Investigation of Altered Spontaneous Brain Activity Patterns In Herpes Zoster Keratitis Using The Percent Amplitude of Fluctuation Method: A Resting-State Functional Magnetic Resonance Imaging Study

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Research Article

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Abstract

Purpose: The purpose of this study was to use the percent amplitude of fluctuation (PerAF) to study the changes in brain activity and nerve function of herpes zoster keratitis (HZK) patients.

Methods: We recruited 20 HZK patients and 20 healthy controls (HCs). Each of these groups included ten males and ten females and were matched in weight and age. All participants underwent resting-state functional magnetic resonance imaging (rs-fMRI). The percent amplitude of fluctuation (PerAF) method was used for analysis and detected differences between the two groups in the neurological function of brain areas. We also applied the receiver operating characteristic (ROC) curve to analyze the two groups and did a correlation analysis between the PerAF value, anxiety, and depression score, and visual acuity.

Results: The PerAF signal at the right putamen and right precentral gyrus were significantly higher in patients than in HCs. However, the PerAF value of the left inferior temporal was lower in patients than in HCs. In addition, the HZK patients' anxiety and depression score (HADS) and visual acuity (VA) negatively correlated with the PerAF value at the left inferior temporal gyrus.

Conclusion: HZK patients had some changes in brain regions, and the changes were also related to their mood and visual acuity. These findings might contribute to other studies in the potential pathological mechanism, disease development, prognosis, and brain function in HZK patients.

Introduction

Herpes zoster keratitis (HZK) was caused by varicella-zoster virus infection[1]. When the human body's immune system weakens or when the human body lacks nutrition and rest, the virus, latent in the trigeminal ganglion, might be activated and cause disease. Patients with immunodeficiency, such as AIDS patients, were more susceptible to varicella-zoster virus infection and more likely to relapse than ordinary immune function people. varicella-zoster virus infection had a high incidence rate in China, approximately 7/1000[2]. It usually occured after the appearance of a skin rash. HZK sometimes would combine with other eye diseases, such as blepharitis, conjunctivitis, keratitis, scleritis, uveitis, and retinopathy [3]. varicella-zoster virus could cause immune-mediated damage in all corneal layers and might lead to corneal scarring, thinning, and neovascularization. Finally, HZK patients might have a visual impairment and become blind. Thus, HZK could cause a severe burden on patients' quality of life and the economy.

In this study, functional magnetic resonance imaging (fMRI) technology was performed to analyze the changes in human brain structure and function when patients suffered HZK. Resting-State Functional Magnetic Resonance Imaging (Rs-fMRI) differed from other types of fMRI due to its advantages of easier signal acquisition, easier functional brain area identification, and minimum requirements for patients. The amplitude of low-frequency fluctuation method was commonly used to study changes in brain activity[4]. Another novel and advanced method of analysis was regional homogeneity[5], which involves

analysis of the functional state of the brain as a whole within a single period. Its disadvantage was that it could not accurately reflect the activity and function of the neuron in a specific integrin. The method we applied in the present research was the percentage amplitude of fluctuation. It could be used both with and without dividing the whole-brain mean value. [6] PerAF has been applied successfully in scientific research on the brain[7]. Another technique used in this study was mean PerAF, which involves measurement of the PerAF of a single voxel as a fraction of the whole brain, and has better inter-scanner reliability.[8] Thus, the method of PerAF had excellent potential for analyzing the whole brain, and appeared to be superior to the amplitude of low-frequency fluctuation method and regional homogeneity methods.

Few studies have focused on using percentage amplitude of fluctuation to analyze changes in human brain structure in HZK. It was the first study to use PerAF in HZK and analyze the functional differences in HZK patients' brain areas. The study aimed to contribute to further research on the development and prognosis of HZK and implicate the brain function changes in HZK patients.

