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Featured Article

# Cross-Species Convergence of Functional Connectivity Changes in Thalamic Pain Across Human Patients and Model Macaques


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**Abstract:** **Thalamic pain can be understood as a network reorganization disorder. This study aimed to investigate functional connectivity (FC) in human patients and a macaque model of thalamic pain. In humans, resting-state FC was compared between patients with thalamic pain and healthy individuals. Furthermore, resting-state FC was compared in macaques, before and after the induction of thalamic pain in the same individuals. FC between the amygdala of the unaffected hemisphere and the brainstem was significantly higher in patients with thalamic pain. More specifically, a significantly higher FC was observed between the basolateral amygdala and the ventral tegmental area, which also significantly predicted the value of a visual analog scale of pain intensity in individual patients. The macaque model of thalamic pain also exhibited a significantly higher FC between the amygdala of the unaffected hemisphere and the brainstem, particularly between the basolateral amygdala and the midbrain. Furthermore, the previously reported significantly higher FC between the amygdala and the mediodorsal nucleus of the thalamus in macaques with thalamic pain was also reproduced in the human patients. Therefore, the present results suggest that the FC changes in the regions associated with emotion, memory, motivation, and reward are part of the underlying mechanisms of thalamic pain onset present in both human patients and model macaques. This cross-species convergence provides new insights into the neurological mechanisms underlying thalamic pain, paving the way for further studies and the development of therapeutic strategies.**

***Perspective:*** ***This article presents that the FC changes in the regions associated with emotion, motivation, and reward are part of the underlying mechanisms of thalamic pain in humans and macaques.***



***Key Words:*** *Cross-species, functional connectivity changes, thalamic pain, human, macaques*

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## Introduction

Thalamic pain is a type of central poststroke pain (CPSP) first described by Déjerine and Roussy as "Le syndrome thalamique."[1] CPSP has an incidence rate of 1 to 12% and is a central neuropathic pain caused by a lesion in the central somatosensory nervous system, including the lateral medulla, pons, midbrain, thalamus, posterior limb of the internal capsule, lenticular nucleus, posterior insular cortex, and secondary somatosensory cortex.[2–4] Thalamic pain can occur particularly in lesions of the somatosensory relay nucleus of the thalamus.[5–7] The reported incidence of CPSP in patients with thalamic stroke is 18%.[8] Thalamic pain accounts for over half of all CPSP cases.[9] It is typically an intractable chronic pain that substantially impairs activities of daily living and quality of life. Potential underlying mechanisms of thalamic pain include 1) the central imbalance of the facilitatory and inhibitory systems, 2) central sensitization resulting in hyperexcitation of neuronal activity and increased sensitivity, and 3) disinhibition of the medial system of pain pathways from the lateral system.[4,10] The pathophysiology of thalamic pain is a progressive, maladaptive mechanism involving plasticity and reorganization of the pain network. Therefore, the thalamic pain is best understood as a network reorganization disorder leading to a maladaptive central pain state.[2]

Neuroimaging methods assessing functional connectivity (FC) using functional magnetic resonance imaging (fMRI) have become widely used.[11,12] FC analysis using resting-state fMRI (rs-fMRI) evaluates the temporal correlation of spontaneous neural activity between brain regions and has been used to investigate functional brain networks in pain studies.[13] There is limited evidence on FC changes associated with thalamic pain in clinical cases and nonhuman models. In humans, some specific brain regions and networks are associated with thalamic pain.[14–16] It is difficult to isolate phenomena that are caused by thalamic pain because pain is influenced by multiple factors in human studies, including stroke comorbidities and psychosocial factors. Animal models allow more controlled interference with a specific brain region to observe electrophysiological and histopathological changes at the neuron level consequent to that lesion. However, differences in the brain structure and function between humans and nonhuman species limit the translational potential of the obtained results. To explore commonalities in the pain circuit between humans and nonhuman species, nonhuman primates are more suitable compared with other species because of similarities with humans in both cerebral structure and function. By using nonhuman primates, we can intervene in the relevant brain regions to observe the FC changes associated with the development of pain within the same individual, which provides a causal link between the pain-inducing intervention and the observed FC changes. Moreover, the effect of interventional neuromodulation on FC normalization and pain relief can be tested to examine its clinical efficacy. Therefore, cross-species comparison of pain-related FC changes between human patients and nonhuman primate models of the same thalamic pain is a promising approach for causally elucidating clinically relevant changes in brain networks associated with thalamic pain. This study aimed to identify the cross-species convergence of FC changes associated with thalamic pain using rs-fMRI in both human patients and model macaques.

## Methods

### Study Overview

The aim of this study was to investigate the alterations in FCs caused by thalamic pain in both human and macaque models. In human analyses, we compared FCs between patients with thalamic pain and healthy individuals. In macaque analyses, we compared FCs before and after the injection of collagenase to induce thalamic pain. In both analyses, we used brain regions defined as having the same names across species as our regions of interest (ROIs). To identify common brain circuits associated with thalamic pain in both humans and macaques, we employed a 3-step approach. In the first step, we conducted ROI-to-ROI analysis across the whole brain to identify regions with differences in FC between healthy controls and patients with thalamic pain and between macaques before and after collagenase injection. In the second step, ROIs with significant differences in the first step were divided into subdivisions and analyzed using those subdivisions to focus on more specific brain regions. In the final step, we cross-referenced the findings from humans and macaques to determine whether the results observed in one species were consistent with those in the other.

### Patients With Thalamic Pain and Healthy Controls

We included 14 patients with thalamic pain and 15 age-matched healthy controls after an MRI quality check. All participants, both patients and controls, are of Japanese descent. We recruited patients aged ≥20 years diagnosed with central neuropathic pain due to thalamic stroke (Fig 1, Supplementary Fig 1) based on the terminology of the International Association for the Study of Pain[4,17] and experiencing continuous pain refractory to medication for neuropathic pain. On average, patients had a stroke 50 months previous to enrollment, which subsequently led to the onset of CPSP syndrome (Table 1).

We excluded patients with dementia, severe aphasia or higher brain dysfunction, major psychiatric disorders, or an inability to complete the questionnaires. Patients with thalamic pain were recruited from the outpatient clinic of the Department of Neurosurgery at Osaka University Hospital. Healthy controls were recruited through the distribution of recruitment flyers at Osaka University.

