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ORIGINAL RESEARCH

Functional and Structural Changes in Postherpetic Neuralgia Brain Before and Six Months After Pain Relieving

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Objective: Multimodal magnetic resonance imaging (MRI) was used to detect whether 6 months after pain relieving, the structural and functional abnormalities in the brain of postherpetic neuralgia (PHN) patients are changeable.

Methods: Fifteen successfully treated PHN patients were enrolled; the brain activity and structural abnormalities were detected and compared before and 6 months after treatment. The functional parameters were evaluated with resting-state functional MRI technique, i.e., the regional homogeneity (ReHo) and fractional amplitude of low-frequency fluctuation (fALFF). Structural changes were detected with voxel-based morphometry (VBM) and diffusion kurtosis imaging (DKI).

Results: Six months after pain relieving, PHN brain showed different ReHo and fALFF values in the frontal lobe, caudate, supramarginal gyrus, anterior cingulate cortex (ACC), cuneus, middle temporal gyrus, and cerebellum. In addition, VBM intensity in the cerebellum increased; DKI values decreased in the thalamus and increased in the temporal lobe after successful treatment.

Conclusion: Six months after pain relieving, functional and structural changes exist in PHN brain. Changes in some differential areas in PHN brain, such as ACC, frontal lobe, thalamus, and temporal lobe indicate that the central plasticity may be reversible after chronic pain relieving.

Keywords: postherpetic neuralgia, PHN, functional magnetic resonance imaging, regional homogeneity, ReHo, fractional amplitude of low-frequency fluctuation, fALFF

Introduction

Herpes zoster causes many complications, among which postherpetic neuralgia (PHN) is the most common and refractory one.[1] PHN is one kind of neuropathic pain lasting more than one[2] or three months[1,3] after the outbreak of herpes zoster (shingles). PHN has been an economic burden of the gradually aging society.[4] In China, the estimated prevalence rates of herpes zoster and PHN from hospital patients were 7.7% and 2.3%, respectively.[5] PHN not only affects patients' quality of life[6] but also increases the risks of anxiety, depression, and suicide.[7,8] Unfortunately, the mechanisms of PHN are still not fully understood.[9]

By using functional magnetic resonance imaging (fMRI), accumulating evidence showed functional abnormalities in PHN brain.[10–14] For example, functional connectivity analysis revealed altered connections between putamen and other regions in PHN brain.[11] Small-world network detection showed decreased local

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efficiency in sense, memory, and emotion-related brain areas in PHN brain.[12] Our previous work showed functional abnormalities in PHN brain in the pain matrix (frontal lobe, insular and cerebellum etc.), occipital lobe, temporal lobe, and brainstem.[15–17]

Chronic pain causes central sensitization and plasticity changes in the brain.[18,19] Multimodal MRI studies indicate microstructure abnormalities in the gray and white matter of PHN brain.[20,21] Compared with healthy brain, PHN brain exhibited significantly decreased DKI values in the gray matter,[20] and reduced diffusion tensor imaging (DTI) values in white matter,[21] which means abnormal microstructural integrity. Of note, compared with healthy brain, gray matter volume (GMV) changes have been found in many areas in PHN brain, such as insula, middle frontal gyrus, cerebellar posterior lobe, parahippocampal gyrus, and so on.[22] Furthermore, two studies compared VBM values between PHN and herpes zoster brain; GMV differences were found in limbic lobe (hippocampus and parahippocampal gyrus), frontal lobe, thalamus, occipital lobe, parietal lobe, cerebellum, etc.,[17,22] which suggest that pain duration of herpetic neuralgia influences GMV.

Whether the structure and function of these abnormal brain areas can recover after successful treatments and pain relief is of interest. Geha et al[10] found that after 6 h or two-week treatment of PHN patients with 5% lidocaine patch, the spontaneous pain was significantly reduced, and for most of the pain-activated areas, the brain activities were significantly reduced.[10] The ventral striatal and amygdala activity, which was modulated by longer-term treatment, reflected changes in neuropathic pain score.[10] Six months after the effective treatment of chronic low back pain, the abnormal functional connection between the insula and prefrontal lobes began to recover,[23] and the cortex thickness of the dorsolateral prefrontal lobes increased significantly.[24] When the chronic pain of patients with osteoarthritis was relieved after joint replacement, 9 months after operation, the decreased GMV of thalamus recovered,[25] and the decreased GMV of anterior motor cortex and auxiliary motor cortex gradually recovered one year after operation.[26] However, whether successful treatment can reverse the microstructural damage and GMV changes in PHN brain has not been reported.

