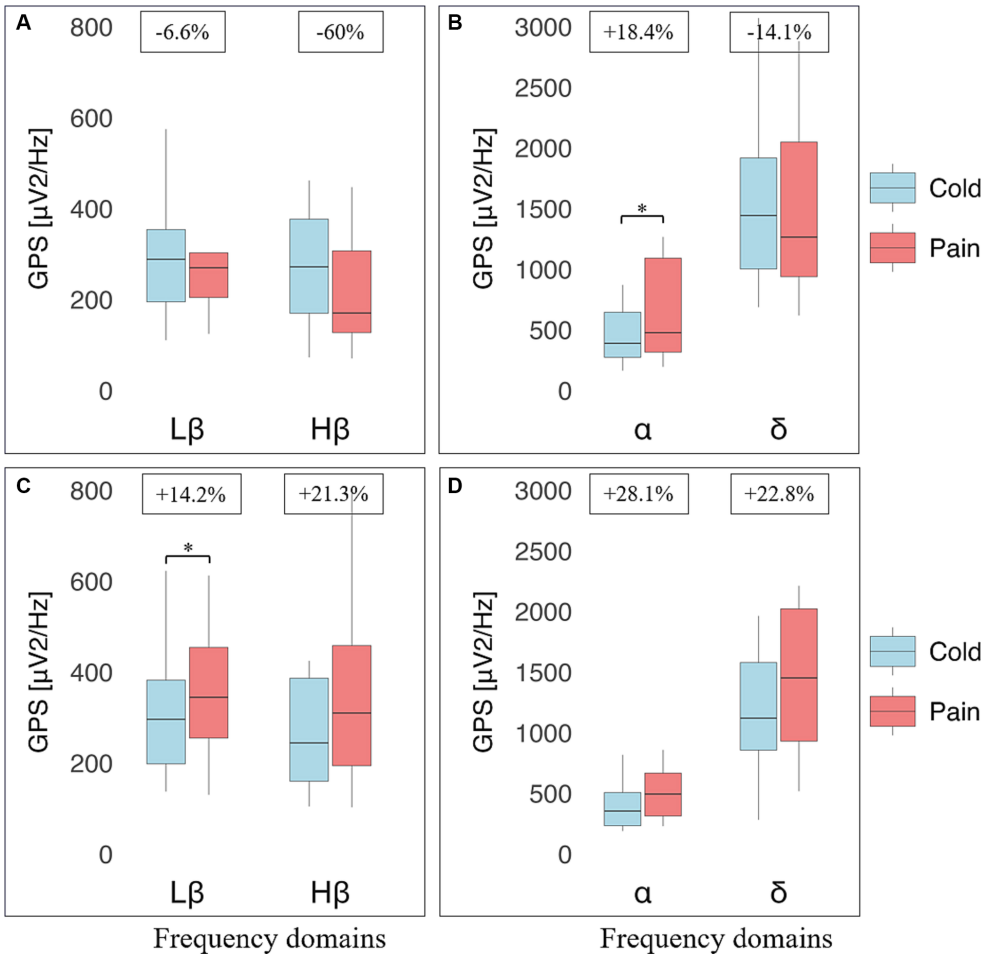

FIGURE 4
Electroencephalographic (EEG) global power spectra (GPS) according to frequency bands during cold and pain perceptions in resistant athletes (RA) and non-resistant non-athletes (NRNA). GPS (in $\mu V^2/Hz$) are presented on the y-axis as median (horizontal black line) and interquartile range (IQR, upper and lower edges of the box), while grey whiskers indicate minimum and maximum values. GPS during cold and pain perceptions are, respectively, shown in light blue and light red colors. Different frequency bands are represented on the x-axis: Low Beta (Lβ; 13–20 Hz) and High Beta (Hβ; 20–30 Hz) in A and C graphs; Alpha (α; 8–12 Hz) and Delta (δ; 2–4 Hz) in B and D graphs. The numbers at the top indicate GPS decrease (–) or increase (+) between cold and pain in percentage (%) normalized to the value during pain perception. RA (top panels) showed a decrease in GABAergic markers **(A)**; respectively from 288 (159) to 270 (98.1) $\mu V^2/Hz$, (Lβ, $p = 0.975$) and from 275 (207) to 170 (180) $\mu V^2/Hz$ (Hβ, $p = 0.183$), as well as δ GPS (from 1443 (915) to 1264 (1109) $\mu V^2/Hz$; $p = 0.874$). In contrast, an increase was observed in the α band (from 389 (371) to 477 (774) $\mu V^2/Hz$; $p = 0.045$) **(B)**. NRNA (bottom panels) displayed an increase in all frequency bands: Lβ (from 296 (184) to 345 (199) $\mu V^2/Hz$; $p = 0.030$) and Hβ (from 244 (226) to 310 (264) $\mu V^2/Hz$; $p = 0.734$) **(C)**; α (from 355 (274) to 494 (354) $\mu V^2/Hz$; $p = 0.072$) and δ (from 1120 (722) to 1452 (1091) $\mu V^2/Hz$; $p = 0.057$) **(D)**. *Indicates significant results ($p < 0.05$, 95% CI) from a repeated ANOVA and a Tukey tested for post-hoc differences, while at the same time correcting for multiple testing.

dynamics of GABAergic EEG markers (Hβ and Lβ power), in contrast to the increase noticed not only in other EEG indicators (α and δ power), but also in all EEG markers in NRNA.