Patients underwent a battery of assessments using the following: a visual analog scale (VAS; scaled

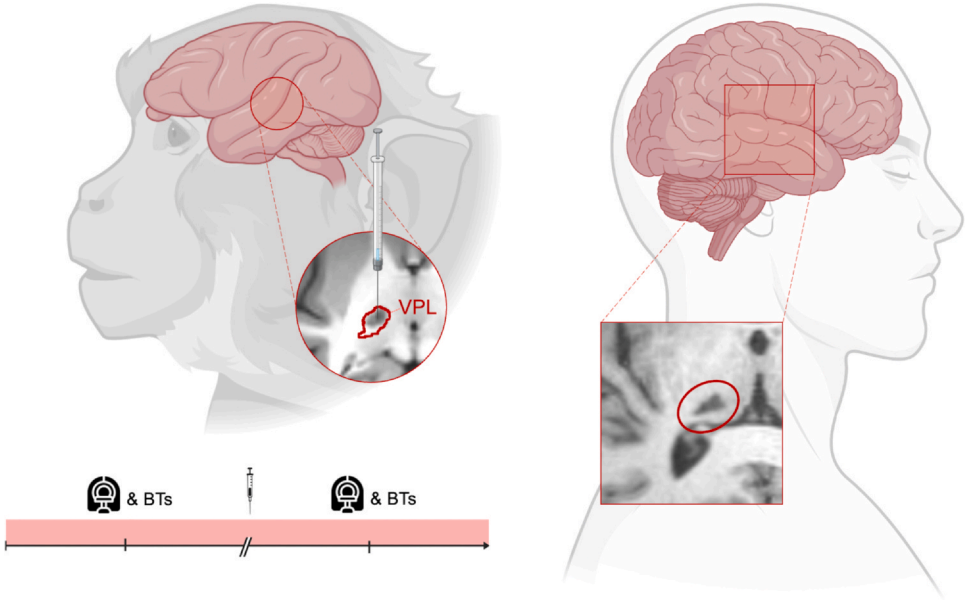


**Figure 1.** Cross-species comparison of resting-state functional MRI data obtained from human patients with thalamic pain and model macaques. A macaque brain with an axial T1 image shows a ventral posterolateral nucleus (VPL) lesion made by collagenase injection (Left). The region demarcated by the red line (VPL) was the target of the collagenase injection. The timeline represents the entire process from the beginning of the experiment to postoperative period in the macaque. An MRI icon indicates MRI scanning, and a syringe icon indicates the injection of collagenase into the VPL to establish a lesion for the development of thalamic pain. Behavioral tests were conducted concurrently with MRI scanning. A human brain with an axial T1 image shows a thalamic lesion (red circle) of a patient with thalamic pain (Right). See Supplementary Fig 1 for T1 images of all the patients. Abbreviation: BTs, behavioral tests.

0–100 mm) of pain intensity, the Japanese version of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ2; scaled 0–220, with 4 subscales, namely, continuous pain, intermittent pain, neuropathic pain, and affective descriptors),[18] the Beck Depression Inventory-Second Version (BDI-II; scaled 0–63), and the Intelligence Quotients estimated by the Japanese Adult Reading Test.[19] Healthy controls underwent a battery of assessments, including BDI-II and Intelligence Quotients estimated by the Japanese Adult Reading Test evaluation. These tools were assessed immediately before the MRI scans. Table 1 presents the characteristics of the participants. The human participant section of this study followed the Declaration of Helsinki and the Japanese ethical guidelines for clinical studies. The study protocol was approved by the Ethics Committee of Osaka University Hospital (approval number: 13384), and written informed consent was obtained from all participants.

## Table 1. Characteristics of the Study Participants

| CHARACTERISTICS | PATIENTS WITH THALAMIC PAIN (N = 14) | | HEALTHY CONTROLS (N = 15) | | P VALUE |
|---|---|---|---|---|---|
| | MEAN/N | SD/N% | MEAN/N | SD/N% | |
| Age (years) | 62.9 | 8.5 | 59.3 | 12.1 | .36 |
| Sex (male) | 5 | 35% | 11 | 73% | .07 |
| Thumb (right)* | 104.1 | 12.9 | 111.6 | 6.5 | .07 |
| BDI-II score (0–63) | 7.9 | 8.9 | 3.4 | 4.2 | .09 |
| Poststroke period (month) | 50.2 | 30.2 | | | |
| Stroke type (hemorrhage)* | 9 | 64% | | | |
| Pain site (upper limb) | 13 | 93% | | | |
| VAS score (0–100) | 75.2 | 12.9 | | | |
| SF-MPQ2 score (0–220) | 78.4 | 47.2 | | | |
| Continuous pain† | 3.9 | 2.2 | | | |
| Intermittent pain† | 3.4 | 2.4 | | | |
| Neuropathic pain† | 3.9 | 2.3 | | | |
| Affective descriptors† | 2.8 | 2.4 | | | |

Abbreviation: IQ-JART25, Intelligence Quotients estimated using the Japanese Adult Reading Test; SD, standard deviation.
NOTE. Subscales of the SF-MPQ2: continuous pain, intermittent pain, neuropathic pain, and affective descriptors.
*Hemorrhage or infarction in the thalamus.
†A subscale of the SF-MPQ2 was described as an average of the items of each subscale.

## Monkey Thalamic Pain Model

In this study, we used rs-fMRI data from 2 macaque monkeys, which were originally acquired for our previous study.[20] Briefly, 2 adult male Japanese monkeys (*Macaca fuscata*), weighing 8.0 (macaque 1) and 7.4 kg (macaque 2), were used to create the thalamic pain models by stereotactic microinjection of type-IV collagenase into the left ventral posterolateral nucleus of the thalamus, as previously described.[21] Monkeys were provided by the National Bio-Resource Project at Kyoto University Primate Research Institute (Inuyama, Japan) with support from the Japan Agency for Medical Research and Development (Tokyo, Japan). The validation of the thalamic pain models was conducted to confirm the reduction in withdrawal thresholds for both mechanical and thermal stimulations in both hands following collagenase injection. MRI data were collected as a baseline condition before the development of thalamic pain, and subsequently after the onset of thalamic pain (for macaque 1: between 14 and 23 weeks post lesion; for macaque 2: between 15 and 23 weeks post lesion). In this study, we used propofol as the anesthetic. Although it has minimal analgesic effects, its impact on brain function cannot be ignored.