Results

Demographic characteristics

The average age of patients in the HZK group was 54.21 years, and their average weight was 65.32 kg. The patients were right-hand dominant. The average duration of the disease was about 25 days. The mean monocular best-corrected visual acuities were 0.24 (left) and 0.51 (right). In the HCs group, the average age was 54.21 years, and the average weight was 67.16, with right-hand dominance. The mean monocular best-corrected visual acuities were 1.01 (left) and 1.04 (right). No significant difference was found between the two groups in terms of gender, age, weight, or dominant hand ($P>0.05$), but there was a significant difference between the groups in visual acuity of the left eye ($p=0.005$) and the right eye ($p=0.022$). (Table 1)

PerAF Differences

For the HZK group, the PerAF signal values in the brain regions of the right putamen and the right precentral gyrus were significantly higher than those of the HCs group ($P<0.05$). In contrast, the PerAF signal value in the left inferior temporal gyrus was significantly reduced compared with the HCs group ($p<0.05$). (Fig. 1) (Table 2)

ROC Curve Analysis

The ROC curve analysis results showed that the signal value of the mean PerAF in the left inferior temporal gyrus might be used as a potential diagnostic marker for HZK. The area under the ROC curve was 0.956; the 95% confidence interval was 0.889–1.000; $p<0.0001$. (Fig. 2)

Correlation Analysis

Linear correlation analysis showed that the HADS scores were negatively correlated with the PerAF value in the left inferior temporal gyrus (r = 0.8687, P <0.0001). As explained above, in HZK patients, the PerAF value at the left inferior temporal gyrus was reduced, suggesting that these patients experienced greater anxiety and depression. (Fig. 3a) Visual acuity was negatively correlated with the PerAF value in the left inferior temporal gyrus (r=-0.6523, p=0.0018), indicating that the HZK patients had poorer visual acuity. (Fig. 3b)

Discussion

We used the method of percent amplitude of fluctuation, a theoretically more reliable and accurate method than the low-frequency fluctuation amplitude and regional homogeneity methods, to study the neural activity in different brain regions of HZK patients compared with healthy controls. Our results showed a relatively high PerAF value at the right putamen and the right precentral gyrus and a low value at the left inferior temporal gyrus in HZK patients. (Fig. 4)

The putamen was a large, complex brain structure closely related to sports feedback.[9] The right putamen had been the focus of many studies, one of which shows a positive correlation between age and the volume of the right putamen in patients with a history of suicide attempts. Their results indicated that adolescents with a history of suicide attempts might have atypical maturation in the subcortical area of the right putamen, which may lead to suicidal behavior[10]. Research by Maeda et al. showed that the right putamen is related to subjective well-being, with a negative correlation between subjective well-being and the average diffusion rate in the area around the right putamen[11]. Another study found a significant functional change in the right putamen of patients who had undergone vertical sleeve gastrectomy, and the change was also related to weight loss[12]. The right putamen had also featured in eye research. A study in 2015 found that the amplitude of low-frequency fluctuation value of the right putamen in patients with optic neuritis was significantly lower than that in healthy people[13]. Our study found that at the right putamen, the signal intensity of PerAF was higher in HZK patients than in healthy controls. The changes at the right putamen might reveal the pathological mechanism of HZK and its effects on the brain and might be useful to understand the emotional changes in HZK patients.

The right precentral gyrus was located in the frontal lobe between the central sulcus and the central anterior sulcus. It contained many large pyramidal cells and was the center for movement control. [14]In patients with bipolar disorder, glucose metabolism in the right precentral gyrus increases and might affect the disease and dysfunction, perhaps with links to emotional and cognitive impairment[15]. One recent study showed that the cortex in the right precentral gyrus in some progressive neurodegenerative disorders was becoming thinner such as amyotrophic lateral sclerosis[16]. The emotional eating disorder has also been related to the right precentral gyrus, symptoms being negatively correlated with the volume of the gyrus[17]. This region also featured in eye research, patients with iridocyclitis reportedly having a significantly lower the amplitude of low-frequency fluctuation value in this region than healthy controls[18].

