Observational Study

Abnormal Local Brain Activity Beyond the Pain Matrix in Postherpetic Neuralgia Patients: A Resting-State Functional MRI Study

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Background: Postherpetic neuralgia (PHN) patients suffer debilitating chronic pain, hyperalgesia, and allodynia, as well as emotional disorders such as insomnia, anxiety, and depression. The brain structure and functional basis of PHN are still not fully understood.

Objectives: To identify the changes of regional brain activity in resting-state PHN patients using regional homogeneity (ReHo) and fractional aptitude of low-frequency fluctuation (fALFF) methods. Correlations between spontaneous pain intensity and ReHo or fALFF were analyzed.

Study Design: Observational study.

Setting: University hospital.

Methods: ReHo, fALFF change was analyzed in 19 PHN patients and 19 healthy controls to detect the functional abnormality in the brains of PHN patients. Correlations between ReHo, fALFF, and PHN pain intensity were assessed in the PHN group.

Results: PHN patients exhibited significantly abnormal ReHo and fALFF intensity in several brain regions, including the brainstem, thalamus, limbic system, temporal lobe, prefrontal lobe, and cerebellum compared with healthy controls. Correlation analysis showed that most of the ReHo values of the aforementioned brain regions positively correlated with visual analog scale (VAS) values. But much less correlation was found between fALFF and VAS.

Limitations: (a) No specific emotional assessment was given for PHN patients before fMRI scans, therefore we cannot exclude whether the emotional disorders exist in these patients. (b) Relatively short pain duration (mean 5.4 months) and small sample size (n = 19) for the PHN group.

Conclusions: For PHN patients, the local brain activity abnormality was not restricted to the pain matrix. Besides regions related to pain perception, areas in charge of affective processes, emotional activity, and pain modulation also showed abnormal local brain activity in a resting state, which may suggest complicated supraspinal function and plasticity change in PHN patients. ReHo was more closely correlated with pain intensity of PHN patients than fALFF. This work indicates that besides physical and emotional pain perception, mood disorder and pain modulation could be characteristics of PHN patients. This also supports the potential use of therapeutic interventions not only restricted to pain alleviation, but also those that attempt to ameliorate the cognitive and emotional comorbidities.

Key words: Postherpetic neuralgia, resting-state fMRI (rs-fMRI), mood disorder, limbic system, fractional aptitude of low-frequency fluctuation (fALFF), regional homogeneity (ReHo)

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Postherpetic neuralgia (PHN) is a neuropathic pain (NP) syndrome usually defined as chronic pain lasting more than 3 months following an outbreak of shingles (acute herpes zoster). This sharp, burning, or stabbing pain profoundly affects the quality of life (1). Moreover, PHN may increase the risk of development of anxiety, depression, and suicide (2,3). Due to its complicated pathogenesis, traditional analgesics are not satisfactory, and new supplementary therapies, such as psychotherapy, are still needed. Understanding the changes in brain activity in PHN patients will help to develop strategies in prevention and treatment of PHN.

However, the basis of the brain structure and function in PHN is not clear. A few studies have explored PHN's effects on brain functional activity using functional magnetic resonance imaging (fMRI) (4-6). It's reported that besides regions of the affective and sensory-discriminative areas (primary [S1] and secondary somatosensory [S2], thalamus, insula, and anterior cingulated cortices) (7), brain areas associated with emotion, affective processes, hedonics, and reward, such as the striatum, amygdala, and frontal cortex were also activated by spontaneous PHN (4). In addition, increased cerebral blood flow (CBF) was found in the S1, inferior parietal lobule, thalamus, striatum, insula, and amygdala, while CBF was decreased in the frontal cortex in PHN patients (8). Functional connectivity (FC) analysis indicated that connections between several regions and the putamen were altered in PHN patients (5). By graphing theoretic approaches, Zhang et al (6) analyzed the small-world network (graphs with dense local connections and a few long connections) alterations in PHN patients. PHN patients exhibited decreased local brain efficiency compared with healthy controls. In addition, regional nodal efficiency in areas related to sense (postcentral gyrus, inferior parietal gyrus, and thalamus), memory, affective processes (parahippocampal gyrus), and emotion (putamen) was significantly affected (6). To date, there is little information about the local brain synchronization in PHN patients during the resting state.

The spontaneous local brain activity can be quantitatively measured by regional homogeneity (ReHo) (9,10) and fractional amplitude of the low frequency fluctuations (fALFF) (11,12). Both of them are powerful and reliable indices in evaluating resting-state brain activity (13-15). ReHo was first proposed by Zang et al (9). Calculated by Kendall's coefficient of concordance (KCC), ReHo evaluates similarities between time series of a given voxel and its nearest neighbors, so ReHo reflects the local coherence of local spontaneous neuronal activity. The power of low frequencies (e.g., 0.01 – 0.08 Hz) is proportional to the amplitudes of the blood oxygen level dependent (BOLD) signal. On the other hand, fALFF is measured by dividing the chosen low frequency band (e.g., 0.01 – 0.08 Hz) by all frequencies measured, which was proved to be more gray matter-specific and sensitive to BOLD signal (11).