The experimental procedures undertaken in this study with macaque subjects were approved by the Committee for Animal Experiments at Osaka University and the National Bio-Resource Project and were conducted in compliance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

## Magnetic Resonance Imaging Data Acquisition

### Humans

Structural MRI and rs-fMRI were conducted using a 3-T MR scanner (MAGNETOM Trio, A Tim System 3T; Siemens Healthineers, Erlangen, Germany) in patients with thalamic pain (Fig 1) and healthy controls. T1-weighted images were acquired using the following parameters: repetition time/echo time (TR/TE), 1,900/2.52 ms; flip angle (FA), 9° field of view (FOV), 256 × 256 mm; matrix, 256 × 256; slice thickness, 1.2 mm, 192 slices; and voxel size, 1 × 1 × 1 mm. Prior to the rs-fMRI scan, participants were asked to keep their eyes open and fixate on the cross-symbol positioned in front of them throughout the duration of the scan. rs-fMRI data were acquired using echo-planar images (single-shot) with the following parameters: TR/TE, 2,500/30 ms; FA, 80° FOV, 212 × 212 mm; matrix size, 64 × 64; slice thickness, 3.2 mm, 40 slices; voxel size, 3.3 × 3.3 × 4 mm; and scan time, 10 minutes.

### Macaques

Structural MRI and rs-fMRI were conducted in the 2 macaques using a 7-T MR scanner (7T Magnetom; Siemens Healthineers). The macaques were anesthetized with propofol, and their heads were fixed with a urethane foam headrest. MRI data were collected before and after the development of thalamic pain models. For macaque 1, 2 sets of MRI scans were obtained for the baseline (healthy condition) and 3 sets for the thalamic pain condition. For macaque 2, 3 sets of scans were obtained for each condition. T1-weighted images were acquired with the following parameters: TR/TE, 2,200/1.94 ms; FA, 5° FOV, 128 × 128 mm; matrix, 192 × 192; slice thickness, .7 mm, 128 slices; and voxel size, .67 × .67 × .70 mm. rs-fMRI data were acquired with the following parameters: TR/TE, 1,000/20 ms; FA, 55° FOV, 150 × 150 mm; matrix size, 100 × 100; slice thickness, 1.5 mm, 42 slices; voxel size, 1.5 × 1.5 × 1.5 mm; and scan time, 30 minutes (except for 1 baseline dataset of macaque 1, which was acquired for 20 minutes).

## Analysis of FC

To ensure credibility in comparing the results, we strived to maintain consistent conditions and methods in the analyses of both humans and macaques. MRI images of patients with stroke in the right hemisphere were flipped before preprocessing to align the stroke lesion to the left side, ensuring that the lesions were consistent with those in the macaques. Moreover, we used the same version of software and adhered to uniform principles in our analysis model to interpret and summarize the MRI scans. Data were analyzed using the CONN toolbox version 18.b (Gabrieli Lab at MIT McGovern Institute for Brain Research, Cambridge, MA; https://web.conn-toolbox.org) implemented with MATLAB Runtimes version 9.5 (MathWorks, Natick, MA). To eliminate sources of spurious brain-wide correlations, we performed denoising in humans using the General Linear Model by regressing out several noise components from the blood oxygen level dependent signal. These components included 1) the first 5 principal components analysis components of the whole-brain blood oxygen level dependent signal within the white matter and cerebrospinal mask, a method known as "aCompCor" 2) the 6 motion parameters from the realignment procedure; and 3) the scrubbing regressor from the ART toolbox. We set thresholds at a global-signal z-value of 5 and a subject-motion threshold of .9 mm, and used the "Use diff global," "Use diff motion," and "Use comp motion" options in the ART settings. For macaques, denoising was conducted using "effect of rest" and "cerebrospinal fluid" as confounds. We removed the "effect of rest" to minimize non-experiment-related activity and enhance the specificity of our FC analyses. The rs-fMRI data were then temporally band-pass filtered over a range of .008 to .09 Hz in humans and .01 to .18 Hz in macaques to reduce the effects of low-frequency trends associated with scanner drift and high-frequency physiological noise due to respiration and pulse.

### Preprocessing of Human MRI Data

We used the CONN toolbox to preprocess the MRI data. This process began with the removal of the first 6 rs-fMRI images to allow the signal to reach steady state, followed by realignment to the anatomical image and

unwarping for geometric distortion. We then performed slice-timing correction and identified outlier scans using Artifact Detection Toolbox-based scrubbing. Functional and anatomical data were normalized to the standard Montreal Neurological Institute space and segmented into distinct tissue classes, including gray matter, white matter, and cerebrospinal fluid. Finally, after segmenting and normalizing the structural data, we smoothed the functional data using an 8-mm full width at half maximum Gaussian filter.

Quality control was performed to ensure data reliability and validity. This included visual inspection for artifacts and structural abnormalities, head motion assessment using the framewise displacement method,[22] and the exclusion of scans with framewise displacement values exceeding 1.6 mm.

## Preprocessing of Macaque MRI Data

Prior to analysis in macaque data, rs-fMRIs underwent preprocessing, which included motion correction and normalization using advanced normalization toolboxes (http://stnava.github.io/ANTs/), followed by smoothing with SPM12 (The Wellcome Centre for Human Neuroimaging, University College London Queen Square Institute of Neurology, London, UK). We generated a time-averaged image to align the fMRIs and correct head motion. The motion correction parameters employed were as follows: the metric used was Mutual Information; the transformation type was Rigid; and the gradient step was set at .1. The rs-fMRI images were then registered to these time-averaged images. Next, we computed the transformations from the time-averaged images to the subject-specific T2-weighted images, and from these T2-weighted images to the atlas b0 image (with a radius of 4 and spine distance of 26) using advanced normalization toolboxes. The resulting normalized images, once transformed, were further smoothed using a Gaussian kernel in SPM12, with a full width at half maximum of 3 mm for the smoothing.

