NeuroImage 221 (2020) 117186

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Deficits in ascending and descending pain modulation pathways in patients with postherpetic neuralgia

Hong Li[a,b], Xiaoyun Li[b,c], Yi Feng[d], Fei Gao[d,*], Yazhuo Kong[a,b,**], Li Hu[b,c]

[a] CAS Key Laboratory of Behavioral Science, Institute of Psychology, Beijing 100101, China
[b] Department of Psychology, University of Chinese Academy of Sciences, Beijing 100049, China
[c] CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing 100101, China
[d] Department of Pain Medicine, Peking University People's Hospital, Beijing 100044, China

ARTICLE INFO

Keywords:
Postherpetic neuralgia
Pain
Thalamus
Periaqueductal gray matter (PAG)
Magnetic resonance imaging (MRI)
Anxiety
Depression

ABSTRACT

Postherpetic Neuralgia (PHN), develops after the resolution of the herpes zoster mucocutaneous eruption, is a debilitating chronic pain. However, there is a lack of knowledge regarding the underlying mechanisms associated with ascending and descending pain modulations in PHN patients. Here, we combined psychophysics with structural and functional magnetic resonance imaging (MRI) techniques to investigate the brain alternations in PHN patients. Psychophysical tests showed that compared with healthy controls, PHN patients had increased state and trait anxiety and depression. Structural MRI data indicated that PHN patients had significantly smaller gray matter volumes of the thalamus and amygdala than healthy controls, and the thalamus volume was negatively correlated with pain intensity (assessed using the Short-form of the McGill pain questionnaire) in PHN patients. When the thalamus and periaqueductal gray matter (PAG) were used as the seeds, resting-state functional MRI data revealed abnormal patterns of functional connectivity within ascending and descending pain pathways in PHN patients, e.g., increased functional connectivity between the thalamus and somatosensory cortices and decreased functional connectivity between the PAG and frontal cortices. In addition, subjective ratings of both Present Pain Index (PPI) and Beck-Depression Inventory (BDI) were negatively correlated with the strength of functional connectivity between the PAG and primary somatosensory cortex (SI), and importantly, the effect of BDI on PPI was mediated by the PAG-SI functional connectivity. Overall, our results provided evidence suggesting deficits in ascending and descending pain modulation pathways, which were highly associated with the intensity of chronic pain and its emotional comorbidities in PHN patients. Therefore, our study deepened our understanding of the pathogenesis of PHN, which would be helpful in determining the optimized treatment for the patients.

1. Introduction

Postherpetic neuralgia (PHN) is a typical neuropathic pain, which develops after the resolution of the herpes zoster mucocutaneous eruption (Peng et al., 2017). PHN patients are clinically characterized by extreme pain, usually accompanied by various abnormal sensory symptoms (Kost and Straus, 1996) and emotional comorbidities, such as anxiety and depression (Hunt and Mantyh 2001; Geha et al., 2007). The duration of PHN varies from a few months to a lifetime. Evidence from both animal models and human studies showed that PHN was not only related to peripheral neuropathy, but also associated with abnormal subcortical/cortical alterations (Woolf and Salter 2000; Hunt and Mantyh 2001; Wu et al., 2001).

These subcortical/cortical alterations in PHN patients could be quantified using advanced neuroimaging approaches. Structurally, pathological changes in the brain could be evaluated using diffusion tensor imaging (DTI), diffusional kurtosis imaging (DKI), or voxel-based morphometry (VBM) techniques (Zhang et al., 2016; Chen et al., 2017; Cao et al., 2018; Liu et al., 2019). When applying the VBM technique, Liu et al. (2019) reported that PHN patients exhibited abnormal gray matter density in several brain regions, including the thalamus, bilateral insula, right middle frontal gyrus, left postcentral gyrus, and cerebellum. In addition, Zhang et al. (2016) adopted the DKI technique and observed microstructure changes in the superior temporal gyrus and bilateral insula in PHN patients. Functionally, resting-state functional MRI was widely used to evaluate regions and regional interactions that were

* Corresponding author at: Department of Pain Medicine, Peking University People's Hospital, Beijing 100044, China
** Corresponding author at: Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China
E-mail addresses: gaofei19780318@sina.com (F. Gao), kongyz@psych.ac.cn (Y. Kong).

https://doi.org/10.1016/j.neuroimage.2020.117186
Received 21 August 2019; Received in revised form 18 May 2020; Accepted 19 July 2020
Available online 22 July 2020

associated with pathological changes. Using regional homogeneity and fractional amplitude of low-frequency fluctuations, it has been revealed that in PHN patients, functional changes in a series of brain regions were related to their spontaneous pain, including the insula, somatosensory cortices, thalamus, anterior cingulate cortex, limbic system, prefrontal lobe, and temporal lobe (Jiang et al., 2016; Cao et al., 2017). Moreover, Jiang et al. (2016) have identified decreased homotopic connectivity in the dorsolateral prefrontal cortex, precuneus, and posterior cingulate cortex, indicating disrupted intrinsic connectivity within the default-mode network (DMN) in PHN patients. While previous neuroimaging studies have reported pathological changes in brain structure and function in PHN patients, ascending and descending pain modulation pathways have not been investigated thoroughly.

It has been suggested that abnormal sensory symptoms in chronic pain patients could be caused by impairments of the ascending and descending pain modulation circuits (Apkarian et al., 2011). Thalamus is a key node in the ascending pain pathway, and widespread nociceptive information accesses somatosensory cortices through the spinothalamic projection (Monconduit and Villanueva 2005). MRI studies have shown that the volume of thalamus decreased in individuals with neuropathic pain, who also displayed decreased thalamic baseline activity or decreased thalamic response (Apkarian et al., 2004; Gustin et al., 2011). The descending pain modulation system provides a mechanism through which cortical and subcortical regions could influence pain, and the periaqueductal gray (PAG), which receives inputs from higher brain regions, is the primary control center for the descending pain modulation (Mason 2012). Altered functional connectivity of the descending pain modulation system was widely observed in various chronic pain conditions, such as migraines (Mainero et al., 2011; Marciszewski et al., 2018), low back pain (Yu et al., 2014), and painful diabetic neuropathy (Segerdahl et al., 2018). However, the neural mechanism by which the ascending and descending pain modulation systems contribute to PHN is poorly understood. In addition, the interaction between these pain modulation systems and pain-related emotional comorbidities is not well studied.

In this study, we combined psychophysics with structural and functional MRI techniques to investigate brain alternations in ascending and descending pain pathways in PHN patients. We assessed the relationship between these brain alternations and pain intensity as well as pain-related emotional comorbidities. With these efforts, our study could deepen our understanding of the pathogenesis of PHN, which would help provide a solid basis for the mechanism-based diagnosis of PHN patients.

2. Materials and methods

2.1. Subjects

24 right-handed PHN patients (9 males; mean age 63.78±7.79 years) and 23 well-matched right-handed healthy controls (8 males; mean age 60.73±8.01 years) participated in the study. Patients fulfilled the International Association for the Study of Pain (IASP) criteria for PHN (Merskey and Bogduk, 1994), and in accordance with recent guidelines (Scholz et al., 2019), the diagnosis was performed by experienced clinicians based on clinical symptoms (including medical history, typical scars, pain severity, and types) (Fields et al., 1998). All PHN patients were requested to stop taking any painkillers one week before the MRI scan. Exclusion criteria included histories of neurological diseases or dementia, psychiatric disorders, or inabilities to complete the testing procedures and MRI scans. One patient was excluded because of illness during the MRI scan. All included patients reported pain that lasted for at least a month after the resolution of the herpes zoster eruption (Kost and Straus 1996). All subjects gave their informed consent, and the Ethics Committee at the Institute of Psychology, Chinese Academy of Sciences, approved the study. Independent samples *t*-test was used for detecting differences in age and year of education between PHN patients and healthy controls. A Chi-square test was applied to assess the difference in gender between PHN patients and healthy controls.

