Altered Hippocampal Functional Connectivity Is Closely Related to Pain and Catastrophic Thinking Habits in Patients With Postherpetic Neuralgia

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Research Article

Keywords: Postherpetic neuralgia (PHN), hippocampal functional connectivity, pain, catastrophic thinking habits, patients

Posted Date: September 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-882573/v1

Abstract

Postherpetic neuralgia (PHN) is a chronic pain condition after a cure of herpes zoster. Patients with PHN often suffer from physical pain and psychological distress. We investigated the relationship between functional alternations in the brains of patients with PHN and their clinical manifestations using resting-state fMRI. We acquired resting-state fMRI data from 17 patients with PHN and matched healthy controls. We performed seed-based functional connectivity (FC) analysis and statistical comparisons in FC. We also performed correlation analysis between FC strengths and clinical scores about pain intensity, anxiety, depression and pain catastrophizing. In FC analysis, brain regions in the salience, default mode, sensorimotor and reward network were set as seeds. FC between the medial prefrontal cortex (mPFC) and hippocampus increased in PHN group. In contrast, FC between the hippocampus and primary somatosensory cortex (SI) decreased in PHN group. Furthermore, the SI-hippocampus FC was negatively correlated with pain intensity and the mPFC-hippocampus FC was positively correlated with pain catastrophizing tendency. Our findings indicate that the hippocampus is related to pain perception and catastrophic thinking habits in patients with PHN. Functional alteration of the hippocampus may have a major role in the development and maintenance of chronic pain condition in patients with PHN.

Introduction

Chronic pain often has negative effects on various aspects of daily life[1]. Postherpetic neuralgia (PHN) is a typical chronic neuropathic pain that develops after a cure of herpes zoster[2]. Although pain in PHN originates from damage of peripheral nerves[3], central mechanisms are thought to be involved in its pain as with central neuropathic pain[4] and other chronic pain conditions[5]. Therefore, attention has recently been given to alterations of functional coupling in the central nervous system as the pathophysiology of neuropathic pain, including PHN. The brain activity of patients with PHN has been investigated in several studies[6–8]. However, the relationship between pain in PHN and altered functional coupling among brain regions is still poorly understood.

Various brain regions are known to serve pain processing. The primary somatosensory cortex, the posterior insular cortex and the thalamus are thought to process the sensory aspect of pain[9]. On the other hand, the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC) are involved in cognition of pain experience[10]. Limbic regions are also known to be related to pain experience. Pain experiences have been reported to affect the functional and morphological properties of the amygdala and the hippocampus, which are involved in fear, anxiety[11], and memory[12]. In clinical practice, patients with chronic pain often show heightened fear of pain, excessive anxiety, and deteriorated memory function. They also show functional and structural alterations of the amygdala and hippocampus. For example, a study has shown that patients with pelvic pain had increased resting-state functional connectivity (FC) between the ACC and the hippocampus[13]. In another study, patients with chronic fibromyalgia showed a significant decrease in gray matter volume in the prefrontal cortex, amygdala, and ACC compared with that in healthy controls[14].

As mentioned above, the differences in brain activity between PHN patients and healthy people were investigated in several studies. However, those studies only focused on brain regions related to cognitive control[7] or somatosensory processing[8]. Several lines of evidence indicate that functional and structural

alterations of other brain regions are closely related to chronic pain conditions. Voxel-based morphometry studies have shown that gray matter volume was decreased in areas related to central pain control including the prefrontal cortex[15] and default mode network (DMN)[16]. In patients with fibromyalgia, activity of the amygdala and the ACC was reduced and dysfunction of emotional regulation, which is considered to be a cause of chronic pain behaviors, was observed[14]. The gray matter volume of the reword system, which is responsible for the dopaminergic central analgesic mechanism, was also reduced in patients with chronic pain[17]. Taking into account the importance of these brain regions in the development and maintenance of chronic pain, we investigated functional alterations of these regions in patients with PHN by using resting-state fMRI (rs-fMRI) and seed-based FC analysis. We hypothesized that (1) patients with PHN would show different functional coupling among brain regions related to the development and maintenance of chronic pain or between such regions and other brain regions compared with that in healthy people and (2) the altered functional coupling would be related to individual pain intensity and psychological features of PHN patients.

