

# Altered EEG Brain Networks in Patients with Acute Peripheral Herpes Zoster

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**Objective:** To investigate whether the brain networks changed in patients with acute peripheral herpes zoster (HZ).

**Methods:** We reviewed the EEG database in Jianyang People's Hospital. Patients with acute HZ (n=71) were enrolled from January 2016 to December 2020. Each included subject underwent a ten-minute and 16-channel EEG examination. Five epochs of 10-second EEG data in resting-state were collected from each HZ patient. Five 10-second resting-state EEG epochs from sex- and age-matched healthy controls (HC, n=71) who reported no history of neurological or psychiatric disorders and visited the hospital for routine physical examinations were collected. Brain network and graph theory analysis based on phase locking value parameter and functional ICA were performed using a self-writing Matlab code and the LORETA KEY tool.

**Results:** Compared with the HC group, the HZ patients showed significant altered brain networks. The graph theory analysis revealed that the clustering coefficient and local efficiency of full band in HZ patients were lower than those in HC group ( $P<0.05$ ). In beta band, the global efficiency and local efficiency of HZ patients group decreased, compared with healthy group ( $P<0.05$ ). The functional ICA showed that three components showed significant differences between the two groups. In component 2, HZ patients showed excess superior frontal gyrus (BA10) neuro oscillation in delta band and less medial frontal gyrus (BA 11) neuro oscillation in beta and gamma bands than that in HCs. And for component 3, the alpha band of the HZ patients presented increased neuro activities in superior frontal gyrus (BA 11) and decreased neuro activities in occipital lobe (BA 18). In component 4, the inferior frontal gyrus (BA 47) showed excess activity in the left hemisphere and reduced activity in the right hemisphere in delta band, compared with HC group.

**Conclusion:** Altered brain networks exist in resting-state EEG data of patients with acute HZ. The changes of EEG brain networks in HZ patients are characterized by decreased global efficiency and local efficiency in beta band. Moreover, the spontaneous oscillation of some brain regions involving pain management and the connectivity of default mode network changed in HZ patients. Our study provided novel understanding of HZ from an electrophysiological view, and led to converging evidence for treatment of HZ with neural regulation in future.

**Keywords:** herpes zoster, brain network, graph theory analysis, independent component analysis, phase locking value

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## Introduction

Peripheral herpes zoster (HZ) is mainly characterized by blistering dermatomal rash along the nerve and moderate to severe pain in a variety of skin, such as burning, stabbing, soreness, bloating, or allodynia.<sup>1</sup> It is caused by the reactivation of latent

varicella zoster virus (VZV) in spinal or cranial sensory ganglia of people who have been primary infected with VZV.<sup>2</sup> The incidence rate of HZ ranged 3–5/1,000 per year<sup>3</sup> and 29.8% of HZ patients leave over the postherpetic neuralgia,<sup>4</sup> which could cause negative effects on the mood and sleep quality of HZ patients.<sup>5</sup>

The question how pain is processed in the brain has been an enduring puzzle. A large number of studies focused on changes in pain modulation pathways and brain regions in HZ patients.<sup>6,7</sup> Recently, an increasing number studies have recognized that pain may reorganize the brain networks.<sup>8,9</sup> The brain network was used to describe the connectivity between interest nodes of the brain regions,<sup>10,11</sup> which has been widely used in brain network research of neurological diseases such as epilepsy and Alzheimer's disease.<sup>12–16</sup> Some studies using functional magnetic resonance imaging (fMRI) have found altered functional networks patients with peripheral HZ, which may indicate that the pain processing in HZ patients were different from normal subjects.<sup>17,18</sup> These studies on HZ are biologically meaningful considering that their findings may provide new understandings on the multiple dimensions of pain processing. However, few studies concentrated on brain function changes and pain modulation mechanisms in patients with acute HZ using EEG.

A widely accepted brain network analysis method: Independent component analysis (ICA) is a classical electroencephalogram (EEG) signal analysis technique, which separates scalp electrical signals into their additive independent or source components.<sup>19</sup> All the components activated in the results are statistically independent of each other to identify independent spatial brain networks and their interactions in frequency bands.<sup>20</sup> Another commonly used phase interaction measure is the Phase Locking Value (PLV), the absolute value of the mean phase difference between two signals from pairs of electrodes as a complex unit-length vector.<sup>21</sup> The PLVs reflect information transfer from one brain region to other regions.<sup>22</sup> In addition, graph theory analysis applied to the constructed PLV matrices is useful in identifying differences in brain network patterns.<sup>23</sup> Considering that EEG signals are a complex sum of several sources of electrical brain activity, we may acquire a deeper understanding of the neurobiological mechanisms of HZ using these analysis methods involving brain networks. Therefore, we decided to use ICA, PLV, and graph theoretical analysis to explore the changes of brain networks in patients with acute HZ.

