Research Paper

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Neural mechanisms of pain relief through paying attention to painful stimuli

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Abstract

A commonly held belief suggests that turning one's attention away from pain reduces it, whereas paying attention to pain increases it. However, some attention-based therapeutic strategies for pain, such as mindfulness-based interventions, suggest that paying attention to painful stimuli can reduce pain, resulting in seemingly contradictory conclusions regarding attention and pain. Here, we investigated the analgesic effects of attention modulation and provide behavioral and neural evidence that paying attention to pain can reduce pain when attention is directed toward the specific features of painful stimuli. The analgesic effects of paying attention to painful stimuli were mediated by the primary somatosensory cortex and goal-directed attention regions in the prefrontal and parietal cortex. These findings suggest that suppressing early somatosensory processing through top–down modulation is the key mechanism of the analgesic effects of paying attention to painful stimuli, providing evidence that pain itself can be used as a component of pain management.

Keywords: Pain, Attention, Psychophysics, fMRI, Mediation analysis

1. Introduction

About a fifth of the population suffers from chronic pain.[14] Although opioids have been widely used for pain relief, the development of nondrug interventions for pain will be highly beneficial, as deaths from opioid overdose are on the rise. A straightforward way to relieve pain is to divert attention away from painful stimulation.[5,8,13,29,43,49,50] By contrast, pain usually increases when attention is paid to painful stimulation.[16,37] In patients with chronic pain, painful spells last a long time,[39] making it difficult for patients to divert their attention from the pain. Therefore, it would be beneficial if these patients could reduce their pain by focusing their attention on the pain, rather than turning their attention away from it.

It has been suggested that the brain mechanisms that process features of noxious stimuli and those that process pain experience are not identical.[21,38] Any successful attention system should be open to the possibility that current engagement could be interrupted at any time by imposing a new superordinate goal to protect organs from harm,[40] and pain is an ideal example to illustrate this model.[15] Although it has been debated as to whether pain is a unique percept, distinct from salience,[31] there is a consensus that the processing of pain stimuli is automatically boosted by bottom–up attention.[15,33,50] On the other hand, the processing of task-relevant stimuli can be boosted voluntarily by top–down attention.[34,50] In addition, when top–down attention and bottom–up attention occur simultaneously, competition could arise between these 2 types of attention.[34] Therefore, we hypothesized that enhancing the former mechanism by directing attention to specific sensory features of stimuli could suppress the latter process, thereby reducing pain. To test this hypothesis, it is essential to dissociate the system activated by a focused top–down attention to the features of the pain stimulus from the attention system generally triggered by the pain stimulus.

Here, we designed a psychophysical experiment in which subjects were instructed to divert their attention away from pain or pay attention to specific sensory features of the painful stimuli while we dynamically modulated the heat intensity they were subjected to over time. We collected subjective pain intensity ratings for each trial and monitored the brain activity induced by painful stimulation with functional magnetic resonance imaging (fMRI). During each trial, both thermal and visual stimulation were presented alongside a task in which we asked participants to detect whether the thermal or visual stimuli were changed over time. The thermal task brought attention to the sensory features of the painful thermal stimuli, whereas the visual task directed participants' attention to the sensory features of the visual stimuli and diverted their attention away from the painful stimuli. There were also trials in which the thermal and visual stimuli were given without tasks to provide a baseline condition. Then, we examined brain regions that mediate the effects of attention on pain perception using whole-brain, multilevel mediation analysis.[3,56,57]

2. Methods

2.1. Participants

Thirty-four healthy adults (mean age = 27.1 years, SD_{age} = 6.22; 10 females) participated in the fMRI experiment. Subjects

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

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provided informed consent in accordance with the Declaration of Helsinki, as approved by the Institutional Review Board of Sungkyunkwan University (IRB file number: 2017-05-001-010). All subjects had normal or corrected-normal vision and had no history of psychological, neurological, or pain disorders. All participants were reimbursed for their participation.

2.2. Materials and procedures

2.2.1. Thermal stimulation

Thermal stimulation was delivered to the volar surface of the left forearm using a 30 × 30 mm Peltier thermode (CHEPs; Medoc Ltd, Ramat Yishai, Israel).

2.2.2. Thermal stimulation type

2.2.2.1. Constant

The stimulation lasted 3 seconds and consisted of a 0.5-second ramp-up period, a 0.5-second ramp-down period, and 2 seconds at the target temperature of 48°C. The baseline temperature was 36°C.

2.2.2.2. Modulation

The first target temperature of 48°C was maintained for 0.3 seconds after it was reached from the baseline temperature, and then, the temperature was decreased to the second target temperature (see below). The second target temperature was maintained for ~ 1 second, and then, the temperature was increased to the first target temperature again. The first target temperature was maintained once again for 0.3 seconds, and then, the temperature was lowered to baseline (36°C). The temperature was raised or lowered at a rate of 30°C/second. The second target temperature had 7 levels (44°C, 45°C, 45.5°C, 46°C, 46.5°C, 47°C, and 47.5°C), one of which was selected for each participant according to their behavior during the adaptive staircase procedure.

2.2.3. Visual stimulation

An oriented Gabor patch at fixation (subtending 4° of visual angle, 1 c/°) was generated on a gamma-corrected, PROPixx DLP LED projector (75-Hz refresh).[27] All aspects of the experiment-display generation, trial sequences, and staircase procedure were controlled using MATLAB and the Psychphysics Toolbox running on a MacBook Pro.[28] For each trial, one of 16 possible orientations, from 10° to 180° at 10° intervals except for 90° and 180°, was randomly selected.

2.2.4. Visual stimulation type

2.2.4.1. Constant

The oriented Gabor patch lasted 3 seconds without contrast change (0.6 contrast ratio).