## Selection of ROIs

We used ROIs for the initial whole-brain analyses in both humans and macaques (Supplementary Table 1). We selected these ROIs from neurosynth.org (https://www.neurosynth.org) as regions associated with chronic pain. The set of human ROIs was generated from the Harvard-Oxford cortical and subcortical structural atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and a histological thalamic atlas.[23] The set of macaque ROIs was generated from a diffusion tensor image-based atlas of rhesus macaques (https://www.civm.duhs.duke.edu/rhesusatlas)[24] (see Supplementary Materials for details on ROI selection). To align the ROIs between the human and macaque atlases, we merged regions when an ROI from the human atlas corresponded to multiple regions in the macaque atlas. For example, since the amygdala is represented by 14 distinct nuclei in the macaque atlas, we combined these into a single ROI as "amygdala" (see Supplementary Table 2 for the correspondence to the anatomical labels in the macaque atlas). We utilized SPM12 and the FMRIB Software Library (FSL 6.0.5, the University of Oxford, Oxford, UK, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) for ROI extraction and spatial normalization. ROIs were extracted and exported as Neuroimaging Informatics Technology Initiative files, then spatially normalized to the standardized space compatible with CONN. All ROIs were ensured to be compliant with CONN's format before analysis (https://andysbrainbook.readthedocs.io). When large regions significantly related to thalamic pain were found in the initial whole-brain analyses, these regions/ROIs were divided into as many subdivisions as possible. Consequently, the amygdala was divided into the basolateral amygdala (BLA) and the central nucleus of the amygdala, and the brainstem was divided into the midbrain, pons, and medulla. The midbrain was further divided into the following 8 nuclei: dorsal raphe, locus coeruleus region, medial raphe, periaqueductal gray, parabrachial complex, pontine reticulum oral, pedunculopontine nucleus, and ventral tegmental area (VTA). The human ROIs of the subdivision were derived from the CIT168 amygdala atlas,[25] Talairach Daemon atlas,[26] and Harvard ascending arousal network atlas.[27] The subdivisions of macaque ROIs were sourced from the subcortical atlas of the rhesus macaque.[28] In cases where there were differences in the ROIs due to interspecies differences, we ensured anatomical consistency by combining regions and using a single ROI. We incorporated the BLA and central nucleus of the amygdala as subdivisions of the amygdala because these 2 regions are commonly found to be involved in pain processing across both species.[29–31]

## ROI-to-ROI and Seed-to-Voxel Analyses

For the statistical analyses, we used analysis of covariance to compare differences in FC between patients with thalamic pain and healthy controls with a covariate of "age," and between thalamic pain and healthy condition macaques with covariates of "subject" and "time." For the analysis of human subjects, there was a sex imbalance between patients with thalamic pain and healthy participants. For sensitivity analysis, we included both age and sex as confounding variables (Supplementary Materials). The initial whole-brain analyses were performed using ROI-to-ROI analysis of the 52 ROIs related to chronic pain, with a significance level of $P < .05$ for the analysis-level correction (Supplementary Table 1), which is a false discovery rate (FDR) correction over the total number of connections included in the analysis. The significance level of the ROI-to-ROI analyses with subdivisions of the initial ROIs was set at a less-stringent level ($P < .05$, uncorrected) for the seed level to explore FC-related thalamic pain in detail. The significant FCs obtained from these ROI-to-ROI analyses were examined for correlation with the pain scales (VAS and SF-MPQ2) in patients with thalamic pain using partial correlations with age as a covariate. Furthermore, seed-to-voxel analyses were performed on the ROIs with significant FCs to explore the detailed brain regions associated with thalamic pain. The significance level of the seed-to-voxel analysis was set at $P < .001$ (uncorrected) for voxel levels. In addition, we

set the extent threshold for humans at cluster size (k) > 20 voxels (160 $mm^3$) according to the expected number of voxels per cluster using SPM12 and that for macaques at cluster size (k) > 5 voxels (16.9 $mm^3$) according to our previous study[20] (see Supplementary Materials for details on the cluster size thresholds).

## Results

In humans, there was no significant age difference between patients with thalamic pain and healthy controls. There was a nonsignificant tendency toward female predominance, lower intelligence quotient, and higher BDI-II scores in the patient group compared with the control group (Table 1). ROI-to-ROI FC analysis in the whole human brain was conducted to identify the regions where FCs differed between the 2 groups. This analysis revealed a significantly higher FC between the amygdala on the nonaffected side and the brainstem in patients with thalamic pain compared with healthy controls (t[26] = 5.30, FDR adjusted p-value [p-FDR] = .019) (Fig 2).

Subsequent more detailed analyses with subdivisions of the amygdala and brainstem showed higher FCs specifically between the BLA on the nonaffected side and the midbrain (t[26] = 2.61, uncorrected $P = .015$) and between the BLA and VTA (t[26] = 2.07, uncorrected $P = .048$). Based on these results, we defined the amygdala on the nonaffected side, BLA, and VTA as seed regions for the following seed-to-voxel FC analysis; note that the brainstem was not included because it seemed to be too heterogeneous as a single seed. In the seed-to-voxel analysis with the amygdala on the nonaffected side as a seed region, the voxels with significantly higher FC in patients were located in the medial thalamus bilaterally (Fig 3), midbrain tegmentum, and bilateral central part of the pons (Supplementary Fig 2).

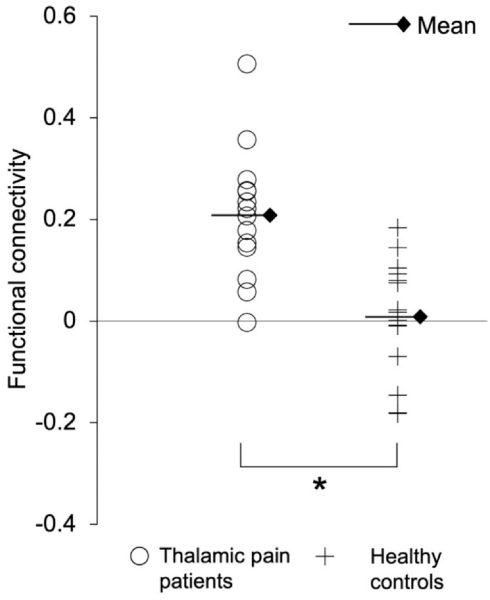


**Figure 2.** FC between the amygdala on the nonaffected side and the brainstem in human patients with thalamic pain and healthy controls. Significant differences in FC values (z-scores) between the amygdala and brainstem were observed (t[26] = 5.30, p-FDR = .019). *$P < .05$. Abbreviation: p-FDR, FDR adjusted p-value.

Voxels with significantly higher FC contained the VTA when the BLA on the nonaffected side was used as a seed region (Fig 4A). Conversely, when the VTA was used as a seed region, voxels with significantly higher FC contained the BLA (Fig 4B). Thus, significantly higher FC between the BLA on the nonaffected side and VTA in patients was indicated by 2 mutual seed-to-voxel FC analyses.

FC values of individual patients between the BLA on the nonaffected side and VTA exhibited a significant positive correlation with VAS score (r = .72, p-FDR = .005), continuous pain (r = .58, p-FDR = .039), and affective descriptors (r = .63, p-FDR = .022) of SF-MPQ2 subscales (Fig 5). FC values between the amygdala on the nonaffected side and the brainstem did not significantly correlate with any clinical score.