4.2 Characterization of RA and differentiation from NRNA

Since RA and NRNA differed mainly by the intensity of their training regime, our results suggest that the observed differences in their pain-related behavior, response to cold-induced pain and GABAergic dynamics could be attributed to long-lasting intensive endurance sport, thereby further supporting our hypothesis. The meaningful element could be the endurance itself or another (unknown) training element not related to endurance (please also refer to the paragraph on the clinical applicability for further discussion). This finding is in accordance with existing literature suggesting reduced pain perception and improved pain-copying strategies upon acute and regular physical training (Ellingson et al., 2012; Naugle et al., 2012; Koltyn et al., 2014; Sluka et al., 2018; Vaegter and Jones, 2020) and confirms that our experimental frame was appropriate to reliably study exercise-induced pain reduction, in particular through characterization of the newly disclosed category of RA.

The RA group, while displaying significantly lower fear of pain than NRNA exhibited non-significant decrease (although moderate in size effect) in other pain-related behavioral indicators (i.e., central sensitization and pain catastrophizing features). The practice of endurance sport is associated with the ambition to go beyond one's

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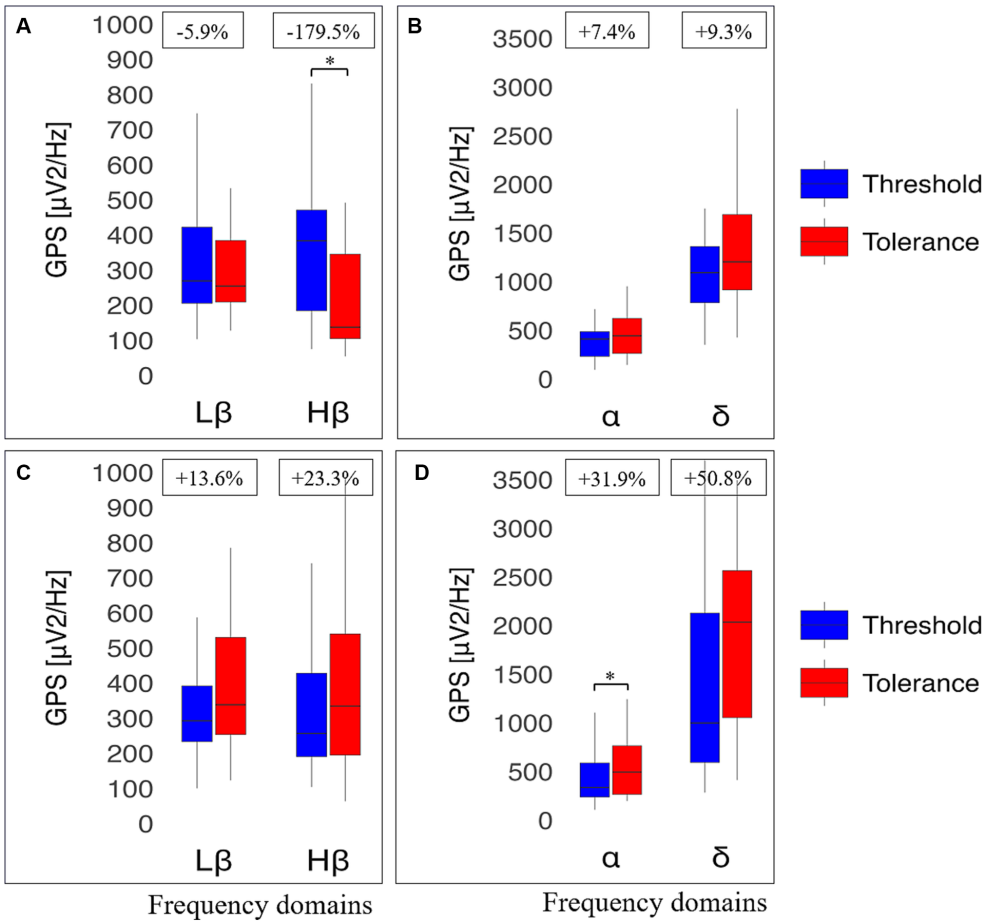