We recently detected microstructrural changes in several regions of the pain matrix, including the occipital lobe, caudate, and parahippocampal gyrus in PHN patients (16). Given the FC alterations among pain-related brain areas (5,8), local brain efficiency reduction (6), and microstructural abnormality of PHN brains, we hypothesize that PHN patients possess abnormal local brain synchronicity and activity. In this study, we employ ReHo and fALFF to detect local brain synchronicity and activity in PHN patients, then the correlations between intrinsic neural activity and pain intensity were assessed.

Methods

Participants

This fMRI study was approved by the Ethics Committee of the local hospital. Informed consent was obtained from all participants. Twenty-one right-handed PHN patients with lesions on the left were recruited from the Pain Medicine Department of the local hospital. The diagnosis of PHN was based on the International Association for the Study of Pain (IASP) criteria for Post Herpetic Neuralgia (17). Spontaneous PHN intensity was assessed using the visual analog scale (VAS). All PHN patients reported persistent pain for more than 3 months after the herpes zoster rash. All participants had neither a history of psychiatric nor neurological disorder. Two patients were excluded for remarkable cerebral infractions or head movement. Finally, data from 19 patients were analyzed: 11 men and 8 women, ranging in age from 46 to 77 (mean 64.4 year). Nineteen age-, gender- matched right-handed healthy volunteers (8 men and 11 women, ranging in age from 53 to 68, mean 61.4 year) were recruited as healthy controls. All volunteers in the control group were free from pain, brain structural abnormalities, and neuropsychiatric disorders.

Image Acquisition

fMRI experiments were implemented on a GE Signa

HDxT 3.0 T MRI scanner (General Electric Company, USA) with a standard 8 channel head coil. rs-fMRI data were acquired using an echo-planar image (EPI) sequence with parameters as follows: thickness/gap = 4.0/0 mm, matrix = 64 × 64, TR = 2000 ms, TE = 40 ms, flip angle = 90°, field of view (FOV) = 240 × 240 mm. A total of 210 time points and 33 axial slices were obtained in 7 minutes. High-resolution anatomic 3-D T1 (TR = 5.8 ms, TE = 1.8 ms, flip angle = 12°, thickness/gap = 1.0/0 mm, 196 sagittal slices, FOV = 256 × 256 mm, matrix = 256 × 256) images were also acquired.

Image Processing

Preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF, http://rest.restfmri.net/forum/DPARSF) (18) and SPM8 (Wellcome Department, University College of London, UK) software based on MATLAB R2012a (MathWorks, USA). DPARSF was used for the following steps: To allow for scanner calibration and participants' adaptation to the scan, the first 10 volumes were discarded. The remaining 200 volumes were further analyzed. Processing steps included slice timing, head-motion correction, spatial normalization in the Montreal Neurological Institute (MNI) space, and resampling with a 3 × 3 × 3 mm3 resolution. Patients in pain may invariably move in the scanner; participants with head motion > 2.0 mm of translation or > 2.0° of rotation in any direction were excluded from further processing. The linear trend of the fMRI data was removed. For ReHo, the band-pass filtering (0.01 – 0.08 Hz) was conducted to discard high-frequency physiological noise and the frequency drift lower than 0.01 Hz (19). The Resting State fMRI Data Analysis Toolkit (REST, http://rest.restfmri.net) 1.8 (12) was then used for the following steps: Individual ReHo map was generated by calculating the KCC of the time series of a given voxel with those of its neighbors (26 voxels) in a voxel-wise way (9,20). Afterwards, a whole-brain mask was adopted to remove the non-brain tissues. For standardization purposes, the individual ReHo maps were divided by their own global mean KCC within the whole-brain mask. Then spatial smoothing was performed on the standardized individual ReHo map with a Gaussian kernel of 4 mm full-width at half maximum (FWHM) (21). After the preprocessing, fALFF were computed as previously described (11,14). First, the resampled images were smoothed with a Gaussian kernel of 4 mm. Then the frequency band filtering was set as 0.01 – 0.08 Hz, and the time courses were converted to the frequency band using a Fast Fourier Transform. The mean and standard deviation of each individual's ReHo and fALFF value was calculated by DPARSF within the thresholded whole brain mask. Z scores were then calculated in a voxel-wise way by subtracting the mean ReHo or fALFF values from each voxel's value, and then dividing by the standard deviation of ReHo or fALFF value, respectively. In this way, the Z score represents a voxel's ReHo or fALFF value in relation to all voxels in the whole brain. Therefore, the positive Z score represents higher synchronicity (ReHo) or activity (fALFF) in that individual's brain. Likewise, a negative Z score represents lower synchronicity or activity.