To test these hypotheses, we compared FCs of brain regions included in the salience network, DMN, sensorimotor network, and reward network between patients with PHN and healthy controls. Moreover, we examined the relationships between individual pain intensity and psychological features of PHN patients and the strength of FC that was significantly different in between-group comparisons.

Results

Patients with PHN

In the patients with PHN, the average NRS score was 3 and the average duration of illness was 35 months. Demographics of the PHN patients, including HADS and PCS scores, are shown in Table 1.

Table 1
Demographic and clinical characteristics of patients with PHN.

PHN patients	Age (years)	Gender	Pain duration (months)	Pain intensity (NRS)	Location of PHN	HADS-D	HADS-A	PCS	Medication
1	75	Male	28	3	Rt. T4–5	3	0	13	A, P, T
2	58	Male	8	5	Lt. T1–3	4	1	23	D, P
3	84	Female	99	1	Lt. C4	5	6	27	D, P
4	69	Female	16	4	Rt. T1–2	1	1	1	P, T
5	77	Female	3	7	Lt. C7 - T2	2	4	35	D, N
6	70	Female	166	5	Rt. T3–4	1	10	17	D
7	76	Male	34	1	Lt. C8 - T1	0	1	0	A
8	82	Male	15	5	Rt. V1	1	7	46	N, P
9	77	Female	46	2	Rt. T5	0	1	3	P
10	61	Male	20	0	Rt. V1	16	12	32	D, P
11	55	Male	6	3	Lt. T4	4	0	8	P
12	76	Male	18	1	Rt. L3	0	0	13	D, P
13	75	Female	19	1	Lt. T10–11	1	2	10	D, P
14	74	Male	22	2	Rt. V1	1	3	11	P
15	76	Male	33	2	Lt. C5–6	1	3	11	P
16	70	Male	60	1	Rt. T2–3	0	0	2	D, P
17	62	Male	8	0	Rt. C2	0	0	0	P

PHN, postherpetic neuralgia; NRS, numeric rating scale; HADS-D, depression score of hospital anxiety and depression scale; HADS-A, anxiety score of hospital anxiety and depression scale; PCS, pain catastrophizing scale; T, level of thoracic vertebrae; C, level of cervical vertebrae; V1, level of first division of the trigeminal nerve; L, level of lumber vertebrae; Rt, right, Lt, left; A, Amitriptyline; P, Pregabalin; T, Tramadol; D, Duloxetine; N, Neurotropin.

Increased FC and decreased FC in the PHN group compared with those in the HC group

The PHN group showed significant increases in FC in several brain regions compared with the HC group. Table 2 shows MNI coordinates and t-values of local maxima in clusters showing a significant FC increase. The mPFC

seed showed a significant increase of its FC to the right hippocampus, right cerebellum lobule VIII, and right cerebellum crus. The right thalamus seed also showed a significant increase of its FC to the right cerebellum lobule VIII. The FC between the left anterior insula and posterior cingulate gyrus also significantly increased.

Table 2
Brain regions in which clusters of functional connectivity were increased in the patient group.

Seed	Brain region	MNI coordinates (mm)	number of voxels	peak t-values
mPFC	Rt. Hippocampus	40, -26, -14	288	5.36
	Rt. Cerebellum VIII	14, -60, -48	798	5.28
	Rt. Cerebellum Crus	18, -86, -34	437	4.56
Rt. Thalamus	Rt. Cerebellum VIII	28, -46, -42	1513	5.21
Lt. Anterior Insula	PCC	14, -40, 26	2000	5.49

MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; Rt, right; Lt, left

In addition to the significant FC increase, we also observed that several brain regions showed a significant decrease of their FC in the PHN group compared with that in the HC group. Table 3 shows MNI coordinates and t-values of local maxima in clusters showing a significant FC decrease. The left hippocampus showed a significant decrease of its FC to the left and right primary somatosensory cortices compared with that in the HC group. The left nucleus accumbens and bilateral amygdala also showed significant decreases in FC to the left putamen.

Table 3
Brain regions in which clusters of functional connectivity were decreased in the patient group.