FIGURE 5
Electroencephalographic (EEG) global power spectra (GPS) according to frequency bands at pain threshold (THR) and at pain tolerance (TOL) in resistant athletes (RA) and non-resistant non-athletes (NRNA). GPS (in $\mu V^2/Hz$) are presented on the y-axis as median (horizontal black line) and interquartile range (IQR, upper and lower edges of the box), while grey whiskers indicate minimum and maximum values. GPS at THR and TOL are, respectively, shown in bright blue and bright red colors. Different frequency bands are represented on the x-axis: Low Beta (Lβ; 13-20 Hz) and High Beta (Hβ; 20-30 Hz) in A and C graphs; Alpha (α; 8–12 Hz) and Delta (δ; 2–4 Hz) in B and D graphs. The numbers at the top indicate GPS decrease (–) or increase (+) between cold and pain in percentage (%) normalized to the value during at TOL. RA (top panels) showed a decrease in GABAergic markers **(A)**; respectively from 269 (217) to 254 (176), $\mu V^2/Hz$ (Lβ, $p = 0.653$) and from 383 (287) to 137 (240) $\mu V^2/Hz$ (Hβ, $p = 0.039$). In contrast, an increase was observed in the α band (from 411 (254) to 444 (361) $\mu V^2/Hz$; $p = 0.853$) and in δ GPS (from 1091 (577) to 1203 (775) $\mu V^2/Hz$; $p = 0.658$) **(B)**. NRNA (bottom panels) displayed an increase in all frequency bands: Lβ (from 292 (159) to 338 (276) $\mu V^2/Hz$; $p = 0.061$) and Hβ (from 256 (238) to 334 (345) $\mu V^2/Hz$; $p = 0.905$) **(C)**; α (from 336 (350) to 494 (499) $\mu V^2/Hz$; $p = 0.037$) and δ (from 999 (1534) to 2034 (1510) $\mu V^2/Hz$; $p = 0.655$) **(D)**. *Indicates significant results ($p < 0.05$, 95% CI) from a repeated ANOVA and a Tukey tested for post-hoc differences, while at the same time correcting for multiple testing.

limits, which implies, among other challenges, resisting to potentially painful conditions (Scott and Gijsbers, 1981; Lentini et al., 2021) and even giving them a positive meaning (i.e., not linking them to a potential threat or to a disease) in order to be performant (Geva and Defrin, 2013; Kakiashvili et al., 2016). Lower fear of pain becomes thus fully meaningful in this modified behavioral paradigm. The significantly negative correlation with large effect size between pain catastrophizing features and the number of training hours per week in RA, although disappearing with multiple testing correlation, would further suggest, if confirmed, the link between the pain-related behavioral change and the training regime.

The GABAergic markers (Hβ and Lβ power) were similar at baseline and in all explored perceptions between RA and NRNA. However, not only they differently evolved through key CPT steps compared to other EEG markers (α and δ power) in RA, but their modifications were different between the RA and the NRNA groups. Indeed, a significant interaction was observed between GABAergic markers at cold and pain perceptions, as well as at THR and TOL time-points when comparing the two groups. Careful observation of post-hoc testing results suggests that interaction between cold and pain in Lβ frequency domain could be explained by increase in the NRNA group, and interaction in Hβ domain between THR and TOL by decrease in the RA group. Interestingly, the direction of the remaining GABAergic EEG modifications, although not reaching statistical significance, was similar to significant results (i.e., decrease in RA and increase in NRNA). Given the close similarities noticed in GABAergic decreasing (or non-increasing) trends between cold and pain perception and between THR and TOL, we interpreted them as being part of the same physiological process, and specifically induced by the experiment; highly suggesting differential modifications of the GABAergic signaling in RA and NRNA in response to cold-induced pain.

TABLE 3 Comparative analysis of response to the cold pressor test between RA and NRNA.

Variables		RA ($n = 13$)	NRNA ($n = 22$)	p	Cohen's d
NRS [/10] Threshold	Intensity	3.0 (2.0) (1–5)	3.0 (3.0) (0–9)	0.481	0.238
	Unpleasantness	4.0 (1.0) (1–6)	4.0 (3.0) (0–10)	0.938	0.026
NRS [/10] Tolerance	Intensity	**7.0 (1.0) (5–9)**	**8.0 (1.75) (1–10)**	**0.023**	**0.779**
	Unpleasantness	8.0 (3.0) (5–10)	8.0 (2.0) (5–10)	0.683	0.148
Pain appearance time [s]		26.2 (15.4) (8.09–146)	18.6 (16.9) (8.09–54.6)	0.257	0.454
Pain perception time [s]		**214 (15.4) (94–232)**	**29.2 (44.8) (1.29–126)**	**<0.001**	**4.555**

Data are shown as median (InterQuartile Range, IQR). The p values result from the independent samples Welch's t-test. Values in bold indicate significant differences ($p < 0.05$, 95% CI). The Cohen's d evaluated the effect size as following: small effect ($d \sim 0.2$), moderate effect ($d \sim 0.5$) and large effect ($d > 0.8$). NRS, numerical rating scale; RA, Resistant Athletes; NRNA, Non-Resistant Non-Athletes.

