Research Paper

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Vigilance-related attention systems subserve the discrimination of relative intensity differences between painful stimuli

Sung-Ling Yang, Ting-Wei Wu, Ming-Tsung Tseng*

Abstract

Humans require the ability to discriminate intensities of noxious stimuli to avoid future harm. This discrimination process seems to be biased by an individual's attention to pain and involves modulation of the relative intensity differences between stimuli (ie, Weber fraction). Here, we ask whether attention networks in the brain modulate the discrimination process and investigate the neural correlates reflecting the Weber fraction for pain intensity. In a delayed discrimination task, participants differentiated the intensity of 2 sequentially applied stimuli after a delay interval. Compared with nonpain discrimination, pain discrimination performance was modulated by participants' vigilance to pain, which was reflected by the functional connectivity between the left inferior parietal lobule and the right thalamus. Of note, this vigilance-related functional coupling specifically predicted participants' behavioral ability to differentiate pain intensities. Moreover, unique to pain discrimination tasks, the response in the right superior frontal gyrus linearly represented the Weber fraction for pain intensity, which significantly biased participants' pain discriminability. These findings suggest that pain intensity discrimination in humans relies on vigilance-related enhancement in the parieto-thalamic attention network, thereby allowing the prefrontal cortex to estimate the relative intensity differences between noxious stimuli.

Keywords: Pain, Functional magnetic resonance imaging, Psychophysical interaction analysis, Discrimination, Working memory

1. Introduction

The ability to accurately discriminate differences in intensity of sequentially applied noxious stimuli on the body is essential for humans to avoid subsequent damage. As a salient feature of sensory-discriminative aspects of pain, the processing of pain intensity has traditionally been proposed to engage the lateral thalamic nuclei and somatosensory cortices.[63] However, studies of primates show that the physical attributes of somatosensory stimuli are gradually processed in frontal and parietal association cortices during perceptual decisions.[18,56] Although previous neuroimaging research has characterized a set of brain regions responsive to noxious stimuli,[2] it remains unclear whether and how the decision-related fronto-parietal areas interact with pain-related networks to subserve pain discrimination processes.

It is well recognized that the response to pain is largely shaped by individual differences in pain-relevant characteristics.[17,27,52] Regarding intensity discrimination, evidence points to an important role of attention in processing painful stimulation. Selective attention to pain has been shown to facilitate pain discrimination performance.[13,17,61] Intriguingly, compared to innocuous stimulation, attentional modulation appears to preferentially influence perceptual decisions in the noxious range.[13] Given a delayed discrimination requires attention,[29,55] these observations suggest that the neural systems for attentional control during a perceptual decision, particularly the inferior parietal lobule (IPL) and superior frontal gyrus (SFG),[15,22,31,38] possibly contribute to the pain discrimination process. Although pain instantaneously captures more attention than nonpain,[17] whether intensity discrimination of pain entails increased engagement of the attentional networks, through which pain-vigilant individuals exhibit better pain discriminability, remains elusive.

In addition to the potential influence of attention, the ability of humans to detect differences between somatic stimuli, including those that are painful, has been documented to parallel the ratio of the intensities, that is, Weber fraction.[51,54,67] Intriguingly, within the attentional networks mentioned above, the SFG has been reported to scale with Weber fractions of somatosensory stimuli[51] and to respond during discrimination of painful stimuli.[45] These observations raise the possibility that the SFG would reflect the modulation of Weber's law during pain discrimination process. Here, using functional magnetic resonance imaging (fMRI), we investigated brain responses while healthy volunteers performed a delayed discrimination task. In contrast to previous studies,[1,37,45] both pain and nonpain trials were included, and the difficulty levels between pain and nonpain discrimination were controlled. Moreover, a control decision task (ie, categorization task) was added to ensure the specific effect of pain vigilance on the discrimination process. We assumed that pain discrimination required increasing levels of attentional processing and that an individual's vigilance to pain would influence pain discriminability

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Graduate Institute of Brain and Mind Sciences, National Taiwan University College of Medicine, Taipei, Taiwan

**Corresponding author. Address: Graduate Institute of Brain and Mind Sciences, National Taiwan University College of Medicine, 1 Jen-Ai Road Section 1, Taipei 10051, Taiwan. Tel.: (886)-2-23123456 ext 88870; fax: (886)-2-23224814. E-mail address: mingtsungtseng@ntu.edu.tw (M.-T. Tseng).*

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by modulating attention-related neural streams, particularly the IPL and SFG. We further posited that distinct areas within the fronto-parietal attention network would reflect the Weber fraction for pain intensity.

2. Materials and Methods

2.1. Subjects

Twenty-five healthy right-handed volunteers who had never participated in pain studies before were enrolled in this study. Three participants were excluded from analyses: 1 reported no painful sensation to electrical stimulation, 1 did not follow the rating procedures during scanning, and 1 had a suboptimal practice. To ensure that the second stimulus in pain discrimination and categorization trials (ie, Stim2 in **Figs. 1A and B**) was perceived as clearly painful, 4 additional participants were excluded from further analysis because of a rating of less than 40 (ie, just painful) during scanning. Therefore, data from 18 participants (11 women and 7 men; age range: 20-26 years; mean ± SD: 22.3 ± 1.8) were analyzed. The study protocol was approved by the Ethics Committee of National Taiwan University Hospital, Taipei, Taiwan. All participants provided written informed consent prior to the experimental procedures. Before scanning, each participant's vigilance level to pain and state and trait anxiety levels were assessed with the self-reported Pain Vigilance and Awareness Questionnaire (PVAQ)[40] and State Trait Anxiety Inventory.[62] To examine whether the influence of these personality traits on behavioral and imaging data differed between pain discrimination trial and other trial types, a median split of the scores was used to dichotomize participants into 2 groups.

2.2. Stimuli

Painful and nonpainful electrocutaneous stimuli were generated by a bipolar constant-current stimulator (DS5; Digitimer, Hertfordshire, United Kingdom). Stimuli were delivered to the degreased skin of the left volar forearm via a pair of leads (LEAD108; Biopac Systems Inc, Goleta, CA) and silver chloride surface electrodes (EL-508; Biopac Systems Inc). All leads and electrodes were MRI-compatible. Each stimulus consisted of a single monophasic 0.5-millisecond pulse. In this experiment, all stimulus presentation and data collection were controlled by laptop computers equipped with Presentation software (Neurobehavioral Systems, San Francisco, CA).

2.3. Behavioral session

To determine proper stimuli and to control for the confounding effects of task difficulty and performance on brain activity, each participant took part in a behavioral session before scanning, during which a four-step procedure was adopted to determine the stimulus content of the first (Stim1) and second (Stim2) stimuli for discrimination and categorization trials in the formal experiment (**Figs. 1A and B**). First, the ascending method of limits approach was used to define the detection threshold and pain threshold for each participant. The average of the detection threshold and pain threshold (designated as "$Stim1_{non\text{-}pain}$") was defined as the stimulus intensity of Stim1 for nonpain trials. Second, participants performed 2 series of nonpain delayed discrimination trials, with the trial structure identical to the formal experiment (**Fig. 1A**; detailed below). Each trial comprised the $Stim1_{non\text{-}pain}$ followed by a second nonpainful stimulus, which consisted of an ascending or descending series of stimuli (starting from $Stim1_{non\text{-}pain}$; step: 0.3 mA). After each trial, participants were asked to rate the task difficulty on a 0 to 100 visual analogue scale (VAS; anchored at left with "easy" and at right with "hard"). Subsequently, we determined 2 intensities, 1 higher (designated as "$High_{non\text{-}pain}$") and 1 lower (designated as "$Low_{non\text{-}pain}$") than $Stim1_{non\text{-}pain}$, that were easy (with a difficulty rating less than 20/100) for the participant to differentiate from $Stim1_{non\text{-}pain}$. Then, 2 stimulus magnitudes corresponding to the 10th and 90th