Here, we focus on the brain activity and structural changes in PHN patients who recovered for 6 months after treatment. The brain activity, GMV, and microstructural damages were detected with multimodal MRI.

Methods

Participants

This study was approved by the ethics committee of the Affiliated Hospital of Zunyi Medical University, and conducted in accordance with the Declaration of Helsinki. Written informed consents were obtained from all patients. All of the 15 right-handed patients were recruited from the Department of Pain Medicine of the local hospital. The diagnosis of PHN was based on the International Association for the Study of Pain (IASP) criteria.[27] Spontaneous pain intensity was evaluated with visual analogue scale (VAS), and depression level of PHN patients was evaluated with Beck depression inventory (BDI). Patients were treated with combination therapy as guidelines recommended,[28] including: i) Antiepileptic drugs; ii) Opioid analgesics; iii) Neurotrophic drugs; iv) Paravertebral nerve block; and v) Physical therapy. PHN patients were discharged when the pain was relieved (VAS score < 3). Only PHN patients claimed: i) intense thoracic herpetic neuralgia (VAS scores ≥ 5) on the right side on the admission day; ii) herpetic neuralgia relieved (VAS < 3) for 6 months after treatment; iii) with no depression symptoms and with low BDI scores (<10) were enrolled. No opioid analgesics, antidepressants, or antipsychotic drugs were taken one month before MRI scans. All patients showed no visible structural abnormalities from brain MRI images. Patients in the present study received twice MRI scan: first time was on the admission day, before treatments (T1), and the second one was 6 months after enrollment and treatment (T2). After discharging, all patients did not receive additional treatment.

Image Acquisition

MRI images were acquired as reported,[15,16] patients were scanned with a GE Signa HDxT 3.0 T MRI scanner (GE company, USA) with a standard 8-channel head coil. fMRI images 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. DKI images were acquired using spin-echo single-shot echo-planar imaging sequences, with TR/TE = 10,000/99.3 ms, thickness/gap = 4.0/0 mm, FA: 15°, FOV: 240 × 240 mm^3, matrix: 128 × 128, scan time is 530 s, and a total of 1820 images were collected for DKI analyses. High-resolution anatomic 3D T1 images were

acquired with the TR = 5.8 ms, TE = 1.8 ms, flip angle = 12°, thickness/gap = 1.0/0 mm, FOV = 256 × 256 mm, matrix = 256 × 256, 146 sagittal slices were collected.

Image Processing

The fMRI mages were processed with the Data Processing Assistant for Resting-State fMRI (DPARSF, http://rest.restfmri.net/forum/DPARSF)[29] and SPM8 (Wellcome Department, University College of London, UK) software based on MATLAB R2012a (MathWorks, USA).

The processes with DPARSF were as follows: the first 10 volumes of the fMRI images were discarded considering scanner calibration and participants adaptation during the scan, then the remaining 200 volumes were further analyzed for slice timing, head-motion correction, spatial normalization to the Montreal Neurological Institute (MNI) space and resampling with a 3 × 3 × 3 mm^3 resolution. Patients with a head motion > 2.0 mm or >2.0° of rotation in any direction were excluded, and linear trends of the MRI data were removed. For ReHo analyses, to discard high-frequency physiological noise and the frequency drift lower than 0.01 Hz, the band-pass filtering was set as 0.01–0.08 Hz.[30] The Resting State fMRI Data Analysis Toolkit (REST, http://rest.restfmri.net)[31] was used for the subsequent analyses: 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.[32,33] Then, a whole-brain mask was adopted to remove the non-brain tissues. The individual ReHo maps were divided by their own global mean KCC within the whole-brain mask to assure standardization. Afterward, spatial smoothing was performed on individual standardized ReHo map with a Gaussian kernel of 4 mm full-width at half maximum (FWHM).[34]

fALFF analysis was performed as previously described.[35,36] Firstly, the resampled images were smoothed with a 4 mm Gaussian kernel and filtered with a 0.01–0.08 Hz frequency band, then the time courses were filtered with this frequency band using a Fast Fourier Transform. The mean and standard deviation of individual's ReHo and fALFF value were calculated by DPARSF within the whole-brain mask.