Seed	Brain region	MNI coordinates (mm)	number of voxels	peak t-values
Lt. SI	Lt. Hippocampus	-34, -12, -24	487	5.97
Rt. SI	Lt. Hippocampus	-34, -12, -14	552	6.21
Lt. NAc	Lt. Putamen	-22, 12, 2	371	4.45
Lt. AMY	Lt. Putamen	-28, 0, -4	486	6.05
	Rt. Putamen	32, -4, 2	520	5.48

MNI, Montreal Neurological Institute; Rt, right; Lt, left; SI, primary somatosensory cortex; NAc, nucleus accumbens; AMY, amygdala

Correlations between FC and pain intensity, HADS, and PCS

Of FCs showing significant between-group differences, we found that some of them have significant correlations with pain intensity and PCS. As shown in Fig. 1, FC between the mPFC and the right hippocampus showed a significant positive correlation to individual PCS score (MNI coordinates of the local maximum: 40,

-26, -14; r = 0.48, p = 0.049). FC between the left SI and the left hippocampus showed a significant negative correlation to individual pain intensity (Fig. 2; MNI coordinates of the local maximum: -34, -14, -16; r = -0.52, p = 0.03). FC between the right SI and the left hippocampus also showed a significant negative correlation to pain intensity (Fig. 3; MNI coordinates of the local maximum: -34, -12, -14; r = -0.51, p = 0.04). There was no FC showing a significant correlation to HADS.

Discussion

The main findings of this study are hippocampal FC showed the between-group difference and it was correlated with catastrophic thinking as well as pain intensity. In addition, the patients with PHN showed increased FC among emotional pain regions and the cerebellum and decreased FC in the basal ganglia.

In this study, the hippocampus, cerebellum, and PCC showed significant FC increases in the PHN group compared with those in the HC group. Generally, the hippocampus engages in memory and learning[12], the cerebellum is involved in motor control[18], and the PCC is a core region of the DMN[19]. These regions are also involved in progression and maintenance of chronic pain. The hippocampus is thought to be a key structure involved in the development of chronic migraine[20]. It is well known that the hippocampus is associated with pain-related emotional coping as well as learning of emotional memory including pain experience[21]. Moreover, when transition from acute pain to chronic pain occurs, the FC of the hippocampus increases[22]. A study on trigeminal neuralgia showed that the hippocampal volume was decreased in the patient group[23]. Such functional and morphological changes of the hippocampus are implicated in the development of chronic PHN. In addition to the hippocampus, the PCC is also thought to have a key role in the development of chronic pain. Increased FC with the insula, which is known to process affective elements of pain, is considered as a form of maladaptive neuroplasticity leading to the development of chronic pain[24]. Our results correspond to this concept.

Our study revealed that FC between the bilateral primary somatosensory cortices and the left hippocampus was decreased in the PHN group. In a previous study, patients with high frequency migraine showed significant decreases in FC between the hippocampus and other brain regions that are involved in pain processing[20]. Although our finding is consistent with the results of the previous study in terms of hippocampal FC decrease in chronic pain conditions, it is a novel finding that FC between the hippocampus and primary somatosensory cortices was decreased in chronic pain patients. This finding could explain why patients with PHN show hypoesthesia.

The basal ganglia are also thought to have a critical role for chronic pain[25]. The basal ganglia receive nociceptive inputs from the cingulate cortex, dorsolateral prefrontal cortex, hippocampus, and amygdala[26]. Previous studies have shown a relationship between activities of the basal ganglia and pain in patients with fibromyalgia[27] and patients with complex regional pain syndrome[28]. In the present study, the patients with PHN showed significant decreases in FC between the nucleus accumbens and the putamen and FC between the amygdala and the putamen. These results suggest that the basal ganglia also have a key role in the development of PHN. Specifically, these changes may be related to aberrant emotional regulation in patients with PHN. In fact, patients with PHN have a high tendency to develop anxiety and depression[29].