The GABAergic decrease (or absence of increase) in the presence of cold-induced pain in RA is against our initial working hypothesis that was based on the GAD upregulation subtending EIH and on the decrease of GABAergic signaling and increased brain excitability observed in CP conditions. It appears therefore, at first sight, hard to coherently relate our results to exercise-induced analgesia. However, GABAergic markers were negatively and highly correlated to the sensory pain at TOL (the only pain indicator that was lower in RA than in NRNA in a significant way) and to pain catastrophizing features in RA (although non-significantly upon multiple-testing correction). All these findings highly suggest a GABAergic contribution to reduce experimental pain and to modify pain-copying strategies in RA.

The lowering of GABAergic markers in RA recalls the decrease of many other physiological and metabolic indicators (e.g., heart rate, blood pressure) after several weeks of endurance training (Wilmore et al., 2001), possibly suggesting a similar link between our results and the long-lasting endurance training. In this perspective, the observed decrease could be understood as a counterpart of the neural efficiency reported in highly trained athletes (Li and Smith, 2021). Unfortunately, there is no report of a decreased brain inhibition under regular training conditions in the literature. In contrast, short-term increased brain cortical excitability and decreased GABAergic inhibition have been consistently observed upon acute PE (Lulic et al., 2017; Monda et al., 2017; El-Sayes et al., 2020; Nicolini et al., 2021; Hendy et al., 2022) in association with antinociception and subsequent increase in THR and reduced pain perception in healthy populations (Tang et al., 2009; Pagano et al., 2012; Moloney and Witney, 2014; Granovsky et al., 2019). Interestingly, in the HERITAGE Family study mentioned above (Wilmore et al., 2001), the decrease of metabolic indicators noticed after several weeks of training was enhanced upon additional but more acute and effort-demanding exercise series, suggesting a similarity of effects between the short-term and the long-lasting PE, possibly cumulating one with another. By analogy, this could also apply to brain GABAergic signaling modifications in RA. We could not verify this assumption because RA were not submitted to acute exercise in our study. In case our hypotheses were confirmed, the GABAergic decrease could mediate regular exercise-induced analgesia (Ellingson et al., 2012; Sluka et al., 2018; Vaegter and Jones, 2020) as well. In this scenario, exercise-induced lowering of the GABAergic signaling could be considered as an adaptive beneficial mechanism against pain and pain-related aberrant behaviors, possibly related to the above-mentioned neural efficiency.

Nevertheless, it is difficult to reconcile this interpretation with the antinociception associated with GAD upregulation in experimental animal models upon acute PE (Kami et al., 2016; Senba and Kami, 2020). Accordingly, there are indications that endurance athletes increase their resting-state EEG β power in all brain areas when submitted to acute PE at maximal load, irrespective of their neural efficiency (Ludyga et al., 2016). In this perspective, the observed lowering of GABAergic markers in an acute exercise context would possibly be part of training-related body adaptations, allowing a broader range of performance increase under (acute) extreme training conditions (Bjørnstad et al., 1993).

On the other hand, the increased GAD activity and expression (and the subsequent enhancement of the GABAergic signaling) were observed in neuropathic pain animal models and were interpreted as a therapeutic strategy rescuing deficient GABAergic neurotransmission. Furthermore, in patients suffering from fibromyalgia-related CP, a decrease in Hβ functional connectivity was correlated to the affective pain in the basolateral area of the amygdala (interpreted as participating to CP pathological mechanisms), whereas Lβ increased as a function of pain intensity in the prefrontal cortex (seen as a compensatory mechanism) (Makowka et al., 2023).

Overall, these results and related discussions suggest that exercise-related modifications in brain GABAergic signaling could be different not only between differently trained healthy populations, but possibly also between pain-free and pain-affected individuals. Consequently, the GABAergic decrease, while being beneficial upon long-lasting endurance training (regardless of its interpretation), could be part of pathophysiological mechanisms in CP conditions.

Considering these multifaceted GABAergic changes in pain-free and CP conditions, and the supposedly antinociceptive effect of PE, it was interesting to further discuss differences between RA and NRNA