Statistical Analysis

Demographic and clinical data were analyzed using Prism 6.0 (GraphPad Software Inc, USA). Two-sample t-tests were used for detecting the differences in the age, VAS scores, and pain duration between PHN patients and health controls. χ^2 test was applied for comparison of gender. The criteria for all statistical significance were set as $P < 0.05$.

For ReHo and fALFF comparison between 2 groups, 2-sample t-tests were conducted in a whole-brain voxel-wise way with REST 1.8. To determine the significance of ReHo and fALFF, multiple comparison correction was performed by Monte Carlo simulations (22) using the REST AlphaSim utility (12). Voxels with $P < 0.05$ (2-tailed, corrected by AlphaSim, rmm = 4 mm, cluster size > 1458 mm^3 (54 voxels); http://afni.nih.gov/afni/docpdf/AlphaSim.pdf) were regarded as showing a significant difference between 2 groups. For correlation analysis between ReHo and VAS, and fALFF and VAS, Pearson's correlations were performed in a whole-brain voxel-wise way with REST toolbox. $P < 0.05$ (2-tailed, AlphaSim corrected) was set as the threshold of a significant difference.

REST Slice Viewer, which is routine for displaying results (12), was used to generate graphs. The brain areas can be overlaid on structural brain images. A color-bar was set to illustrate the threshold (16).

Results

Demographic and Clinical Features

Clinical characteristics of PHN patients are shown in Table 1. There were no remarkable differences in age and gender between PHN and healthy group (P = 0.21 and 0.33, respectively).

Comparison of ReHo between Two Groups

As shown in Table 2 and Fig. 1, the PHN group showed significantly increased ReHo, mainly in the vast region of the pons, nucleus basalis, thalamus, right cerebellum, frontal lobe (medial frontal gyrus and middle frontal gyrus), insula, and limbic system (cingulate gyrus, limbic lobe, hippocampus). Lower ReHo was observed mainly in the temporal lobe (middle temporal gyrus, superior temporal gyrus), left cerebellum, occipital lobe, temporal lobe, and right parietal lobe (paracentral lobule).

Table 1. *Demographic and clinical characteristics of participants.*

	PHN patient N = 19	Healthy control N = 19	*P*
Age (year, mean ± SEM)	64.4 ± 2.1	61.4 ± 1.1	0.21 (two-sample t test)
Gender (male:female)	11:8	8:11	0.33 (χ^2 test)
Pain duration (month, mean±SEM)	5.4 ± 1.3	-	-
VAS score (mean±SEM)	6.3 ± 0.4	-	-

PHN: postherpetic neuralgia; VAS: visual analog scales; SEM: standard error of mean.

Comparison of fALFF between Two Groups

As shown in Table 3 and Fig. 2, the PHN group showed significantly increased fALFF mainly in the pons, occipital lobe (precuneus), limbic lobe, nucleus basalis, thalamus, right cerebellum, frontal lobe (medial frontal gyrus and middle frontal gyrus), insula, and limbic system (cingulate gyrus, limbic lobe, hippocampus). Lower fALFF was observed mainly in the vast region of the prefrontal cortex (middle frontal gyrus, superior frontal gyrus, and medial frontal gyrus) and parietal lobe (inferior parietal lobule, superior parietal lobule).

Table 2. *Clusters of different ReHo values between PHN and control group (Con).*

Region (R: right; L: left)	Peak MNI coordinate			Peak T value	Voxel size	Brain volume (mm^3)
	x	y	z			
PHN > Con						
Cerebelum Posterior Lobe _R	18	-63	-51	2.86	80	2160
Pons (bilateral)	12	-21	-30	3.90	191	5157
Lentiform Nucleus_L	-21	-12	6	3.40	262	7074
Cerebellum Anterior Lobe_R	12	-51	-15	3.51	63	1701
Extra-Nuclear_R	15	-6	6	3.78	168	4536
Middle Frontal Gyrus_R	27	36	-3	2.93	65	1755
Middle Temporal Gyrus_L	-36	-87	21	2.92	64	1728
Occipital Lobe_R	12	-75	21	4.10	161	4347
Limbic Lobe_R	15	3	45	3.37	171	4617
Medial Frontal Gyrus_L	-30	24	39	4.25	618	16686
PHN < Con						
Cerebelum Posterior Lobe _L	-36	-60	-45	-3.84	83	2241
Middle Temporal Gyrus_R	51	-33	-30	-4.68	497	13419
Middle Temporal Gyrus_R	54	-3	24	-3.69	104	2808
Fusiform Gyrus_L	-39	-42	-9	-3.11	56	1512
Limbic Lobe_L	-21	-36	-9	-3.58	61	1647
Superior Temporal Gyrus _L	-63	-21	-9	-5.32	343	9261
Postcentral Gyrus_L	-51	-21	21	-3.60	116	3132
Inferior Parietal Lobule_R	57	-15	18	-3.10	141	3807
Prentral Gyrus_R	54	-6	42	-4.22	65	1755
Inferior Parietal Lobule_L	-36	-57	60	-3.20	107	2889

ReHo: regional homogeneity; PHN: postherpetic neuralgia; MNI: Montreal Neurological Institute.