2.2.4.2. Modulation

The contrast (ratio) of the oriented Gabor patch was updated every 0.1 second as a function of the difference between 0.6 and the probability density function of the normal distribution, with the mean and standard deviation sigma falling in the range of [−16, 16]. For each subject, the mean value was 0 and the standard deviation sigma value was selected from the following values of [1.0, 2.0, 2.5, 3.0, 3.5, 3.75, 4.0, 4.25, 4.50, 4.75, 5.00, 5.25, 5.50, 6.00] through the adaptive staircase procedure.

2.3. Functional magnetic resonance imaging task design

Subjects lay in the fMRI scanner and viewed the visual stimuli presented on the screen through a mirror attached to the head coil while a thermode was attached on the volar side of their left forearm (**Fig. 1A**). A response box for tasks and pain rating was held in the subjects' right hand. Each trial started with a 1-sec cue (randomly selected from visual task, thermal task, or passive) followed by a concurrent presentation of noxious heat and a sinusoidal grating for 3 seconds by the thermode and the screen, respectively. A word cue was presented in the center of the screen. The cues included "thermal change detection task," "visual change detection task," and "no stimulus change detection task," which provided the task information for the trial. When a response prompt (red dot) appeared a few seconds (3, 5, or 7 seconds) after the stimulus disappeared, the subjects reported whether the stimulus was modulated or constant by pressing key 1 or key 2, respectively, on the response box during the thermal or visual tasks. In the case of the passive condition, the subjects did not respond. Immediately after, subjects reported how much pain they felt under all 3 conditions by moving an arrow on a horizontal line using the 2 buttons on the button box. Given that pain intensity could vary within a trial, participants were instructed to report the average pain rating for each trial. For pain rating, we used a generalized labeled magnitude scale, which is a semantic scale of perceptual intensity characterized by a quasilogarithmic spacing of its verbal labels.[6,17,36]

The stimuli presented in each trial satisfied one of the following 4 conditions. (1) Both the thermal and visual stimuli were modulated. (2) The thermal stimulus was modulated, whereas the visual stimulus was constant. (3) The thermal stimulus was constant, whereas the visual stimulus was modulated. (4) Both the thermal and the visual stimuli were constant (**Fig. 1B**). Participants completed 5 runs consisting of 20 trials each, for a total of 100 trials. In each run, 80% were task trials (40% visual task trials and 40% thermal task trials), whereas the remaining 20% were passive trials (**Fig. 1C**). During the thermal and visual task trials, each of the 4 stimulus conditions was presented at the same rate. On the other hand, during the passive trials, only stimuli that satisfied condition 2 were presented (**Fig. 1C**). The order of each condition was randomized, reducing the impact of previous trials. To avoid skin damage caused by the transmission of harmful heat, the thermode was relocated to a different skin site for each of the 20 trials.

2.4. Staircase procedure

It has been suggested previously that there is a correlation between the degree of difficulty of a given task and the degree of attention that participants pay to it.[18] Therefore, if there is a significant difference in difficulty between the visual and thermal tasks, the degree of attention paid during the 2 tasks may be also different. Therefore, a staircase procedure was performed before the fMRI experiment to find the contrast values of visual and thermal stimuli that matched the 2 tasks' attention levels.[12] Subjects performed each of the visual and thermal tasks described above in a total of 80 trials (40 trials for each task) without pain rating. We designed both of the visual and thermal tasks to approach a correct answer rate of ~90% through a seven-down one-up staircase procedure in which the stimulus amplitude decreased after 7 correct responses and increased when 1 response was incorrect. During the actual fMRI tasks, the correct