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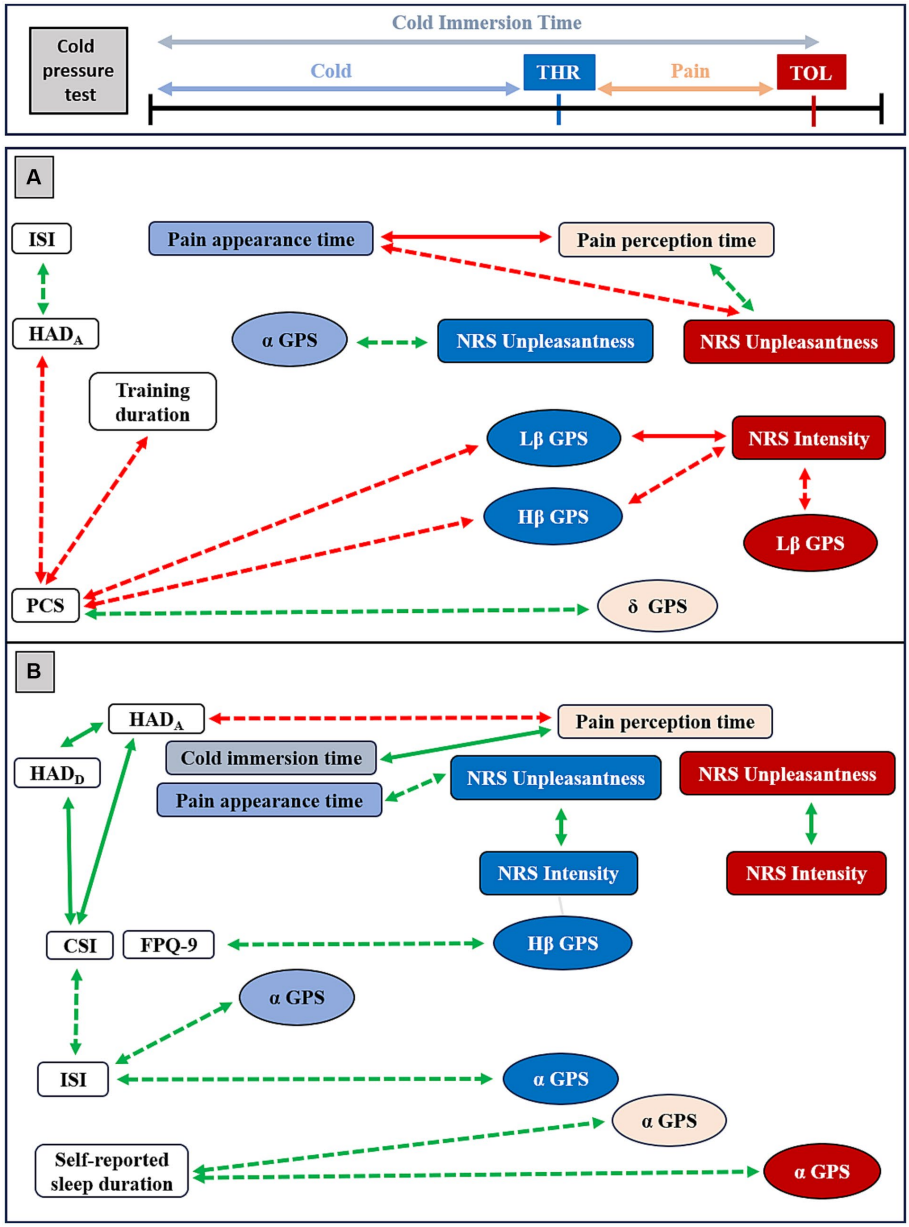

FIGURE 6
Overview of Spearman Rho (r_s) correlations between clinical indicators, psychophysical data and EEG markers in resistant athletes (RA) and in non-resistant non-athletes (NRNA). Red arrows represent negative correlations and green arrows the positive ones. Plain arrows correspond to significant correlations persisting after Benjamini Hochberg (BH) correction, while dashed arrows indicate large-effect size significant correlations that disappeared upon correction. Indicators labeled in light blue and light red were evaluated, respectively, during cold and pain perceptions; those in dark blue and dark red were calculated at threshold (THR) and tolerance (TOL) time-points, respectively. HAD=Hospital Anxiety and Depression scale for anxiety (HAD_A) and for depression (HAD_D), PCS=Pain Catastrophizing Scale, CSI=Central Sensitization Index, NRS=Numeric Rating Scale, ISI=Insomnia Severity Index. In RA (**A**, top panel), PCS correlated to the weekly training duration (r_s=−0.569, p=0.043) and to HAD_A (r_s=−0.563, p=0.045). HAD_A was correlated to ISI (r_s=0.619, p=0.024). Pain appearance time and pain perception time were correlated one to each other (r_s=−1.0, p<0.001) and both with NRS Unpleasantness at TOL (r_s=−0.674, p=0.011 and r_s=0.674, p=0.011, respectively). In addition, Lβ GPS at THR correlated with NRS Intensity at TOL (r_s=−0.780, p=0.002) and PCS (r_s=−0.637, p=0.019). Lβ GPS at TOL correlated with NRS Intensity at TOL (r_s=−0.588, p=0.034), Hβ GPS at THR with PCS (r_s=−0.692, p=0.009) and NRS Intensity at TOL (r_s=−0.693, p=0.009). A correlation was noticed between α GPS during cold and NRS Unpleasantness at THR (r_s=0.566, p=0.044) and between δ GPS during pain and PCS (r_s=0.640, p=0.018). In NRNA (B, bottom panel), CSI was correlated to HAD_A (r_s=0.740, p<0.001) and to HAD_D (r_s=0.658, p<0.001), the latter being correlated to the other (r_s=0.599, p=0.003). CSI correlated with ISI (r_s=0.528, p=0.012). NRS Intensity and NRS Unpleasantness were, respectively, correlated to each other at THR (r_s=0.732, p<0.001) and at TOL (r_s=0.723, p<0.001). Pain perception time correlated with HAD_A (r_s=−0.534, p=0.022) and pain appearance time correlated with NRS Unpleasantness at THR (r_s=0.599, p=0.004). In addition, pain perception time correlated with the cold immersion time (r_s=0.887, p<0.001). A correlation was seen between Hβ GPS at THR and FPQ-9 (r_s=0.540, p=0.017), and between α GPS during cold (r_s=0.523, p=0.022) and at THR (r_s=0.540 p=0.017) with ISI, between α GPS during pain (r_s=0.560, p=0.013) and at TOL (r_s=0.576, p=0.001) with the self-reported sleep duration per night.