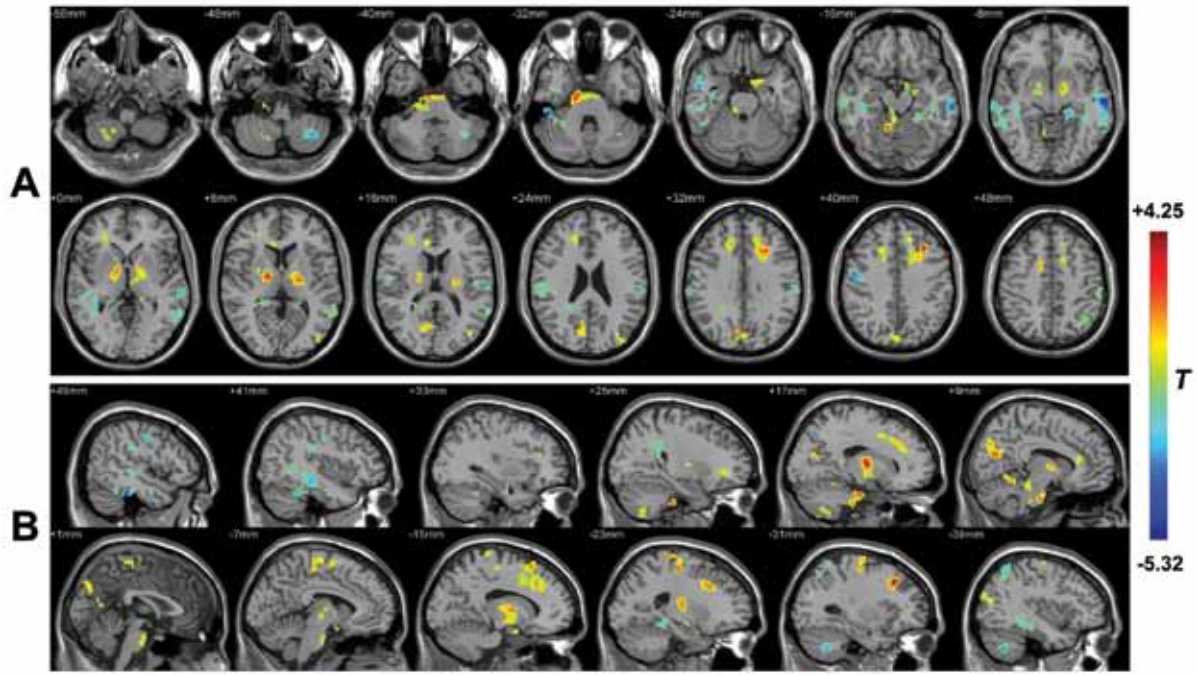

Fig. 1. *Significant differences in ReHo between PHN patients and healthy controls in axial (A) and sagittal (B) slices. The warm colors indicate higher ReHo and cool colors indicate lower ReHo in PHN patients than healthy controls ($P < 0.05$, corrected). Brain images are displayed in radiology convention (e.g., the left in the figure represents the right side of patients' brains and vice versa).*

Correlation between ReHo and VAS

As shown in Table 4 and Fig. 3, the mean correlation coefficient figure (R value map) displayed a trend similar to the differential ReHo map (T value map, Fig. 1). The ReHo values of the brainstem, limbic system, thalamus, and frontal lobe were significantly and positively correlated with VAS score, while for the temporal lobe, occipital lobe, and parietal lobe, the correlation was negative.

Correlation between fALFF and VAS

Only a small part of the right temporal lobe, right limbic lobe, and right frontal lobe showed a positive correlation with VAS value, while a small part of the left cerebellum displayed a negative correlation with VAS value (Fig. 4).

Discussion

As we expected, PHN patients showed abnormal local connectivity and activity in many brain regions evidenced by ReHo and fALFF analysis. These regions are not limited to the pain matrix, which was defined as a distributed set of brain regions that exhibited a reliable activation in response to increasing levels of pain (7,23-25). The pain matrix is composed of the insula, somatosensory area (S1 and S2), anterior cingulate gyrus (ACC), thalamus, forebrain, posterior parietal cortex, striatum, cerebellum, periaqueductal grey, and supplementary motor area (26,27), which are generally associated with physical and affective pain. Tables 2 – 3 and Figs. 1 – 2 revealed that besides the regions belonging to the pain matrix, the brainstem (pons) and some other regions of the limbic system (limbic lobe, nucleus basalis area, hippocampus, parahippocampal gyrus, amygdala, and mammillary body) were also involved. Our results suggest more complex brain mechanisms participated in PHN pathogenesis. Given the general function of these brain areas, we predict that abnormal mood/emotion related brain mechanisms exist in PHN pathophysiology. These brain areas detected by local brain activity analysis may indicate the origin of affective disorder for PHN patients, although we didn't find apparent symptoms of mood disorders in PHN patients in the present study.