2.2. Pain characteristics

Before the MRI scan, subjects were instructed to complete the Short-form of the McGill pain questionnaire (SF-MPQ) (Dworkin et al., 2009). This questionnaire contains (1) A Pain Rating Index (PRI), consisting of 15 descriptors ranging from 0 (none) to 3 (severe), which represents pain intensity in the past month; (2) A Present Pain Intensity (PPI) index ranging from 0 (no pain) to 5 (unbearable pain), which evaluates the present pain intensity; (3) A 10-cm Visual Analogue Scale (VAS), which measures the intensity of averaged daily pain during the past 2 weeks. The SF-MPQ total score is the sum of the three indices. In addition, for PHN patients, the duration of pain was measured in years, and the site of shingles was recorded.

2.3. Psychophysical characteristics

Psychological characteristics were assessed using the following validated questionnaires: State and trait anxiety were evaluated by the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970), and depression was evaluated by the Beck-Depression Inventory (BDI) (Beck et al., 1996). Kolmogorov-Smirnov normality test was used to examine if pain and psychological characteristics were normally distributed, and independent samples *t*-test was used for detecting differences in pain and psychological variables between PHN patients and healthy controls. Pearson's correlation analysis was performed to assess the relationship between pain intensities and psychological characteristics in PHN patients.

2.4. MRI acquisition

All PHN patients and healthy controls lay supine on the bed of a 3T MR750 GE-MRI scanner with their head immobilized in a tight-fitting head coil. Standard T1-weighted 3D anatomical data were acquired using gradient echo (3D SPGR) sequence (TR/TE = 6.9/2.9 ms, FA= 8°, FOV = 256 mm × 256 mm, matrix = 256 × 256, slices = 192, slice thickness = 1.0 mm). Resting-state fMRI data were acquired with an echo planar imaging (EPI) sequence (TR/TE = 2000/30 ms, flip angle: 90°, FOV = 220 mm × 220 mm, matrix = 64 × 64, slice thickness = 4 mm, slices = 37, 300 volumes).

2.5. Surface-based morphology analysis (SBM)

To extract the cortical and subcortical volumes, structural MRI data were analyzed using FreeSurfer (version 5.2.0, http://surfer.nmr.mgh.harvard.edu), a freely available software suite for analyzing human brain MRI images. The technical details of the SBM analysis were described in previous studies (Dale et al., 1999; Fischl and Dale 2000), and its accuracy in identifying cortical and subcortical volumes was validated in several publications (Rosas et al., 2002; Salat et al., 2004). Briefly, preprocessing steps included intensity normalization, skull stripping, Talairach transformation, hemispheric separation, and segmentation of the gray matter/white matter (GM/WM) tissues. The cortical thickness at each vertex was calculated by measuring the shortest distance between the white and pial surfaces. The surface area was the total area of triangles that were connected to the vertex (Fischl and Dale, 2000). The volume at each vertex was quantified by the product of cortical thickness and surface area. Then, each subject's cortex was anatomically parcellated, and all sulci and gyri were labeled and aligned to the FreeSurfer's average surface map according to cortical folding patterns and smoothed using

a 10-cm full-width half-maximum (FWHM) Gaussian spatial smoothing kernel. The subcortical volumes were obtained from the automated segmentation for the brain structures implemented in FreeSurfer (Liu et al., 2016). We extracted 40 labeled subcortical structures (e.g., brainstem, caudate, thalamus, pallidum, putamen, hippocampus, and amygdala) from each hemisphere of the brain (Fischl et al., 2002). The volumes of five subcortical structures (i.e., thalamus, caudate, putamen, hippocampus, and amygdala) that were proved to be closely related to chronic pain were selected and compared between PHN patients and healthy controls using one-way analysis of covariance (ANCOVA) after controlling the effects of age, gender, and total brain size by adding them as covariates (Davis et al., 2017; Reddan and Wager 2018). The significant level was set at $p < 0.01$, adjusted with Bonferroni correction for multiple comparisons. Pearson's correlation analysis was performed to assess the relationship between pain intensities and subcortical volumes in PHN patients.

2.6. Resting-state fMRI data pre-processing

Resting-state fMRI data were analyzed using FMRI Expert Analysis Tool (FEAT), version 5.98, which is a part of the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). Pre-processing of resting-state fMRI data was performed as follows: motion correction using MCFLIRT (Jenkinson et al., 2002), removal of nonbrain structures using Brain Extraction Tool (Smith et al., 2002), spatial smoothing using a Gaussian kernel with a 5-mm FWHM, and high-pass temporal filtering (cutoff: 100 s). Time-series autocorrelation was performed using FMRIB's Improved Linear Model (FILM). Resting-state fMRI data were co-registered to each participant's structural data (T1-weighted) using a boundary-based registration procedure (Greve and Fischl 2009). Subsequently, they were spatially normalized to the MNI-152 2-mm standard brain using an initial linear registration (FLIRT, FMRIB's Linear Image Registration Tool) (Jenkinson et al., 2002), followed by a nonlinear registration (FNIRT, FMRIB's Non-Linear Image Registration Tool) (Andersson et al., 2007).

2.7. Seed-based functional connectivity analysis

Given that the thalamus and PAG are key nodes in the ascending and descending pain pathways respectively, they were chosen as seeds for the functional connectivity analyses of resting-state fMRI data. To keep consistency across all subjects in alignment with standard fMRI analysis pipelines, the thalamus seed was defined from the Harvard Oxford subcortical structural atlas (90% threshold), which is a population-based probability atlas in MNI-152 standard space (Frazier et al., 2005). The PAG seed was defined from the Duvernoy's atlas of the Human Brainstem and Cerebellum in MNI-152 standard space (Ezra et al., 2015). Both masks were then warped back to individual fMRI space using applywarp, one of the FSL tools.

Resting-state seed-based functional connectivity analysis was performed through a general linear model (GLM) framework following the standard procedures (Fox et al., 2006). CSF and WM masks were drawn within a ventricular region of interest and a region centered in the white matter in the MNI space (center points of CSF in both hemispheres: [9, −14, 20] and [−9, −14, 20]; center points of WM in both hemispheres: [33, −13, 27] and [−33, −13, 27]), and registered back to each subject's individual space. Mean time series of the two seeds and nuisance regions for CSF and WM were then extracted for each subject. Time series of each individual subject's seed was modeled as an explanatory variable in the first level analysis, and the time series of CSF and WM were entered as nuisance variables. Parameter estimates and variances were passed up to group level using a mixed-effect FLAME approach (FLAME, FMRIB's Local Analysis of Mixed effects). The differences in the seed-based functional connectivity between PHN patients and healthy controls were assessed using independent samples *t*-test. In addition, pain intensities and psychological variables across subjects in each experimental group were demeaned (zeroing set to mean), and included as regressors to determine the associated functional connectivity after controlling the effects of age and gender. The statistical images were thresholded using cluster-forming correction determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

2.8. Mediation analysis

A bootstrapped mediation analysis was performed to assess the mediatory relationship between pain intensity, psychological variables, and seed-based functional connectivity. The PROCESS macro (www.processmarcro.org, version 2.16.3) in SPSS (IBM, version 23.0.0) was used with 2000 bootstrap samples, which identified 95% confidence intervals for model components. The mediation analysis was aimed to evaluate whether there was a significant difference between the total effect (path c) and the direct effect (path c′) that account for the mediator (M) (Fig. 5). With the PAG-SI functional connectivity was designated and entered as the mediator, we tested two models: 1) BDI ratings as the independent variable and pain intensities (PPI) as the outcome, 2) pain intensities (PPI) as the independent variable and BDI ratings as the outcome. A significant mediation occurs when bootstrapped upper and lower 95% confidence intervals (CIs) do not include zero (Hayes and Preacher 2014).