Correlation analysis revealed that the FC of the hippocampus is related to pain intensity and psychological status of PHN patients. In the present study, a higher tendency of catastrophic thinking about pain was correlated with increased connectivity between the mPFC and the right hippocampus. The mPFC, which encompasses the rostral ACC, is a region involved in transition from acute pain to chronic pain[30], and this region connects with limbic structures such as the amygdala and the ventral striatum[31]. The mPFC is also known to be a part of the DMN. Whereas the DMN shows deactivation while individuals focus on the external environment, it is activated when individuals do not engage in behavioral/cognitive tasks[32]. The hippocampus has a close relationship with the transition from acute pain to chronic pain[20]. Generally, sensitivity to pain is correlated with FC between brain areas associated with the DMN, including the PCC, mPFC and hippocampus, and pain regions[33]. Our results are consistent with this fact. Meanwhile, it is a new finding that FC of the mPFC has a relationship with catastrophizing thinking about pain. FC between bilateral SI and left hippocampus negatively correlated with pain intensity in PHN patients. This finding provides a new evidence about pathophysiology of PHN and supports the notion that maladaptive plastic changes in the central nervous system play an important role in the development and maintenance of chronic pain. SI is known to process the sensory aspect of pain[9]. On the other hand, the hippocampus is known to be involved in emotion and emotional memory including pain experience. Our result suggests that pain in patients with PHN is exaggerated by emotional modulation, and that its magnitude of modulation is related to the strength of SI-Hippocampus connectivity. In fact, previous studies has reported that the amygdala that densely connects with the hippocampus was related to emotional modulation of pain[34] and that the amount of SI FC to other brain regions was related to pain in chronic low back pain condition[35].

In the present study, the strength of SI-Hippocampus FC negatively correlated with pain intensity. That is, the patients with stronger pain showed weaker SI-Hippocampus FC. This relationship is counterintuitive. However, when a correlation between FC strength and variables is discussed, it is necessary to consider actual FC strength. In this study, the strength of SI-Hippocampus FC in the patients with weaker pain was around zero. In contrast, its strength in the patients with stronger pain were negative values. Therefore, although meaning of negative FC remains controversial, our result can be considered that patients with stronger pain showed stronger SI-Hippocampus FC.

We must consider limitations in this study. As mentioned above, the rs-fMRI data for the HC group and that for the PHN group were acquired at different institutions. As a result, even though the scanning parameters were almost the same in the two institutions, there was a possibility that the between-group differences we observed in this study merely reflect inter-scanner differences. However, this possibility can be ruled out because there were correlations between several FCs showing significant between-group differences and symptoms of PHN, particularly pain intensity and catastrophic thinking. Second, there is a possibility that analgesics prescribed for the patients with PHN, such as pregabalin, affected their rs-FC, as shown in a previous study[36]. Indeed, some of our patients with PHN were prescribed pregabalin for treatment of PHN. Therefore, we could not exclude the possible effects of pregabalin for the brain networks.

To conclude, we identified alterations in FC with the hippocampus in the patients with PHN compared with FC in the HC group. Furthermore, FC with the hippocampus was correlated with individual pain intensity and tendency of catastrophic thinking about pain. Our results suggest that functional alterations of the hippocampus are

related to not only pain perception but also the pain-related cognitive process, especially catastrophizing, in patients with PHN as in patients with other types of chronic pain.

Methods

Participants

This study was approved by the Wakayama Medical University Ethics Committee (No. 1606), and all of the participants provided written informed consent in line with the Declaration of Helsinki. The protocol of our study was registered at the UMIN Clinical Trials Registry (UMIN-CTR, No. UMIN00023604; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000027176). We recruited patients with PHN who had received care at the outpatient pain clinic of Wakayama Medical University Hospital. As a result, 17 patients with PHN (ages, 55 to 84 years; mean age, 72 years; male/female = 10/7) participated in this study. They reported a history of persistent pain for at least 3 months after the resolution of an acute outbreak of episodes of shingles. Patients with PHN were allowed to continue with their stable medical treatment. Medications which they took at MRI data acquisition are shown in Table 1. Sixteen age- and gender-matched healthy adults (ages, 54 to 82 years; mean age, 72 years; male/female = 10/6) also participated in this study as a healthy control (HC) group. All participants were right-handed. At the time of study entry, none of the participants were suffering from psychiatric or neurological disorders. None of them had neurological symptoms. In addition, no pathological changes were found on structural MRI in any of the participants.

Pain intensity and questionnaires

The patients with PHN completed the following measurement and questionnaires before MRI scanning. Clinical pain intensity of the patients with PHN was assessed using a numeric rating scale (0–10, where 0 is no pain and 10 is the maximum pain imaginable). The degree of anxiety and depression in the patients was assessed with the Hospital Anxiety and Depression Scale (HADS)[37]. A tendency to catastrophize pain in the patients was assessed with the Pain Catastrophizing Scale (PCS)[38]. All of those data were used as variables in correlation analysis.