Next, we conducted the analysis of FC change in a macaque model of thalamic pain with reference to the pain-related FC change observed in human patients. The FC between the amygdala on the nonaffected side and the brainstem became significantly higher following the development of thalamic pain compared with the baseline measured before making a thalamic lesion in the same monkeys (t[16] = 2.40, uncorrected $P = .029$). More specifically, the FC between the BLA on the nonaffected side and midbrain exhibited a significant increase following the development of thalamic pain (t[16] = 2.70, uncorrected $P = .016$). However, VTA in the midbrain did not show significant pain-related FC change with the BLA (t[16] = 1.56, uncorrected $P = .14$). Seed-to-voxel FC analysis revealed the voxels to have a significant FC increase with the BLA on the nonaffected side following the pain development located at the medial thalamus on the nonaffected side and midbrain tegmentum on the nonaffected side (Fig. 6A and 6B).

Based on the macaque dataset, we conducted a whole-brain ROI-to-ROI analysis of the FC change associated with the development of thalamic pain in model macaques. This analysis demonstrated a pain-related FC increase between the amygdala on the affected side and the mediodorsal thalamus (MD) of the affected side (t[16] = 5.92, p-FDR = .029) (Fig 7).

The FCs between the subdivisions of the amygdala and MD in the thalamic pain condition were not significantly different from those in the healthy condition. We thus defined the amygdala and MD on the affected side and selected these as seed regions for subsequent seed-to-voxel FC analyses. The voxels showing significant FC increase with the amygdala on the affected side in the thalamic pain condition were located in the central part of the MD. The corresponding analysis with the MD as a seed region revealed a significant FC increase with voxels in the BLA, basomedial, and medial parts of the amygdala, thus replicating the above results as described in Kadono et al.[20]

We examined whether human patients with thalamic pain exhibited the FC changes in amygdala and MD observed in macaque models. The ROI-to-ROI FC analysis revealed that patients with thalamic pain

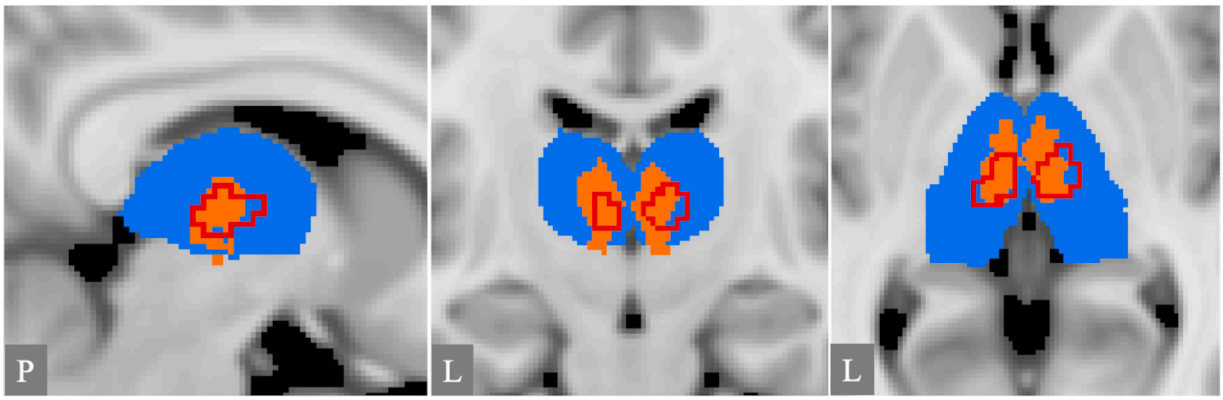


**Figure 3.** Seed-to-voxel FC analysis in humans with the amygdala on the nonaffected side as a seed region. The red lines delineate the boundary of the voxel clusters where functional connectivity exhibited significant changes (uncorrected $P < .001$, $k > 20$; center coordinate: 8.04, −16.70, 2.90). Blue and orange areas depict the thalamus and mediodorsal thalamic nucleus, respectively. Abbreviations: P, posterior; L, left.