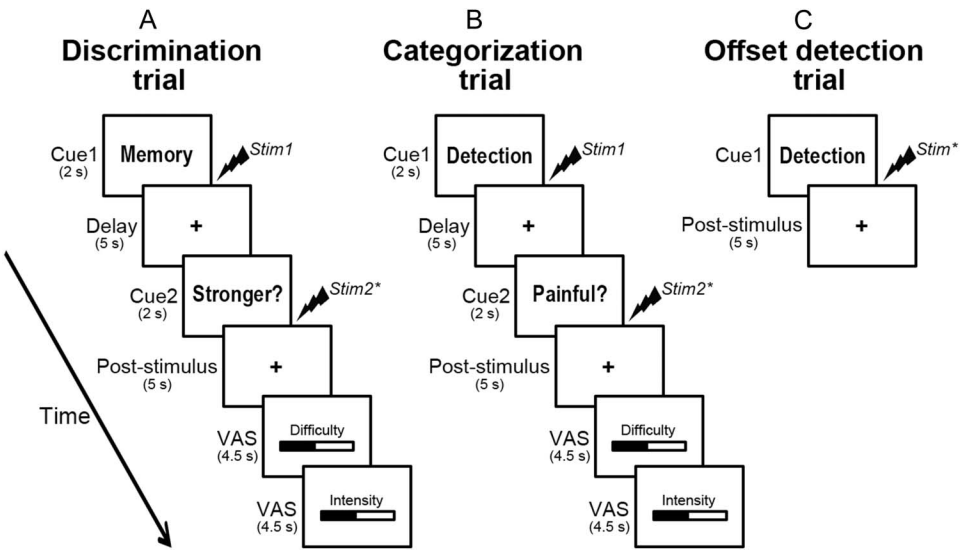

Figure 1. Experimental paradigm. A written cue (Cue1) indicated the beginning and the type of each trial. (A and B) In discrimination and categorization trials, participants received the first stimulus (Stim1) and, after a delay interval, the second stimulus (Stim2) followed another written cue (Cue2). In discrimination trials, participants decided whether or not Stim2 had a higher intensity than Stim1. In categorization trials, participants judged whether Stim2 was painful or not. After decisions, participants used VAS to rate the task difficulty and intensity of Stim2. (C) In offset detection trials, only 1 stimulus (Stim) was applied, and participants simply had to detect its termination. The intertrial interval was jittered between 3 and 5 seconds. *In both pain and nonpain trials, Stim2 in discrimination and categorization trials and Stim in offset detection trials consisted of 4 stimulus intensities presented in random order, with each intensity occurring equally often. See Methods for detailed descriptions.

percentile between $Stim1_{non\text{-}pain}$ and $Low_{non\text{-}pain}$, and another 2 stimulus magnitudes between $Stim1_{non\text{-}pain}$ and $High_{non\text{-}pain}$ were estimated by linear interpolation. The third and fourth steps followed the first and second steps except that a rating of moderate pain, that is, 50 to 75 on a 0 to 100 pain VAS (anchored at left with "no pain" and at right with "unbearable pain"), was measured and defined as the stimulus intensity of Stim1 for pain trials, which was followed by 2 series of pain delayed discrimination trials. In total, 2 stimulus magnitudes (1 painful, 1 nonpainful) for Stim1 and 8 stimulus magnitudes (4 painful, 4 nonpainful) for Stim2 were defined to constitute the stimulus content in discrimination and categorization trials (**Table 1**). The offset detection trial (**Fig. 1C**) contained only 1 electrical stimulus, which was with the set of stimuli identical to that for Stim2.

2.4. Practice session

After determination of stimulus parameters, participants performed a practice session to familiarize themselves with the 3 trial types used in the formal fMRI experiment (described below). The practice session included 4 repetitions of each trial type. Experimental conditions were presented in a random order in the practice session. Participants were required to achieve a minimum correct response rate of 90% to proceed to the fMRI session.

2.5. Experimental paradigm

The fMRI paradigm encompassed 2 decision trials (ie, discrimination and categorization trials; **Figs. 1A and B**) and 1 nondecision trial (ie, offset detection trial; **Fig. 1C**). The main interest of the current study focused on the discrimination trials. In this trial type, the decision is preceded by a mnemonic process associated with the internal representation of the first stimulus during the delay period, and a discrimination response is believed to be made against this memory trace.[55] In this report, fMRI signals associated with these temporally separate periods are termed delay- and discrimination-related activity, respectively. The decision made in categorization trials did not require a comparison with a memory trace of the preceding stimulus and hence acted as a decision control condition to examine whether pain vigilance specifically affected the discrimination-related process. The offset detection trials did not involve any discrimination or categorization process related to the stimulus intensity and thus served as the control condition for both decision trials.

Critically, to ensure that participants compared Stim2 with Stim1 in discrimination trials but concentrated solely on Stim2 in categorization trials, they were told that the whole experiment contained 3 different tasks heralded by 3 written cues: "Memory," "Painful?," and "Detection." The cue "Memory" indicated the start of a discrimination trial (**Fig. 1A**). After a delay interval and a second cue ("Stronger?"), participants received Stim2 and had to determine whether or not Stim2 was of higher intensity than Stim1. When "Painful?" emerged, participants were required to decide whether or not the following electrical shock (ie, Stim2) was painful. If the cue was "Detection," participants were not asked to make any decision. To make sure that Stim1 intensity was encoded in discrimination trials but not in the other 2 trials, for the electrical stimulus following "Memory" (discrimination trials) and "Detection" (categorization and offset detection trials), participants were trained to signal the termination of the electrical stimulus by pressing any button on an MR-safe button box with their right hand. Immediately after the offset of the stimulus following "Stronger?" and "Painful?," participants were instructed to press either the right middle finger ("yes") or right index finger ("no") once they were confident in their decision. Fifty percent of the "Detection" cues were followed by "Painful?" to constitute categorization trials. Another 50 percent of the "Detection" cues were followed only by an electrical stimulus to constitute offset detection trials. Because the type of stimulus intensity (ie, 4 painful and 4 nonpainful stimulus intensities) for Stim2 in discrimination and categorization trials and Stim in offset detection trials was actually identical (**Fig. 1**), and each of the 8 stimulus intensities appeared randomly and with equal frequency in each trial type, participants should have the same expectations about the upcoming stimulus across the 3 trial types but use different cognitive processes (ie, discriminating stimulus intensities, categorizing the quality of the stimulus, or detecting the termination of the stimulus) to perform the tasks.

The fMRI experiment consisted of 3 scanning runs, with each run containing 48 trials (8 repetitions of pain and nonpain conditions for each trial type). Trial types were presented in randomized order. Participants were asked to rate the level of task difficulty (described above) in both decision trials. They were also requested to rate the stimulus intensity of Stim2 after each decision trial on an on-line VAS presented on the monitor during scanning. Here, to examine the behavioral and neural responses across a range of innocuous and noxious stimuli, a 0 to 100 rating scale (anchored at left with "no pain," at 40/100 with "just painful," and at right with "unbearable pain"), which is capable of reflecting a linear relationship between stimulus magnitude and subjective perception,[9] was used as the unidimensional measure of stimulus intensity.