MRI data acquisition

Structural and functional brain images were acquired from patients with PHN by using a 3 Tesla MRI (PHILIPS, the Netherlands) with a 64-channel head coil (SENSE-Head-64CH) at Wakayama-Minami Radiology Clinic. MRI scans for healthy controls were performed with a 3.0 Tesla MRI scanner (GE, Discovery MR750, Milwaukee, USA) at Osaka University. Headphones and earpieces were used to reduce the scanner noise. The following parameters were applied to T1-weighted structural image scanning: TR = 7 ms, TE = 3.3 ms, FOV = 220 mm, matrix scan = 256, slice thickness = 0.9 mm, and flip angle = 10 degrees. A gradient-echo echo-planar pulse sequence sensitive to BOLD contrast[39] was applied to the rs-fMRI scan with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 220 mm, matrix scan = 64, slice thickness = 3 mm, and flip angle = 90 degrees. Each participant underwent a single 5-min rs-fMRI scan. The participants were instructed to close their eyes, not to move their heads, and not to fall asleep during rs-fMRI data acquisition.

MRI data preprocessing

The functional images were preprocessed using SPM12 software ver.7219 (available at: http://www.fil.ion.ucl.ac.uk/spm) and CONN 17.b (Functional Connectivity Toolbox; https://www.nitrc.org/projects/conn)[40] implemented in MATLAB (MathWorks, Inc., Natick, Massachusetts). The first 5 volumes were discarded to eliminate the T1 equilibrium effect. Thus, the remaining 145 consecutive volumes were entered into the preprocessing and analysis.

Preprocessing steps consisted of motion correction (realignment to the first image of the time series), slice timing correction, segmentation of the anatomical image (gray matter, white matter, and cerebrospinal fluid), normalization to the Montreal Neurological Institute (MNI) template including reslicing (generating 2 x 2 x 2 mm resolution images), and smoothing (convolution with a 6-mm full width at half maximum Gaussian kernel). In the denoising step, body movement-related and non-neural physiological activity-related components were eliminated from rs-fMRI data by linear regression. The latter components were calculated by the component-based noise correction method (CompCor), which is built in the CONN. Outliers on rs-fMRI data were eliminated by scrubbing. Low-frequency drift (< 0.01 Hz) and high-frequency noises (> 0.1 Hz) were eliminated by band-pass filtering (0.008–0.09 Hz).

Seed-based FC analysis

We performed a seed-based FC analysis. Based on previous findings[19,41], we selected the following brain regions that are related to pain-processing as seeds for the FC analysis: (1) the ACC and the right and left anterior insula as salience network seeds, (2) the mPFC and the posterior cingulate cortex (PCC) as DMN seeds, (3) bilateral primary sensory cortex (SI) and bilateral thalamus as sensorimotor network seeds, and (4) bilateral amygdala and bilateral nucleus accumbens as reward network seeds.

To compute seed-to-voxel FC maps, we applied a whole brain seed-to-voxel FC analysis to each seed. Then we entered these maps into between-group comparisons (two-sample t-tests). Statistical significance was set as a voxel-wise uncorrected p-value < 0.001 and a cluster-level familywise error corrected p-value < 0.05. Since we performed a between-group comparison for multiple seeds, we additionally applied a Bonferroni's multiple comparison correction procedure to the cluster-level threshold.

Correlation analysis between FC and pain intensity, HADS, and PCS

We performed correlation analysis for FC that showed significant between-group differences. In this analysis, we extracted individual FC strengths (transformed into z scores) from the peak voxels of the significant clusters. Then we calculated Spearman's correlation coefficients between FC strengths and pain intensity, HADS-anxiety, HADS-depression, and PCS in the PHN patients.

All statistical analyses were performed using MATLAB R2017a (https://jp.mathworks.com/products/matlab.html). Significance level was set at $p < 0.05$.

Declarations

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

We would like to thank Mr. Yuji Nakao, Mr. Yasuo Tanaka, Ms. Yumi Okazaki and Mr. Koji Tsuchihashi for the MRI data acquisition.

This work was supported by Grant-in-Aid for Early-Career Scientists from the Japan Society for the Promotion of Science (18K16494) to HK and by Japan Agency for Medical Research and Development (JP16ek0610002).