3. Results

3.1. Demographic, pain, and psychological characteristics

Demographic (gender, age, and year of education), pain (PRI, PPI, VAS, and SF-MPQ total score), and psychological (SAI, TAI, and BDI) characteristics in PHN patients and healthy controls were summarized in Table 1. Whereas the gender, age, and year of education were not significantly different between the two groups, the intensity of pain, as quantified by PRI ($t = 7.281$, $p < 0.001$), PPI ($t = 7.257$, $p < 0.001$), VAS ($t = 8.138$, $p < 0.001$), and SF-MPQ total score ($t = 8.460$, $p < 0.001$) were significantly larger in PHN patients than healthy controls (Table 1, Fig. 1, top row). In addition, psychological variables, as measures by SAI ($t = 5.627$, $p < 0.001$), TAI ($t = 4.923$, $p < 0.001$), and BDI ($t = 4.178$, $p < 0.001$), were significantly larger in PHN patients than healthy controls (Table 1, Fig. 1, middle row). Other characteristics of PHN patients were summarized in Supplementary Table 1.

3.2. Correlations between pain intensities and psychophysical factors

For PHN patients, Pearson's correlation analyses revealed that both SAI and BDI scores were positively correlated with SF-MPQ total scores

Table 1
Comparison of demographic, pain, and psychological variables between PHN patients and healthy controls (mean ± SD).

	PHN patients	Healthy controls	t	p
Female/Male	15/9	15/8	–	–
Age, y	63.78 ± 7.79	60.73 ± 8.01	1.305	0.199
Education, y	10.65 ± 3.42	11.87 ± 2.28	−1.420	0.163
PRI	20.07 ± 12.50	0.87 ± 1.86	7.281	<0.001
PPI	3.13 ± 1.57	0.39 ± 0.89	7.257	<0.001
VAS	5.41 ± 2.70	0.47 ± 1.07	8.138	<0.001
SF-MPQ	28.61 ± 14.81	1.73 ± 3.55	8.460	<0.001
SAI	43.17 ± 13.78	26.04 ± 4.82	5.627	<0.001
TAI	41.91 ± 8.70	30.96 ± 6.17	4.923	<0.001
BDI	6.43 ± 4.18	2.18 ± 2.34	4.178	<0.001

PRI, Pain Rating Index; PPI, Present Pain Intensity; VAS, 10-cm Visual Analogue Scale; SF-MPQ, Short-form McGill pain questionnaire; SAI, State-Anxiety Inventory; TAI, Trait-Anxiety Inventory; BDI, Beck-Depression Inventory.

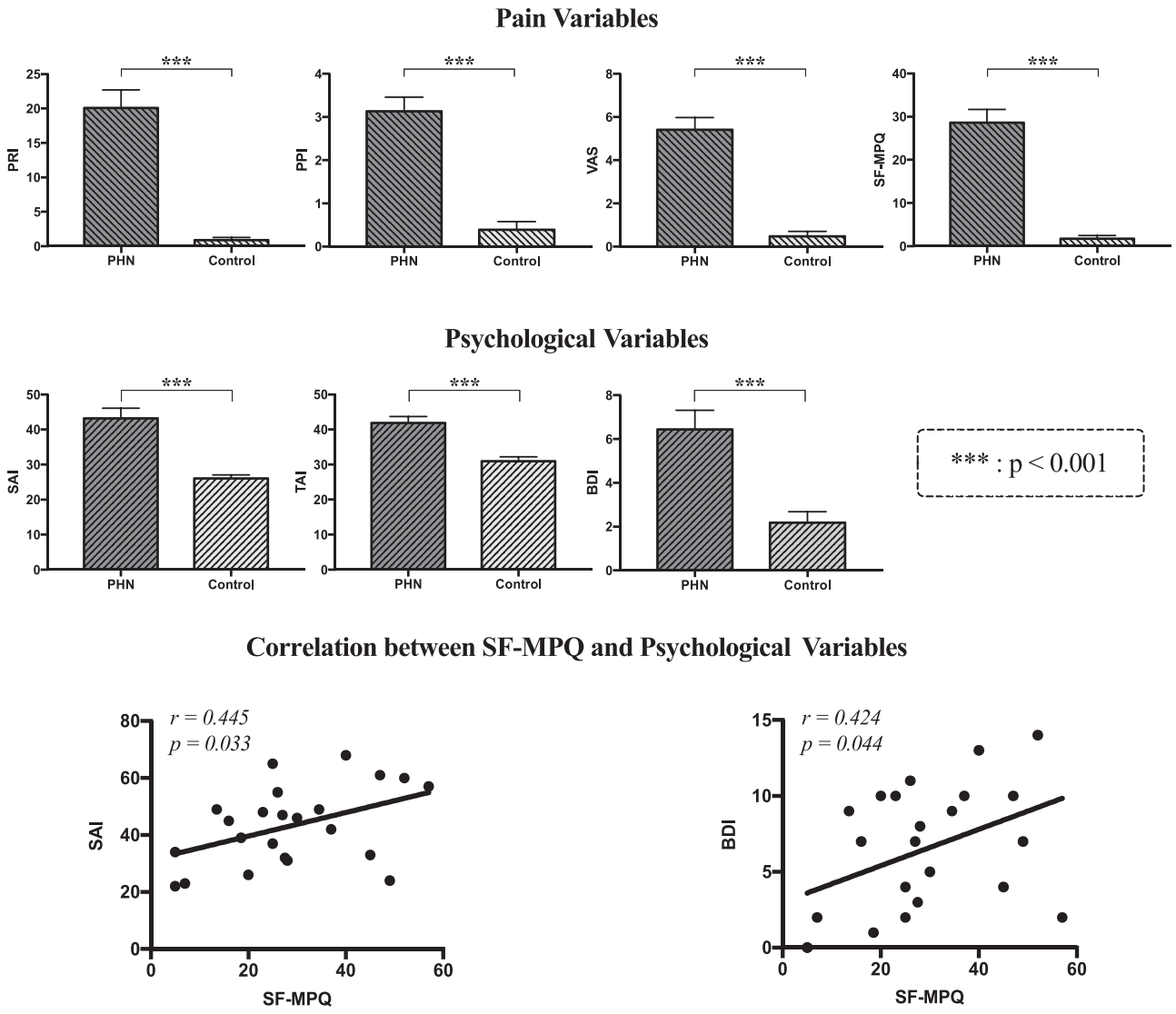

Fig. 1. Comparison of pain intensities (i.e., PRI, PPI, VAS, and SF-MPQ) and psychological variables (i.e., SAI, TAI, and BDI) between PHN patients and healthy controls, and the correlation between pain intensities and psychological variables in PHN patients.
Top row: Pain intensity ratings (i.e., PRI, PPI, VAS, and SF-MPQ) were significantly larger in PHN patients than in healthy controls. PRI = Pain Rating Index; PPI = Present Pain Index; VAS = 10-cm Visual Analogue Scale; SF-MPQ = Short-form McGill pain questionnaire. *Middle row:* Psychophysical variables (i.e., SAI, TAI, and BDI) were significantly larger in PHN patients than in healthy controls. SAI = State-Anxiety Inventory; TAI = Trait-Anxiety Inventory; BDI = Beck-Depression Inventory. *Bottom row:* SF-MPQ ratings were significantly correlated with both SAI and BDI in PHN patients.

(SAI vs. SF-MPQ: $r = 0.445$, $p = 0.033$; BDI vs. SF-MPQ: $r = 0.424$, $p = 0.044$) (Fig. 1, bottom row).

3.3. Cortical and subcortical gray matter volumes

After controlling the effects of age, gender, and total brain size, we observed that the gray matter volumes of the amygdala and thalamus were significantly smaller in PHN patients than in healthy controls (amygdala: $F = 7.400$, $p = 0.002$; thalamus: $F = 5.199$, $p = 0.009$; Table 2). In addition, the gray matter volume of the thalamus was negatively correlated with SF-MPQ total scores in PHN patients ($r = -0.474$, $p = 0.026$, Fig. 2). No significant differences in other subcortical and cortical volumes were observed between PHN patients and healthy controls (caudate: $F = 3.504$, $P = 0.039$; putamen: $F = 1.562$, $p = 0.222$; hippocampus: $F = 2.445$, $p = 0.099$; Table 2; the significant level was set at $p < 0.01$, adjusted with Bonferroni correction for multiple comparisons).