Our study found that in HZK patients, the PerAF signal intensity was significantly higher in both the right precentral and the right putamen areas than healthy controls, further demonstrating altered brain activity.

The inferior temporal gyrus was related to visual processing, perception, facial perception, and digital recognition. One study has shown that inferior temporal gyrus damage impacts attention[19]. For corneal ulcer patients, Our previous studies also have demonstrated that the regional homogeneity levels were increased in the inferior temporal gyrus [20]. For patients with monocular blindness, compared with a healthy control group, the signal value of degree centrality of the left inferior temporal gyrus was increased [21]. In the present study, HZK patients had decreased PerAF signal intensity than healthy controls in the left inferior temporal gyrus. Our results might help diagnose HZK and understand its underlying pathological mechanism.

Overall, the PerAF value at the left inferior temporal gyrus was significantly decreased in HZK patients compared with healthy controls. This reduced value suggested that related brain areas' functional activities had become inactive, causing impaired visual perception and cognition. However, the PerAF values at the right putamen and right precentral brain areas significantly increased, indicating that some functional activities were enhanced in these two brain regions. We speculated that the change in the brain area of HZK patients might affect their visual processing, perception, sensory cognition, and emotional cognition. Our findings might help understand the disease, including treatment, cognition, affect, underlying pathological mechanism, and diagnosis. (Fig. 5)

Conclusion

The brain's regional signal strength changes might reflect related body functions. (Table 3) A limitation of this study was the small sample size. However, the use of the PerAF method enhanced the quality of the research. Our findings helped in the prognosis in HZK patients and revealed potential brain regional damage.

Methods

Subjects

20 HZK patients (10 males and 10 females) were recruited from the Department of Ophthalmology, the First Affiliated Hospital of Nanchang University. The inclusion criteria for the HZK group included:(1) Age from 30 to 65 years; (2) Unilateral facial rash or skin with a history of residual scars or brown deposits; (3) Keratitis; (4) Macrophages and nuclear eosinophilic inclusion bodies identified in the acute phase of corneal epithelial scraping; (5) No contraindications to MRI scanning. The exclusion criteria included: (1) Patients with other eye diseases such as cataracts or glaucoma; (2) Patients who have received eye surgery treatments such as myopia surgery, cataract surgery, or glaucoma surgery; (3) The presence of severe systemic disease. Healthy controls were matched in age and weight. The control group was also composed of 10 males and 10 females. The inclusion criteria for the healthy controls group included:(1)

binocular uncorrected visual acuity >0.8; (2) No eye diseases; (3) No systemic diseases; (4) No MRI scan contraindications.

Parameters for MRI

In this study, we used the Trio 3-Tesla scanner. [22]Firstly, we obtained the structural image and then the functional image. Parameter modulation and 3D deformed gradient echo pulse sequence were used. All participants were instructed to remain quiet with their eyes closed during the scan. (Table 4)

Functional magnetic resonance imaging Data Analysis

On obtaining the MRI image, the data were analyzed using MRIcro software. [23]Then the DPARSFA 4.0 and SPM8 were used to process the data, including filtering.[24] The image was smoothed in the digital image communication system using a 3 × 3 × 3 mm^3 Gaussian at full width half maximum of 6 mm. If the head movement were greater than 1.5 mm in any dimension, it would be corrected. [25]. In this study, the mean value of the whole time series was used to optimize the mean PerAF measurement. The specific calculation method was shown below: 'xi'='i' time point signal intensity; 'n'=total number of time points in the time series; μ=average time series.

$$PerAF=\frac{1}{N}\sum_{i=1}^{n}\left|\frac{x_i-\mu}{\mu}\right|\times 100\%$$

$$\mu=\frac{1}{n}\sum_{i=1}^{n}x_i$$

Correlation Analysis

We tested HZK patients' anxiety and depression scores using the Hospital Anxiety and Depression Scale (HADS). Using Pearson correlation analysis, we separately analyzed the correlations between PerAF signal intensity in the left inferior temporal gyrus, anxiety and depression scores, and visual acuity. The visual acuity was expressed as Logarithm of the Minimum Angle of Resolution (LogMAR).