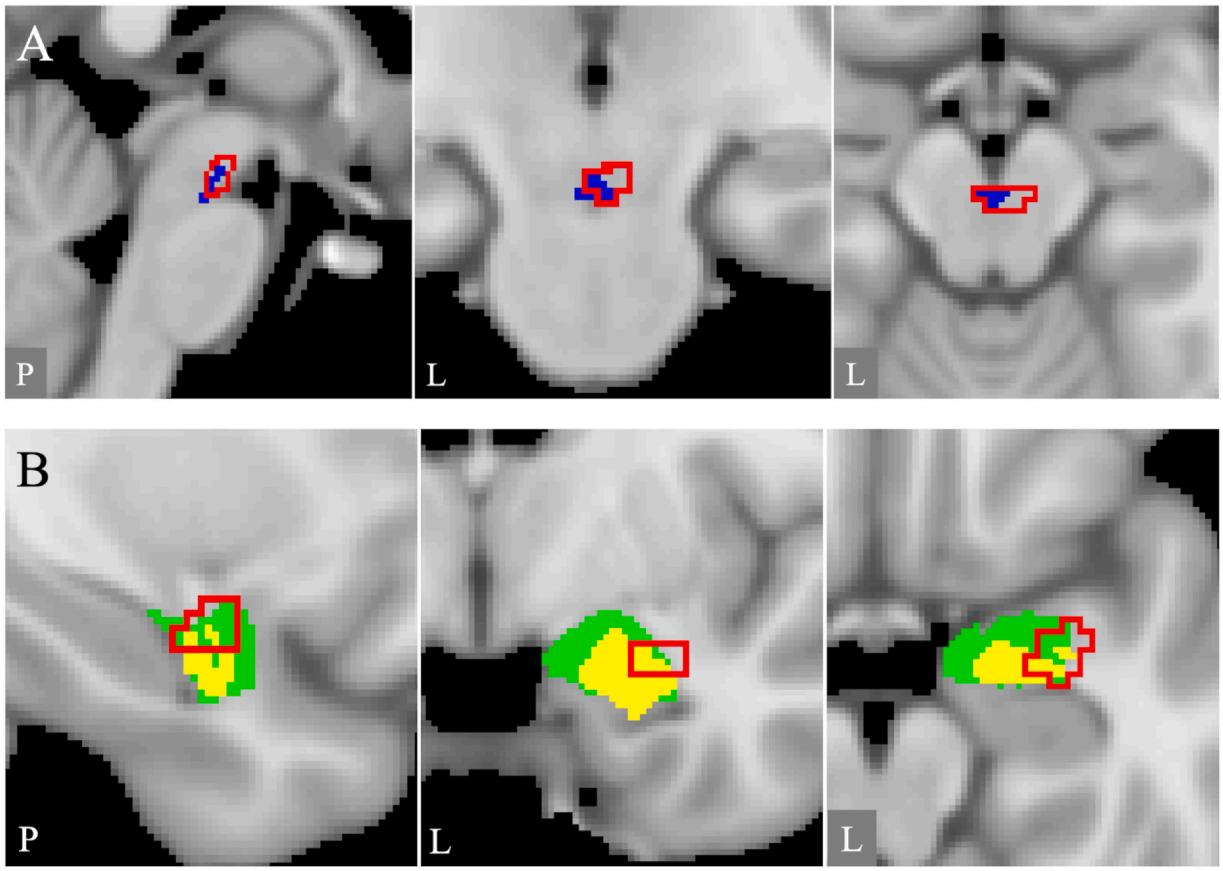


**Figure 4.** Seed-to-voxel FC analyses in humans with the BLA on the nonaffected side and VTA as seed regions. Voxels showing significant FC with the BLA on the nonaffected side (**A**) and VTA (**B**) as a seed region, respectively, are shown. Red lines delineate the boundary of the voxel clusters where FC exhibited significant changes (uncorrected $P < .001$, $k > 20$; center coordinate: 2.13, −23.11, −16.04, and 29.90, −5.40, and −19.00 for (**A**) and (**B**), respectively). Blue, green, and yellow areas depict the VTA, amygdala, and BLA, respectively. Abbreviations: P, posterior; L, left.

exhibited increased FC between the amygdala on the nonaffected side and bilateral MD compared with healthy controls (MD on the affected side: $t[26] = 2.67$, uncorrected $P = .013$; MD on the nonaffected side: $t[26] = 3.06$, uncorrected $P = .005$). More specifically, the FC between the BLA on the nonaffected side and MD on the nonaffected side increased in patients with thalamic pain ($t[26] = 2.15$, uncorrected $P = .04$). Voxels showing a significant increase in FC with the amygdala on the nonaffected side were located bilaterally in the MD in the patients as described above (Fig 3). These FC changes in human patients were well-aligned with those that were obtained in a macaque model of thalamic pain.

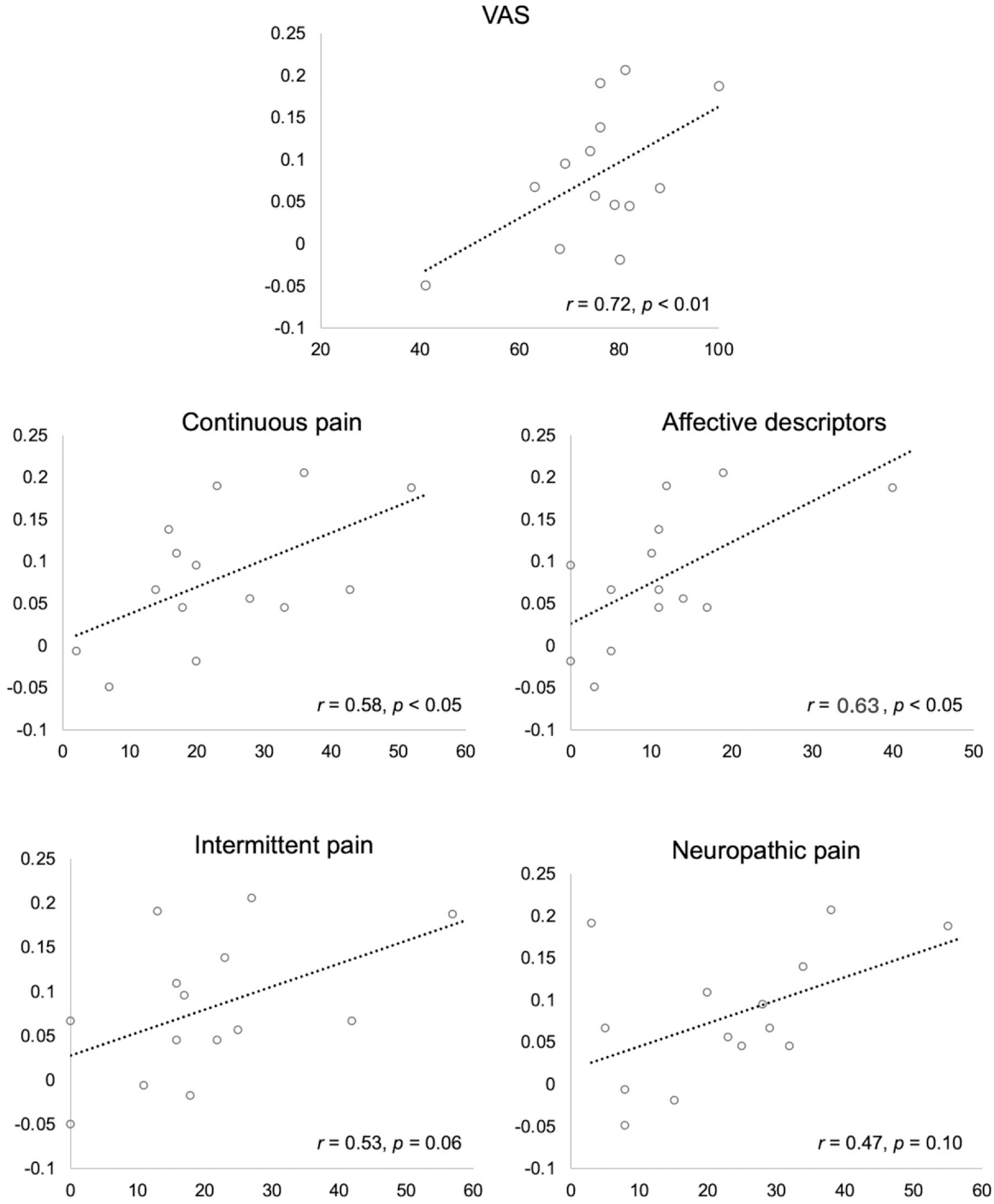


**Figure 5.** Correlation analysis between FC values of the BLA on the nonaffected side—VTA and pain scores in patients with thalamic pain. X and Y axes depict scores for each pain assessment and FC value, respectively. Continuous pain, intermittent pain, neuropathic pain, and affective descriptors are subscales of the Japanese version of the Short-Form McGill Pain Questionnaire 2.