2.6. Statistical analysis

Statistical analyses were conducted using SPSS (Chicago, IL) and GraphPad Prism (GraphPad Software, San Diego, CA). One-

Table 1

Stimulus intensity and perceptual ratings on visual analogue scale (VAS).

	Stim1	Stim2			
	Mean ± SD	Mean ± SD			
Nonpain					
Intensity (mA)	3.7 ± 2.4	2.3 ± 1.9	3.8 ± 2.4	4.2 ± 2.5	6.1 ± 2.9
VAS rating	—	11.4 ± 9.1*	16.9 ± 8.8*	19.5 ± 8.8*	26.5 ± 8.6*
Pain					
Intensity (mA)	13.6 ± 9.1	11.0 ± 9.1	13.5 ± 9.5	14.1 ± 9.6	16.1 ± 10.6
VAS rating	—	47.4 ± 6.3†	51.8 ± 8.3*	52.2 ± 8.1*	58.3 ± 8.9*

This table shows the electrical stimulus intensity of the first (Stim1) and second (Stim2) stimulus as well as perceptual ratings to Stim2.

* The *P* value indicates the statistical comparison with the score of "just painful" (ie, 40 on a 0-100 VAS; $P < 0.0001$).

† The *P* value indicates the statistical comparison with the score of "just painful" (ie, 40 on a 0-100 VAS; $P = 0.0001$).

SD, standard deviation.

sample *t*-tests were used to examine whether the task performance was significantly different from chance level (ie, 50%). Paired *t* tests were used to compare perceptual ratings between pain and nonpain trials and the reaction time between different trial types. The main effects of stimulus type and task type on the task difficulty, reaction time, and correct rate, as well as their interactions, were analyzed by a 2-way repeated-measures analysis of variance. To examine the influence of personality traits on the decision process, pain vigilance or anxiety was included as a between-subject variable in 2-way repeated-measures analyses of variance. Pearson's correlation test was used to examine the linear relationship between 2 variables. Analysis of covariance was used to compare the slopes of linear regression lines.

2.7. Functional magnetic resonance imaging data acquisition

All images were collected using a 3.0 T S (Erlangen, Germany) Prisma MRI scanner equipped with a 64-channel head coil. Foam padding was used to minimize head movement. Blood oxygen-level dependent (BOLD) data were acquired using a gradient-echo T2*-weighted echo planar imaging (EPI) sequence (TR = 2000 milliseconds; TE = 30 milliseconds; flip angle = 90°; FOV = 224 × 224 mm; a GRAPPA acceleration factor of 2; slice thickness = 3.9 mm; acquisition matrix = 64 × 64; voxel size = 3.5 × 3.5 × 3.9 mm). A total of 37 horizontal slices without slice gap were obtained covering the whole brain. The first 4 EPI volumes were discarded to allow for magnetization equilibration. To correct image distortions caused by magnetic field inhomogeneities,[32] a map of the static magnetic field using the same slice geometry as EPI images was acquired using a double gradient-echo sequence (TR = 600 milliseconds, TE_1 = 10.00, TE_2 = 12.46 milliseconds). For registration purposes, a T1-weighted, high-resolution (0.88 × 0.88 × 0.89 mm), magnetization-prepared rapid acquisition gradient echo image and a structural T2-weighted scan coplanar with the functional images, but with higher in-plane resolution (256 × 256), were additionally acquired.

2.8. Functional magnetic resonance imaging data analysis

Image data were analyzed using Statistical Parametric Mapping (SPM8; Welcome Department of Imaging Neuroscience, London, United Kingdom) implemented in MATLAB (Mathworks, Sherborn, MA). All EPI images were adjusted for timing differences between slices, unwarped using field maps, realigned to the first volume in each scan sequence, and re-sliced with a fourth-degree b-spline interpolation to correct for motion artifacts. The resulting mean functional image was co-registered with the participant's T2-weighted anatomical image, which in turn was aligned with the T1-weighted image. To enable between-subject analyses, the T1-weighted image was then normalized to the standard Montreal Neurological Institute (MNI) template,[14] and the normalization parameters were then applied to the co-registered functional data. Functional images were resampled to a resolution of 2 × 2 × 2 mm and finally smoothed using a 3D isotropic Gaussian kernel with an full-width at half maximum of 6 mm. All participants' structural images were averaged for overlay of statistical parametric maps. A high-pass filter with 128 seconds cutoff was used to remove low-frequency noise.

At the first level, the BOLD response at each voxel was analyzed using the general linear model,[25] in which the fMRI time-series was modeled as a sequence of events convolved with the canonical hemodynamic response function implemented in SPM8. The current study focused on discrimination-related regressors (ie, discrimination of pain [PD] and nonpain [ND]), with the 2 categorization regressors for pain (PC) and nonpain (NC) and the 2 offset detection regressors for painful (PO) and nonpainful (NO) stimuli serving as the control condition. Duration of these 6 regressors was set from the onset of the second stimulus to the time participants indicated their decisions. Additional regressors included the first visual cue (all conditions collapsed to 1 regressor), first stimulus (4 regressors), delay (4 regressors), second visual cue (1 regressor), post-stimulation rating (1 regressor), and motion parameters (6 regressors) from the realignment procedure (Friston et al., 1996). Each individual's first-level *t*-contrasts were then entered into a second-level random-effects group analysis.[30] To factor out the potential confounding effects of age[64] and sex[28] on imaging data, both variables were included as covariates of no interest in all group activation maps reported in the current study.

We first analyzed pain-related brain activations during the first painful stimulus in categorization trials (ie, Stim1 in **Fig. 1B**; consisting of 1 painful stimulus intensity) and the painful stimulus in offset detection trials (ie, Stim in **Fig. 1C**; consisting of 4 painful stimulus intensities; regressor PO) in a whole-brain analysis. Activations during the first painful stimulus of discrimination trials and the second stimulus of both types of decision trials were not included, to avoid contamination of memory- and decision-related brain responses.[1] Because the present study focused on the sensory-discriminative feature (ie, stimulus intensity) of pain, we also examined whether BOLD signals during pain trials were enhanced as compared to nonpain trials by performing small-volume corrections (SVCs) in regions of interest (ROIs) involved in sensory dimensions of pain,[63] which included the contralateral thalamus, contralateral primary somatosensory cortex, and bilateral secondary somatosensory cortex (supplementary Table 1, available online at http://links.lww.com/PAIN/A493).

The first aim of the present study is to investigate the role of attention-related fronto-parietal regions in the intensity discrimination of pain. For this purpose, we first compared the average BOLD signal during the first stimulus and the delay periods between discrimination and categorization tasks to isolate brain activity pertaining to the maintenance of the memory trace for the first stimulus, given that the BOLD signal related to this mnemonic process followed the signal produced by the first stimulus instantaneously in discrimination trials and was difficult to separate out. For the discrimination process, contrasts "PD > PO" and "ND > NO" were used to identify brain activity related to the intensity discrimination of pain and nonpain, respectively. Given that the SFG and IPL have been implicated in attentional control during perceptual decisions,[15,22,31,38] SVCs in the bilateral SFG and IPL were conducted in all contrasts related to the delay and discrimination periods. Because these analyses revealed an important role of the left IPL in pain discrimination process, we further posited that individual vigilance to pain modulated pain processing by predicting the interaction between the left IPL and pain-related brain regions. To this end, we assessed a psychophysiological interaction (PPI) model (described below) with a subsequent intersubject linear regression analysis in SPM 8 using the PVAQ score as a covariate. Small-volume corrections in pain-related ROIs (mentioned above; supplementary Table 1, available online at http://links.lww.com/PAIN/A493) were conducted in this PPI analysis.