In the present study, we hypothesized that brain networks altered in those patients with acute HZ. Thus, we aimed to investigate whether and how EEG brain networks changed in HZ patients. This is practical considering that in future we may adopt novel neural regulation protocols to treat acute HZ.

## Materials and Methods

### Participants

Seventy-one patients who were diagnosed with acute HZ from January 2016 to December 2020 in Jianyang People's Hospital were included. Inclusion criteria: 1) a diagnosis of acute herpes zoster by specialized clinicians and aged 30–80 years; 2) the onset time of acute HZ less than 14 days; 3) the patients reported no other diseases might affect their EEG patterns; 4) no previous history of nervous system disease, mental disease, or head trauma; and 5) MRI scanning on brain showed negative intracranial results. Additionally, 71 age- and sex-matched healthy control subjects who visited our hospital for routine physical examinations were enrolled as the healthy control (HC) group. No history of neurological or psychiatric disorders was reported in the controls. All included subjects were right-handed. No identifiable features for all subjects were reported in the current study. Written informed consent was obtained from the included subjects before data collection and review of the medical records. The study was approved by the Ethics Committee of the Jianyang People's Hospital. This study was conducted following the 2008 Helsinki declaration.

### EEG Data Acquisition

Ten-minute scalp EEG data were collected from all included subjects. The EEG data were recorded using a 16-channel analog recorder (NT9200, Xintuo, China) continuously for ca. 10 minutes according to the international 10–20 system. The electrodes (FP1, FP2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, and O2) were placed using a quantified ruler. The impedance of each electrode was kept at less than 10 k $\Omega$ . The sampling rate was 500 Hz. During the recording time, subjects were asked to keep relaxed with their eyes closed.

### EEG Preprocessing

All the original EEG data were exported as European Data Format (EDF). The EEG was bandpass filtered between 1 Hz and 45 Hz using a hamming window after the FIR filter. Then the electromyogram artefacts and muscle

artifacts were completely removed using an EEGLab plugin-in AAR (<http://germangh.com>). In this tool, the blind source separation algorithm was employed to perform electrooculogram (fast ICA algorithm) corrections automatically. The EEG matrix with a low fractal dimension would be identified as electrooculogram components and would be removed automatically.<sup>24</sup> And the blind source separation algorithm based on canonical correlation analysis also performed electromyogram (fast ICA algorithm) corrections automatically.<sup>25</sup>

Then, the EEG was recomputed to the common average reference. The preprocessed EEG data was cut out and translated to text format for subsequent analysis. We obtained five 10-second-epochs of EEG in the resting state for each subject. The EEG data were preprocessed using EEGLab (v14.1.1, <http://sccn.ucsd.edu>).

## PLV Based Brain Network Analysis

Electrophysiological signals can be usefully characterized in terms of their oscillatory components, through band-pass filtering into the standard frequency bands (delta, theta, alpha, beta, and gamma). Interactions can then be analyzed using measures of within and between frequency-band coupling between electrode pairs.<sup>26</sup> Since the brain is a nonlinear dynamical system, we can use phase locking to quantify the interactions of pairs of electrodes.

The absolute value of the average phase difference between two signals is characterized by PLV, which can be used to measure the degree of synchronization of EEG signals in a certain frequency band. This method has been described in other studies.<sup>27,28</sup> In brief, the PLV is defined as

$$PLV(t) = \frac{1}{N} \left| \sum_{n=1}^N \exp(j(\Delta\varphi_n(t))) \right| \quad 1$$

where  $N$  denotes the total number of sampling points, and  $\Delta\varphi_n(t) = (\varphi_x(t) - \varphi_y(t))$  is the instantaneous difference between signal  $x$  and  $y$  at time  $t$ . The PLV takes values on  $[0, 1]$  with 0 reflecting the case where there is no phase synchronization and the two signals are independent and have no obvious synchronization, and 1 where the degree of synchronization between the two signals is the strongest.