The VBM[37] and DKI analysis[20] were performed with SPM8, DKE toolbox,[38] and FMRIB Software Library (Oxford University, UK) as reported. The procedures included the following steps: i) checking for scanner artifacts and gross anatomical abnormalities for each subject; ii) setting the image origin to the anterior commissure; iii) segmenting the images into gray matter, white matter, and cerebrospinal fluid (CSF) images; iv) using the DARTEL toolbox on SPM8 to produce a high-dimensional normalization protocol; and v) checking for homogeneity across the sample and applying a 8 mm FWHM Gaussian kernel standard smoothing. After this pre-processing, modulated, smoothed, and normalized images were obtained for statistical analysis.

DKI analyses included the following steps: each DKI parameter was estimated from the DKI image by DKE software. The parameters mainly include: DKI oriented mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), and fractional anisotropy (FA); DTI oriented FA, mean diffusion tensor (MD), axial diffusion tensor (AD), and radial diffusion (RD).

Statistical Analysis

Clinical data of PHN patients were analyzed using Prism 7.0 (GraphPad Software Inc, USA). Paired t-tests were used for detecting the VAS score differences. $P < 0.05$ was considered as statistically significant.

Paired t-tests were conducted with REST in whole-brain voxel-wise way for ReHo, fALFF, VBM, and DKI comparisons between two time points. To further determine the significances, multiple comparison correction was performed with Monte Carlo simulations[39] with the REST AlphaSim utility.[31] Voxels with $P < 0.05$ (two-tailed, with AlphaSim correction: http://afni.nih.gov/afni/docpdf/AlphaSim.pdf) were regarded as brain areas of significant difference.

REST Slice Viewer was employed to display statistic results[31] and images. Brain areas were overlaid on brain MRI template images. A color-bar was set to illustrate the statistic values.[20]

Results

Demographic and Clinical Features

Clinical characteristics of 15 PHN patients (female: male = 8:7) are listed in Table 1. The comparison of VAS score indicates that 6 months after treatment, patients had significantly lower VAS scores: 7.1 ± 1.2 vs 0.7 ± 0.8, $P < 0.0001$.

Comparisons of ReHo Before and After Treatment

The ReHo values of multiple regions in the brain of PHN patients significantly changed 6 months after comprehensive

Table 1 Demographic and Clinical Variables of 15 PHN Patients Before Treatment and Six Months After Pain Relieving

No.	Age (Year)	Gender	Location of Lesion	VAS Score		Pain Duration (Month)
				T1	T2	
1	66	F	Right T8–10	8	0	1.5
2	65	F	Right T3–5	8	0	2.0
3	66	M	Right T4–6	7	1	3.0
4	60	F	Right T6–8	6	2	8.0
5	76	M	Right T7–9	8	2	6.0
6	71	M	Right T4–6	5	1	7.0
7	73	F	Right T2–4	8	0	2.0
8	67	M	Right T3–5	7	0	3.0
9	55	F	Right T3–5	8	0	2.0
10	50	M	Right T6–8	7	0	3.0
11	58	F	Right T4–6	6	0	1.0
12	63	M	Right T3–5	5	2	9.0
13	72	F	Right T8–10	9	0	1.0
14	66	F	Right T7–9	8	1	2.0
15	54	M	Right T9–11	7	1	3.0

Notes: T1: time of enrollment; T2: 6 months after enrollment and treatment.
Abbreviations: M, male; F, female; T, thoracic; VAS, visual analogue scale.

treatment. These areas are shown in Figure 1 and Table 2. After treatments, ReHo value increased in temporal lobe, cerebellum, cingulate gyrus, and precuneus, while part of temporal lobe, cingulate gyrus, and frontal lobe showed decreased ReHo after treatments ($P < 0.05$, AlphaSim correction). Detailed information of these differential areas is listed in Table 2.