3.4. Seed-based functional connectivity

Compared with healthy controls, thalamus exhibited significantly stronger functional connectivity with the primary and secondary somatosensory cortices (SI and SII) and weaker functional connectivity with the posterior cingulate cortex (PCC) and precuneus in PHN patients ($Z>2.3$, $p<0.05$ cluster-wise corrected; Table 3, Fig. 3, top panel). PAG exhibited significantly stronger functional connectivity with the thalamus, PCC, and precuneus and weaker functional connectivity with the rostral anterior cingulate cortex (rACC) and prefrontal gyrus in PHN patients than in healthy controls ($Z>2.3$, $p<0.05$ cluster-wise corrected; Table 3, Fig. 3, bottom panel).

Importantly, PPI ratings were negatively correlated with the functional connectivity between PAG and SI (and frontal gyrus, parietal lobule) ($Z>2.3$, $p<0.05$ cluster-wise corrected; Table 4, Fig. 4, top panel), and BDI ratings were negatively correlated with the functional connectivity between PAG and SI in PHN patients ($Z>2.3$, $p<0.05$ cluster-wise corrected; Table 4, Fig. 4, bottom panel). No significant correlations

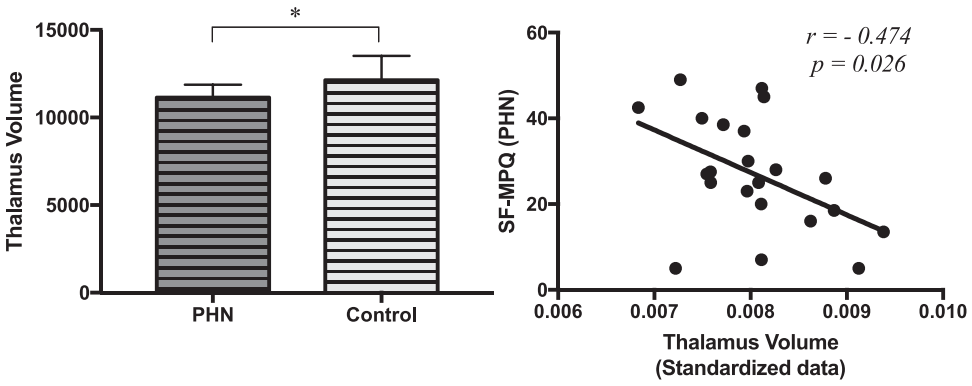

Fig. 2. Comparison of thalamus volume between PHN patients and healthy controls, and the correlation between thalamus volume and pain intensity in PHN patients.
Left panel: The gray matter volume of the thalamus was significantly smaller in PHN patients than in healthy controls (*: $p < 0.05$). *Right panel:* Thalamus volume was negatively correlated with SF-MPQ ratings in PHN patients. SF-MPQ = Short-form McGill pain questionnaire.

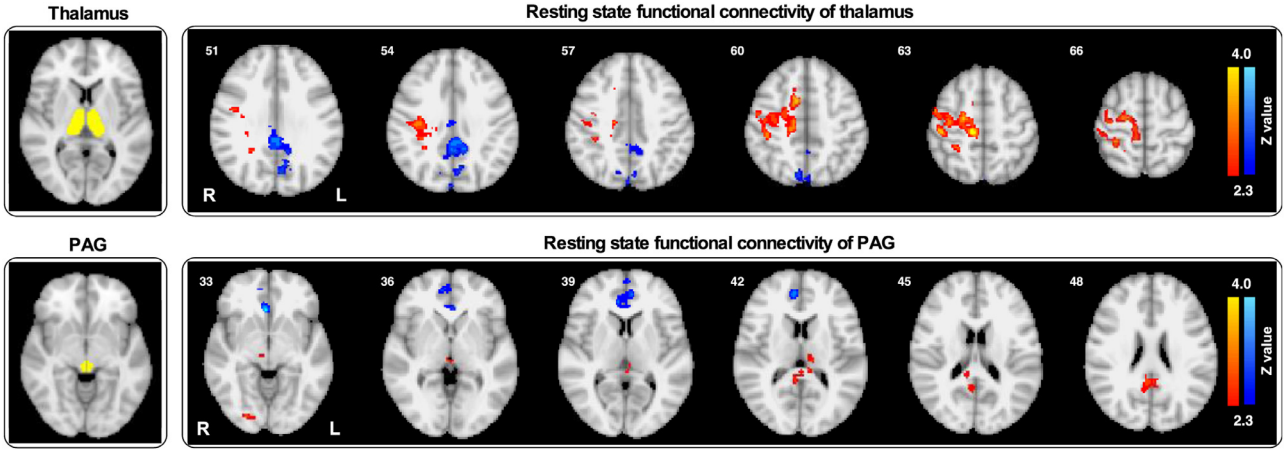

Fig. 3. Resting-state functional connectivity of the thalamus and PAG.
Top panel: Thalamus exhibited stronger resting-state functional connectivity with the SI/SII and weaker resting-state functional connectivity with the PCC and precuneus in PHN patients than in healthy controls. *Bottom panel:* PAG exhibited stronger resting-state functional connectivity with the thalamus, PCC, and precuneus and weaker resting-state functional connectivity with the rACC and prefrontal gyrus in PHN patients than in healthy controls.

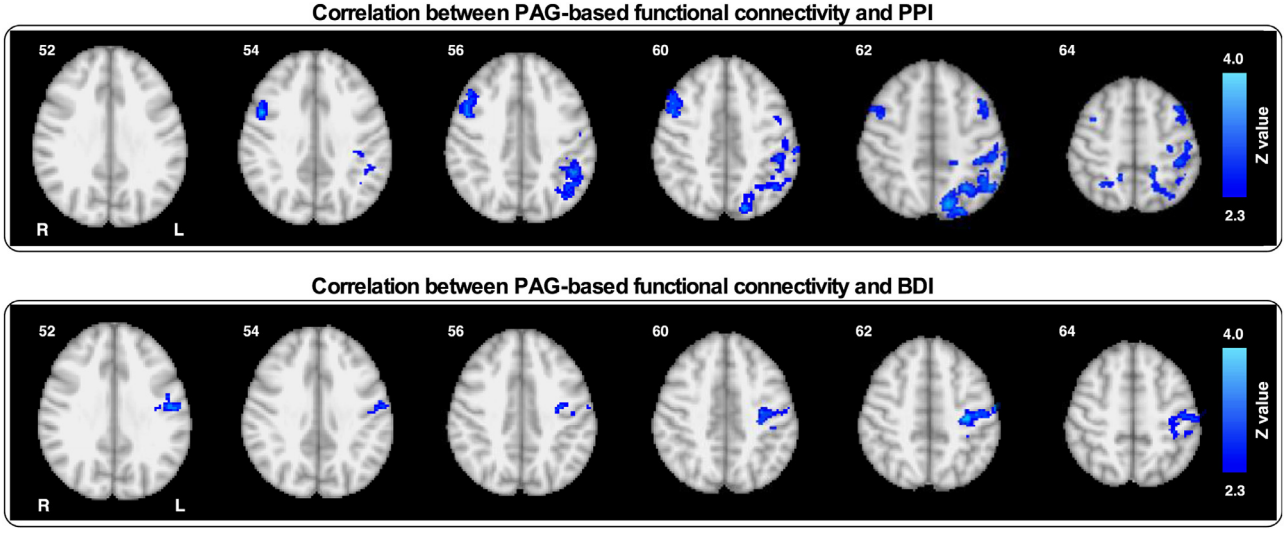

Fig. 4. Correlation between PAG-based functional connectivity and psychological variables (i.e., PPI and BDI) in PHN patients.
Top panel: Resting-state functional connectivity between PAG and SI (as well as the frontal gyrus and parietal lobule) was negatively correlated with PPI in PHN patients. PPI = Present Pain Index. *Bottom panel:* Resting-state functional connectivity between PAG and SI was negatively correlated with BDI in PHN patients. BDI = Beck-Depression Inventory.