In this study, seven frequency bands were defined: delta band (1–4 Hz), theta band (4–8 Hz), alpha1 band (8–10 Hz), alpha2 band (10–13 Hz), beta band (13–30 Hz), gamma band (30–45 Hz), and full band (1–45 Hz).

Then, a  $16 \times 16$  PLV matrix was constructed for each subject and used for later graph theory analysis.

## Graph Theory Analysis

In this study, the 16 EEG channels were used as nodes for each subject in each frequency band. And the previously constructed  $16 \times 16$  PLV matrix was used for graph theory analysis. We selected the path length, global efficiency, clustering coefficient, and local efficiency of the PLV network attribute for characterizing brain network topology. The path length, which referred to the average distance between any two nodes, represented the ability of the network to transmit signals. The global efficiency referred to the reciprocal average of the shortest path length, which represented the efficiency of signal transmission between network nodes and the local efficiency was the trend to measure the clustering of nodes with strong connections in a network. These graph-based indices were computed using MATLAB functions embedded in the Brain Connectivity Toolbox (<http://www.brain-connectivity-toolbox.net>).

## The Functional Independent Component Analysis (fICA)

To analyze the differences of resting state functional network between two groups, an exact Low Resolution Electromagnetic Tomography (eLORETA) functional ICA method was employed. eLORETA is a widely used method to localize multiple distributed cortical sources of EEG data in three-dimensional space.<sup>29</sup> The LORETA method has been previously validated in many real human EEG data. The present used eLORETA (v20190226) is an improvement over earlier related versions of LORETA<sup>29</sup> or Standardized LORETA (sLORETA).<sup>30</sup> ICA is a mathematical decomposition method that separates the EEG signal into a set of statistically independent components. All the technical details can be found in other papers.<sup>31,32</sup>

In brief, first, the EEG signals were transformed to cross-spectral EEG matrix for each frequency band using the discrete Fourier transform. Then, these transformed files were used for computing the spectral density for each cortical voxel and for each frequency band using the algorithm described in detail in previous literature.<sup>31,33</sup> Thus, we obtained six eLORETA images of cortical spectral density across six frequency bands (delta band (1–4 Hz), theta band (4–8 Hz), alpha1 band (8–10 Hz), alpha2 band (10–13 Hz), beta band (13–30 Hz), gamma band (30–45 Hz)). These data

correspond to a “function” of space (cortical voxel) and frequency. After that, the data from each subject in two groups is concatenated. Thus, a matrix including two dimensions was created, in which one dimension corresponds to different subjects, and the other dimension corresponds to space-frequency. This process was known as functional data analysis. When independent component analysis is used to this matrix, general networks are found. This method is defined as functional ICA. Each functional network is composed of six images, one for each frequency band.<sup>32</sup> Those components with *Z* scores larger than or equal to “3” were selected.

The present study was intended to achieve an optimal number of components. We tested a series number from “6” to “16” and found 12 components would obtain the maximum differences between two groups. Thus, the optimal number of components were defined as “12” in this study.

## Statistical Evaluations

Measurement data were represented by mean±standard error of the mean (SEM). Two sample *t*-tests were used for detecting the age differences and Chi-square test was applied for comparison of gender ratio. Two sample *t*-tests with FDR correction were used for comparison of the PLV connections, network properties, and ICA components between the two groups.  $P < 0.05$  was considered as statistically significant.

## Results

### Demographic results

Seventy-one HZ patients (aged 53.56±14.58 years) were included in this study. At the same time, 71 cases matched for age and sex served as healthy controls (aged 53.55±15.11 years). All 71 HZ patients received acyclovir 0.5 gram Q.8H. treatment. There was no significant difference in gender and age between the two groups (Table 1).

### Brain Network Connectivity

Compared with the healthy group, the connections between bilateral anterior temporal and right central regions in herpes zoster patients were decreased in beta band (Figure 1A). No significant survival different connections were found in other frequency bands after FDR corrections between the two groups (not shown).