regarding their respective associations between clinical variables and between clinical and EEG indicators. From a clinical standpoint, pain-catastrophizing features negatively correlated with the anxiety score and the latter to the sleep dysfunction score in RA, suggesting that the known association between both anxiety (and depression), and pain catastrophizing in CP patients (Dong et al., 2020) could be disrupted

in RA. A positive correlation between central sensitization and mood indicators was present in NRNA, similarly to reports in CP syndromes (Proença et al., 2021; Valera-Calero et al., 2022; Fernández-de-Las-Peñas et al., 2023). The NRNA appeared thus to have a pain-related behavior closer to CP patients and differed from the improved behaviors noticed in RA.

During the CPT, pain sensitivity was negatively correlated to pain resistance (indicated by the pain perception time) in RA, implying that the more the latter were sensitive to the induced pain, the more they resisted to it, as if higher sensitivity to induced pain primed or prepared to better resist to it. Supporting this interpretation, pain intensity at TOL was indeed significantly lower in RA. This behavioral mechanism of pain resistance seemed to engage the affective dimension of pain (which increased along with pain resistance but was reversely associated with pain sensitivity), consistently with the involvement of affective inputs and related brain pathways reported in EIH (Kami et al., 2022). In NRNA, however, the cold immersion time positively correlated to the pain perception time, which tended to minimize the role of the pain appearance time. Sensory and affective pain indicators evolved in a linear way between THR and TOL in NRNA (but not in RA), with positive correlations noticed between them at both experimental steps. Of notice, pain resistance was negatively associated to the anxiety score in NRNA, but not in RA. These observations suggest that, compared to NRNA, RA decoupled their THR from their TOL pain level in order to better resist to high pain level. In fact, TOL experimental step exhibited the most meaningful differences between RA and NRNA (sensory pain level) and affective pain level associations (negative with pain sensitivity and positive with pain resistance) in RA.

As stated above, NRNA showed an increase in one GABAergic EEG marker from cold to pain perception with significant interaction, contrary to RA. Furthermore, NRNA displayed positive correlation between one GABAergic marker and fear of pain, whereas correlations between GABAergic markers and pain catastrophizing, as well as with pain intensity at TOL were systematically negative in RA.

These observations suggest that in NRNA, GABAergic increase paralleled perceived pain and pain-related fear; as if NRNA simply adapted their GABAergic signaling and behavior to pain, while RA went a step beyond, decreasing their GABAergic neurotransmission as part of mechanisms attenuating their maximal sensory pain level during the CPT and counteracting meaningful pain-related behavior (namely pain catastrophizing). In this new interpretative frame, non-trained CP patients would be unable to increase their GABAergic signaling as a function of experienced pain, due to chronic-pain-related pathophysiological changes. This plausible dual role of brain hyperexcitability (and therefore of GABAergic decrease) in trained pain-free population versus in CP patients further illustrates the above-hypothesized multifaceted role of GABAergic changes according to the training regime and to the existence of pain. Interestingly, the increase in brain-derived neurotrophic factor (BDNF), which is considered as a marker of a "virtuous" brain neuroplasticity (e.g., following PE; Nicolini et al., 2021), participates at the same time to the (neuropathic) pain pathological neuroinflammatory cascade resulting in the nervous hyperexcitability (Sikandar et al., 2018; Thakkar and Acevedo, 2023). Thus, nociception and pain regulation players could differently change according to homeostatic conditions and their modifications should be interpreted with caution.