The second aim of the present study is to examine the neural representation of Weber fraction for the pain intensity. Based on Weber's law,[67] we hypothesized that the intensity discrimination

mechanisms would involve a brain center estimating the Weber fraction–the ratio of the change in stimulus intensity to the reference stimulus (ie, | Stim2 − Stim1|/Stim1). We adopted a parametric modulation approach[11] to model trial-by-trial Weber fractions in a separate general linear model. To eliminate the potential confounding of activations related to the task difficulty during perceptual decision making,[29] the parametric modulators of hemodynamic responses during discrimination tasks contained first, the trial-wise task difficulty levels and second, the Weber fraction. Small-volume correction was performed in the bilateral SFG because this region has been reported to reflect the Weber fraction for a somatic stimulus[51] and to respond during discrimination of painful stimuli.[45]

2.9. Psychophysiological interaction analysis

Psychophysiological interaction analysis examines context-dependent changes in the temporal correlation between BOLD signals of different brain regions.[24] As mentioned above, a PPI analysis was conducted to examine the functional connectivity with the left IPL during pain discrimination (ie, contrast: "PD > PO"). We used a generalized PPI toolbox for SPM (http://www.nitrc.org/projects/gppi).[41] In each participant, we extracted deconvolved time courses of activity averaged over all voxels in a sphere of 6-mm radius centered on the peak coordinate of the left IPL (MNI coordinates *x/y/z* = −48, −50, 47). In the general linear model for a PPI analysis, an experimental condition (ie, regressors PD, PC, PO, ND, NC, and NO) served as the psychological regressor, the seed-region time course was used as the physiological regressor, and their interaction terms constituted a PPI regressor. Each individual's PPI maps were entered into a second-level random-effects group analysis.

In the current study, SVCs were conducted in SPM using a voxel-wise threshold of $P < 0.05$, family-wise-error (FWE) rate corrected for all ROI analyses. For ROIs involved in the sensory-discriminative aspects of pain, the ROI for the right thalamus was defined as a sphere of 6-mm radius centered at the coordinates with greatest likelihood of activation in response to painful stimuli applied to the left side of the body (supplementary Table 1, available online at http://links.lww.com/PAIN/A493).[19] Considering the somatotopic organization of the nociceptive system,[7] the ROIs for the primary and secondary somatosensory cortices were defined as a 5-mm sphere centered on the MNI coordinates, as in a previous fMRI study applying painful stimuli to the left volar forearm (supplementary Table 1, available online at http://links.lww.com/PAIN/A493).[39,58] With regard to delay- and discrimination-related ROIs, the automated anatomical labeling ROI library in the SPM MarsBar toolbox[65] was used to define the ROI for the bilateral IPL and SFG. Because distinct connectivity patterns and function networks for the superior frontal area have recently been demonstrated,[36] the SFG ROI was defined as the intersection between the automated anatomical labeling anatomical mask and a sphere with a radius of 12 mm centered on connectivity-based MNI coordinates (supplementary Table 1, available online at http://links.lww.com/PAIN/A493) to enhance the specificity. The mean BOLD signal change and the parameter estimates in brain areas showing significant PPI effects were extracted from each ROI using the MarsBaR toolbox.[10] In addition to SVCs in ROIs, random-effects whole-brain analyses were also conducted to complement all hypothesis-driven ROI analyses discussed above in the present study. Given that the whole-brain analyses were regarded as exploratory and to ensure optimal statistical power and control of false positives in group-level whole-brain analyses,[21] a nonparametric permutation-based approach[44] implemented in the statistical nonparametric mapping toolbox (SnPM13; http://warwick.ac.uk/snpm) with 5000 permutations and without variance smoothing was used. Inferences were drawn using the FWE-corrected cluster-level $P < 0.05$.

3. Results

3.1. Behavioral results

All participants perceived the Stim2 in nonpain and pain decision trials as nonpainful and painful, respectively (average VAS rating: 18.6 ± 7.7 for nonpain trials and 52.4 ± 6.9 for pain trials; both $P < 0.0001$ as compared to a just painful score of 40; **Table 1**). There was a main effect of stimulus (pain vs nonpain, $F_{(1,17)} = 165.371$, $P < 0.001$) but no significant main effect of task (discrimination vs categorization, $F_{(1,17)} = 0.024$, $P = 0.878$) or stimulus-by-task interaction ($F_{(1,17)} = 0.167$, $P = 0.688$). In all trial types, participants' performance was significantly different from chance (ie, 50%; correct rate: pain discrimination, 68.28 ± 13.83%; nonpain discrimination, 67.25 ± 12.21%; pain categorization, 81.07 ± 11.74%; nonpain categorization, 76.96 ± 16.58%; all $P < 0.0001$). Importantly, the correct rate ($P = 0.789$; **Fig. 2A**) and difficulty level ($P = 0.363$; **Fig. 2B**) between painful and nonpainful stimuli in discrimination trials did not reach statistical significance, suggesting that our experimental control for the task difficulty and performance between pain and nonpain discrimination trials was successful.

For the reaction time to detect the termination of Stim1, there was no significant difference between painful and nonpainful stimuli in discrimination trials (0.76 ± 0.32 seconds for pain and 0.78 ± 0.27 seconds for nonpain; $P = 0.694$), which indicated that participants paid comparable attention to encode the first stimulus for later comparisons during pain and nonpain discrimination tasks. For the response latency of decision, the reaction time in discrimination trials (1.25 ± 0.26 seconds) was significantly longer than that in offset detection trials (0.77 ± 0.29 seconds; $P < 0.001$). Notably, the reaction time of pain discrimination was significantly shorter than that of nonpain discrimination (1.19 ± 0.28 seconds for pain and 1.31 ± 0.24 seconds for nonpain; $P = 0.037$; **Fig. 2C**), suggesting the allocation of greater attention to intensity discrimination of pain relative to nonpain.

We then examined how personality traits biased decision performance, and whether the task performance followed Weber's law. Unique to pain discrimination, participants scoring high on the PVAQ (scores >41, n = 9, correct rate: 74.99 ± 13.27%) showed a significantly better task performance as compared with those having low PVAQ scores (scores <41, n = 9; correct rate: 61.57 ± 11.37%; $P = 0.035$, 2-tailed; **Fig. 2D**). The detection thresholds and pain thresholds measured before scanning did not significantly differ between these 2 groups (high PVAQ vs low PVAQ; both $P > 0.535$). Pain vigilance had no effect on intensity discrimination of nonpain ($P = 0.330$) or on categorization of pain and nonpain ($P = 0.382$). Importantly, significant 2 × 2 interactions were detected (1) between pain vigilance (high PVAQ vs low PVAQ) and the stimulus type in discrimination trials (pain vs nonpain; $F_{1,16} = 9.545$, $P = 0.007$), and (2) between pain vigilance and the task type in pain trials (discrimination vs categorization; $F_{1,16} = 5.536$, $P = 0.032$), indicating that the impact of pain vigilance was of a significantly different magnitude between the discrimination of pain and nonpain as well as between discrimination and categorization of painful stimuli. There was also a trend towards a stimulus (pain vs nonpain) × task (discrimination vs categorization) × pain vigilance (high PVAQ vs low PVAQ) interaction ($F_{1,16} = 3.991$, $P = 0.063$). Correct response rates, reaction times, and task difficulty in discrimination tasks did not differ between different levels of state and trait anxiety