Author contributions

H.K., S.K., M.S. and T.K. conceived and designed the study. H.K., S.K. and M.T. performed MRI data acquisition, preprocessing, and data analysis. H.K. and S.K. wrote the main manuscript text and prepared figures 1 – 3. H.K., S.K., M.S. and T.K. finalized the paper for submission. All authors reviewed the manuscript.

Additional Information (including a Competing Interests Statement)

The authors have declared that no competing interests exist.

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Figures

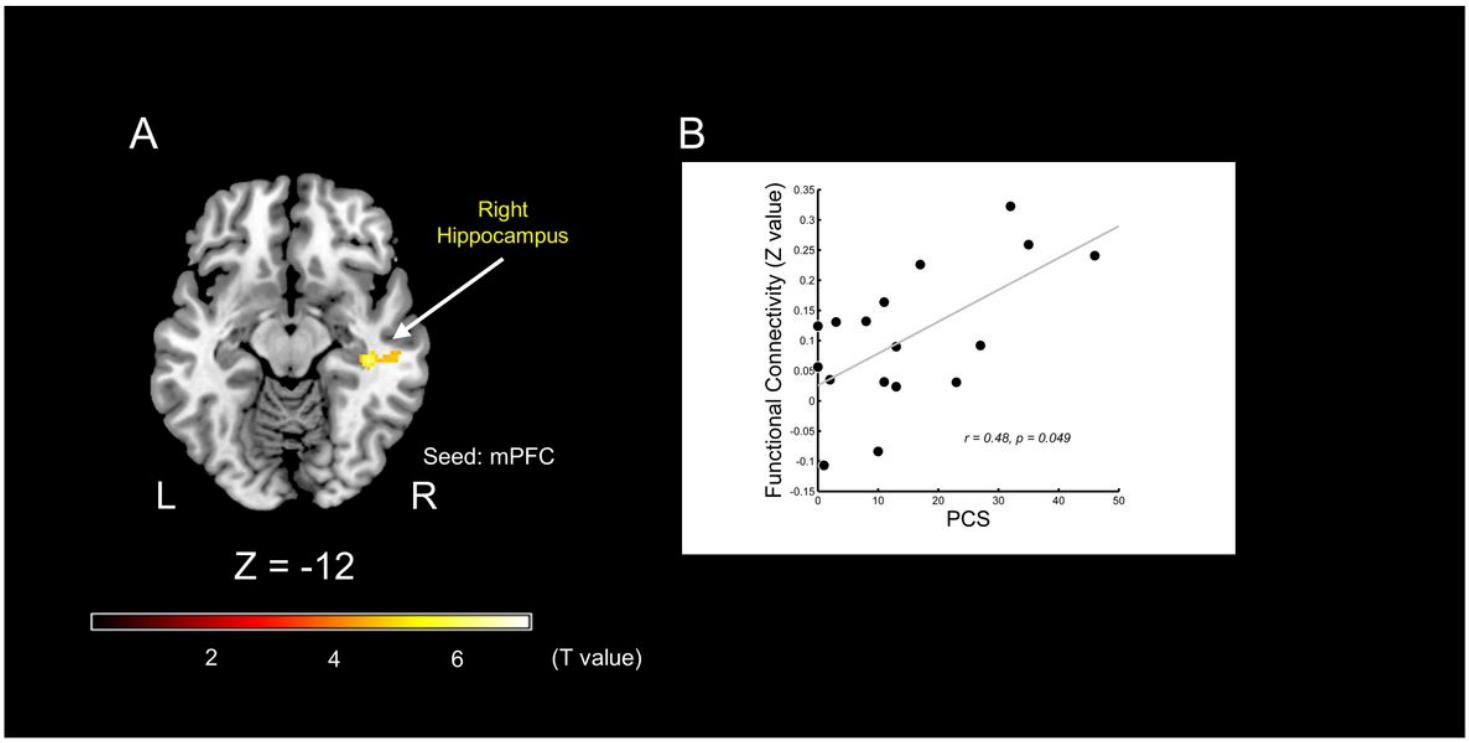

Figure 1

(A) Functional connectivity (FC) map of the medial prefrontal cortex (mPFC) seed. Functional connectivity between the mPFC and right hippocampus showed a significant increase in PHN patients compared with that in HC. (B) Correlation between individual functional connectivity strengths and scores of Pain Catastrophizing Scale (PCS). There was a significant positive correlation between them (r = 0.48, p = 0.049, by Spearman's method). PHN, postherpetic neuralgia; HC, healthy controls.