4.3 Potential clinical applicability and translation of obtained results

The present study was conducted in highly trained athletes (≥ 7 h of weekly training), who do not represent the typical profile of CP patients (subject to aberrant behavior toward pain and movement; see the introduction; Vlaeyen and Linton, 2000; Crombez et al., 2012; Zale and Ditre, 2015), or even the trends of PE intensity in the general population. Therefore, one important question is to know whether obtained results would be applicable in populations targeted by PE as an analgesic therapy.

At this point, there is no direct indication that our results would apply to non-athlete populations (including CP patients). However, it should be remembered that resistant individuals were also present among non-athletes, albeit at a lower proportion. We could not characterize them for this reason, but in case they would display a similar profile as RA, this would open a possibility to translate the observations made in RA to less trained individuals. On the other hand, if we take into consideration the observed involvement of the GABAergic neurotransmission associated with modified pain response and pain-related behaviors, recent data show that acute highly- versus moderately intense exercise do not seem to differ regarding brain excitability in low fit individuals (El-Sayes et al., 2020). Further, when submitted to acute PE sessions upon several week-physical training, low fit individuals exhibit brain excitability decrease as measured by an indicator of brain cortical inhibition (Lulic et al., 2017; El-Sayes et al., 2020). These observations suggest the combination of acute PE and prior long-lasting training as the most suitable regime to impact brain excitability (thereof, brain GABAergic signaling) in non-athletes, provided that obtained modifications are associated with the desired analgesia (which was not investigated in above-mentioned studies). In summary, the response to acute training (which was not measured in this study) and the issue of a minimal necessary dose or a dose-dependent effect of PE eliciting the beneficial modification of pain response should be further investigated prior to translation into clinical practice. Additionally, the acute pain, which corresponds better to the physiological nociceptive model (Sneddon, 2018) and would be more suitable to the experimental pain model in general, should also deserve some interest in the perspective of EIH, and more broadly to the analgesic effect of PE.

Another interesting question is how meaningful the endurance component of the training to RA resistance to cold-induced pain is (and hence possibly to the effectiveness of PE-induced analgesia). In comparison to strength athletes, endurance athletes display significantly higher tolerance to pain and lower fear of pain (Assa et al., 2019), which supports the importance of endurance, although one cannot exclude the possibility that another independent training factor (to be further investigated) may play a role. In complement, the implication of the GABAergic signaling would open a way for synergy between endurance training and GABA-modifying analgesic treatments.

The variability of EIH observed among chronic pain patients (Rice et al., 2019) should also be analyzed under the lenses of possible differences in brain GABAergic dysfunction between CP syndromes, calling for a mechanism-based classification of CP diseases before applying a given therapy modifying a precise pathway (here, the GABAergic signaling). Thus, future studies investigating

exercise-induced GABA-mediated analgesia in different CP syndromes should also compare the involvement of the GABAergic neurotransmission in the pathological process to better target responsive individuals (or syndromes).

5 Study limitations

Despite interesting observations discussed above, and for the potential clinical applications of our findings, a number of limitations have to be stated. First, because our data were purely experimental and collected in pain-free individuals, their confirmation in pain-diseased patients should be warranted before effective clinical translation. Second, despite a moderate to high theoretical study power, we cannot exclude the role of the modest sample size in the variability of our results, especially when data lost significance upon correction from multiple testing or showed no significant differences or correlations. Third, excluding females from the sample, although reducing the variability of collected data by avoiding sex-related bias in pain response (Bartley and Fillingim, 2013), limited generalization and translation of obtained results, considering also that women are more affected by any type of pain than men (Osborne and Davis, 2022). Thus, our findings should be confirmed in more inclusive and larger samples. In particular regarding the sample size estimation, the key endpoints should be significant differences between resistant athletes and non-resistant non-athletes, regarding clinical (mainly pain unpleasantness and, albeit to a lesser extent, pain intensity) and EEG data (Lβ and Hβ GPS) modifications in response to the CPT. More specifically, their differences at THR and TOL, as well as differences in their respective modifications between THR and TOL. Most probably, a compromise should be found between the clinical and the electrophysiological perspective, given the difference of sample size derived from similar statistical power in existing studies (see the discussion above). Fourth, athletes were overall significantly younger than non-athletes. Although this difference was not anymore significant when comparing RA to NRNA, it could account for some differences observed between athletes and non-athletes (and more specifically between RA and NRNA). Thus, obtained results should be confirmed comparing equally aged groups in order to exclude a potential age-related bias.

In addition, we made a number of indirect assumptions based on studies of brain hyperexcitability performed using a different method (transcranial magnetic stimulation) (Mooney et al., 2016; Monda et al., 2017; Moscatelli et al., 2021) or based on the assumed analogy between metabolic changes upon long-lasting endurance training and our results (Wilmore et al., 2001), while we did not directly assess them, neither have we found such indications in the literature. We should therefore be cautious about stated similarities. Finally, our experimental settings could be subject to a number of biases. Immersing the participant's hand in warm water before proceeding to the CPT could constitute a conditioning step vanishing some discriminating features between or within the studied groups during the experiments. Also, we evaluated behavioral data only at baseline, not during or just upon the CPT, while they could be measurably modified and further influence pain response. Data from RA were most probably biased by the imposed limit of 4 min immersion time, which could impact all performed analyses (Årnes et al., 2023).