Comparisons of fALFF Before and After Treatment

As shown in Figure 2 and Table 3, the fALFF values of multiple regions in the brain of PHN patients significantly changed 6 months after comprehensive treatments. The areas where the fALFF value increased after treatments were: bilateral frontal lobe and bilateral caudate, while the right supramarginal gyrus and lingual gyrus showed decreased fALFF after treatments ($P < 0.05$, AlphaSim corrected). The MNI space coordinates, T value, and corresponding voxels are listed in Table 3.

Changes of GMV in PHN Patients Before and After Comprehensive Treatment

The VBM method was used to compare and analyze GMV of PHN brain before and after treatments. The GMV of the left cerebellum (Cerebelum_Crus1_L (aal)) increased significantly after treatments ($P < 0.001$, cluster size = 58), as shown in Figure 3.

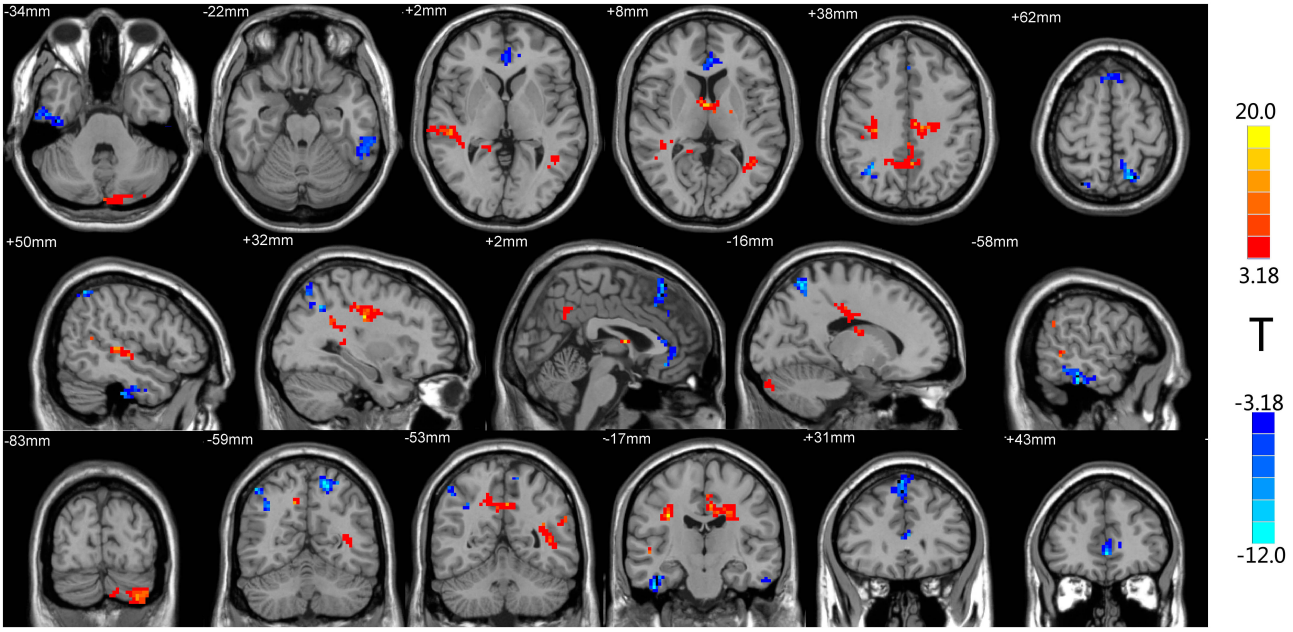

Figure 1 Brain regions with differential ReHo values after treatment. The distribution of ReHo differential brain areas in the transversal sections (upper row), sagittal sections (middle row), and coronal sections (third row) after treatment. The red and yellow colors indicate higher ReHo value, while blue colors indicate lower ReHo in PHN brain 6 months after treatment, compared with the admission day ($P < 0.05$, AlphaSim corrected, paired *t*-test, n=15). Brain areas with increased ReHo mainly in the temporal lobe, cerebellum, cingulate gyrus, and precuneus. Lower ReHo values were detected in the temporal lobe, anterior cingulate gyrus, and frontal lobe (Table 2).