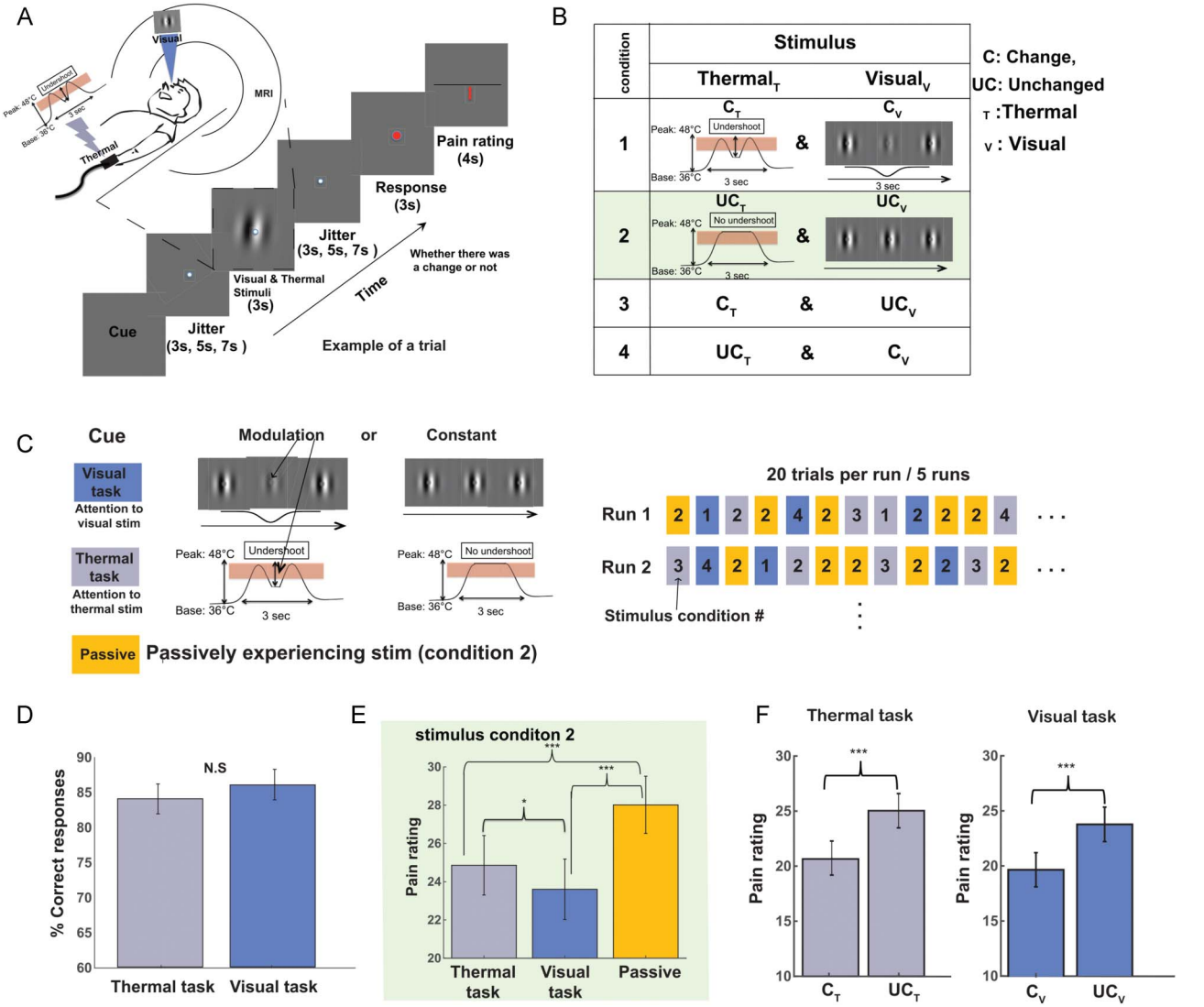

Figure 1. Experimental design and behavioral results. (A) Example of a trial. Visual and thermal stimuli were presented at the same time, and participants were asked to pay attention to visual or thermal stimuli according to the presented cues. (B) There were 4 conditions depending on the pairs of thermal and visual stimulus types. (C) Task description. During the task, participants were asked to detect changes in visual or thermal stimuli depending on the task cues. If the cue was passive, participants were asked to passively experience stimuli without performing any tasks. (D) Average performance scores of the tasks. (E) Average pain ratings for each task condition for the trials from the stimulus condition 2 in Fig. 1B (ie, when both stimuli were kept constant). (F) Comparisons of mean pain ratings between the heat-change vs heat-constant conditions (the left plot was for the thermal task, and the right plot was for the visual task).

answer rate was close to ~85% because of environmental differences, such as the narrowness of the MR scanner and the inconvenience of the task when performed lying down (**Fig. 1D**).

2.5. Functional magnetic resonance imaging acquisition and preprocessing

2.5.1. Data acquisition

Whole-brain fMRI was acquired on a 3 T Siemens Prisma Scanner at the Center for Neuroimaging Research at Sungkyunkwan University. Responses were made with participants' right hand through an MRI-compatible button box. Structural images were acquired for slice placement and registration with an magnetization prepared rapid gradient echo sequence as follows: echo time/repetition time = 2.28/2300 ms, inversion time = 900 ms, 192 slices, flip angle = 8°, and voxel size = 1 × 1 × 1 mm^3. Functional echo-planar images were acquired with the following parameters: echo time/repetition time = 30/2000 ms, 72 slices, flip angle = 90°, field of view = 224 mm, 112 × 112 matrix, and voxel size = 2 × 2 × 2 mm^3.

2.5.2. Preprocessing

Functional magnetic resonance imaging data processing was performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, which is part of the FMRIB's Software Library (www.fmrib.ox.ac.uk/fsl). Registration to high-resolution structural or standard space images was performed using FLIRT (FMRIB's Linear Image Registration Tool).[22,23] Registration from high-resolution structural to standard space was then further refined using FNIRT nonlinear registration.[1,2] The following prestatistics processing was applied: motion correction using MCFLIRT (Motion Correction FLIRT) ,[22] nonbrain removal using Brain Extraction Tool,[47] spatial smoothing using a Gaussian kernel of full width at half maximum 5 mm, grand-mean intensity normalization of the entire 4D data set by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares straight-line fitting, with sigma = 50.0 seconds). After preprocessing, the functional scans were registered to the Montreal Neurological Institute 152 standard space (MNI152 T1 2 mm) using affine registration (FLIRT), 6 degrees of freedom between the echo-planar images and the T1 structural scan, and 12 degrees of

freedom from this to the Montreal Neurological Institute standard. Time series statistical analysis was performed using FMRIB's Improved Linear Model with local autocorrelation correction.[58]

2.6. Functional magnetic resonance imaging analysis

2.6.1. Single-trial analysis

Previous studies have shown that single-trial analysis is reliable and increases sensitivity when modeling response to pain.[57] Thus, we used this analysis to measure the brain response to each trial, in each voxel, for each subject.[3,57] We quantified single-trial response magnitudes by constructing a Generalized Linear Model design matrix with separate regressors for each trial, as in the beta series approach of Rissman et al.[45] For each run, boxcar regressors, convolved with the canonical hemodynamic response function, were constructed to model a 3-second pain event (visual and thermal stimulation periods shown in **Fig. 1A**). To obtain single-trial beta images through GLM analysis, we included a trial-specific regressor for each trial, as well as nuisance covariates (cerebrospinal fluid&white matter signals and motion). Using FEAT (FMRIB's Software Library's general linear modeling fMRI analysis tool) for this GLM analysis, a total of 100 beta images were obtained from 5 runs per participant. We also calculated a trial-by-trial variance inflation factor (a measure of design-induced uncertainty because, in this case, of collinearity with nuisance regressors) to mitigate artifacts due to sudden motion, scanner pulses, etc. Any trials with variance inflation factors that exceeded 2.5 were excluded from all analyses.[3,57]