Statistical Analysis

Statistical analysis was conducted using SPSS 25.0 https://www.ibm.com/products/spss-statistics. The independent-samples t-test was used for comparison between the two groups. The ROC curve was used to analyze the mean value of PerAF signal intensity in the left inferior temporal gyrus brain region of the HZK group and the HCs group.

Abbreviations

HZK, herpes zoster keratitis; HCs, healthy controls; PerAF, percent amplitude of fluctuation; R, right; L, left; AUC, area under the curve; ROC, receiver operating characteristic; HADS, Hospital Anxiety and Depression

Scale; BA, Brodmann's area; MRI, magnetic resonance imaging; N/A, not applicable; VA, visual acuity; MNI, Montreal Neurological Institute; rs-fMRI, resting-state functional magnetic resonance imaging; LogMAR, logarithm of minimum angle of resolution;

Declarations

-Consent to participate

All subjects were informed of the purpose, method, potential risks and signed an informed consent form.

-Consent for publication

Not applicable.

-Availability of data and material

Not applicable.

- Code availability

Not applicable.

Conflict of Interest Statement: This was not an industry-supported study. The authors report no conflicts of interest in this work.

Ethical Statement: All research methods were approved by the medical ethics committee of the First Affiliated Hospital of Nanchang University and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors' contributions

Xu-Lin Liao wrote the main manuscript text; Ting Su, Qiu-Yu Li, Yi-Cong Pan, Hui-Ye Shu, Li-Juan Zhang did data collection and analysis; Chu-Qi Li, Qian-Min Ge, Li-Ying Tang prepared figures and tables; Yi Shao provided guidance. All authors reviewed the manuscript.

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Tables

Table 1 Basic Information of Participants

Condition	HZKs	HCs	t	P-value*
Male/Female	10/10	10/10	N/A	>0.99
Age (years)	54.21±5.53	54.21±6.96	0.086	0.883
Weight (kg)	65.32±9.21	67.16±9.98	0.092	0.871
Handedness	20R	20R	N/A	>0.99
Duration of HZK (days)	25.74±6.43	N/A	N/A	N/A
Best-corrected VA-left eye(LogMAR)	0.24±0.06	1.01±0.16	-0.812	0.005
Best-corrected VA-right eye(LogMAR)	0.51±0.21	1.04±0.18	-0.984	0.022

Note: Independent t-tests comparing two groups.

Abbreviations: HCs, healthy controls; HZK, herpes zoster keratitis; N/A, not applicable; VA, visual acuity; LogMAR, logarithm of minimum angle of resolution.

Table 2 Brain Areas with Significantly Different PerAF Values Between the HZK and HCs

Note: The statistical threshold was set at a voxel level with P<0.005 for multiple comparisons using Gaussian random field theory (AlphaSim corrected at cluster >99 voxels, p<0.05).

Abbreviations: PerAF, percent amplitude of fluctuation; HZK, herpes zoster keratitis; HCs, healthy controls; BA, Brodmann area; MNI, Montreal Neurological Institute.

Table 3 Brain Region Alternation and Its Potential Impact

Brain areas	MNI coordinates			B.A.	Number of voxels	T value
	X	Y	Z			
Patients > HCs						
Right Putamen	30	6	-3	74	4528	7.894
Right Precentral	33	-12	51	2	106	5.0579
Patients < HCs						
Left Inferior Temporal	-48	-48	-24	89	436	-5.8829

Brain Regions	Experimental result	Brain function	Anticipated Results
Right Putamen	HZK > HCs	Affect sports behavior, strengthen learning, and emotion regulation	Movement disorders and concentration disorders [26]
Right Precentral gyrus	HZK > HCs	Primary motor cortex, motor skills learning	Paralysis on the opposite side of the body[27]
Left Inferior Temporal gyrus	HZK < HCs	High cognitive function, visual understanding, language understanding and emotion regulation	Visual comprehension disorders, visual processing and classification barriers, semantic defects[28]

Abbreviations: HZK, herpes zoster keratitis; HCs, healthy controls.