Table 2 Clusters with Different ReHo Values Six Months After Treatment

Region (R: Right; L: Left)	Peak MNI Coordinate			Peak T Value	Voxel Number	Brain Volume (mm^3)
	x	y	z			
T2 > T1						
Cerebellum Posterior Lobe_L(aal)	−11	−93	−30	10.8	112	3024
Temporal_Mid_L (aal)	−30	−45	15	15.1	60	1620
Temporal_Sup_R (aal)	51	−27	3	12.8	63	1701
Cingulum_Mid_L (aal)	−6	−18	39	11.7	53	1431
Precuneus_R (aal)	−3	−54	39	12.2	46	1242
T2 < T1						
Temporal_Inf_R (aal)	45	−18	−36	−22.1	45	1215
Temporal_Inf_L (aal)	−55	−32	−20	−14.7	66	1782
Cingulum_Ant_L (aal)	−3	46	−2	−10.8	50	1350
Frontal_Sup_Medial_L (aal)	0	24	42	−36.6	24	648
Frontal_Sup_Medial_R (aal)	3	30	57	−7.9	36	972

Abbreviations: MNI, Montreal Neurological Institute; aal, anatomical automatic labeling.

Analyses of DKI Before and After Treatment in PHN Patients

Comparison of DKI parameters before and after treatments in 15 PHN patients indicated that AD values of the right thalamus were significantly reduced after treatments (Figure 4A). In addition, the FA value of the right superior temporal gyrus (Temporal_Sup_R (aal), Figure 4B) and the AK values of the right temporal gyrus (Temporal_Mid_R (aal), Figure 4C) increased after treatments (P <0.05, AlphaSim correction). No significant change of DKI was found in other brain regions.