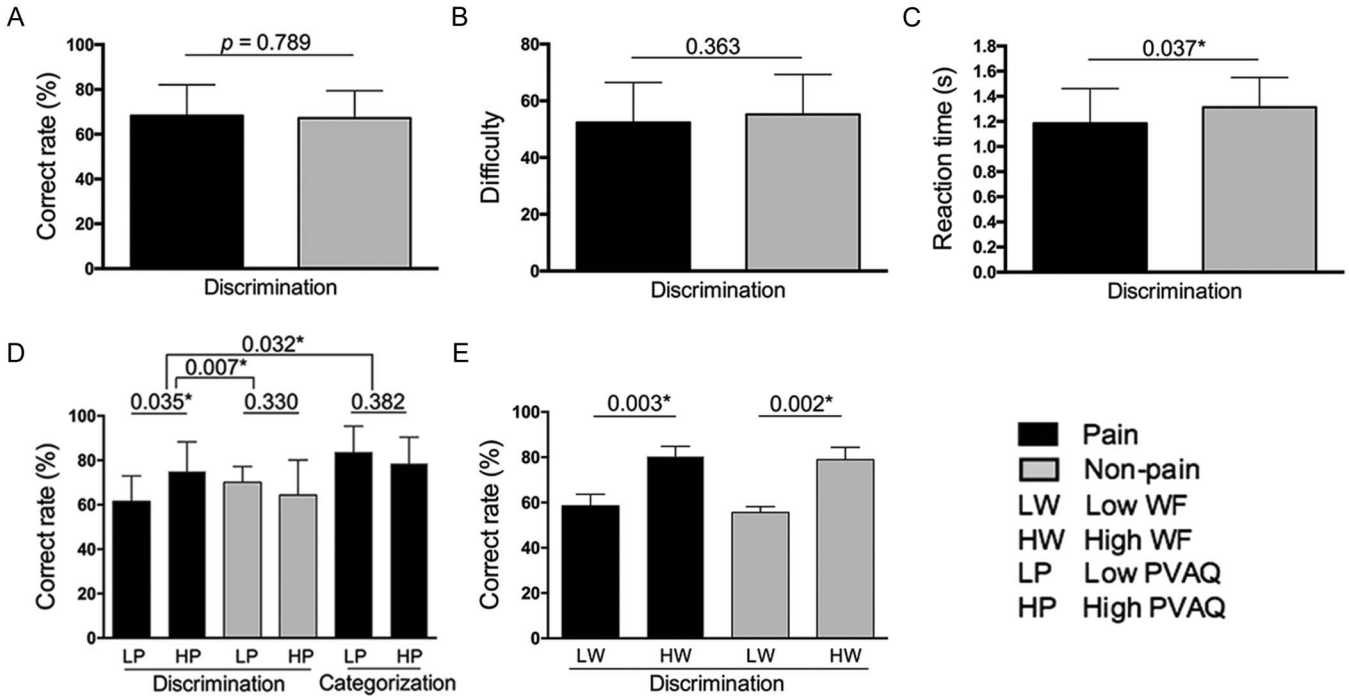

Figure 2. Behavioral results. (A and B) For discrimination tasks, the correct rate (%) and task difficulty were not significantly different between painful and nonpainful trials. (C) Intensity discrimination of pain entailed a faster reaction time (s) than nonpain discrimination. (D) Compared with participants having a lower Pain Vigilance and Awareness Questionnaire (PVAQ) score, those with a higher PVAQ score exhibited a higher correct rate during the discrimination of pain, but not during the discrimination of nonpain and categorization of pain. (E) A larger Weber fraction (WF) for stimulus intensity was associated with a higher correct rate. *$P < 0.05$. Error bars indicate SDs.

(all $P > 0.100$). With regard to Weber's law, there was a main effect of Weber fraction ($F_{1,\ 17} = 29.500$, $P < 0.001$), with a larger Weber fraction associated with a higher correct response rate (**Fig. 2E**). The stimulus-by-Weber fraction interaction ($F_{1,\ 17} = 0.028$, $P = 0.869$) was not significant. Taken together, these findings clearly suggest a specific effect of pain vigilance and the modulation by Weber's law on the intensity discrimination of pain.

3.2. Brain activation related to pain

Painful stimuli produced brain activation within pain-processing regions,[2] which included the thalamus, primary and secondary somatosensory cortices, insular cortex, and anterior cingulate cortex (**Fig. 3** and supplementary Table 2; available online at http://links.lww.com/PAIN/A493). Compared with nonpainful stimuli, painful stimuli elicited higher BOLD signals in brain regions related to the sensory-discriminative aspects of pain processing, including the right primary somatosensory cortex (peak MNI coordinates *x/y/z* = 30/−38/57, $t_{(1,15)} = 3.21$, $P = 0.028$; SVC FWE-corrected) and the left secondary somatosensory cortex (*x/y/z* = -54/-24/21, $t_{(1,15)} = 3.03$, $P = 0.049$; SVC FWE-corrected). A trend towards an increase in activation during painful stimuli was also observed for the right secondary somatosensory cortex (*x/y/z* = 62/−18/19, $t_{(1,15)} = 2.91$, $P = 0.059$; SVC FWE-corrected).

3.3. Brain activation during the delay period

Previous research has demonstrated that delayed discrimination decisions involve the short-term maintenance of the preceding sensory experience.[29,55] Hence, we first examined fMRI data

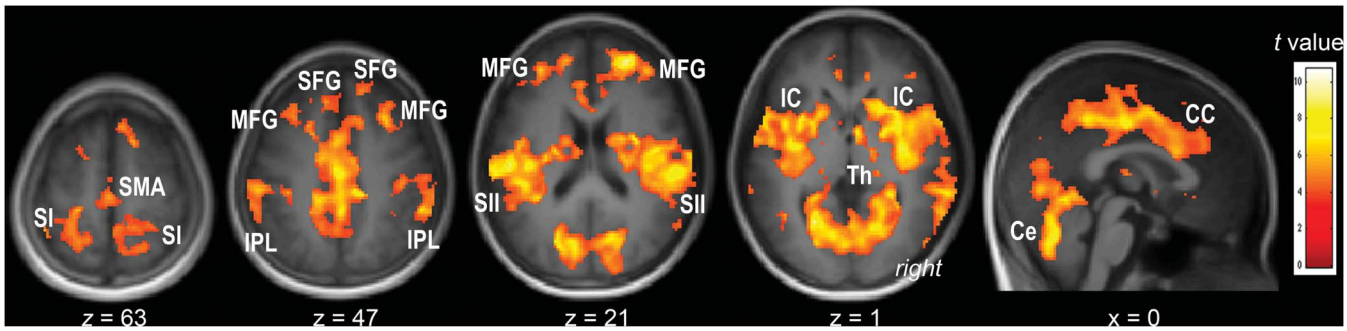

Figure 3. Brain activation to painful electrical stimulation. Compared with the baseline, painful stimulation to the left volar forearm evoked activation in the primary (SI) and secondary (SII) somatosensory cortices, supplementary motor area (SMA), superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior parietal lobule (IPL), insular cortex (IC), thalamus (Th), anterior cingulate cortex (CC), and cerebellum (Ce). Activations were thresholded at $P < 0.05$, FWE corrected across the whole brain and overlaid on an average structural image. The bar on the right side shows the range of *t* scores for SPM 8. FWE, family-wise-error.