Table 4 MRI Parameters

Data Acquisition	Metamorphic Gradient	3D Metamorphic Gradient
Scan parameters	Echo Sequence	Echo Pulse Sequence
Repetition time/echo time	1900/2.26 ms	2000/30 ms
Thickness/gap	1.0/0.5 mm	4.0/1.2 mm
Acquisition matrix	256×256	64×64
Field of view	250×250 mm	220X220mm
Flip angle	90°	90°

Abbreviation: MRI, magnetic resonance imaging.

Figures

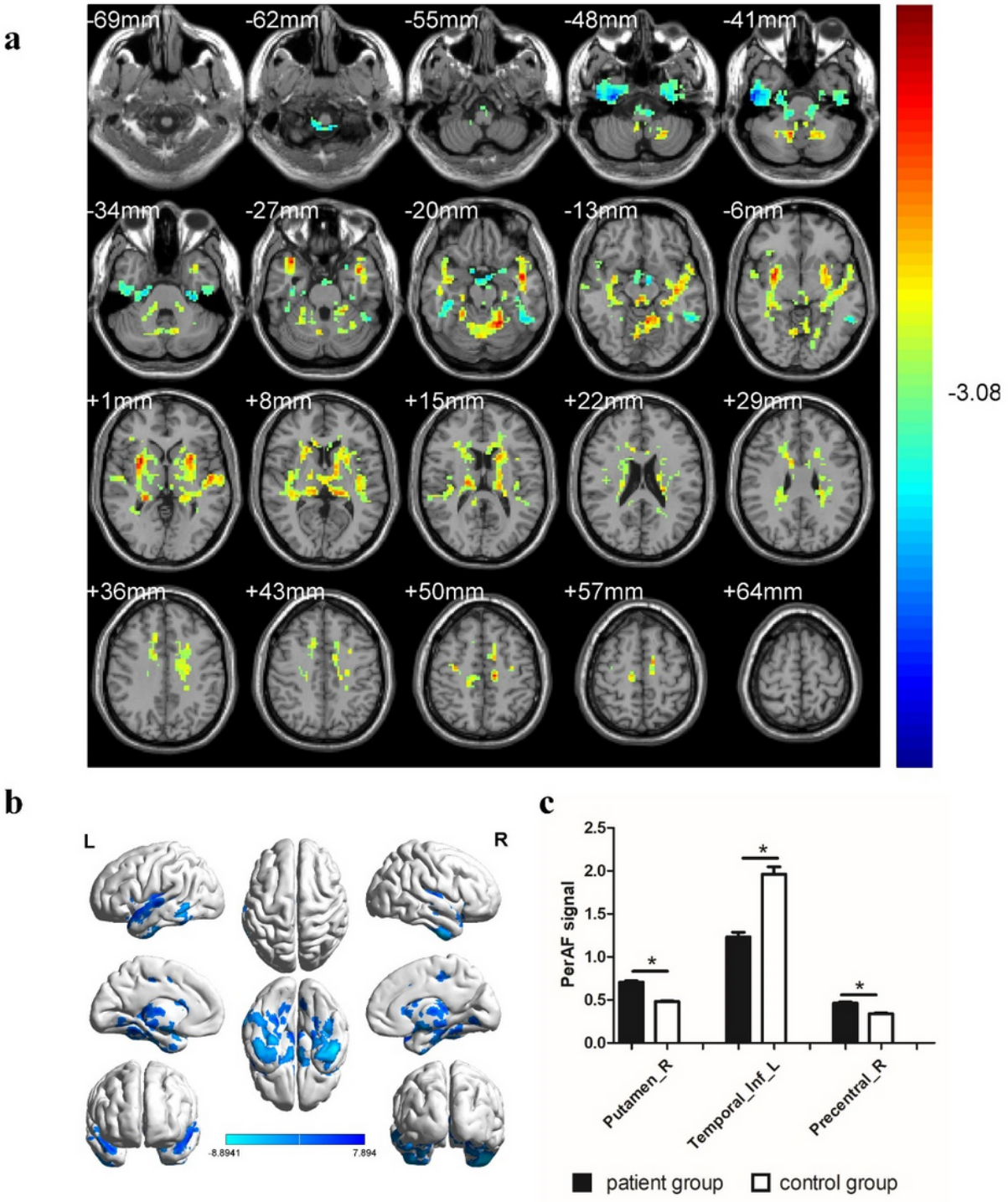

Figure 1

(a and b) Spontaneous brain activity in HZK and HCs. Red, blue, and yellow shadows represented the strength of the signals. The Right Putamen and Right Precentral gyrus exhibited higher signals, while the Left Inferior Temporal exhibited lower signals (P<0.005 for multiple comparisons using Gaussian random field theory, cluster >99 voxels, AlphaSim corrected). (c) The mean PerAF signal value between the HZK and HCs groups. Note: Compared with HCs, the asterisk means the statistical significance P < 0.05.

Abbreviations: HZK, herpes zoster keratitis; HCs, healthy controls; PerAF, percent amplitude of fluctuation; R, right; L, left.