Table 2
Comparison of subcortical volumes between PHN patients and healthy controls (mean ± SD).

Region	Subcortical volume (mm^3)		F	p	η_p^2
	PHN patients	Healthy controls			
Thalamus	11,142.9 ± 725.8	12,132.9 ± 1387.7	5.199	0.009*	0.202
Caudate	6714.5 ± 809.1	6770.1 ± 882.7	3.504	0.039	0.146
Putamen	8833.5 ± 973.2	9418.6 ± 1334.1	1.562	0.222	0.071
Hippocampus	6814.3 ± 666.6	7485.5 ± 810.5	2.445	0.099	0.107
Amygdala	2568.3 ± 287.0	2960.6 ± 408.4	7.400	0.002*	0.256

* : $p < 0.01$ (Bonferroni corrected).

Table 3
Clusters that exhibited significant resting-state functional connectivity differences of the thalamus and PAG between PHN patients and healthy controls.

Area	Side	Brodmann's area	MNI coordinates Peak x/y/z	Z value	Voxels
Thalamus as the seed					
PHN patients > Healthy controls					
SI	R	BA6	46 −26 54	3.57	261
SI	R	BA6	30 −36 62	2.99	34
SII	R	BA70	56 −34 16	3.72	46
PHN patients < Healthy controls					
PCC	L	BA35	−2 −38 34	3.22	693
PCC	L	BA47	−8 −48 4	3.4	362
precuneus	L	–	−6 −70 28	3.12	381
PAG as the seed					
PHN patients > Healthy controls					
PCC	R	BA50	4 −46 24	2.9	126
thalamus	L	–	−10 −22 10	2.82	45
precuneus	R	BA50	6 −52 16	2.78	45
PHN patients < Healthy controls					
rACC	R	BA52	8 44 12	3.08	131
rACC	R	BA22	4 32 −8	3.25	38
prefrontal gyrus	L	BA19	−2 60 4	2.91	55

SI, primary somatosensory cortex; SII, secondary somatosensory cortex; PCC, posterior cingulate cortex; rACC, rostral anterior cingulate cortex; L, left; R, right; MNI, Montreal Neurological Institute.

Table 4
Clusters that exhibited significant correlations between PAG-based functional connectivity and psychological variables (i.e., PPI and BDI) in PHN patients.

Area	Side	Brodmann's area	MNI coordinates Peak x/y/z	Z value	Voxels
PPI					
SI	L	BA5	−40 −36 56	3.34	404
SI	L	BA7	−26 −30 72	2.96	99
SI	R	BA8	18 −30 66	3.22	49
frontal gyrus	R	BA12	48 6 38	4.33	398
frontal gyrus	L	BA11	−46 −6 60	3.13	362
parietal lobule	R	BA14	30 −50 58	3.33	122
parietal lobule	L	BA65	−38 −40 56	2.92	42
BDI					
SI	L	BA7	−50 −20 50	3.15	228
SI	L	BA7	−50 −10 32	3.17	85

SI, primary somatosensory cortex; L, left; R, right; MNI, Montreal Neurological Institute.

were observed between PAG-SI functional connectivity and pain intensities/psychological variables in healthy controls (PAG-SI vs. PPI: $Z<2$; PAG-SI vs. BDI: $Z<2$).

3.5. Mediation analysis

The effect of BDI on pain intensity (quantified by PPI) was mediated by the PAG-SI functional connectivity (direct effect = 0.166, $p < 0.05$; indirect effect = 0.068, 95% confidence interval: [0.002,0.255], Fig. 5, left panel). Please note that the SI region used in the mediation analysis was extracted from the conjunction of the regions displayed in Fig. 4 top and bottom panels. In contrast, the effect of pain intensity (quantified by PPI) on BDI was not mediated by the PAG-SI functional connectivity (direct effect = 1.364, $p < 0.05$; indirect effect = 0.082, 95% confidence interval: [−0.741, 0.769], Fig. 5, right panel).

4. Discussion

Chronic pain neuroimaging, until recently, has been dominated by studies mapping the effects of pain modulation (May 2007; Reddan and

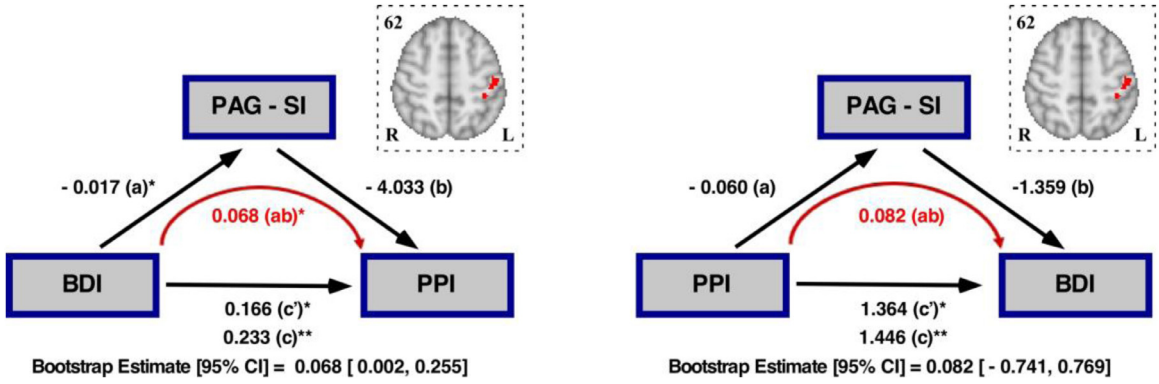

Fig. 5. Mediation analysis.
Left panel: The effect of BDI on PPI was mediated by the PAG-SI functional connectivity. Path c is the total effect of BDI on PPI; path c' is the direct effect of BDI on PPI after controlling for the PAG-SI functional connectivity; the product of a and b (ab) is the indirect effect of BDI through the PAG-SI functional connectivity on PPI. *Right panel:* The effect of PPI on BDI was not mediated by the PAG-SI functional connectivity. Path c is the total effect of PPI on BDI; path c' is the direct effect of PPI on BDI after controlling for the PAG-SI functional connectivity; the product of a and b (ab) is the indirect effect of PPI through the PAG-SI functional connectivity on BDI. PPI = Present Pain Index; BDI = Beck-Depression Inventory. *: $p < 0.05$, **: $p < 0.01$.

Wager 2018). Focus has primarily been on the pain-related brain regions and its pain modulation pathways. The pain-related brain regions are comprised of a general set of brain areas involved in the encoding of pain experience that include the thalamus, ACC, insula, SI, SII, and PAG, and are often extended to include prefrontal cortices, as well as the basal ganglia and amygdala (Melzack 2001). Neuroimaging approaches to the study the modulation pathways often assess the complex interactions between these brain regions and the functional roles of these interactions (Reddan and Wager 2018). In the present study, we combined psychophysics with structural and functional MRI techniques to assess the pathological changes in PHN patients compared to healthy controls. The main finding of this study is that PHN patients demonstrated severe psychophysical consequences, such as increased state and trait anxiety and depression, and structural and functional abnormalities within the pain-related brain network, compared to healthy controls. In addition, subjective ratings of PPI and BDI were negatively correlated with the strength of functional connectivity between PAG and SI in PHN patients, and importantly, the effect of BDI on PPI was mediated by the PAG-SI functional connectivity. Altogether, these findings suggested that PHN patients were characterized by deficits in ascending and descending pain modulation pathways, which could influence the relationship between the intensity of chronic pain and its emotional comorbidities.