**Table 1** Demographics of Subjects Included in the Study

	HZ Group (n=71)	HC Group (n=71)	$\chi^2/t$	P
Male:female <sup>#</sup>	29/42	32/39	0.259	0.61
Age (years, mean±SD) <sup>###</sup>	53.56±14.58	53.55±15.11	-0.01	0.99
Acyclovir	71/71	-	-	-

**Note:** <sup>#</sup>Chi-square test, <sup>###</sup>Two sample *t*-test.

**Abbreviations:** HZ, herpes zoster; HC, healthy control.

## Network Properties

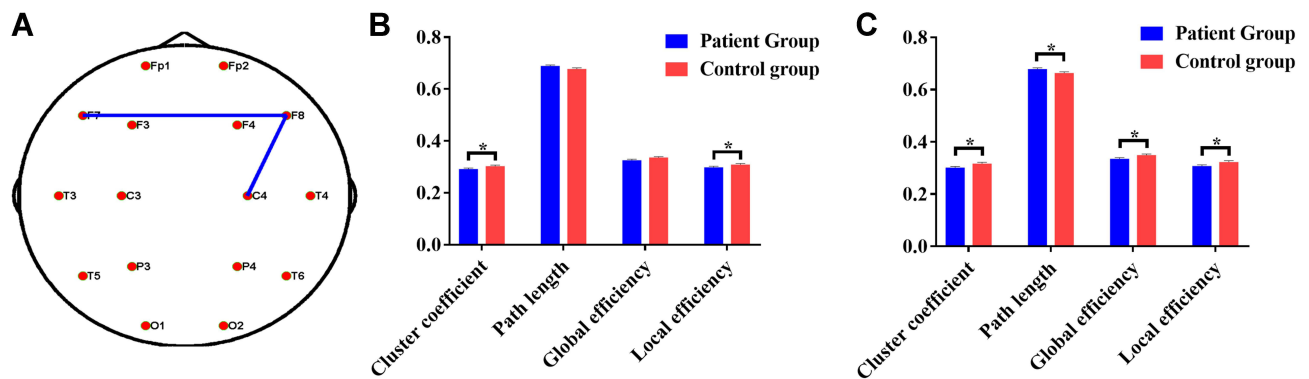
We computed four parameters of network properties, which were based on the constructed PLV weighted matrix, including clustering coefficient, shortest path length, global efficiency, and local efficiency. Compared with the HC group, the clustering coefficient and the local efficiency of HZ patients decreased in full band (1–45 Hz) and the clustering coefficient, the global efficiency, and the local efficiency of HZ patients group decreased in beta band (13–30 Hz). The shortest path length, however, increased in HZs in this band (Figure 1B and C). For other frequency bands, no significant differences were found between the two groups.

## ICA Networks

Three components, numbered 2, 3, and 4, with the maximum differences between HZ and HC groups were obtained in the ICA analysis. There were greatest differences in delta, beta, and gamma band between two groups in component 2 ( $P < 0.05$ ,  $t = 2.42$ ). Compared with HCs, superior frontal gyrus (SFG) (BA10) in HZs showed excess beta oscillation, and medial frontal gyrus (BA 11) showed reduced neuro oscillation in beta and gamma bands. For component 3, compared with the HC group, the HZ patients in alpha1 and alpha2 bands showed increased activity in SFG (BA 11) and decreased activity in occipital lobe (BA 18) ( $P < 0.05$ ,  $t = 2.13$ ). In component 4 patients with HZ, the inferior frontal gyrus (BA 47) showed excess activity in the left hemisphere and reduced activity in the right hemisphere in the delta band, compared with HC group. Furthermore, left middle frontal gyrus (MFG) presented excess theta activity ( $P < 0.05$ ,  $t = 2.49$ ) (Table 2). For other components, no significant differences were found between the two groups (Figure 2, Table 2).

## Discussion

In the present study, we applied graph theory analysis and ICA analysis to detect the potential abnormal changes of EEG in HZ patients. We confirmed that the brain networks changed in



**Figure 1** Comparisons of PLV network and graph theory properties between HZ and HC patients\*. PLV network connectivity in beta band (13–30 Hz) (**A**); Comparison of network properties in full band (1–45 Hz) (**B**) and beta band (13–30 Hz) (**C**). The blue line in **A** indicates that the connections between bilateral anterior temporal, right anterior temporal, and right central regions in HZ patients decreased when compared with HCs in beta band. No significantly different connection survival was found in other frequency bands after FDR corrections between the two groups. For **B** and **C**, the tail on each bar indicates the corresponding standard error of the mean (SEM). For other frequency bands, no significant differences were found between the two groups (not shown in the figure). \*All the results were computed using two sample t-test and corrected with FDR method at level  $P < 0.05$ .

patients with acute HZ, which was characterized by decreased clustering coefficient, global efficiency, local efficiency, and increased shortest path length in the beta band. Furthermore, some brain regions involved pain management, such as SFG and MFG. These findings deepen our understanding of HZ from brain electrophysiological aspects.