Table 3. *Clusters of different fALFF values between PHN and control group (Con).*

Region (R: right; L: left)	MNI coordinate			Peak T value	Voxel size	Brain volume (mm^3)
	x	y	z			
PHN > Con						
Cerebelum Posterior Lobe _R	21	-66	-60	3.56	97	2619
Pons_(bilateral)	12	-9	-30	3.54	62	1674
Cerebellum Anterior Lobe _R	15	-45	-21	3.78	129	3483
Putamen_R	30	-18	3	4.2	116	3132
Extra-Nuclear_L	-33	-12	-6	3.73	164	4428
Occipital Lobe_R	21	-72	18	5.35	143	3861
Precentral Gyrus _R	36	-12	54	3.78	59	1593
PHN < Con						
Middle Frontal Gyrus (bilateral)	36	54	15	-5.31	1157	31239
Superior Parietal Lobule_L	-30	-69	42	-3.55	69	1863
Middle Frontal Gyrus_R	30	36	39	-4.15	127	3429
Middle Frontal Gyrus_L	-24	36	54	-3.68	100	2700

fALFF: fractional aplitude of low-frequency fluctuation; PHN: postherpetic neuralgia; MNI: Montreal Neurological Institute.

Our study indicated that besides the pain matrix, the limbic system and brainstem were also involved in the local brain activity change. The limbic system participates in many functions such as emotion, long-term memory, and sensory processing. It was deemed that limbic regions of the pain matrix encode the emotional aspects of pain perception and primary sensory regions encode the intensity of pain sensation (28,29). Various chronic pain studies in rodents have detected functional changes in limbic circuitry, including the hippocampus (30-33), amygdala (34), striatum (35), and frontal cortex (36-38). Whole-brain network analysis of neuropathic pain (NP) rats showed FC changes were localized mainly within the limbic system and between the limbic and nociceptive systems (39). Based on these results and on recent human imaging data (4,6,40,41), we predict that PHN patients experience not only physical and affective pain, but are prone to mood disorders compared with normal controls.

The brainstem is another major site of pain processing and modulation of nociceptive input. The brainstem contains many nuclei, which projects to the spinal dorsal horn (DH) and/or vast brain areas. For example, the noradrenergic locus coeruleus (LC), which is located at the pons is a relevant structure in both ascending and