## Discussion

Macaques and humans share a high degree of similarity in brain architecture and function. These similarities have enabled researchers to make significant inferences about human neurobiology based on the results obtained in macaques in a similar context. The analysis of the similarities and differences in human and macaque brain structure and function in the pathological state provides unique insights into the mechanisms underlying brain pathology and the development of therapeutic strategies. The present study identified specific FC changes related to thalamic pain in both human and macaque brains, suggesting potential cross-species relevance. In humans, the FC between the amygdala on the nonaffected side and the brainstem, specifically between the BLA and VTA, significantly increased in the thalamic pain condition. The FC value between the BLA and VTA in individual patients showed a significant positive correlation with pain intensity. A macaque model of thalamic pain mirrored these results

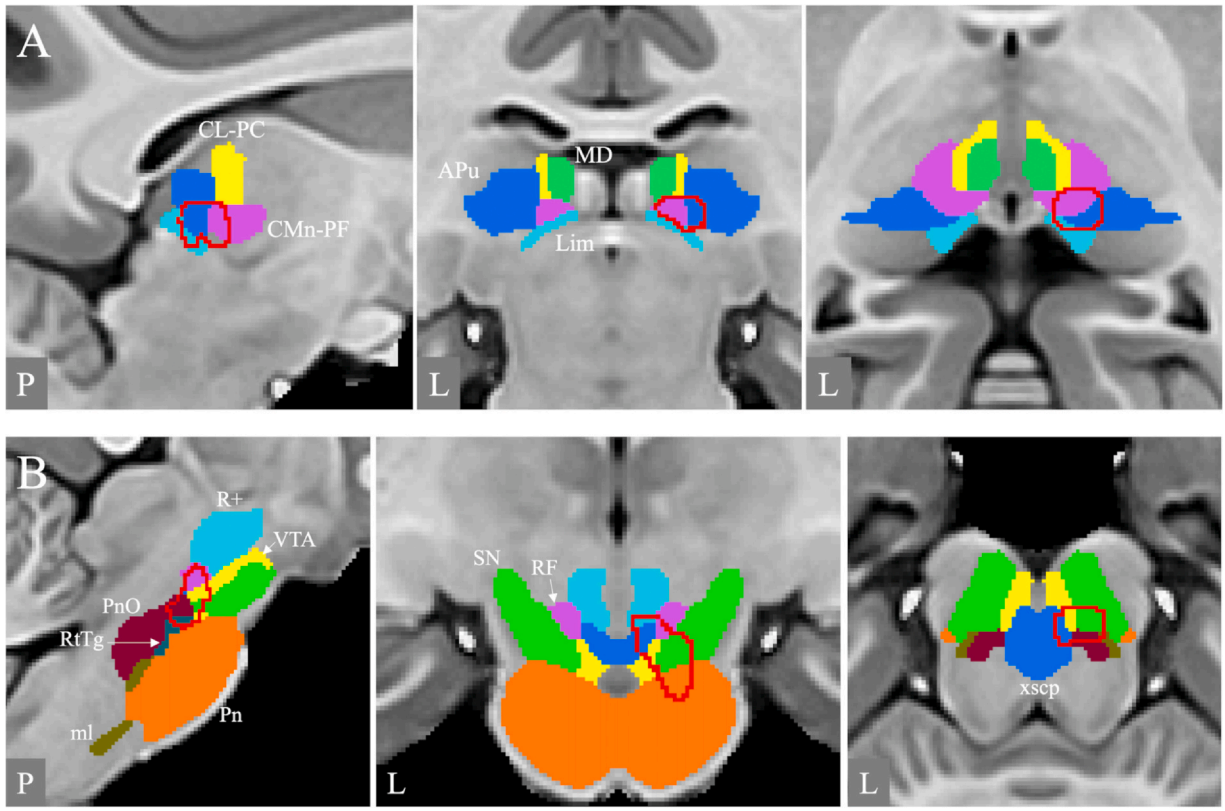


**Figure 6.** Seed-to-voxel analysis of FC changes in a macaque model of thalamic pain with the BLA on the nonaffected side as a seed region. Voxels in the thalamus (**A**) and midbrain (**B**) show significant FC with BLA. Red lines delineate the boundary of the voxel clusters for which a significant FC increase with the BLA seed was observed (uncorrected $P < .001$, $k > 5$; center coordinate: –5.33, 6.60, and 16.25 and –2.42, 7.81, and 6.67 for [**A**] and [**B**], respectively). Abbreviations: CL-PC, centrolateral and paracentral thalamus; CMn-PF, centromedial-parafascicular thalamus; P, posterior; Lim, limitans thalamus (a part of the intralaminar thalamus); APu, anterior pulvinar; L, left; R+, rubral region; PnO, pontine reticulum oral; RtTg, reticulotegmentum; Pn, pontine nucleus; ml, medial lemniscus; SN, substantia nigra; RF, retrorubral field; xscp, superior cerebellar peduncle decussation.

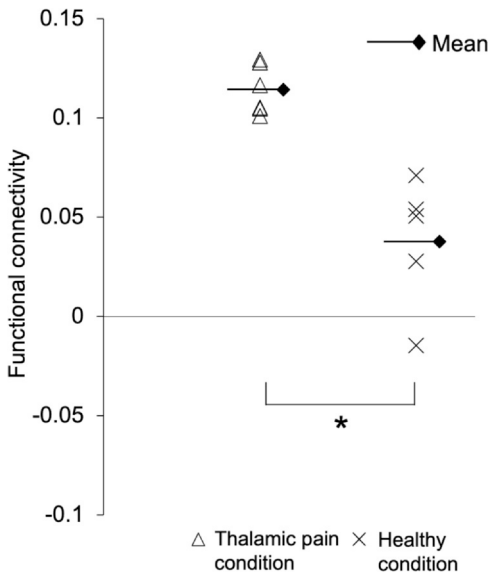


**Figure 7.** FC between the amygdala on the affected side and MD on the affected side of thalamic pain model macaques. A significant increase in FC (z-scores) was observed between the amygdala and MD on the affected side, which was associated with pain development within the same individuals ($t[16] = 5.92$, p-FDR = .029), as reported by Kadono et al.[20] $^{*}P < .05$.

with increased FC between the amygdala on the nonaffected side and brainstem, and more specifically between the BLA and midbrain. Concurrently, no significant results were observed between the BLA and VTA, which might be caused by the substantially small volume of the VTA in macaques. Conversely, a significant pain-related increase in FC between the amygdala and MD, which was the most prominent FC change observed in the macaque model of thalamic pain (Fig 7), was also reproduced in human patients. Altogether, the present results indicate convergent FC changes in the condition of thalamic pain across human patients and model macaques. The obtained cross-species convergence of pain-related FC change allowed us to validate our findings in each species. Furthermore, the results in human patients provided clinical relevance to the corresponding results obtained in macaques. Moreover, we observed changes in the same macaques by comparing their FCs before and after the development of thalamic pain condition. This approach can provide a valuable causal perspective on the findings of pain-related FC changes in human patients.