PLV analysis showed that the synchronization of bilateral anterior temporal and right central EEG signals in  $\beta$ -

band decreased in patients with acute HZ. Previous studies have confirmed that the temporal lobe cortex is involved in the modulation of pain in the brain,<sup>34–36</sup> and the  $\beta$ -oscillation in the central-parietal lobe may play a role in pain perception and processing.<sup>34–37</sup> The decrease of inter-neuronal connectivity in acute HZ plays an important role in pain perception and modulation.

Network property analysis based on graph theory can explain the neural activity in the brain from the perspective of network and information processing.<sup>20</sup> We noted that the acute HZ patients showed reduced global and local efficiency, clustering coefficient, and increased shortest path length in beta band. These findings from graph analysis indicated that acute HZs might show potential deficits in cognition considering that beta was involved in various cognitive functions.<sup>38,39</sup> The change of network attribute in acute HZ patients might be used as a biomarker for identification of cognitive function changes. However, the changes of cognitive function in patients with herpes virus infection of the peripheral nervous system were not well recognized in clinical practice. Further studies should be designed to explore the cognitive function evolutions in patients with HZ.

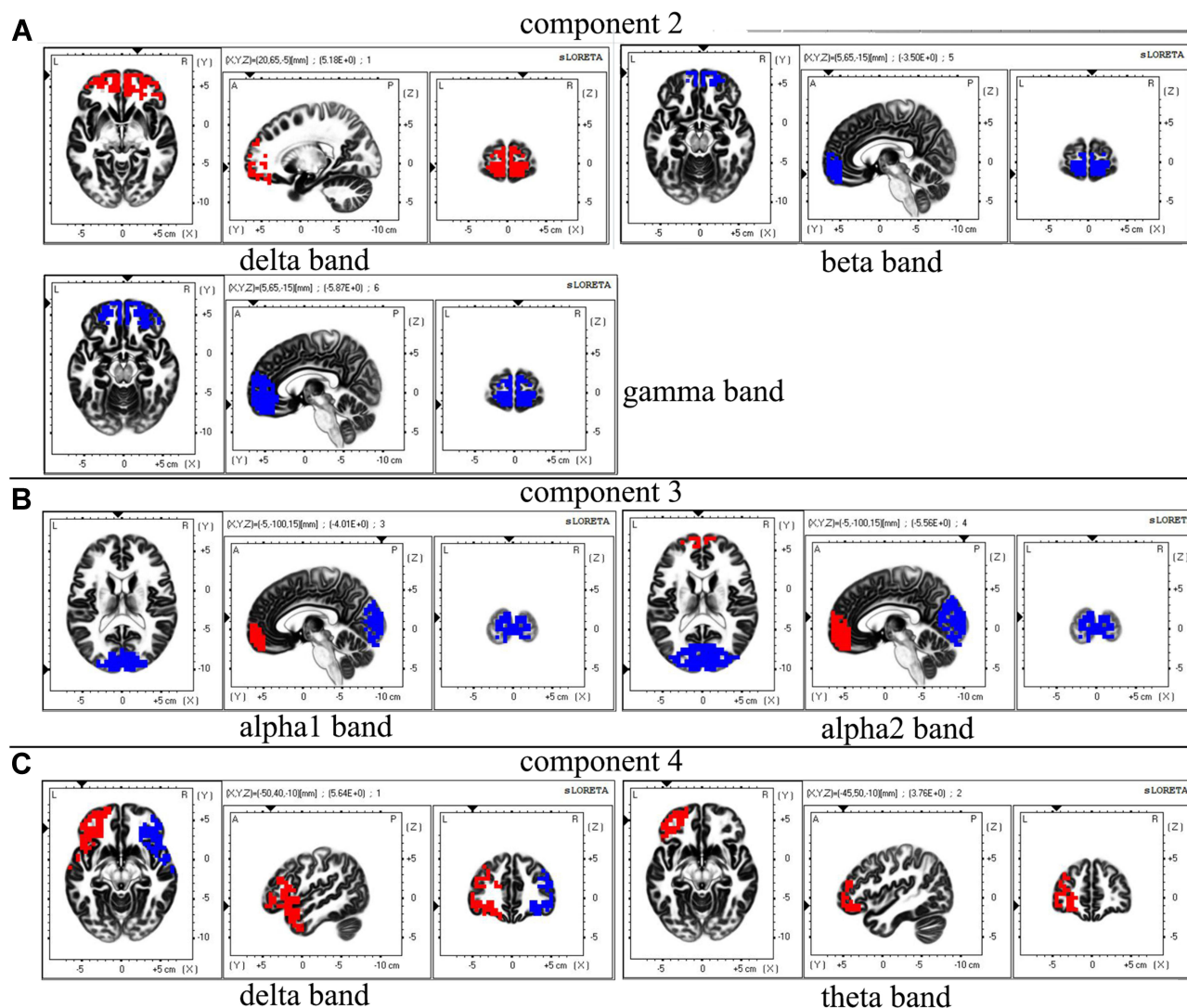
Transient thermal pain stimuli could elicit significant activity in MFG.<sup>40</sup> In present study, however, we noted that the acute HZ patients showed reduced beta and gamma activity in MFG. These differences might be caused by the different nature of pain or detection methods in two studies. Moreover, the reduced beta and gamma oscillation in MFG might indicate that the MFG in HZ patients showed inhibition responses to HZ pain. Another brain region, SFG, also been reported to anticipate some types of pain,<sup>41,42</sup> showed