6 Conclusion

The whole idea behind this study was to better understand mechanisms by which PE would induce analgesia by comparatively investigating pain-related behavior and response to experimental cold-induced pain of highly trained athletes and non-trained individuals. Our results suggest that the most resistant athletes improve their pain-related behavioral features and seem to dissociate the latter from mood and sleep dysfunction. Furthermore, resistant athletes appear more resistant to experimental cold-induced pain, with associated reduction in GABAergic neurotransmission.

Despite its limitations, this study constitutes one of the first investigations enlightening mechanisms underlying exercise-induced hypoalgesia. Furthermore, although the decreased brain GABAergic neurotransmission goes against our working hypothesis, we propose a coherent interpretation by comparatively discussing differences in clinical and GABAergic indicators between the two studied groups, and in light of the current knowledge about the multiple effects of physical exercise (e.g., metabolic changes, modifications in brain excitability). Subsequently, a multimodal profile of GABAergic changes according to homeostatic conditions (namely, the training regime and possibly the presence or absence of pain) is hypothesized. Out of it, a preliminary orientation on the therapeutic applicability of exercise-induced analgesia, based on the GABAergic neurotransmission, can be further investigated in future studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethical Committee of Vaud, Switzerland. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MM: Data curation, Formal analysis, Methodology, Software, Validation, Writing – review & editing. MDP: Data curation, Software, Validation, Writing – review & editing, Methodology. JC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1287233/full#supplementary-material

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Glossary

α	Alpha
ANOVA	Analysis of Variance
BDNF	Brain-Derived Neurotrophic Factor
BH	Benjamin Hochberg
BMI	Body Mass Index
CP	Chronic Pain
CPT	Cold Pressure Test
CSI	Central Sensitization Index
δ	Delta
EEG	Electroencephalography
EIH	Exercice-Induced Hypoalgesia
FPQ-9	Fear of Pain Questionnaire (9 Items)
GAD	Glutamate Acid Decarboxylase
GABA	Gamma-Aminobutyric Acid
GPS	Global Power Spectrum
HAD	Hospital Anxiety and Depression
HAD_A	Hospital Anxiety and Depression subscore for Anxiety
HAD_D	Hospital Anxiety and Depression subscore for Depression
Hβ	High Beta
Hz	Herz
IQR	Interquartile Range
ISI	Insomnia Severity Index
Lβ	Low Beta
NRA	Non-Resistant Athletes
NRNA	Non-Resistant Non-Athletes
NRS	Numeric Rating Scale
NRS_I	Numeric Rating Scale for pain Intensity
NRS_U	Numeric Rating Scale for pain Unpleasantness
PAT	Pain Appearance Time
PCS	Pain Catastrophizing Scale
PE	Physical Exercise
PPT	Pain Perception Time
THR	Threshold
TOL	Tolerance
RA	Resistant Athletes
SD	Standard Deviation
μV	Micro Volt
VO_{2max}	Maximal Oxygen consumption

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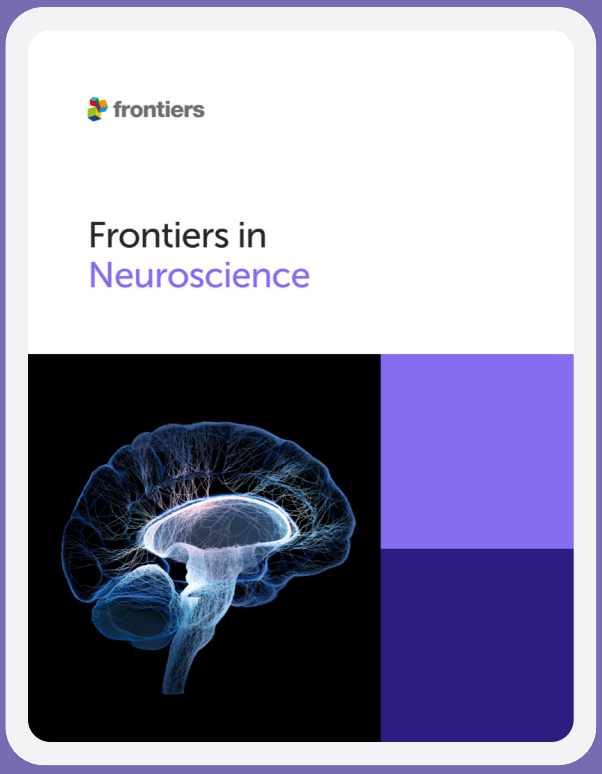

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