2.6.2. Pattern expression analysis

The neurologic pain signature (NPS) response was estimated for each single-trial beta image by taking the dot product of a vectorized activation image with the NPS pattern, yielding a continuous scalar value.[55,57]

2.6.3. Multilevel two-path mediation

Using the Mediation Toolbox, multilevel mediation analyses were performed based on a standard 3-variable path model.[56] In the standard 3-variable path model, the initial variable X is the experimentally manipulated attention (which takes on the value of 1 for the thermal or visual tasks and −1 for the passive condition) and the outcome variable (Y) is the subject's series of pain ratings.[56] The mediating variable (M) is the NPS response (or a single voxel's series of beta images for whole-brain, multilevel mediation analysis). The mediation analysis tests whether a covariance between the X and Y variables can be explained by the mediating variable M. Thus, the mediation test evaluates whether the mediator accounts for a significant amount of the effect of the manipulated variable on the measured outcome.

The formal mathematical description of the first-level mediation model is as follows:

$$y = cx + e_y$$

$$m = ax + e_m$$

$$y = bx + c'x + e'_y$$

where n (trials) × 1 data vectors for each subject contained the outcome (y, reported pain rating), predictor (x, attentional modulation), and data from a candidate mediation voxel (m, activity in single-trial beta images). Note that vector x, y, and m used in the above-mentioned equations corresponds to variable X, Y, and M, respectively. The e_y, e_m, and e'_y vectors denote residual error for the outcome and mediator controlling for x and m, respectively.[56,57] According to standard conventions for mediation analysis, c refers to the overall predictor–outcome relationship, and c' is the direct effect controlling for the mediator. The path a is the estimated linear change in m per unit change in x. Path b is the slope of the mediator–outcome relationship controlling for x. Statistical tests on path coefficients a and b assess the significance of each relationship. A statistical test of $(c - c')$ was performed by testing the significance of the product of the path coefficients $a \times b$.

Based on this model, a multilevel mediation analysis was conducted to account for both within-subject and between-subject variations in the same model by treating the participant as a random effect. The first level describes the relationships between attention (X), brain activity (M), and pain rating (Y) within individual subjects. The second level tests for consistency across individuals to account for known sources of variation in individual pathway strength.[56,57] Whole-brain, multilevel mediation analysis tests the mediation effect on each voxel.[3]

Bootstrapping was used for the significance test, and the distribution of subject-level path coefficients was estimated by randomly sampling 10,000 observations from the path coefficient matrix.[16] Two-tailed P-values were calculated from the bootstrap confidence interval. Resulting statistical maps were thresholded at $q < 0.05$ and false discovery rate corrected across the whole-brain and mediation paths.[3] We then generated additional maps with the conjunction and disjunction of these thresholded statistical images. In addition, we calculated the number of voxels in each superimposed region to delineate the degree of overlap between the thresholded statistical maps and resting-state network masks using a large-scale brain network.[61]

2.6.4. Multilevel three-path mediation analysis

The 3-path mediation analysis can assess relationships among the experimentally manipulated attention (X), 2 different brain mediators (M1 and M2), and pain rating (Y).[56] A detailed explanation of the 3-path mediation model has been published previously.[57] To identify potential pathways connecting the manipulated attention and reported pain, we first selected different M1 and M2 values from the regions of interest (ROI) matrix. The ROI matrix consisted of the 8 significant clusters obtained from the whole-brain, multilevel mediation analysis. We then calculated the averaged activity across voxels within ROIs as M1 and M2 values in each trial.

3. Results

3.1. Analgesic effects of paying attention to the features of painful stimulation

Borrowing the spatial–temporal encoding task paradigm from previous visual perception studies,[10,46] we modulated the thermal and visual stimuli as a function of time (**Fig. 1A**). Specifically, the thermal stimuli presented in the experiment consisted of 2 types, constant or modulated. The "modulated" type stimulus needed a second target temperature, individualized by pain sensitivity, whereas the same temperature was used for the "constant" type. To modulate participants' attention to the sensory features of the thermal or visual stimuli, we kept the contrast of thermal or visual stimuli constant or modulated them dynamically, creating 4 possible combinations of the thermal and visual stimuli (**Figs. 1B and C**). The magnitude of thermal and visual contrast modulation

was adjusted for each individual to obtain an ~85% correct response rate (**Fig. 1D**), thereby achieving a similar level of attention for both stimuli $t(33) = -0.76$, $P = 0.45$, Cohen $d = 0.131$. We used 3 types of cues to induce 1 of 3 attention conditions: (a) attention to visual modulation (visual task), (b) attention to thermal modulation (thermal task), or (c) no attention (passive) (**Fig. 1C**). In the task condition, participants were asked to determine whether the thermal stimulus intensity (in the thermal task) or the visual stimulus contrast (in the visual task) was modulated and to rate perceived pain intensity (**Figs. 1A and C**). In the passive condition, participants assessed only the pain rating without performing the discrimination task. However, even while in the passive condition, the pain-inducing thermal stimuli could attract bottom–up attention. To prevent attention from being captured by modulation of thermal and visual stimuli, the passive condition was consisted of "constant" type of stimuli and was used as a baseline. Similarly, to control for the effects of unintended attentional modulation induced by the thermal and visual stimuli themselves,[11,59] only trials with the constant type were included in the main analyses (ie, stimulus condition 2 in **Figs. B and C**). Because we only included the "constant" type trials in the main analyses, we did not take individualized modulation variables into account.