4.1. Deficits in ascending pain modulation pathway

Structural MRI data indicated that PHN patients had significantly smaller gray matter volumes of the thalamus and amygdala than healthy controls, and moreover, the thalamus volume was negatively correlated with pain intensity in PHN patients. This result is consistent with previous studies showing that neuropathic pain was associated with thalamus anatomy changes, and the extent of which was correlated with pain intensity (Apkarian et al., 2004; Gustin et al., 2010). Growing evidence showed that thalamus is important in the generation and maintenance of neuropathic pain, such as trigeminal neuralgia and chronic back pain (Apkarian et al., 2004; Gustin et al., 2011; Henderson et al., 2013). Reduction in the thalamus volume reported here further extended previous findings, and its atrophy may indicate an abnormality in the ascending pain modulation pathway in PHN patients. The decreased gray matter volume could be explained by the overuse of thalamus caused by excitotoxicity and inflammatory agents (Rommel et al., 2001; Brown and Bal-Price 2003; Mattson 2003; Giesecke et al., 2004). In addition, a reduction of amygdala volume was also observed in PHN patients. Previous evidence suggested that the reduction of amygdala volume was commonly associated with negative affective disorders, and was able to predict the chronification of pain (Gilbertson et al., 2002). However, no significant correlation was observed between the amygdala volume and affective variables (i.e., BDI, STAI) in PHN patients in the present study.

Resting-state functional connectivity analysis revealed that thalamus exhibited stronger functional connectivity with the SI and SII, and weaker functional connectivity with the PCC and precuneus in PHN patients than in healthy controls. This result suggested possible function deficits of the ascending pain modulation pathway in PHN patients. In line with this observation, many previous studies have found that the dysfunction of the thalamocortical network could serve as a promising neurobiological marker of neuropathic pain (Sarnthein et al., 2006; Stern et al., 2006; Moisset and Bouhassira 2007; Henderson et al., 2013). Thalamus is a critical node of the ascending pain modulation pathway, which transmits afferent nociceptive information from nociceptive terminals to the pain-related brain regions (Coghill et al., 1999). It was suggested that the overloaded input of spontaneous pain in the thalamocortical network could enhance the connection from the thalamus to somatosensory cortices (Geha et al., 2008), which might reflect that PHN patients immersed themselves in the state of chronic pain.

It is well known that PCC and precuneus are core regions of the DMN, which remains highly active at rest to continuously gather information from both external and internal milieu (Raichle et al., 2001). Being necessary for monitoring the changes of sensory information, DMN was frequently observed to be functionally disrupted in patients with chronic pain (Baliki et al., 2014), which suggested that the sensory monitoring function may be compromised in these patients (Fox and Raichle 2007; Baliki et al., 2008). In addition, PCC that is structurally connected to the medial temporal lobe memory system plays an important role in negative memory (Vogt et al., 2006). In the present study, the resting-state functional connectivity between the thalamus and DMN (i.e., PCC and precuneus) was reduced in PHN patients, which could reflect that PHN patients with negative memory were characterized with the impaired function of sensory monitoring.

4.2. Deficits in descending pain modulation pathway

In PHN patients, PAG showed weaker resting-state functional connectivity with the rACC and prefrontal areas than healthy controls. Numerous studies have highlighted the role of rACC and prefrontal areas in the inhibition of pain through the descending pain modulation pathway, in which PAG is the primary control center (Bingel et al., 2006). It is well documented that the rACC and prefrontal areas send projections to the PAG and further communicate with the rostral ventromedial medulla (RVM, which sends direct projection to the spinal cord and thus modulates spinal nociception), and this descending pathway is closely related to analgesia (Calejesan et al., 2000; Peng et al., 2019).

The role of PAG in the modulation of pain has been widely investigated in studies of placebo analgesia, which is mediated by the endogenous opioid system through the activation of the μ-opioid receptor in some brain regions, including the rACC and prefrontal areas (Zubieta et al., 2005). The negative correlation between PAG-rACC functional connectivity and BOLD responses in the SII under placebo analgesia indicated that the PAG-rACC functional connectivity was crucial in the modulation of pain (Eippert et al., 2009). Our observation was supported by Mainero et al. (2011), in which the reduced functional connectivity between PAG and prefrontal areas was related to the increased frequency of attacks in migraines. This observation was interpreted as the interictal dysfunction of the descending pain inhibitory system that, in turn, contributed to the development of chronic pain (Tracey 2016). In addition, reduced functional connectivity between PAG and prefrontal areas as well as rACC has been observed in fibromyalgia patients with experimental induced allodynia (Lorenz et al., 2002; Jensen et al., 2013). In line with these previous studies (Geha et al., 2007; Cao et al., 2018), our observation also suggested the dysfunction of the descending pain inhibition system in PHN patients.

Compared to healthy controls, PHN patients showed increased resting-state functional connectivity between PAG and thalamus. A key feature of the descending pain modulation system is that it has the dual capability to inhibit and facilitate pain processing. The PAG is also involved in ascending nociceptive processing, which could modify the magnitude of nociceptive input arriving at the cortex at the level of the dorsal horn of the spinal cord. In chronic pain patients, the increased functional connectivity between the PAG and other pain-related brain regions (e.g., the thalamus and insula) with enhanced hyperalgesia might be related with PAG mediated facilitation of constant spontaneous pain inputs (Coghill et al., 1999; Tracey and Mantyh 2007; Gwilym et al., 2009; Mainero et al., 2011; Segerdahl et al., 2018). In addition, increased resting-state functional connectivity between PAG and brain regions in DMN (i.e., PCC and precuneus) was also observed in PHN patients, which may suggest the possible modulation of DMN on the descending pain modulation system (Jin et al., 2018).

Importantly, we found that in PHN patients, subjective ratings of both PPI and BDI were negatively correlated with the strength of the PAG-SI functional connectivity. In line with previous reports, in which PAG showed decreased resting-state functional connectivity with the somatosensory cortices when the intensity of pain increased, our observations suggested that the dysfunction of the descending pain modulation system was highly associated with the intensity of chronic pain and the emotional comorbidity of depression (Kong et al., 2010; De Felice, Sanoja et al. 2011; Segerdahl et al., 2018). Interestingly, mediation analyses revealed the effect of BDI on PPI was mediated by the PAG-SI functional connectivity, while the effect of PPI on BDI was not mediated by the PAG-SI functional connectivity. It is well known that there is a reciprocal relationship between pain and depression in chronic pain patients (Apkarian et al., 2011; Boersma et al., 2019). In a longitudinal study, Kroenke et al. (2011) observed that pain was a strong predictor of subsequent depression severity, and depression was an equally strong predictor of subsequent pain severity (Kroenke et al., 2011). Here, we observed that the effect of depression on pain severity in PHN patients was mediated by the dysfunction of the descending pain inhibition system, while the effect of pain on depression severity was not. This observation would suggest that even the relationship between pain and depression is reciprocal, causative effects on one another could be achieved through different neural systems. Indeed, the detailed neural mechanisms responsible for the causative effects needs further investigation.

4.3. Limitations and implications

Notably, there are several limitations of our study that merit consideration. First, our findings should be confirmed in a longitudinal study to further strengthen our understanding for the development of PHN. Second, the small sample size involving patients with varying severity and duration of the disease limited our exploration in the relationship between clinical symptoms and subcortical/cortical dysfunctions. Third, there are heterogenous sub-regions within the thalamus and PAG, and nuclei in the thalamus/PAG have multiple cortical connections. However, a precise description of deficits in ascending and descending pain modulation pathways in PHN patients was not explored in the present study. Future studies using ultra-high-field imaging or enhanced acquisition sequences to enable functional neuroanatomical dissection of the thalamus/PAG into its constituent components would help identify differences with a higher spatial resolution between PHN patients and healthy controls. Fourth, what is not clear from this study and previous studies is whether the changes that we observed within the ascending and descending pain modulation pathways can be interpreted as a “brain signature” of PHN, or rather they are shared by other chronic pain conditions (Cauda et al., 2010; Napadow et al., 2010). Finally, it is still not clear whether PHN patients would also be characterized with possible transmission mechanisms from the periphery to the spinal cord, which could be clarified by future work with combined spinal-brain fMRI.