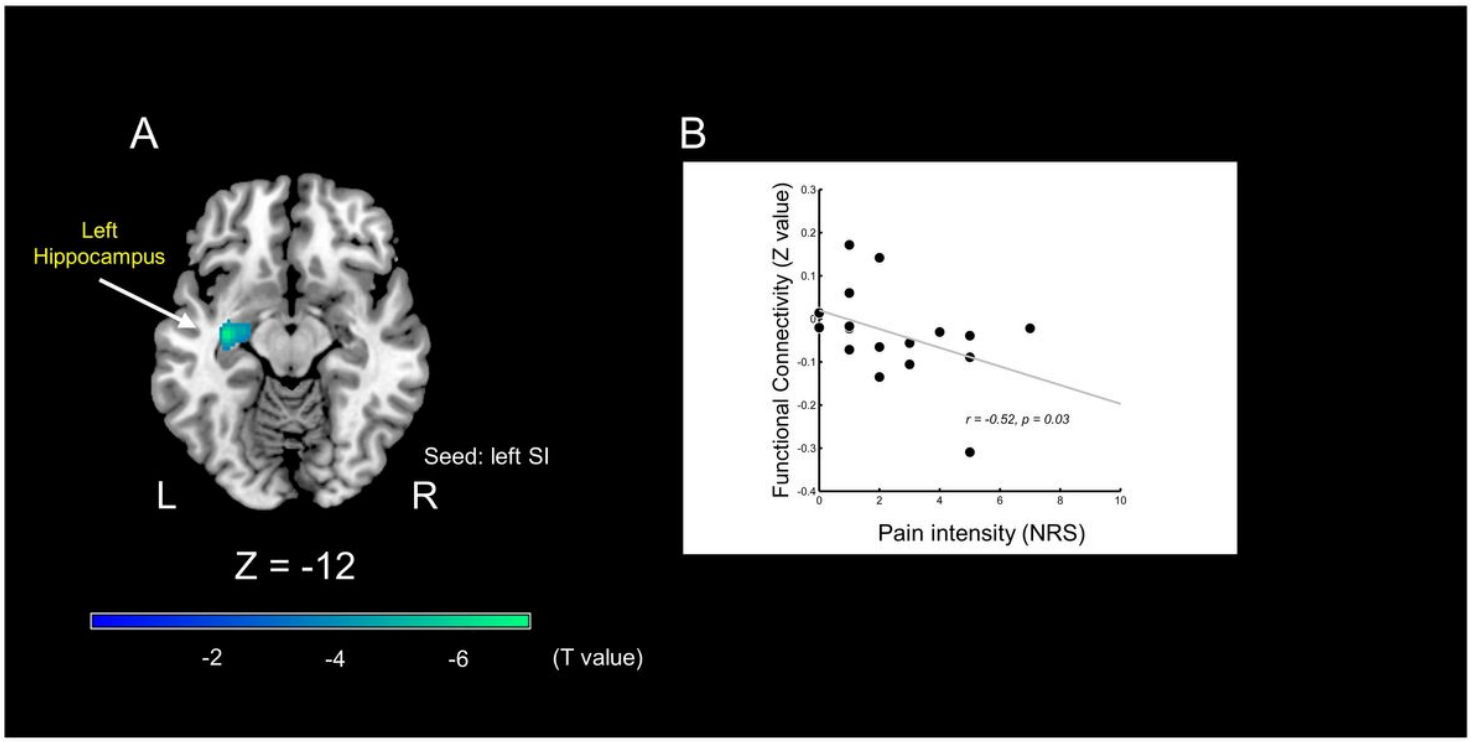

Figure 2

(A) Left SI seed-based functional connectivity analysis. Functional connectivity between the left SI and left hippocampus was significantly decreased in PHN patients compared with that in HC. A cluster with a significant t-value ($p < 0.05$) is shown. (B) Correlation of functional connectivity values between the left SI and left hippocampus with pain intensity is shown in this figure. There is a negative correlation between these values ($r = -0.52$, $p = 0.03$, by Spearman's method). SI, primary sensory cortex; PHN, postherpetic neuralgia; HC, healthy controls.