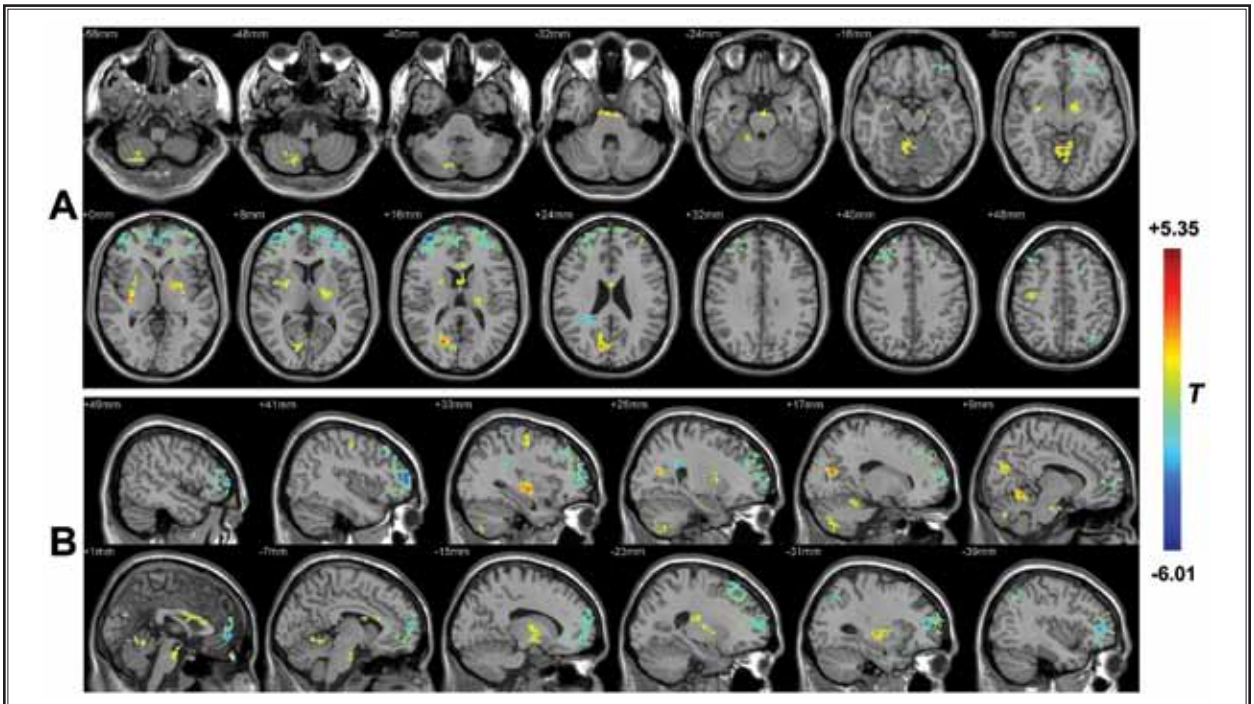

Fig. 2. *Significant differences in fALFF between PHN patients and healthy controls in axial (A) and sagittal (B) slices. The warm colors indicate higher fALFF and cool colors indicate lower ReHo in PHN patients than healthy controls ($P < 0.05$, corrected). Brain images are displayed in radiology convention (e.g., the left in the figure represents the right side of patients' brains and vice versa).*

Table 4. *Correlation between ReHo and VAS.*

Region (R: right; L: left)	Peak MNI coordinate			Peak R value	Voxel size	Brain volume (mm^3)
	x	y	z			
+correlation						
Cerebellum Anterior Lobe _L	0	-24	-51	0.71	377	10179
Medial Frontal Gyrus_R	9	48	-9	0.67	217	5859
Thalamus_L	-15	-33	6	0.74	82	2214
Thalamus (bilateral)	6	-15	3	0.61	59	1593
Limbic Lobe _L	-36	15	45	0.80	1285	34695
Middle Frontal Gyrus _R	24	6	24	0.68	140	3780
Middle Frontal Gyrus_R	21	24	45	0.66	74	1998
Middle Frontal Gyrus_R	24	-12	54	0.67	97	2619
-correlation						
Superior Temporal Gyrus_R	60	-51	15	-0.77	881	23787
Middle Occipital Gyrus _L	-48	-75	-6	-0.70	107	2889
Superior Temporal Gyrus_R	54	-15	12	-0.67	108	2916
Superior Temporal Gyrus_L	-60	-54	12	-0.75	89	2403
Superior Parietal Lobule _R	18	-60	63	-0.74	371	10017
Precuneus_L	-9	-78	42	-0.70	61	1647
Middle Frontal Gyrus _R	30	0	60	-0.69	69	1863
Superior Parietal Lobule_L	-18	-45	72	-0.78	182	4914

ReHo: regional homogeneity; VAS: visual analog scale; MNI: Montreal Neurological Institute