To investigate the effects of attention on pain perception, we compared the pain ratings from the passive condition with the pain ratings from the thermal and visual tasks (**Fig. 1E**). As participants had to provide a pain intensity rating in all trials, including the visual task trials and the passive condition, paying attention to pain was unavoidable, even in the passive condition. However, because the pain assessment process was the same for all conditions, it should not affect the experimental conditions as a confounding factor. The behavioral data showed that the pain ratings during the visual task were lower than those of both the passive and thermal task conditions (**Fig. 1E**), $t(33) = -6.99$, $P < 0.001$, Cohen $d = 1.2$ for the passive condition; $t(33) = -2.14$, $P = 0.04$, Cohen d = 0.367 for the thermal task condition. Importantly, the pain ratings for the thermal task were also significantly lower than those of the passive condition (**Fig. 1E**), $t(33) = -7.37$, $P < 0.001$, Cohen $d = 1.265$, suggesting that paying attention to the sensory features of painful stimulation could also have analgesic effects. It is important to note that there was no physical difference in the stimuli between the thermal and visual task conditions, and the pain ratings changed only according to the task type.

Participants also reported significantly lower pain ratings for conditions in which the thermal stimulus intensity was dynamically changed when compared with conditions in which the thermal stimulus intensity was kept constant (**Fig. 1F**; from the repeated measures ANOVA, the main effect of thermal stimulus modulation, ie, change (C_T) vs unchanged (UC_T), was $F(1,33) = 70.35$, $P < 0.001$, $\eta^2 = 0.505$, and the main effect of task type, that is, visual vs thermal, was $F(1,33) = 12.03$, $P = 0.001$, $\eta^2 = 0.035$, with no significant interaction, $F(1,33) = 0.309$, $P = 0.582$, $\eta^2 = 0.001$). This may be because the overall heat energy was lower when the heat intensity was changed compared with when the heat intensity was kept constant.

3.2. The neurologic pain signature did not mediate the analgesic effects of attention to painful stimuli

One candidate hypothesis was that the reduction in pain would be mediated by the NPS, an a priori fMRI multivariate pattern-based predictive model of pain,[55] a brain marker for primary nociceptive and affective brain responses to the pain experience.[57] To test this hypothesis, we used a multilevel mediation analysis, as depicted in **Figures 2A and B**.[3,56,57] In the path models, the independent variable X was the attention task (thermal [**Fig. 2A**] or visual [**Fig. 2B**]; coded as 1) vs passive experience (coded as −1); the mediation variable M was the single-trial NPS response (see the methods section for further details), and the dependent variable Y was the trial-by-trial pain ratings. In the mediation analysis, only the data from the unchanged (UC) trial types were used to eliminate the confounding effects because of changes in stimulus intensity (**Figs. 2A and B**).

Our results showed that, for the thermal task condition, there was no significant mediation of the NPS (**Fig. 2A**; for path $a \times b$, $\beta = 0.01$, SE = 0.02, $P = 0.61$), indicating that although the NPS response magnitude was associated with increased pain ratings (path *b*), attentional modulation (thermal task vs passive) had no effects on the NPS response (path *a*), and thus, the mediation was not significant. By contrast, the NPS response mediated the analgesic effects induced by visual attentional modulation (**Fig. 2B**; Path $a \times b$: $\beta = -0.26$, SE = 0.05, $P < 0.001$). This is consistent with previous findings that the prefrontal cortex, the ACC, insula, and periaqueductal gray (PAG) are involved in distraction-based pain modulation.[4,52,53]

3.3. Unique brain mediators of attention-induced analgesic effects

We then used a whole-brain multilevel mediation analysis to search for the brain regions that mediated the analgesic effects induced by attention to painful stimuli. This analysis used the same path model as depicted in **Figures 2A and B**, but for the mediator variables, a single-trial blood oxygen level dependent response from each voxel was used instead of the NPS response.

We aimed to identify the brain regions that uniquely mediated the analgesic effects of attention to painful stimuli by excluding the brain regions that also mediated the analgesic effects of attention to visual stimuli. To this end, we obtained disjunction and conjunction maps using the significant mediation results of 2 mediation models. In **Figures 2C and D**, the unique mediators of the 2 models are shown in yellow (thermal unique) and blue (visual unique), whereas the common brain mediators are shown in green (conjunction). We further divided the regions into within and outside of the NPS mask to help interpret the mediation results. The NPS consisted of multivariate patterns of predictive weights, but given that the NPS only used the pain-relevant voxels from a meta-analytic database (neurosynth.org),[60] it also included location information.[55] Here, we used the NPS not only as pattern information for mediation analysis but also as location information for further interpretation of mediation analysis results.

Comparing the number of significant voxels within the NPS mask with the number outside of the NPS mask (pie charts in **Figs. 2C and D**), we found that the ratio of significant voxels within the NPS to those outside of the NPS was much smaller in the thermal unique mediators than in the visual unique mediators (28% vs 53%, respectively), indicating that the thermal unique mediators were mainly located outside of the NPS. When we examined the large-scale brain networks, the thermal unique mediators had the largest overlap with the somato-motor A (SoM A) network, which includes the primary sensory and primary motor cortex (S1 and M1; the location of SoM A is shown in **Fig. 2E**), whereas the visual unique mediators had the largest overlap with the visual central network (VisCent), which includes the early-stage visual cortex (**Fig. 2E**). These results suggest that the S1/M1 regions played an important role in mediating the pain reduction that occurred when attention was paid to pain stimuli.