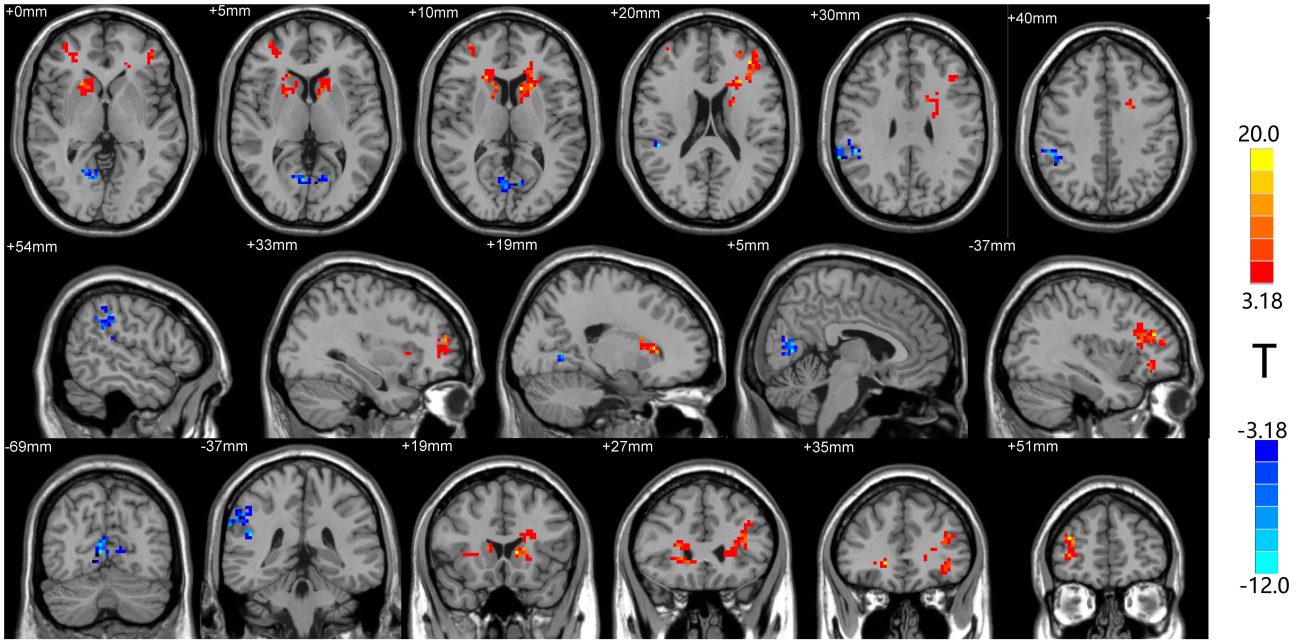

Figure 2 The distribution of fALFF differential brain areas in PHN patients before and after treatment. The warm colors indicate higher fALFF, and cool colors indicate lower fALFF in PHN brain after treatment (P < 0.05, AlphaSim corrected, paired *t*-test, n=15). After treatment, brain showed significantly increased fALFF mainly in the bilateral frontal lobe (bilateral middle frontal gyrus, bilateral inferior gyrus, bilateral caudate). Lower fALFF values were observed in the SupraMarginal_R (aal) and Lingual_R (aal). The detailed information for each cluster and their peak T values and coordinates are listed in Table 3.
Abbreviation: aal, anatomical automatic labeling.

Table 3 Clusters with Different fALFF Values Six Months After Treatment

Region (R: Right; L: Left)	Peak MNI Coordinate			Peak T Value	Voxel Number	Brain Volume (mm^3)
	x	y	z			
T2 > T1						
Frontal_Mid_R (aal)	35	51	3	12.5	51	1377
Frontal_Mid_L (aal)	−39	35	20	8.9	72	1944
Frontal_Inf_Tri_L (aal)	−36	27	18	10.2	46	1242
Frontal_Inf_Orb_L (aal)	−36	36	−9	6.4	23	621
Caudate_R (aal)	21	27	0	9.1	33	891
Caudate_L (aal)	−18	18	9	21.5	43	1161
T2 < T1						
SupraMarginal_R (aal)	48	−42	27	−25.2	89	2403
Lingual_R (aal)	6	−69	6	−10.7	38	1026

Abbreviations: MNI, Montreal Neurological Institute; aal, anatomical automatic labeling.

Discussion

As shown by ReHo, fALFF, VBM, and DKI results, 6 months after the relief of herpetic neuralgia, the brain activity, GMV, and gray matter intensities in several brain regions are different in the 15 PHN patients. All of these differential brain areas, such as the frontal lobe, cerebellum, thalamus, cingulated gyrus, parietal lobe, cuneus, and temporal gyrus were reported as differential brain areas between PHN and healthy subjects.[12,15,16,20,22] These MRI results indicate that a period of time after pain relief (e.g., 6 months), abnormalities in the PHN brain could be reversible.

As expected, most of these differential areas, including the cerebellum, thalamus, cingulated gyrus, and frontal lobe, are parts of the "pain matrix", which was defined as regions that exhibited activation in response to pain.[40–43] This means the changes in the brain of cured PHN patients mostly happen in pain-related brain areas. Decreased ACC, cuneus, and increased frontal lobe activity were found after treatment, which showed a reverse trend in PHN brain compared with healthy brain.[13,16] In addition, after treatment, FA values in the right superior temporal gyrus and AK values in the right middle temporal gyrus increased remarkably, which also showed a reverse trend in PHN brain compared with healthy brain.[20] These changes suggest that after a period of pain relief, for some differential brain regions, the functional and structural abnormalities in PHN brain may be reversible.

In this study, after 6 months of effective treatment, the GMV of the cerebellum was increased, and the previously