Ethics statement

The study was approved by the Ethics Committee at the Institute of Psychology, Chinese Academy of Sciences. All subjects provided written informed consent.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 31671141, 31822025, 81871436), the Informatization Special Project of Chinese Academy of Sciences (No. XXH13506–306), the Scientific Foundation Project of Institute of Psychology, Chinese Academy of Sciences (No. Y6CX021008).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117186.

References

Andersson, J.L.R., Jenkinson, M., Smith, S. FMRIB technical report TR07JA2. 2007. Non-linear registration, aka Spatial normalisation.

Apkarian, A.V., Hashmi, J.A., Baliki, M.N., 2011. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 152 (3 Suppl), S49–S64.

Apkarian, A.V., Sosa, Y., Sonty, S., Levy, R.M., Harden, R.N., Parrish, T.B., Gitelman, D.R., 2004. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J. Neurosci. 24 (46), 10410–10415.

Baliki, M.N., Geha, P.Y., Apkarian, A.V., Chialvo, D.R., 2008. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J. Neurosci. 28 (6), 1398–1403.

Baliki, M.N., Mansour, A.R., Baria, A.T., Apkarian, A.V., 2014. Functional reorganization of the default mode network across chronic pain conditions. Plos One 9(9).

Beck, A.T., Steer, R.A., Ball, R., Ranieri, W.F., 1996. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. J. Pers. Assess. 67 (3), 588–597.

Bingel, U., Lorenz, J., Schoell, E., Weiller, C., Buchel, C., 2006. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 120 (1–2), 8–15.

Boersma, K., Sodermark, M., Hesser, H., Flink, I.K., Gerdle, B., Linton, S.J., 2019. Efficacy of a transdiagnostic emotion-focused exposure treatment for chronic pain patients with comorbid anxiety and depression: a randomized controlled trial. Pain 160 (8), 1708–1718.

Brown, G.C., Bal-Price, A., 2003. Inflammatory neurodegeneration mediated by nitric oxide, glutamate, and mitochondria. Mol. Neurobiol. 27 (3), 325–355.

Calejesan, A.A., Kim, S.J., Zhuo, M., 2000. Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. Eur. J. Pain 4 (1), 83–96.