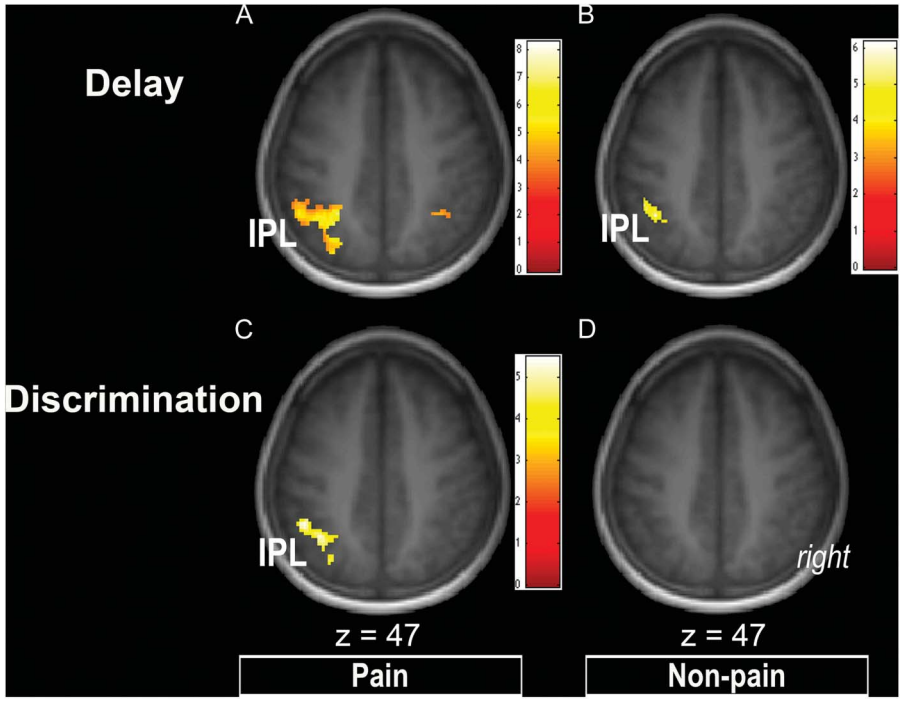

Figure 4. Brain activation during the delay and discrimination periods. (A and C) Both the delay and discrimination phases in painful trials entailed activation in the left inferior parietal lobule [IPL; contrast: "(PD > PO)"; $P < 0.05$ FWE small-volume corrected]. (B and D) For nonpainful stimuli, the left IPL was also activated during the delay period [contrast: "(ND > NO)"; $P < 0.05$ FWE small-volume corrected] but not during the discrimination task. Activation clusters survived small-volume corrections ($P < 0.05$ family-wise error corrected, after an initial height threshold of $P < 0.001$) and were overlapped on an average structural image. The bar on the right side shows the range of *t* scores for SPM 8. FWE, family-wise-error.

during the delay period to clarify whether this process engaged activity within the attentional networks, particularly the IPL and SFG. We found that holding a painful somatosensory experience during the delay period produced activations in the bilateral IPL (left IPL: peak MNI coordinates *x/y/z* = −28/−62/41, $t_{(1,15)} = 8.29$, $P < 0.001$; right PL: *x/y/z* = 34/−54/45, $t_{(1,15)} = 4.69$, $P = 0.047$; SVC FWE-corrected; **Fig. 4A**). Complementary whole-brain analyses further revealed that the delay period of pain discrimination trials indeed entailed activations in the attention-related fronto-parietal network,[15] including the IPL, superior parietal lobule, and middle frontal gyrus (supplementary Figure 1A, available online at http://links.lww.com/PAIN/A493; and **Table 2**). With regard to nonpainful stimuli, the left IPL was also activated during the delay period (*x/y/z* = −40/−54/45, $t_{(1,15)} = 6.16$, $P = 0.010$; SVC FWE-corrected; **Fig. 4B**), and an exploratory whole-brain analysis revealed additional activation in the left premotor area (supplementary Figure 1B, available online at http://links.lww.com/PAIN/A493; and **Table 2**).

3.4. Brain activation related to intensity discrimination of pain

To elucidate the neural underpinning unique to pain discrimination and clarify whether the delay-related activity contributed to the subsequent comparison process, we next assessed brain activation during the discrimination period. Interestingly, the left IPL remained activated in pain trials (contrast: "PD > PO"; *x/y/z*: −48/−50/47; $t_{(1,15)} = 5.50$, $P = 0.024$ SVC FWE-corrected; **Fig. 4C**) but not in nonpain trials (contrast: "ND > NO"; **Fig. 4D**). A direct contrast between painful and nonpainful trials revealed a trend towards an increase in responsivity in the left IPL [contrast: "(PD > PO) > (ND > NO)"; *x/y/z*: −48/−60/49, $t_{(1,15)} = 4.68$, $P = 0.070$ SVC FWE-corrected]. Exploratory whole-brain analyses showed that most delay-related brain areas remained activated during the discrimination phase in both pain and nonpain trials. The intensity discrimination of pain entailed activations in frontal, parietal, and occipital areas (supplementary Figure 1C, available online at http://links.lww.com/PAIN/A493; and **Table 3**), whereas nonpain discrimination activated the left premotor area (supplementary Figure 1D, available online at http://links.lww.com/PAIN/A493; and **Table 3**).

3.5. Modulation of pain vigilance during intensity discrimination of pain

The above findings suggest a pivotal role of the left IPL in intensity discrimination of pain. Given the specific modulation of pain vigilance on pain discrimination behaviors (**Fig. 2D**), and the implication of the IPL in the top-down attentional-control processes during perceptual decisions,[31,37,38] we predicted that individual pain vigilance would modulate the coupling between the IPL and brain areas associated with pain processing, but only when this coupling was required for pain discrimination tasks. Consistent with our prediction, participants with high PVAQ scores (scores > 41, n = 9) exhibited significantly higher strength of functional connectivity from the left IPL to the right thalamus as compared with those having low PVAQ scores (scores < 41, n = 9) during the intensity discrimination of pain (PPI contrast: "PD > PO"; *x/y/z* = 6/−26/3; $t_{(1,14)} = 3.23$, $P = 0.047$ SVC FWE-corrected) but not nonpain. This IPL-thalamus coupling was indeed positively correlated with PVAQ scores during the intensity discrimination of pain (PPI contrast: "PD > PO"; *x/y/z* = 6/−24/1; $t_{(1,14)} = 3.99$, $P = 0.016$ SVC FWE-corrected; **Fig. 5A**) but not

Table 2

Brain activation during the delay period.

Region	Laterality	MNI coordinates (x, y, z)			t	Cluster # (voxels)
Pain						
IPL	Left	−28	−62	41	8.29	1 (5170*)
	Right	34	−54	45	4.69	1
SPL	Left	−32	−70	55	6.95	1
	Right	32	−68	51	5.84	1
Precuneus	Left	−8	−76	45	5.52	1
	Right	8	−72	45	7.49	1
MFG	Left	−52	26	39	6.73	2 (1806*)
PMA	Left	−48	0	37	6.35	2
	Right	30	0	43	4.93	3 (350*)
SMA	Left	−2	8	57	7.41	4 (695*)
	Right	8	14	51	4.70	4
SOG	Right	24	−68	43	7.22	1
MOG	Left	−26	−82	37	7.36	1
	Right	32	−72	39	10.08	1
Cerebellum	Left	−22	−84	−27	7.19	5 (3257*)
	Right	34	−56	−33	9.13	5
Nonpain						
IPL	Left	−40	−54	45	6.16	1 (199*)
PMA	Left	−50	14	31	8.11	2 (430*)

Activated clusters are numbered, and activation foci corresponding to different anatomical regions within the clusters are given as peak MNI coordinates (mm).

* This table shows results of whole-brain analyses ($P < 0.05$ cluster-wise FWE-corrected; cluster sizes are reported in parentheses) during the delay period.