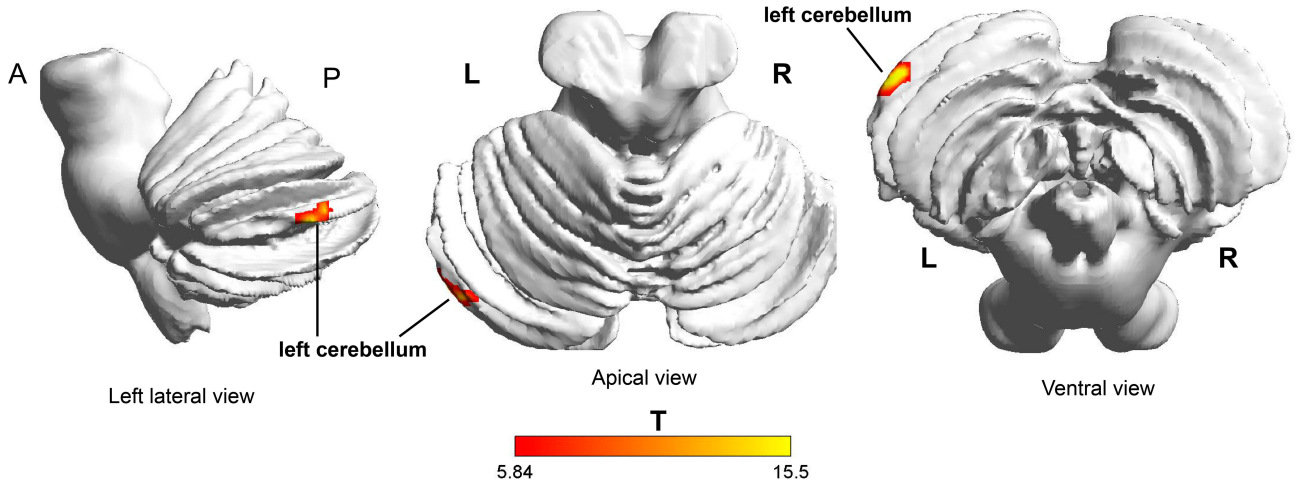

Figure 3 VBM analysis shows brain structural changes in PHN patients after treatment. The left cerebellum (Cerebelum_Crus1_L (aal)) indicated with red and yellow color shows increased GMV after treatment (P <0.05, AlphaSim correction).
Abbreviation: aal, anatomical automatic labeling.