In addition to the SoM A regions, brain areas related to goal-directed attention, such as the ventral intraparietal sulcus (VIP)

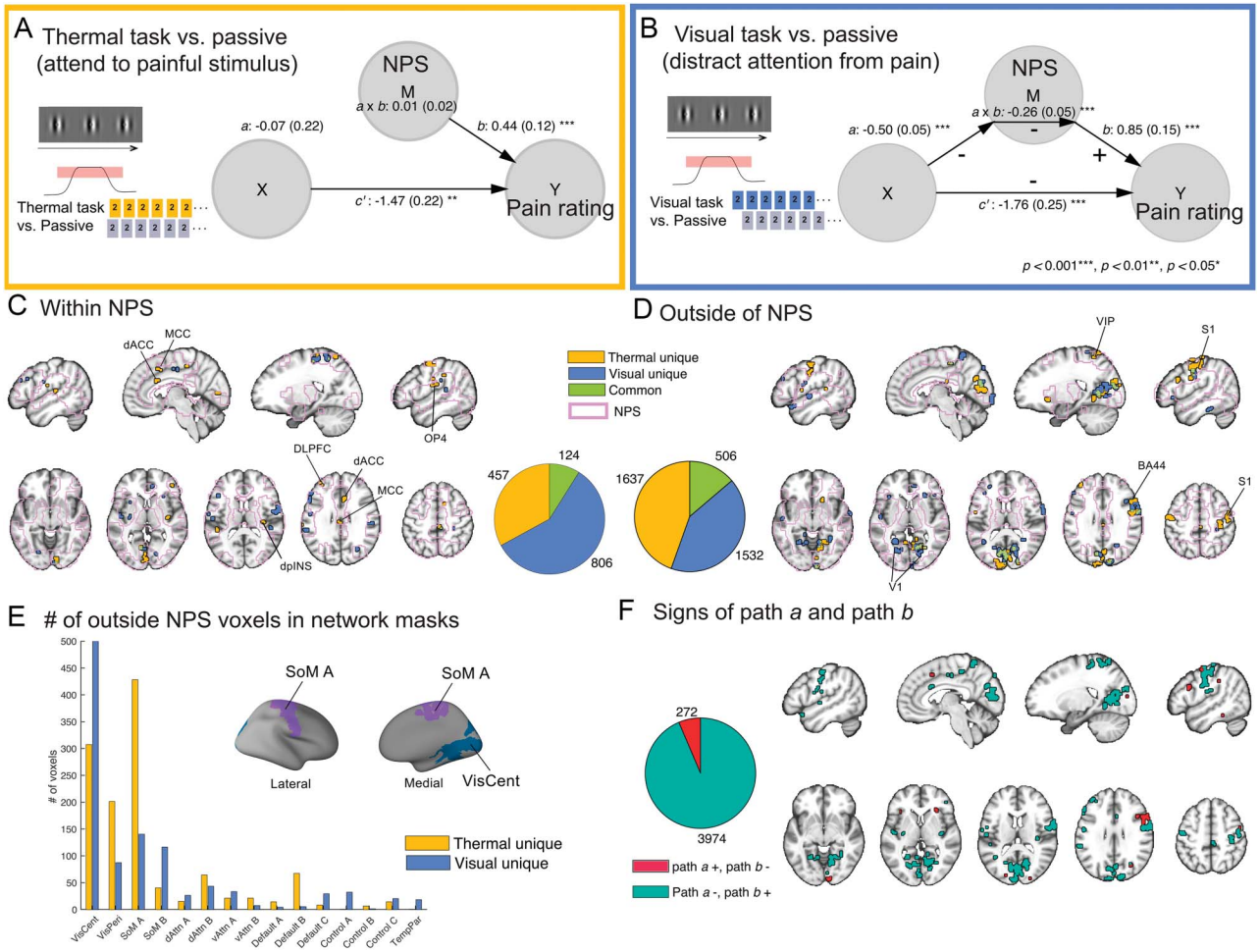

Figure 2. Results of the 2-path multilevel mediation analysis. The path models are depicted in a and b. Mediators were either NPS response (A and B) or single-trial estimates of the whole-brain activity (C and D). a. The NPS response did not mediate the analgesic effects of attention on painful stimuli. (B) The NPS response mediated the analgesic effects of attention on visual stimuli. In c (within the NPS mask) and d (outside of the NPS mask), the regions in yellow indicate the unique brain mediators of the analgesic effects of attention to painful stimuli (thermal unique), whereas the blue regions indicate the unique brain mediators of the analgesic effects of paying attention to visual stimuli (visual unique). The brain regions in green were the common brain mediators of the 2 task types (conjunction) (see the main text for more details). The pie charts show the number of significant voxels within and outside of the NPS under each condition. (E) The number of voxels outside of the NPS mask. (F) Signs of paths *a* and *b*. The red regions indicate the positive path *a* and negative path *b*, whereas the cyan color indicates the negative path *a* and positive path *b*. The pie chart shows the numbers of significant voxels for each color. All clusters were FDR corrected with $q < 0.05$. NPS, neurologic pain signature.

and dorsolateral prefrontal cortex (DLPFC); stimulus-driven attention, such as the inferior frontal gyrus (IFG); and some representative areas within the NPS, such as the dorsal anterior cingulate cortex, middle cingulate cortex, dorsal posterior insula (dpINS), and operculum 4 (OP4), were among the thermal unique mediators. For most of these brain regions, except for the IFG, brain activity was lower during the thermal task than during the passive condition (ie, negative path *a*) (**Fig. 2F**, turquoise) and was positively correlated with pain (ie, positive path *b*). In other words, paying attention to painful stimuli reduced the brain activity in these areas, resulting in reduced pain. Conversely, the IFG showed increased activity when attention was paid to the pain stimuli (ie, positive path *a*), and its increased activity was negatively correlated with pain ratings (ie, negative path *b*) (**Fig. 2F**, red).