FWE, family-wise-error; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MOG, middle occipital gyrus; PMA, premotor area; SMA, supplementary motor area; SOG, superior occipital gyrus; SPL, superior parietal lobule.

nonpain. This thalamic cluster was located within the medial portion of the right thalamus.[5] More importantly, the strength of this IPL-thalamus coupling paralleled an individual's task performance under pain discrimination ($P = 0.017$) but not nonpain discrimination ($P = 0.062$), with the correlation during painful trials significantly stronger than that during nonpainful trials ($P = 0.002$; **Fig. 5B**). These findings strongly indicate that this parieto-thalamic coupling represents the influence of pain vigilance during the intensity discrimination of pain.

Table 3

Brain activation related to intensity discrimination.

Region	Laterality	MNI coordinates (x, y, z)			t	Cluster # (voxels)
Discrimination: pain						
IPL	Left	−48	−50	47	5.50	1 (316*)
IFG	Left	−44	18	33	4.84	2 (461*)
PMA	Left	−26	−14	59	6.48	3 (488*)
		−50	6	33	6.05	2
	Right	34	−14	61	6.58	4 (186*)
SMA	Left	−8	4	59	5.40	3
IOG	Left	−22	−90	−7	6.86	5 (199*)
	Right	20	−92	−7	4.98	6 (178*)
LG	Left	−36	−88	−15	5.48	5
	Right	22	−88	−15	4.71	6
Discrimination: nonpain						
PMA	Left	−34	−10	53	5.92	1 (174*)

Activated clusters are numbered, and activation foci corresponding to different anatomical regions within the clusters are given as peak MNI coordinates (mm).

* This table shows results of whole-brain analyses ($P < 0.05$ cluster-wise FWE-corrected; cluster sizes are reported in parentheses) during the discrimination period.

FWE, family-wise-error; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; IPL, inferior parietal lobule; LG, lingual gyrus; PMA, premotor area; SMA, supplementary motor area.

3.6. Parametric modulation analysis during intensity discrimination of pain

Finally, we explored the neural substrate underlying the modulation of Weber's law on pain intensity discrimination (**Fig. 2E**). Specifically, we tested whether cerebral activity in the attentional networks, especially the SFG, reflected Weber fraction of pain intensity. By implementing the trial-by-trial Weber fraction as a parametric modulator during the discrimination period, we found that the Weber fraction of the pain intensity difference was correlated with the activity in the right SFG (parametric contrast: "PD"; $x/y/z = 18/38/47$; $t_{(1,19)} = 5.31$, $P = 0.009$ SVC FWE-corrected) during pain discrimination tasks (**Fig. 6A**). Note that, by directly contrasting this parametric effect in painful vs nonpainful trials, we observed a cluster in the right SFG (parametric contrast: "PD > ND"; $x/y/z = 18/38/47$; $t_{(1,15)} = 4.59$, $P = 0.025$ SVC FWE-corrected; **Fig. 6B**) overlapping with the cluster identified in the pain discrimination contrast (**Fig. 6A**). In a supplementary analysis, we used an uncorrected threshold ($P < 0.001$ with an extent size of 10 voxels) to scrutinize the extent of activation across the whole brain and found that the maximal t value of the peak voxel was located in the right SFG, not only during the intensity discrimination of pain but also during the direct comparison between painful and nonpainful trials (supplementary Table 3, available online at http://links.lww.com/PAIN/A493). Taken together, these findings suggest that the right SFG is an important brain region that expresses the Weber fraction for pain intensity.

4. Discussion

In the present study, the intensity ratings in pain trials were clearly painful and higher than those in nonpain trials, which was accompanied by increased activations in brain regions processing the sensory-discriminative aspects of pain. These findings ensure that our fMRI results are highly relevant to pain. By controlling the potential confounding of task difficulty between painful and nonpainful trials, we demonstrated, for the first time, the significant influence of attention to pain (ie, pain vigilance) on the intensity discrimination process of pain at both behavioral (ie, task performance) and neural (IPL-thalamus coupling) levels. The IPL-thalamus coupling exclusively predicted an individual's pain discriminability but not nonpain discriminability. Another important finding of the present study is that the estimation of pain intensities was modulated by Weber's law, with the right SFG expressing the Weber fraction during the intensity discrimination process of pain but not nonpain stimuli. Because these neural mechanisms are not observed during innocuous events and categorization tasks, the current study thus characterizes a novel and distinct mechanism underlying the intensity discrimination of pain in humans.

4.1. Enhanced attention during pain discrimination

Compelling evidence points out that the perceptual decision making processes in primates require complex cognitive operations, such as the representation of sensory evidence, the formation of decision variable, available attentional resources, and performance monitoring.[18,26,29] Among these cognitive processes, attention is particularly associated with the task difficulty, with an increase in attention demand and brain responses when the task becomes more difficult.[49,57] This issue is particularly important for pain, because more attention is

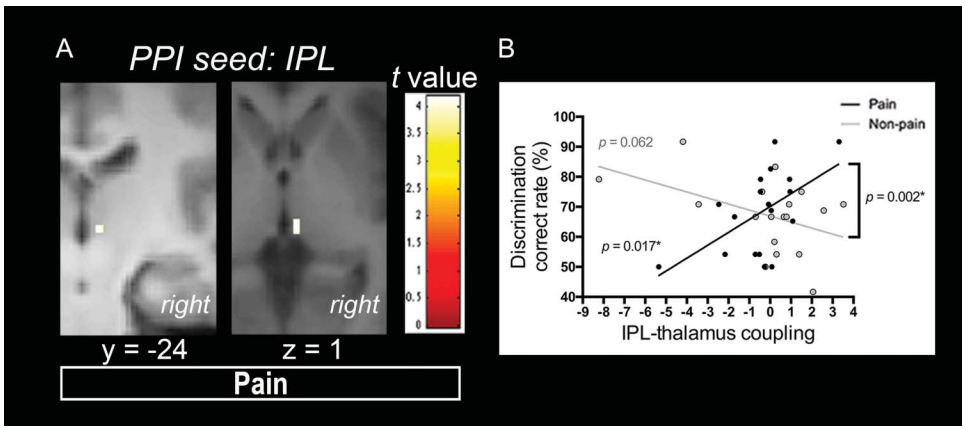

Figure 5. Functional connectivity correlated with pain vigilance during pain discrimination. (A) A psychophysiological interaction (PPI) analysis using the left inferior parietal lobule (IPL) as seed revealed that the correlation between individual pain vigilance (assessed with the Pain Vigilance and Awareness Questionnaire, PVAQ) and the functional connectivity from the left IPL to the right thalamus (PPI contrast: "PD > PO"; $P < 0.05$ FWE small-volume corrected) was significant during intensity discrimination of pain. Activation clusters survived small-volume corrections ($P < 0.05$ family-wise error corrected, after an initial height threshold of $P < 0.001$) and were overlapped on an average structural image. The bar on the right side shows the range of *t* scores for SPM 8. (B) The correlation between the strength of the IPL-thalamus connectivity and task performance was significantly positive during pain discrimination ($r = 0.553$, $P = 0.017$) but not significant during nonpain discrimination ($r = -0.448$, $P = 0.062$), with a significant difference between both correlations ($F_{(1,32)} = 11.302$, $P = 0.002$). FWE, family-wise-error.

involuntarily captured by painful stimuli compared with nonpainful stimuli. In the present study, subjective levels of task difficulty were comparable between pain and nonpain discrimination tasks, which is critical because it allows us to explore the potential role of attention in pain-related discrimination processes. Since the task difficulty was titrated for pain and nonpain discrimination tasks, the differences in activation patterns between pain and nonpain discrimination tasks cannot be accounted for by the relative task difficulty.