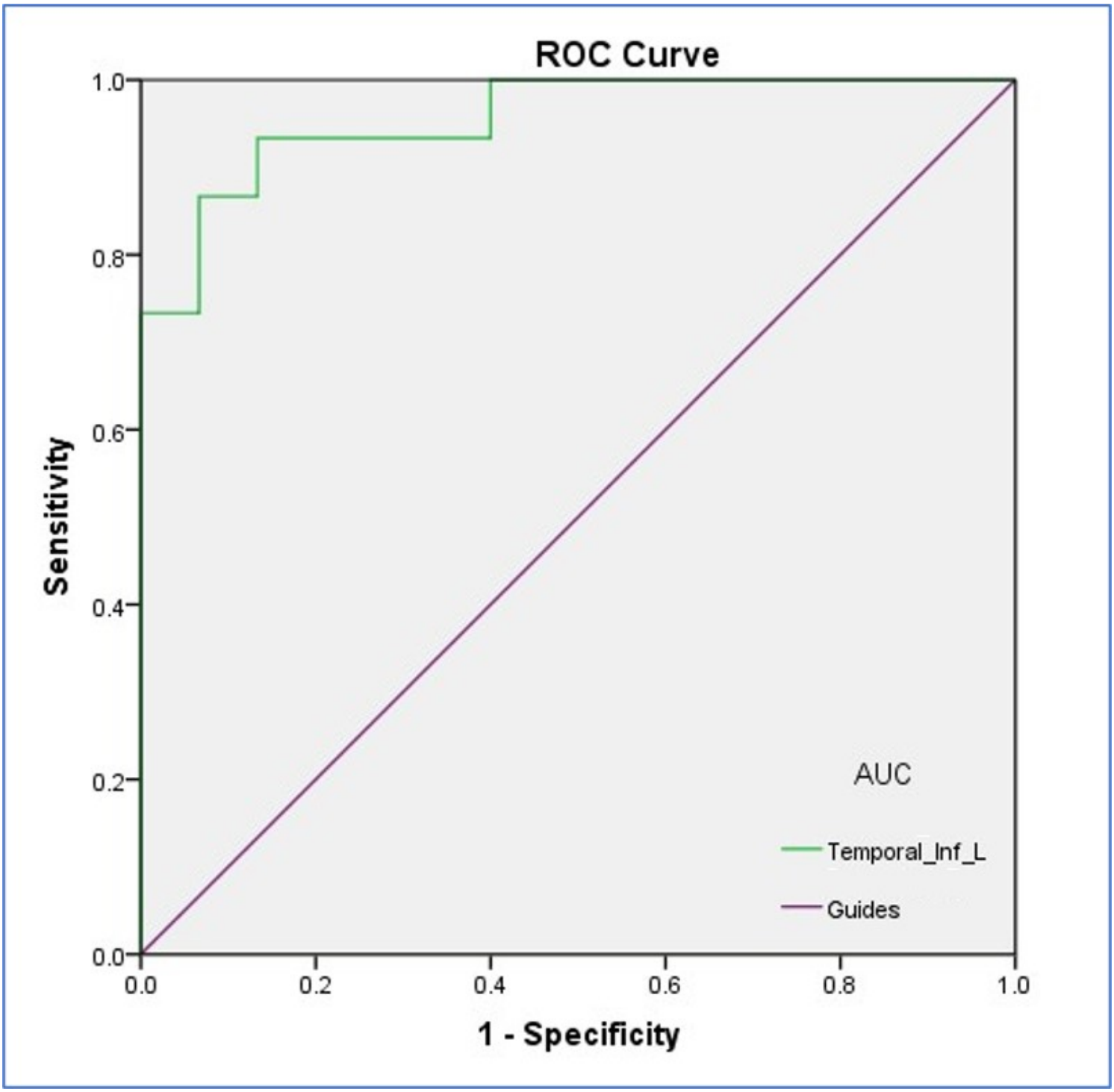

Figure 2

ROC curve analysis of the mean PerAF values for altered brain regions. Notes: The area under the ROC curve was 0.956 (p 0.0001; 95% CI: 0.889-1.000) for the Left Inferior Temporal gyrus. Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

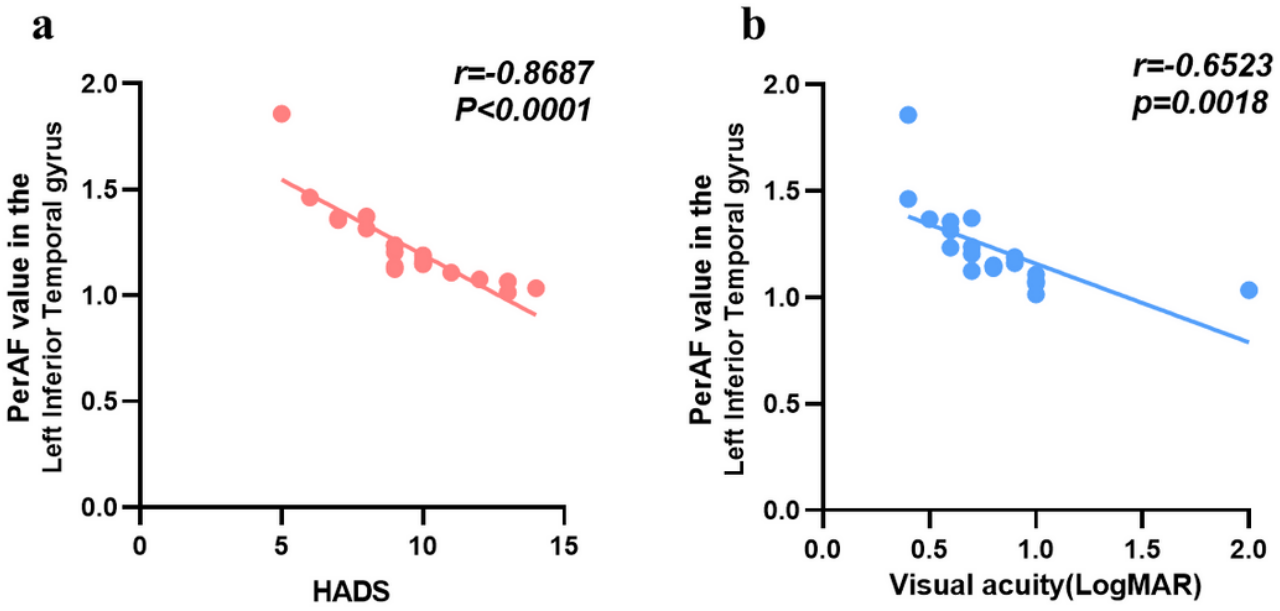

Figure 3

(a) Correlations between the HADS scores and the PerAF signal values of left inferior temporal gyrus in HZK patients. (b) Correlations between the visual acuity (LogMAR) and the PerAF signal values of left inferior temporal gyrus in HZK patients. Abbreviations: HADS, Hospital Anxiety and Depression Scale; PerAF, percent amplitude of fluctuation; HZK, herpes zoster keratitis.