3.4. Top–down pain modulation of the S1-mediated attention-induced analgesic effects

Next, we investigated the relationships between the regions discovered through the whole-brain mediation analysis. To this end, we used 3-path mediation models with 2 potential brain mediators (M1 and M2) (**Fig. 3A**). We first selected the 8 significant ROIs obtained from the thermal unique mediation map. We then used the averaged activity across voxels within the ROIs as the input for the M1 and M2 variables in the mediation models. The **Figure 3B** shows *P* value map of 3-path mediation analysis. The results showed that there were significant negative mediation effects only when the first mediator (M1) was the DLPFC or VIP and the second mediator (M2) was the S1 (**Fig. 3C**; for DLPFC → S1, $\beta_1\beta_2\beta_3 = -0.026$, SE = 0.007, $P < 0.001$; for VIP → S1, $\beta_1\beta_2\beta_3 = -0.030$,SE = 0.009, $P < 0.001$, Bonferroni corrected). For the DLPFC and VIP, the brain activity for the passive condition was greater than that for the thermal task (DLPFC, path $\beta_1 = -9.06$ (2.22), $P < 0.001$; VIP, path $\beta_1 = -7.08$ (1.83), $P < 0.001$) (**Fig. 3C**). This indicates that activity in these regions was suppressed when attention was paid to the pain stimuli. In addition, the brain activity in these areas had a positive relationship with the activity in the S1 (DLPFC, path $\beta_2 = 0.18$ (0.03), $P < 0.001$; VIP, path $\beta_2 = 0.35$ (0.03), $P < 0.001$) (**Fig. 3C**). In other words, when participants paid attention to the pain stimulus, the S1 was suppressed alongside the DLPFC and

VIP. Finally, the S1 response magnitude was directly associated with pain ratings (DLPFC, path $\beta_3 = 0.04$ (0.01), $P < 0.001$; VIP, path $\beta_3 = 0.05$ (0.21), $P < 0.001$) (**Fig. 3C**). When participants paid attention to the pain stimulus, the S1 activity decreased, and the pain ratings were also reduced.

Overall, our results show that these attention-induced analgesic effects are mediated through the activity of S1 from attention networks such as DLPFC and VIP.

4. Discussion

This study demonstrated that focused attention to features of painful stimuli could reduce pain. Furthermore, this analgesic effect of paying attention to painful stimuli was mediated by the primary somatosensory cortex through attention regions in the prefrontal and parietal cortex.

4.1. Methodological differences between our study and previous studies

Contrary to our results, several studies have shown that paying attention to pain intensity increases pain. For example, Bushnell and her colleagues reported that the intensity of pain when paying attention to pain intensity was higher than that when diverting attention from pain stimulation.[8] They also reported that S1 activity was greater when paying attention to pain intensity than when distracting from painful stimuli. However, because the pain was also reduced by distraction, it is unclear whether the significant difference was due to an increase in pain caused by attention to pain stimuli or decreased pain due to distraction. Therefore, in this study, we directly compared the subjective pain rating in the condition where attention is given to the pain stimulus with that in the no task condition.

On the other hand, Peyron and his colleagues directly compared the pain felt when performing a task of detecting subtle intensity changes in painful thermal stimuli with the pain felt when no task was performed on the same stimuli[44] and found no significant difference in pain intensity between the 2 conditions. In that study, however, participants performed a relatively easy task—that is, counting how many times the intensity of the pain stimulus changed in each fMRI run. Therefore, it is possible that participants did not pay attention to the pain stimulus feature enough to reduce pain.

4.2. Neural mechanisms of attention-induced analgesic effects

Previous studies have identified brain regions and networks involved when selective attention is given to spatial or nonspatial features of nociceptive stimuli.[41,42] However, these studies did not directly address whether the pain experience changed when attention was given to specific features of nociceptive stimuli and which brain regions mediated these effects. Here, we identified that the analgesic effects induced by paying attention to features of painful stimuli were mediated by the S1 through the top–down modulation of the DLPFC and VIP.

There is much evidence that the frontal and parietal regions are involved in the top–down regulation of attention to nociceptive