Compared with the estimation of nonpain intensities, we observed that discrimination of pain intensities entailed a faster response latency, suggesting the allocation of more attention to pain discrimination. In line with these behavioral data, we found persistent activation within the left IPL during the delay and discrimination periods of pain. The IPL has been implicated in working memory operations during perceptual decisions[15,22,31,38] and has been shown to be activated when subjects compared pain intensities.[37,45] As a polymodal association region interconnecting with both prefronto-limbic structures[59] and pain-processing regions such as the somatosensory cortices[33] and insula,[42] the left IPL has been implicated in the cognitive processes for nociceptive stimuli, including pain-related attention[53,60] and anticipation.[34] Our data thus extend the function of IPL in pain processing, indicating an essential role for it in differentiating the intensity difference between sequentially applied noxious stimuli. Moreover, our exploratory whole-brain analyses further revealed that the majority of delay-related fronto-parietal activations remained activated during the discrimination phase, which substantiates the notion that the preceding somatosensory experiences are brought online in working memory and are integrated with present stimulus information to form perceptual decisions in a delayed discrimination task.[29,55] Therefore, we postulate that intensity discrimination of noxious stimuli relies on enhanced recruitment of the fronto-parietal attention network, whereby relevant information can be retained online and manipulated on a trial-by-trial basis as the comparison process requires.

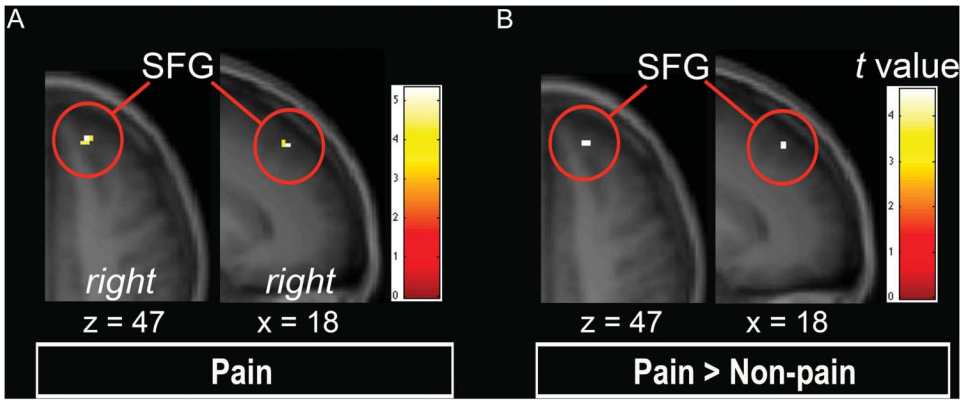

Figure 6. Brain activity parametrically correlated with the Weber fraction during pain discrimination. (A) The right superior frontal gyrus (SFG; $P < 0.05$ FWE small-volume corrected) showed a linear activity increase with the relative intensity difference between stimuli (ie, Weber fraction) during pain discrimination. (B) The correlation in the right SFG ($P < 0.05$ FWE small-volume corrected) during pain discrimination was significantly stronger than that during nonpain discrimination. Activation clusters survived small-volume corrections ($P < 0.05$ family-wise error corrected, after an initial height threshold of $P < 0.001$) and were overlapped on an average structural image. The bar on the right side shows the range of *t* scores for SPM 8. FWE, family-wise-error.

4.2. Modulation of pain vigilance on pain discrimination

During the discrimination process, we also observed that participants who biased their attention to pain exhibited a more accurate pain discriminability, indicating the impact of pain-relevant personality traits. The facilitatory effect of pain vigilance is consistent with previous observations that intentionally directing attention towards pain enhances pain-related responses, such as detecting pain intensity changes[13] and processing facial expressions of pain.[4] The finding that individual pain vigilance did not influence pain sensitivity indicates that the effect of pain vigilance on pain discrimination is due to cognitive rather than sensory processes. Of note, individual differences in attention to pain merely influence the discrimination of stimulus intensities in the noxious range. These findings support the idea that the differentiation of somatic stimulus intensity is prioritized to sensory information with utmost behavioral relevance such as pain.[13,66]

In parallel to these behavioral results, we demonstrated that participants with high levels of pain vigilance had stronger functional connectivity between the left IPL and the right medial thalamus during pain discrimination, suggesting that this functional coupling is primarily involved in the attentional processes associated with pain discrimination. Importantly, this notion is further strengthened by the finding that the strength of this parieto-thalamic coupling specifically predicted pain discrimination performance. Several lines of evidence support the notion that this parieto-thalamic connectivity reflects attentional modulation on the differentiation of noxious stimuli. The thalamus is structurally and functionally connected with the IPL.[33,68] Both structures receive dense noradrenergic innervation form the locus coeruleus, which plays critical roles in selective attention and vigilance.[6] Within the attentional system, evidence has indicated that the IPL and thalamus form the core components of the vigilance network.[22] With regard to pain, the medial thalamus contains nociceptive-specific neurons[16] and has been implicated in mediating the influence of attention on the discrimination of noxious stimuli.[12] Activations within the IPL and thalamus have been demonstrated to increase monotonically with the extent of attention paid to noxious stimuli.[3,48,53] Therefore, our data support the existence of vigilance-related enhancement in the parieto-thalamic network during the intensity discrimination process of pain. Future studies manipulating participants' attention to pain or assessing real-time subjective attention to painful stimuli would be required to further clarify the role of top-down attentional modulation in the pain discrimination process.

4.3. Modulation of Weber fraction during pain discrimination

Although our data suggest an important role of pain-related attention during the intensity discrimination of pain, another consideration is that attention may support another computational mechanism to facilitate the discrimination process. This possibility was assessed by our parametric modulation analysis. Consistent with previous research,[54] we observed the modulation of Weber's law on pain discrimination performance. Notably, our region-of-interest analysis as well as the supplementary whole-brain analysis demonstrated that the right SFG emerged as the key region reflecting the Weber fraction for pain intensity. Previous evidence points to the SFG as an important brain structure for the intensity discrimination process of pain. The SFG is anatomically interconnected with other subregions in the lateral prefrontal and posterior parietal areas to subserve working memory processes,[15,46] which is required for a delayed discrimination process.[29,55] Lesions involving the SFG produced an impairment in perceptual discrimination tasks.[47] For pain, the SFG has been shown to become activated during the discrimination of pain intensities.[45] Taken together, we propose that the heightened attention maintained by the parieto-thalamic network during pain discrimination would allow the SFG to compute the relative intensity difference between painful stimuli to drive the discrimination process.

In conclusion, we highlight a capacity of the human brain to discriminate the intensity difference between painful stimuli as a function of the Weber fraction. This process is subject to an individual's vigilance to pain and involves the collaboration of attention- and pain-related systems. We propose that the pain discrimination mechanisms identified in the present study may play an adaptive and protective role by providing sensory-discriminative information of painful stimuli for humans to cope with potentially life-threatening situations.[8] Because pain-relevant attention varies across individuals, studies should therefore consider the intrinsic interaction of pain and attention networks throughout the brain when subjects perform pain-related cognitive tasks. Clinically, patients with chronic pain often exhibit attentional deficits and have decreased performance on cognitively demanding tasks,[20] including the discrimination of somatic stimulation.[50] This phenomenon implies that the discrimination process for pain intensities may be impaired in these patients, which contributes to the maladaptive state in chronic pain.[35] Given improving sensory discriminability could potentially reverse cortical reorganization and alleviate chronic pain,[23,43] future research investigating the role of pain discrimination in the persistence of chronic pain would provide new insights into the potential mechanisms of therapeutic approaches.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A493.

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