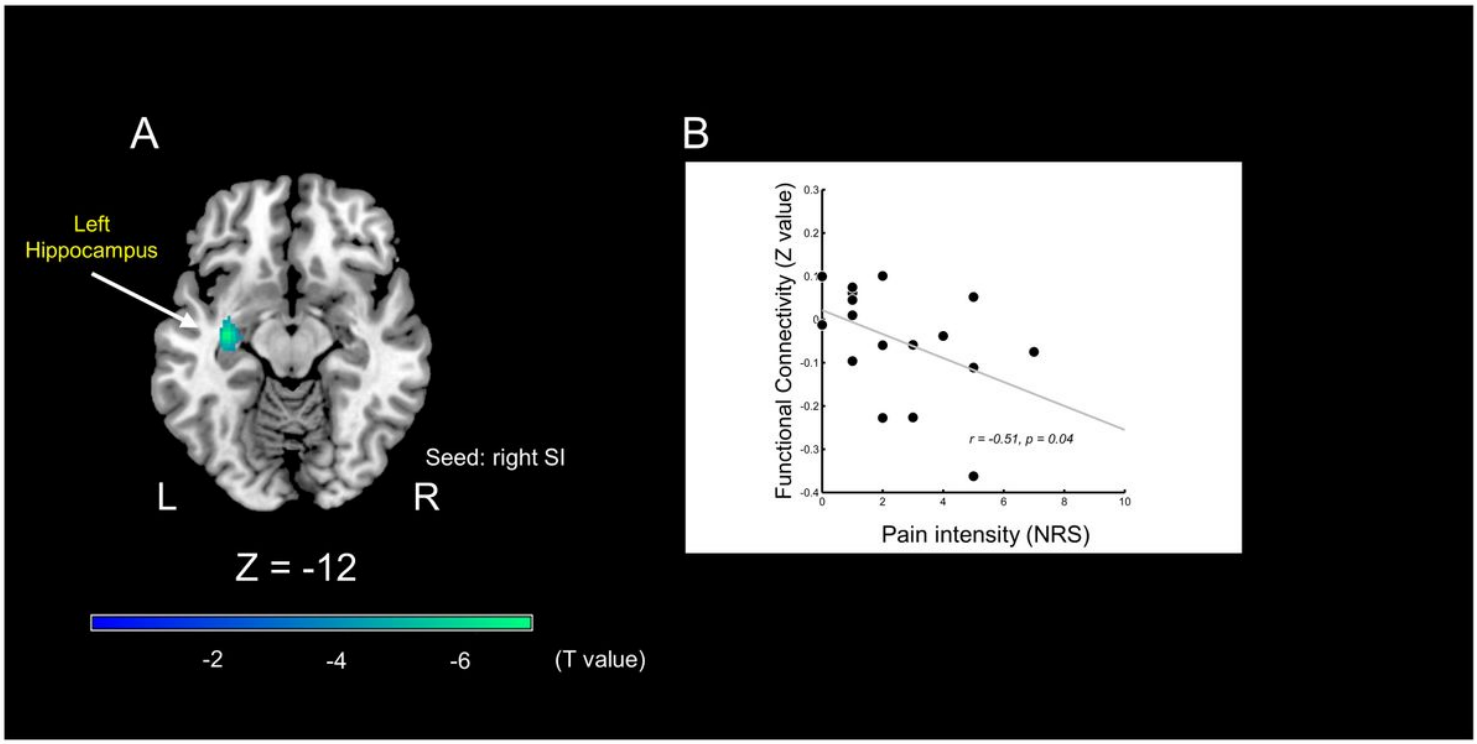

Figure 3

(A) Right SI seed-based functional connectivity analysis. Functional connectivity between the right SI and left hippocampus was significantly decreased in PHN patients compared with that in HC. A cluster with a significant t-value ($p < 0.05$) is shown. (B) Correlation of functional connectivity values between the right SI and left hippocampus with pain intensity is shown in this figure. There is a negative correlation between these values ($r = -0.51$, $p = 0.04$, by Spearman's method). SI, primary sensory cortex; PHN, postherpetic neuralgia; HC, healthy controls.