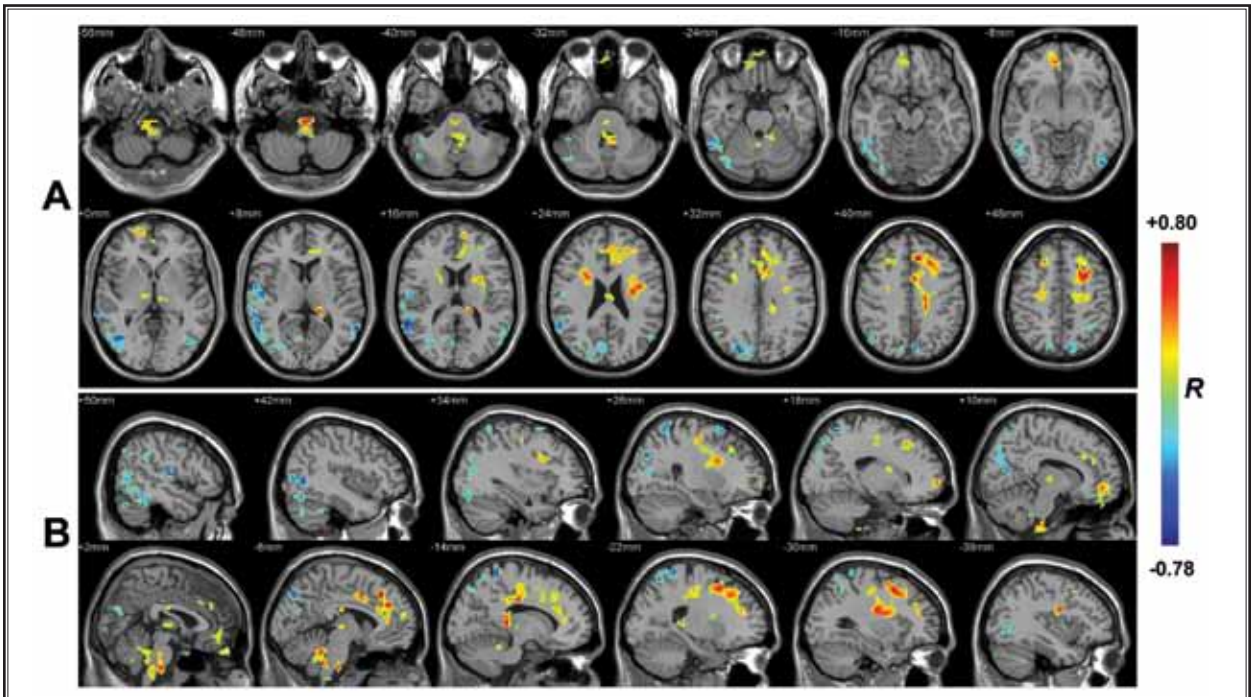

Fig. 3. *Visual analog scale (VAS) value and ReHo correlation. Brain regions with colors showed significant correlation between PHN patients and healthy controls. Their distribution is displayed in axial (A) and sagittal (B) way. The warm colors indicate higher positive correlation while cool colors indicate negative correlation ($P < 0.05$, corrected). Brain images are displayed in radiology convention (e.g., the left in the figure represents the right side of patients' brains and vice versa).*

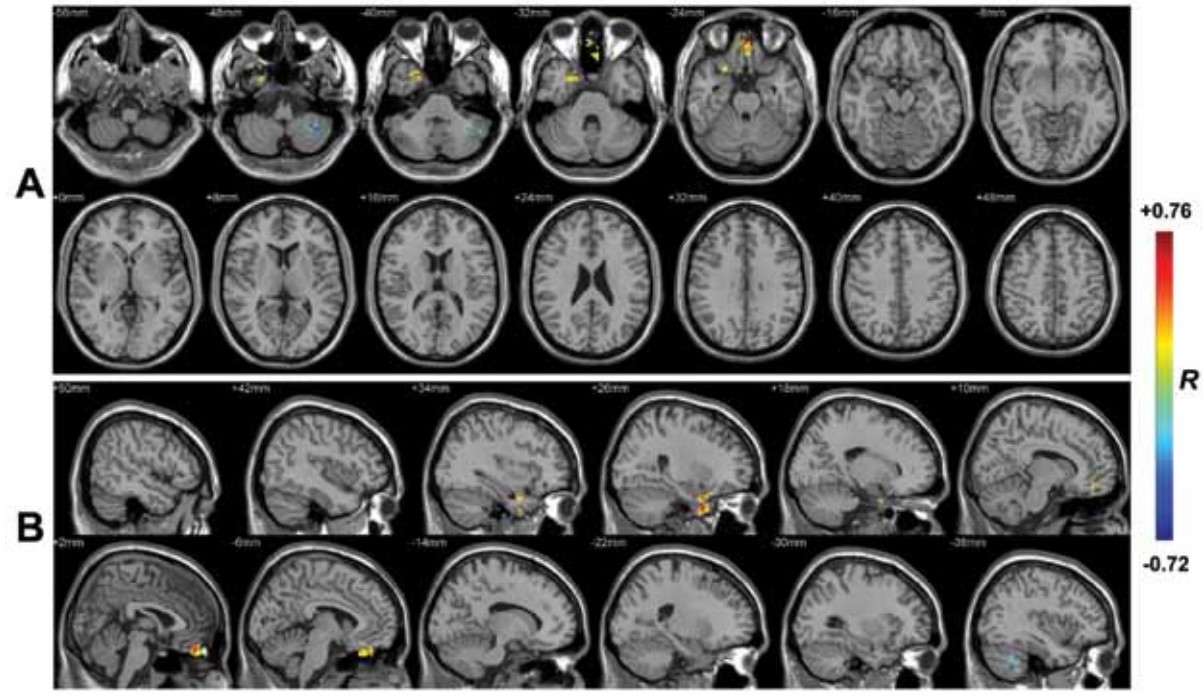

Fig. 4. *Visual analog scale (VAS) value and fALFF correlation. Brain regions with colors showed significant correlation between PHN patients and healthy controls. Their distribution is displayed in axial (A) and sagittal (B) way. The warm colors indicate higher positive correlation while cool colors indicate negative correlation ($P < 0.05$, corrected). Brain images are displayed in radiology convention (e.g., the left in the figure represents the right side of patients' brains and vice versa).*

descending pain modulation. By sending to the DH, it forms one of the noradrenergic pontospinal descending pain inhibition pathways, which influences the spinal transmission of noxious inputs (42-44). In addition, the LC is the primary source of norepinephrine (NE) in the brain. LC produces NE and sends it to vast regions of the brain and maintains cortical activation and behavioral arousal (45). The LC is regarded as the central "stress circuitry" involved in depression and anxiety disorders (46). Previous studies demonstrated plastic changes in the descending noradrenergic inhibitory system in NP rats (47,48). NP could also increase the activity of LC-prefrontal cortex (PFC) noradrenergic neurons (49).