Cao, S., Qin, B.Y., Zhang, Y., Yuan, J., Fu, B., Xie, P., Song, G.J., Li, Y., Yu, T., 2018. Herpes zoster chronification to postherpetic neuralgia induces brain activity and grey matter volume change. Am. J. Transl. Res. 10 (1), 184–199.
Cao, S., Song, G., Zhang, Y., Xie, P., Tu, Y., Li, Y., Yu, T., Yu, B., 2017. Abnormal Local Brain Activity Beyond the Pain Matrix in Postherpetic Neuralgia Patients: a Resting-State Functional MRI Study. Pain Phys. 20 (2), E303–E314.
Cauda, F., D'Agata, F., Sacco, K., Duca, S., Cocito, D., Paolasso, I., Isoardo, G., Geminiani, G., 2010. Altered resting state attentional networks in diabetic neuropathic pain. J. Neurol. Neurosurg. Psychiatry 81 (7), 806–811.
Chen, F., Chen, F., Shang, Z., Shui, Y., Wu, G., Liu, C., Lin, Z., Lin, Y., Yu, L., Kang, D., Tao, W., Li, Y., 2017. White matter microstructure degenerates in patients with postherpetic neuralgia. Neurosci. Lett. 656, 152–157.
Coghill, R.C., Sang, C.N., Maisog, J.H., Iadarola, M.J., 1999. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J. Neurophysiol. 82 (4), 1934–1943.
Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis - I. Segmentation and surface reconstruction. Neuroimage 9 (2), 179–194.
Davis, K.D., Flor, H., Greely, H.T., Iannetti, G.D., Mackey, S., Ploner, M., Pustilnik, A., Tracey, I., Treede, R.D., Wager, T.D., 2017. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat. Rev. Neurol. 13 (10), 624–638.
De Felice, M., Sanoja, R., Wang, R., Vera-Portocarrero, L., Oyarzo, J., King, T., Ossipov, M.H., Vanderah, T.W., Lai, J., Dussor, G.O., Fields, H.L., Price, T.J., Porreca, F., 2011. Engagement of descending inhibition from the rostral ventromedial medulla protects against chronic neuropathic pain. Pain 152 (12), 2701–2709.
Dworkin, R.H., Turk, D.C., Revicki, D.A., Harding, G., Coyne, K.S., Peirce-Sandner, S., Bhagwat, D., Everton, D., Burke, L.B., Cowan, P., Farrar, J.T., Hertz, S., Max, M.B., Rappaport, B.A., Melzack, R., 2009. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). Pain 144 (1–2), 35–42.
Eippert, F., Bingel, U., Schoell, E.D., Yacubian, J., Klinger, R., Lorenz, J., Buchel, C., 2009. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 63 (4), 533–543.
Ezra, M., Faull, O.K., Jbabdi, S., Pattinson, K.T.S., 2015. Connectivity-based segmentation of the periaqueductal gray matter in human with brainstem optimized diffusion MRI. Hum. Brain Mapp. 36 (9), 3459–3471.
Fields, H.L., Rowbotham, M., Baron, R., 1998. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol. Dis. 5 (4), 209–227.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97 (20), 11050–11055.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33 (3), 341–355.
Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. U. S. A. 103 (26), 10046–10051.
Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8 (9), 700–711.
Frazier, J.A., Chiu, S.F., Breeze, J.L., Makris, N., Lange, N., Kennedy, D.N., Herbert, M.R., Bent, E.K., Koneru, V.K., Dieterich, M.E., Hodge, S.M., Rauch, S.L., Grant, P.E., Cohen, B.M., Seidman, L.J., Caviness, V.S., Biederman, J., 2005. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am. J. Psychiatry 162 (7), 1256–1265.
Geha, P.Y., Baliki, M.N., Chiaivo, D.R., Harden, R.N., Paice, J.A., Apkarian, A.V., 2007. Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. Pain 128 (1–2), 88–100.
Geha, P.Y., Baliki, M.N., Wang, X., Harden, R.N., Paice, J.A., Apkarian, A.V., 2008. Brain dynamics for perception of tactile allodynia (touch-induced pain) in postherpetic neuralgia. Pain 138 (3), 641–656.
Giesecke, T., Gracely, R.H., Grant, M.A.B., Nachemson, A., Petzke, F., Williams, D.A., Clauw, D.J., 2004. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum. 50 (2), 613–623.
Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., Pitman, R.K., 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat. Neurosci. 5 (11), 1242–1247.
Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 48 (1), 63–72.
Gustin, S.M., Peck, C.C., Wilcox, S.L., Nash, P.G., Murray, G.M., Henderson, L.A., 2011. Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. J. Neurosci. 31 (16), 5956–5964.
Gustin, S.M., Wrigley, P.J., Siddall, P.J., Henderson, L.A., 2010. Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. Cereb. Cortex 20 (6), 1409–1419.
Gwilym, S.E., Keltner, J.R., Warnaby, C.E., Carr, A.J., Chizh, B., Chessell, I., Tracey, I., 2009. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum. 61 (9), 1226–1234.
Hayes, A.F., Preacher, K.J., 2014. Statistical mediation analysis with a multicategorical independent variable. Br. J. Math. Stat. Psychol. 67 (3), 451–470.
Henderson, L.A., Peck, C.C., Petersen, E.T., Rae, C.D., Youssef, A.M., Reeves, J.M., Wilcox, S.L., Akhter, R., Murray, G.M., Gustin, S.M., 2013. Chronic pain: lost inhibition? J. Neurosci. 33 (17), 7574–7582.
Hunt, S.P., Mantyh, P.W., 2001. The molecular dynamics of pain control. Nat. Rev. Neurosci. 2 (2), 83–91.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17 (2), 825–841.
Jensen, K.B., Srinivasan, P., Spaeth, R., Tan, Y., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C.R., Choy, E., Vitton, O., Gracely, R., Ingvar, M., Kong, J., 2013. Overlapping structural and functional brain changes in patients with long-term exposure to fibromyalgia pain. Arthritis Rheum. 65 (12), 3293–3303.
Jiang, J., Gu, L.L., Bao, D., Hong, S.D., He, W., Tan, Y.M., Zeng, X.J., Gong, H.H., Zhang, D.Y., Zhou, F.Q., 2016. Altered homotopic connectivity in postherpetic neuralgia: a resting state fMRI study. J. Pain Res. 9, 877–886.
Jin, L., Sun, J., Xu, Z., Yang, X., Liu, P., Qin, W., 2018. Intersubject synchronisation analysis of brain activity associated with the instant effects of acupuncture: an fMRI study. Acupunct. Med. 36 (1), 14–20.
Kong, J., Tu, P.C., Zyloney, C., Su, T.P., 2010. Intrinsic functional connectivity of the periaqueductal gray, a resting fMRI study. Behav. Brain Res. 211 (2), 215–219.
Kost, R.G., Straus, S.E., 1996. Postherpetic neuralgia pathogenesis, treatment, and prevention. N. Engl. J. Med. 335 (1), 32–42.
Kroenke, K., Wu, J.W., Bair, M.J., Krebs, E.E., Damush, T.M., Tu, W.Z., 2011. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. J. Pain 12 (9), 964–973.
Liu, J.Q., Gu, L.L., Huang, Q., Hong, S.D., Zeng, X.J., Zhang, D.Y., Zhou, F.Q., Jiang, J., 2019. Altered gray matter volume in patients with herpes zoster and postherpetic neuralgia. J. Pain Res. 12, 605–616.
Liu, P., Yang, J., Wang, G., Liu, Y., Liu, X., Jin, L., Liang, F., Qin, W., Calhoun, V.D., 2016. Altered regional cortical thickness and subcortical volume in women with primary dysmenorrhoea. Eur. J. Pain 20 (4), 512–520.
Lorenz, J., Cross, D.J., Minoshima, S., Morrow, T.J., Paulson, P.E., Casey, K.L., 2002. A unique representation of heat allodynia in the human brain. Neuron 35 (2), 383–393.
Mainero, C., Boshyan, J., Hadjikhani, N., 2011. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. Ann. Neurol. 70 (5), 838–845.
Marciszewski, K.K., Meylakh, N., Di Pietro, F., Mills, E.P., Macefield, V.G., Macey, P.M., Henderson, L.A., 2018. Changes in brainstem pain modulation circuitry function over the migraine cycle. J. Neurosci. 38 (49), 10479–10488.
Mason, P., 2012. Medullary circuits for nociceptive modulation. Curr. Opin. Neurobiol. 22 (4), 640–645.
Mattson, M.P., 2003. Excitotoxic and excitoprotective mechanisms - Abundant targets for the prevention and treatment of neurodegenerative disorders. Neuromolecular Med. 3 (2), 65–94.
May, A., 2007. Neuroimaging: visualising the brain in pain. Neurol. Sci. 28 (Suppl 2), S101–S107.
Melzack, R., 2001. Pain and the neuromatrix in the brain. J. Dent. Educ. 65 (12), 1378–1382.
Moisset, X., Bouhassira, D., 2007. Brain imaging of neuropathic pain. Neuroimage 37, S80–S88.
Monconduit, L., Villanueva, L., 2005. The lateral ventromedial thalamic nucleus spreads nociceptive signals from the whole body surface to layer I of the frontal cortex. Eur. J. Neurosci. 21 (12), 3395–3402.
Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D.J., Harris, R.E., 2010. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 62 (8), 2545–2555.
Peng, W.W., Guo, X.L., Jin, Q.Q., Wei, H., Xia, X.L., Zhang, Y., Huang, P.C., Wang, W.C., Li, S.L., Wang, J.S., Chen, J., Hu, L., 2017. Biological mechanism of post-herpetic neuralgia: evidence from multiple patho-psychophysiological measures. Eur. J. Pain 21 (5), 827–842.
Peng, W.W., Tang, Z.Y., Zhang, F.R., Li, H., Kong, Y.Z., Iannetti, G.D., Hu, L., 2019. Neurobiological mechanisms of TENS-induced analgesia. Neuroimage 195, 396–408.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U.S.A. 98 (2), 676–682.
Reddan, M.C., Wager, T.D., 2018. Modeling Pain using fMRI: from regions to biomarkers. Neurosci. Bull. 34 (1), 208–215.
Rommel, O., Malin, J.P., Zenz, M., Janig, W., 2001. Quantitative sensory testing, neurophysiological and psychological examination in patients with complex regional pain syndrome and hemisensory deficits. Pain 93 (3), 279–293.
Rosas, H.D., Liu, A.K., Hersch, S., Glessner, M., Ferrante, R.J., Salat, D.H., van der Kouwe, A., Jenkins, B.G., Dale, A.M., Fischl, B., 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58 (5), 695–701.
Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S., Busa, E., Morris, J.C., Dale, A.M., Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cereb. Cortex 14 (7), 721–730.
Sarnthein, J., Stern, J., Aufenberg, C., Rousson, V., Jeanmonod, D., 2006. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. Brain 129, 55–64.
Scholz, J., Finnerup, N.B., Attal, N., Aziz, Q., Baron, R., Bennett, M.I., Benoliel, R., Cohen, M., Cruccu, G., Davis, K.D., Evers, S., First, M., Giamberardino, M.A., Hansson, P., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Nurmikko, T., Perrot, S., Raja, S.N., Rice, A.S.C., Rowbotham, M.C., Schug, S., Simpson, D.M., Smith, B.H., Svensson, P., Vlaeyen, J.W.S., Wang, S.J., Barke, A., Rief, W., Treede, R.D.NeuPSIG, 2019. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 160 (1), 53–59.
Segerdahl, A.R., Themistocleous, A.C., Fido, D., Bennett, D.L., Tracey, I., 2018. A brain-based pain facilitation mechanism contributes to painful diabetic polyneuropathy. Brain 141, 357–364.
Smith, S.M., Zhang, Y.Y., Jenkinson, M., Chen, J., Matthews, P.M., Federico, A., De Stefano, N., 2002. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 17 (1), 479–489.

Spielberger, C.D., Gorsuch, R.L., Lushene, R, 1970. Manual for the state-trait anxiety inventory. Palo Alto: Consulting Psychologists' Press..
Stern, J., Jeanmonod, D., Sarnthein, J., 2006. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. Neuroimage 31 (2), 721–731.
Tracey, I., 2016. A vulnerability to chronic pain and its interrelationship with resistance to analgesia. Brain 139 (Pt 7), 1869–1872.
Tracey, I., Mantyh, P.W., 2007. The cerebral signature and its modulation for pain perception. Neuron 55 (3), 377–391.
Vogt, B.A., Vogt, L., Laureys, S., 2006. Cytology and functionally correlated circuits of human posterior cingulate areas. Neuroimage 29 (2), 452–466.
Woolf, C.J., Salter, M.W., 2000. Neuronal plasticity: increasing the gain in pain. Science 288 (5472), 1765–1769.
Wu, G., Ringkamp, M., Hartke, T.V., Murinson, B.B., Campbell, J.N., Griffin, J.W., Meyer, R.A., 2001. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. J. Neurosci. 21 (8), RC140.
Yu, R.J., Gollub, R.L., Spaeth, R., Napadow, V., Wasan, A., Kong, J., 2014. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. Neuroimage Clin. 6, 100–108.
Zhang, Y., Yu, T., Qin, B.Y., Li, Y., Song, G.J., Yu, B.W., 2016. Microstructural abnormalities in gray matter of patients with postherpetic neuralgia: a diffusional kurtosis imaging study. Pain Phys. 19 (4), E601–E611.
Zubieta, J.K., Bueller, J.A., Jackson, L.R., Scott, D.J., Xu, Y.J., Koeppe, R.A., Nichols, T.E., Stohler, C.S., 2005. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J. Neurosci. 25 (34), 7754–7762.