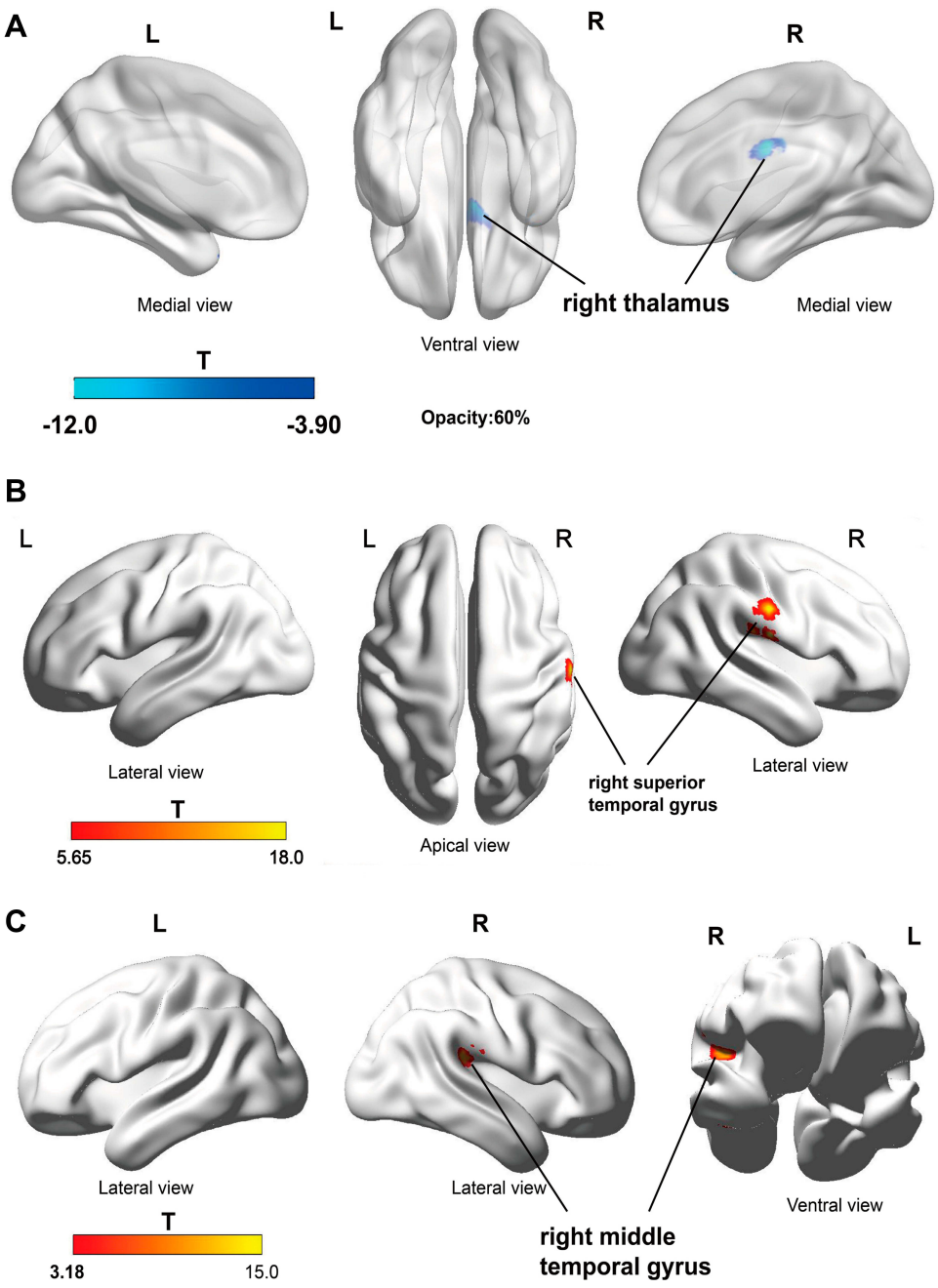

Figure 4 DKI analyses suggest brain structural changes in PHN patients after treatment. (**A**) AD value of right thalamus (Thalamus_R (aal)) was significantly reduced after treatment; (**B**) FA values in the right superior temporal gyrus (Temporal_Sup_R (aal)) increased after treatment; (**C**) AK values in the right temporal gyrus (Temporal_Mid_R (aal)) increased after treatment (P <0.05, AlphaSim correction). The blue color indicates the GMV is significantly reduced after treatment, and the red and yellow colors indicate the GMV is significantly increased after treatment.

Abbreviation: aal, anatomical automatic labeling.

reduced FA and AK values in the temporal lobe[20] were significantly increased, indicating that the GMV loss and microstructural abnormalities in PHN brain were partially recovered after effective treatments. Interestingly, the cerebellum GMV has been reported to be increased in PHN patients compared with healthy controls[22] or herpes zoster patients,[17] furthermore, our data indicate that its volume continued to increase 6 months after herpetic-pain relief. Cerebellum is part of pain matrix and activates in painful events in healthy controls[44] and in patients with chronic pain.[45] It is reported that cerebellar activity correlated well with rat neuropathic pain development in an eight-week longitudinal study.[46] Under the circumstances of chronic pain, the GMV of cerebellum could be increased or

decreased. For example, it was increased in patients with fibromyalgia[47] or cluster headache,[48] but decreased in trigeminal neuralgia[49,50] or burn moth syndrome.[51] Cerebellar direct current stimulation (tcDCS) could modulate pain perception and its cortical correlates;[52] therefore, the cerebellum is thought to be one of the potential targets for chronic pain treatment.

Whether there is a causal relationship between changes in brain structure and chronic pain remains unclear. Rodriguez-Raecke et al[53] found that long-term pain-suffering patients with hip arthritis may develop GMV reduction in brain areas such as ACC, and the GMV loss recovered in patients received hip replacement. DeSouza et al[54] found that the FA, MD, and RD values of the right anterior insular lobe and the gray matter at the entrance of the trigeminal nerve of patients with trigeminal neuralgia were reversible 2–6 months after effective treatment, indicating gradual recovery of the damaged microstructure in the brain. In the present study, 6 months after pain relief, the FA and AK values of temporal lobe significantly increased, indicating that maybe the abnormality of brain microstructure is reversible after effective treatment in PHN patients.

Detections at longer recovery time points (e.g., one year or two years) will be helpful to evaluate the functional and structural changes in the brain of cured PHN patients. It should be realized that a high false-positive rate may exist in fMRI studies using conventional software.[55] Alternative neuroscience methods are warranted to identify functional and structural abnormalities in brains of patients with chronic pain.

Conclusions

Evaluations of ReHo, fALFF, VBM, and DKI indicate that 6 months after the relief of herpetic neuralgia, the brain activity, GMV, and gray matter intensities of PHN brain are different. Successful treatment may partly reverse functional and structural abnormalities in areas such as ACC, frontal lobe, and temporal lobe in PHN brain. These data indicate reversible central plasticity after the relieving of chronic pain.

Data Sharing

No further data will be shared.

Disclosure

The authors report no conflicts of interest in this work.

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