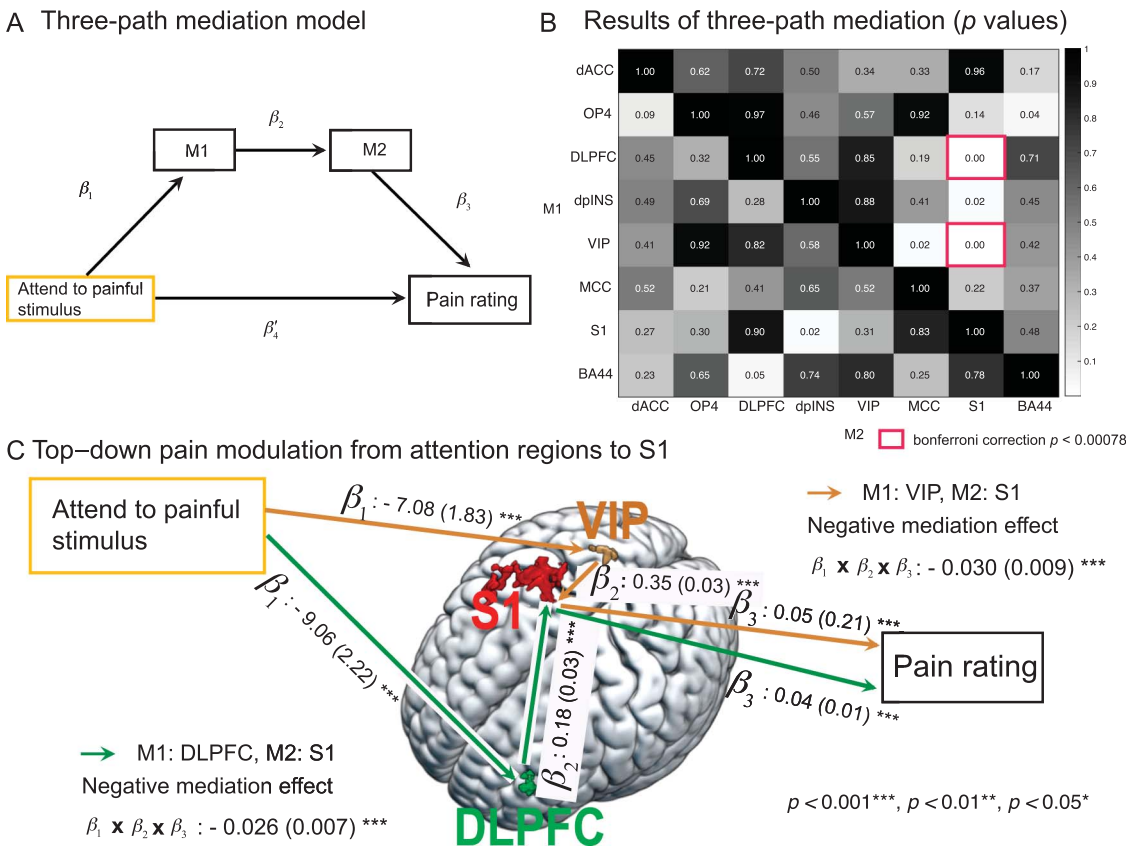

Figure 3. Results of the 3-path multilevel mediation analysis. (A) The overview of the 3-path mediation model. M1 and M2 were the averaged activity across voxels within the ROIs. The ROIs were selected from the significant clusters obtained from the thermal unique mediation map in Figures 2C and D. (B) Results of 3-path mediation analysis (*P* value map). (C) The top–down modulation of the S1 by the attention-related brain regions was associated with pain reduction when participants paid attention to painful stimuli. ROI, regions of interest.

and nonnociceptive stimuli.[33,51] In particular, the DLPFC is known to be involved in prioritizing and maintaining current executive function-related goals, which avoids interference from task-irrelevant information by loading executive functions preferentially into task-related information processing.[30] On the other hand, the intraparietal sulcus (IPS), which contains the VIP as a subregion, is involved in constructing a priority map of attention that orchestrates neural responses in sensory brain regions, favoring responses to specific inputs to which attention is given. It has been proposed that the DLPFC and IPS may help to maintain attention load and attention set, respectively, to prevent attention capture and interference by painful stimuli.[33] Our results showed that the DLPFC and IPS modulated activity in the S1 to control pain that interfered with task performance.

However, it remains difficult to interpret the results that showed that those regions' brain activity was greater in the passive condition than in the thermal task condition, given that those regions are important for the sensory-discrimination aspect of pain stimulation.[54] One possible explanation is the divisive normalization theory of attention. This theory suggests that divisive normalization, defined as the ratio of the response of individual neurons to the summed activity of a pool of neurons, plays a key role in sensory processing in the brain.[9,19,20] The model predicts that when the stimulus intensity is weak to moderate, the mean of the population response in the attended condition is greater than that in the unattended condition. On the other hand, if the stimulus intensity is very strong, the mean population response in the unattended condition is expected to be higher than that in the attended condition. This is because the size of the stimulus is larger than that of the attentional field, and thus, the stronger the stimulus, the greater the influence of the suppressive drive. Because the BOLD signal is known to reflect the net activity of excitatory and inhibitory neuronal activity rather than single cell-level firing rates, the fMRI signal might have captured this inhibitory population response of neurons in those regions induced by the attention to noxious heat.[35] Although further studies are needed to explore this hypothesis, we speculate that the normalization model of attention can partially explain the findings in this study.

4.3. The relevance of our findings and mindfulness meditation

Mindfulness involves focusing on the sensory aspects of pain, and many studies have reported analgesic effects during meditation. In this regard, our results are consistent with the known effects of mindfulness. In recent years, several studies have revealed the mechanism of mindfulness-based analgesia using fMRI.[62–64] Zeidan and his colleagues showed that meditation during noxious heat significantly reduced pain intensity and pain unpleasantness ratings.[63] These behavioral outcomes were associated with activities of the anterior cingulate cortex, orbitofrontal cortex, and the right anterior insula. They also found bilateral thalamic deactivation, suggesting that meditation could reduce pain through fine tuning of nociceptive sensory signaling with top–down control.[63,64] However, mindfulness could be different from our manipulation because mindfulness requires no judgement about the current painful sensation, and thus, the implications that our study has for mindfulness would need more considerations.

4.4. Contributions of lower-level visual cortical regions to the effect of attention on pain

Our results also showed that lower-level visual cortical regions, such as V1 and V2, mediated the effects of attention on pain. Although lower-level visual cortical areas do not belong to the pain network, previous studies have shown that lower-level visual processes, such as contrast perception, are affected by arousal or emotion.[27,32] In particular, our results showed that there were positive correlations between lower-level visual cortical activation and pain ratings. It is also well known that attention modulates V1.[48] Taken together, these results suggest that the V1 region may also contribute to the effects of attention on pain.

4.5. Application to clinical treatment for pain management

It remains challenging to find a cure for chronic pain because of the complexity of its underlying mechanisms. Opioids are widely used for pain relief, and their use has increased exponentially in recent years.[7] However, the use of opioids causes serious problems, such as drug abuse and addiction. Recently, mindfulness meditation has attracted attention as a way to relieve pain without the use of narcotics.[24–26,63,64] However, despite the accumulating evidence of the effectiveness of mindfulness on pain control obtained through numerous clinical trials, the fact that the analgesic effects of mindfulness therapy can vary depending on the level of training of the patient can be a barrier to its clinical use. Current research has shown that even those who have never encountered mindfulness can achieve significant analgesic effects with a simple attention task. Thus, the analgesic effect of focused attention on pain, an interesting phenomenon shown in this study, could potentially be used for pain management in clinical settings.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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