In our results, we demonstrated that many brain regions including the vast area of the superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus showed significant low fALFF value and some areas of the middle frontal gyrus and inferior frontal gyrus showed higher ReHo value in the PHN group. In addition, significantly higher ReHo and fALFF values were shown in the brainstem in the PHN group. These results suggested that when patients suffer from PHN, the neuronal circuitry might be modified. This hypothesis is supported by work by Kim et al (50), as they found that when rats suffered NP, the brainstem, sensorimotor cortex, and the prefrontal cortex became highly connected. The prefrontal-limbic-brainstem areas engage in cognitive/emotional modulation of pain as has been indicated in other studies (51,52).

Additionally, many of the abnormal ReHo and fALFF activity regions perform additional functions besides pain processing. For instance, the prefrontal lobe is associated with depression- and anxiety-like behaviors (53) and the limbic system and brainstem are involved in sleep control (54). Pain is an integrated feeling with sensory, affective, and cognitive dimensions (55). As a neuropathic pain, PHN is not just about somatic and affective pain characteristics. Geha et al (4) recorded the BOLD signal of PHN patients with spontaneous pain and detected that BOLD change was not only restricted to the sensory-discriminative areas (thalamus, primary and secondary somatosensory, anterior cingulate cor-

tices, and insula), but also the emotion, reward, and punishment related brain regions (ventral striatum, orbital frontal cortex, amygdala, and ventral tegmental). It is well known that the occurrence of chronic pain and neuropsychiatric disease such as depression (56) and anxiety (57), cognitive dysfunctions (58), and sleep disorder (59) are highly comorbid. Indeed, up to 50% of patients with chronic pain exhibit symptoms of anxiety or depression (60), whereas in some studies the number even reaches to 75% (61). It's also reported that chronic pain of any kind was associated with the development of major depression within 2 years in 16.4% of patients. Importantly, the prevalence of depression increased with greater pain severity (56). Sleep disorder is another common complication for chronic pain patients. Clinical studies have shown that many patients experience sleep problems after they develop chronic pain; for example, more than half of chronic neck pain patients reported mild to severe insomnia (62). Conversely, inadequate sleep due to NP may contribute to living with chronic pain (63,64).

Although much of the brain imaging studies of PHN were conducted using fMRI, we should notice that mounting evidence indicated that NP resulted in or was accompanied by plastic change or structural abnormality in human (65-69) and murine (70,71) brains. Much of the plastic and structural alterations took place in pain-processing regions. For example, when NP led to anxio-depressive-like behaviors, it impaired the noradrenergic system as evidenced by the plastic change of the LC (72). We also found that PHN patients showed abnormal microstructure in the bilateral insula, superior temporal gyrus, left middle frontal gyrus, occipital lobe, right cerebellum anterior lobe, right thalamus, caudate, and parahippocampal gyrus as evidenced by significantly decreased diffusional kurtosis imaging (DKI) intensity as compared with healthy controls (16). All of the above-mentioned regions showed an activated trend in the PHN group in the present study. Normal anatomic brain structure decides normal brain function, so the detected abnormality can be partly the result of structural or plastic change during PHN. It will be interesting to analyze the cause of these abnormalities, and comparing DKI and ReHo/fALFF differences between acute herpes zoster pain patients and PHN patients will be helpful in shedding light on the causal relationship between functional and structural abnormality.

We assessed the correlations between local brain activity and pain intensity, and found that only ReHo changed in accordance with VAS scores, although ReHo and fALFF results displayed many similar patterns in PHN patients. Although pain intensity is the most key symptom for PHN, which may hold most of the change detected by ReHo and fALFF, other components of PHN, for example, the emotional disturbance and the affective change may have also contributed to local brain activity change, so a poor correlation between VAS and brain activity is understandable. It should be interesting to analyze correlations between mood status and rs-fMRI parameters, such as the ReHo and fALFF.

Limitations

There are some limitations in this study. For the PHN group, the sample size (19 patients) is small, the pain duration range (mean 5.4 months, from 3 to 24 months) is short, and no obvious emotional symptoms were found among PHN patients, so we didn't assess the emotional status of each patient. Nevertheless, we thought emotional status could contribute to the ReHo and fALFF change. We also didn't assess the correlation between ReHo and pain duration or fALFF and pain duration.

Conclusions

Using ReHo and fALFF, we found that PHN patients displayed apparent abnormalities in the brain regions related to sensory as well as emotional and affective processes. ReHo and fALFF change in PHN patients may have shed some light on brain mechanisms underlying PHN patients, perhaps involved in mood disorders.

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