Typically, an increase in FC suggests enhanced cooperative activity between brain regions. However, this does not necessarily imply the generation of pain. Even when increased connectivity is observed in areas

associated with pain, it is not possible to directly infer a causal relationship. Such changes could either be a consequence of experiencing pain or an adaptation to it. Therefore, our discussion primarily focuses on the brain regions that yield significant FC results. The emotional-motor system links the amygdala and hypothalamus, passes through the midbrain, and extends to the lateral tegmentum in the caudal pons and medulla. It controls specific motor actions involved in emotions and pain, heart rate, respiration, vocalization, mating behavior, and pain.[29,32] Using a less-stringent level at the subdivision seed-level analysis may introduce some risk of false discoveries. However, our study tried to identify larger ROI correlations and use seed-to-voxel methods to explore detailed brain regions associated with thalamic pain. Thus, the subdivision findings are preliminary and should be interpreted as exploratory. The BLA receives neuromodulatory inputs from the VTA, which is important for fear response/learning and pain memory.[30,31,33,34] The VTA is an integral component of the mesolimbic dopamine system and plays a pivotal role in motivation and reward processing. Specifically, dopaminergic neurons in the VTA exhibit selective projections to several brain regions, including the medial shell and core of the nucleus accumbens, dorsomedial prefrontal cortex, and BLA.[30,35–37] Trutti et al[38] reported a difference in the distribution of dopamine receptors between humans and macaques, however, the functions of the VTA related to pain in these species are thought to be generally similar.[38–41] The BLA has a similar and critical role in emotional processing (eg, pain, fear, and anxiety) and memory formation in both humans and macaques.[42–45]

Disruption in the thalamic somatosensory relay function can lead to altered sensory processing and pain perception. The imbalance between the lateral and medial pain systems is thought to be the underlying mechanism of thalamic pain.[4,10,20] Specifically, thalamic pain is believed to stem from a lesion in the lateral system, such as in the ventral posterolateral nucleus, which then causes disinhibition in the medial pain system. Supporting this hypothesis, studies have shown a convergent increase in FC between the MD and the amygdala, central to the medial pain system's role in processing the emotional and affective dimensions of pain, in both human patients and a macaque model of thalamic pain.[46,47] These findings are consistent with earlier studies that documented enhanced FC involving the MD thalamus or amygdala in patients with conditions like complex regional pain syndrome and chronic headache compared with healthy individuals.[48,49] Future research should aim to elucidate the mechanisms by which the lateral pain system modulates these medial system nodes during pain development.

It is well-known that each hemisphere has its specialized role within the brain networks. However, the specialized role of each hemisphere in chronic pain remains under debate.[50] In thalamic pain, a brain lesion is present in the affected hemisphere, which is thought to have a greater impact. Indeed, neuromodulation therapies, such as deep-brain stimulation, motor cortex stimulation, and thalamotomy, are applied on the affected hemisphere. Therefore, we flipped the images to match the lesion site to the left in the primary analysis of humans. To mitigate the influence of image flipping, we also performed sensitivity analyses with "lesion side" as a covariate. As a consequence, the main results did not change significantly (Supplementary Materials). The role of each hemisphere in thalamic pain needs further investigation.

The present study has some limitations. First, the findings from this study may encompass not only pain-related phenomena but also those associated with stroke lesions. Including a group of stroke patients or macaque models without pain as a control cohort may help us discriminate between phenomena associated with pain and those associated with stroke lesions. Additionally, an imbalance in biological sex between stroke patients and healthy participants represents another limitation of our study. Although we performed an additional analysis on the data by including sex as a covariate and confirmed that the results did not change significantly (Supplementary Materials), this may have had some impact on the study's results. Future research should focus more on the selection and control of participant groups. Ensuring that control participants are matched for both sex and age is essential for accurately assessing the potential impacts of sex on FC. Second, rs-fMRI data in humans and macaques were acquired with 3- and 7-T scanners, in quiet awake and light anesthesia conditions, respectively, and thus these differences might have affected the observed convergence of FC changes. Third, it is not clear to what degree the pain in the macaque model mirrored that in human patients. In particular, because we evaluated sensitivity to sensory stimuli as the degree of pain in model macaques, it is unclear whether these macaques exhibited spontaneous and/or persistent pain. Finally, although we identified FC changes associated with thalamic pain, it is not clear whether the FC changes were the cause or effect of the pain. Future studies of neuromodulation to directly normalize these FC changes in a macaque model of thalamic pain would clarify whether the observed FC changes are the cause of the pain. The present study showing the cross-species convergence of the pain-related FC changes advances our understanding of the causality of thalamic pain in human patients using a macaque model.

While our imaging data did not encompass other types of MRI sequences, such as diffusion tensor imaging, exploring these was not the focus of our present study. Notably, our previous research demonstrated that a macaque model of thalamic pain exhibited a pain-associated change in the structural connectivity in the somatosensory thalamocortical system, which constitutes the lateral pain system with no overlap with the network in which the FC changes were observed. Therefore, acquiring multiple modalities of MRI data in human patients could be a valuable direction for future studies to provide a more comprehensive understanding of the cross-species convergence of the structural and functional changes associated with thalamic pain. To gain further understanding of the neurobiological basis of thalamic pain and optimize

the development of novel diagnostic and treatment strategies, future studies involving both humans and macaques should be conducted with the following approaches: high-resolution fMRI to obtain more precise localization of relevant brain nodes showing thalamic pain-related FC changes, electrophysiology to record the activity of individual or groups of neurons underlying the observed FC changes, and neuromodulation to test whether the observed FC changes are causally related to pain. Identifying crucial regions, FC, and underlying mechanisms for triggering thalamic pain via using a cross-species approach to examine the FC of regions involved in thalamic pain and identify the mechanisms underlying the development of thalamic pain will contribute to the development of novel therapeutic strategies.

## Conclusions

The present study was designed to identify convergent FC changes across humans and macaques in thalamic pain. Our findings indicate that the FCs between the BLA and the midbrain, and between the amygdala and MD, increase in relation to thalamic pain in both species. The current results suggest that increased FC among regions associated with emotion, memory, motivation, and reward is part of the underlying mechanisms for the onset of thalamic pain consistently in both humans and nonhuman primates.

## Disclosures

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## Data availability

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

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## Appendix A. Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2024.104661.

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