**Table 2** The Location Assignments of Peak Voxels for fICA\*

Components and Frequency Band	Peak MNI Coordinates			Lobe	BA	Structure
	x	y	z			
<b>Components 2</b>						
Delta	20	65	-5	Frontal	10	SFG
Beta	5	65	-15	Frontal	11	MFG
Gamma	5	65	-15	Frontal	11	MFG
<b>Components 3</b>						
Alpha1	-15	65	-15	Frontal	11	SFG
	-5	-100	15	Occipital	18	Cuneus
Alpha2	-15	65	-15	Frontal	11	SFG
	-5	-100	15	Occipital	18	Cuneus
<b>Components 4</b>						
Delta	-50	40	-10	Frontal	47	Left IFG
	50	25	-15	Frontal	47	Right IFG
Theta	-45	50	-10	Frontal	11	MFG

**Notes:** \*These three components showed significant differences between HZ patients and the healthy group ( $P < 0.05$ ). Other components in the two groups showed no significant differences. The macro locations of these regions are shown in Figure 2. The location assignments were performed based on eLORETA methods using LORETA KEY software in MNI space.

**Abbreviations:** SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus.



**Figure 2** ICA components showing significant differences between herpes zoster patients and healthy controls. Component 2 (A), component 3 (B), and component 4 (C). The images are shown in MNI space. The red color indicates increased neuronal activity and the blue color indicates decreased neuronal activity. The small triangles along the coordinate axes indicated the maximum electric neuronal activity. The corresponding peak coordinates are displayed in the upper part of each band image. The location assignments of each component are shown in Table 2.

excessive delta and alpha activity. These findings might suggest that the balance between excitation and inhibition has altered in acute HZ patients.

The changes of brain electrical activity might function in network patterns in HZ. Previous fMRI studies have reported that recuperating from HZ accompanies default model network (DMN) connectivity alterations.<sup>1</sup> In the present study, it was noted that the frontal lobe anti-correlated with occipital lobe in alpha band of component 3. Parts of these regions were assignment within the range of DMN regions. This result suggested that the changes of networks in HZ patients involved DMN. In fact, the altered DMN has been found in multiple pain.<sup>43,44</sup> This change might be related with pain intensity.<sup>45</sup>

Study limitations include a relatively small sample. We did not address longitudinal effects of HZ on EEG, such as the associations between pain intensity and EEG networks. In addition, all patients were treated with acyclovir medication, which may have had an impact on brain networks. In future research, we will continuously collect cases and overcome these limitations for a more comprehensive understanding of HZ from brain electrical activity aspects.

## Conclusions

Our study confirmed that the altered brain networks exist in resting-state EEG data of patients with acute HZ. The changes of EEG brain networks in HZ patients are characterized by decreased global efficiency and local

efficiency in beta band. Moreover, the spontaneous oscillation of some brain regions involving pain management and the connectivity of default mode network changed in HZ patients. Our study provided better understanding the mechanisms of HZ from electrophysiological view, and led to converging evidence for treatment of HZ with neural regulation in future.

## Abbreviations

HZ, Herpes zoster; HC, healthy control; EEG, electroencephalogram; BA, Brodmann area; ICA, Independent component analysis; eLORETA, exact Low Resolution Electromagnetic Tomography; FDR, False Discovery Rate; SFG, Superior frontal gyrus; MFG, middle frontal gyrus; DMN, default model network.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no conflicts of interest.

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