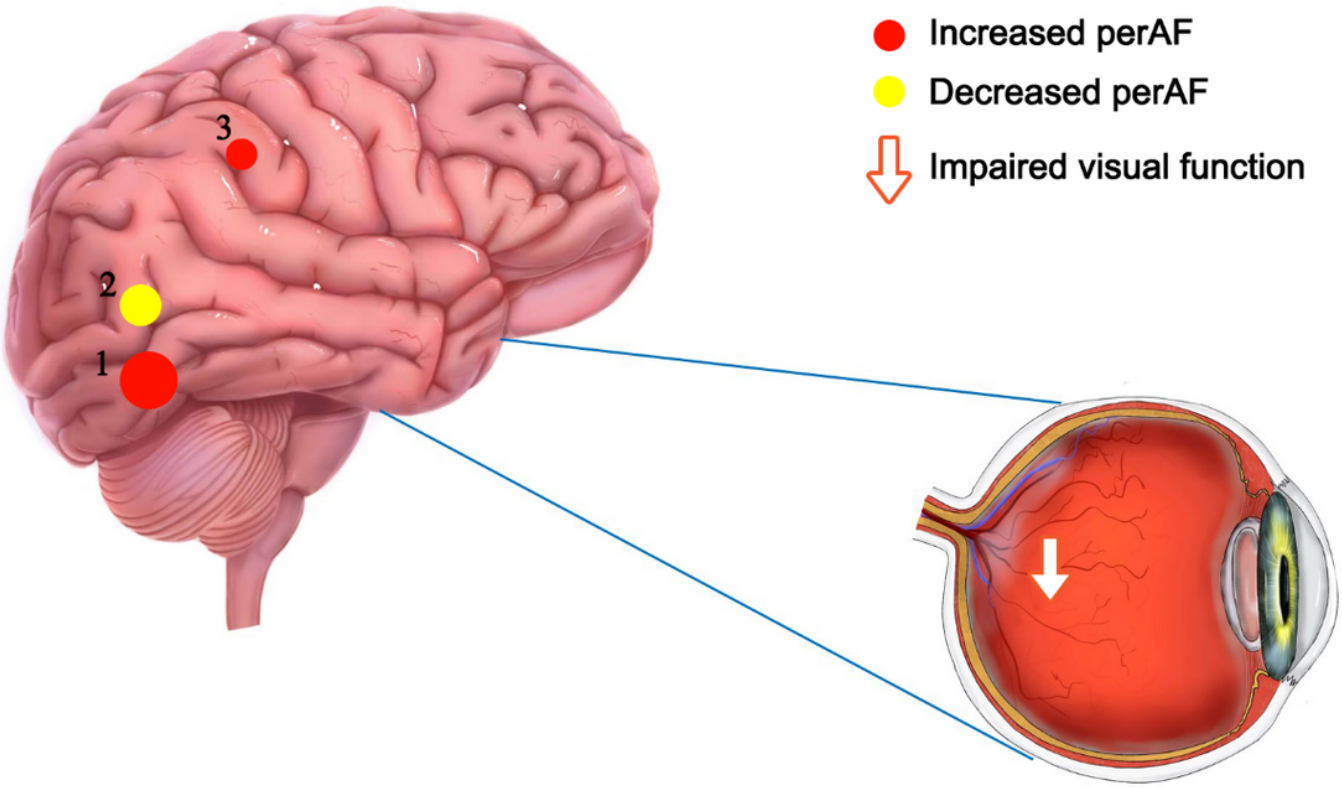

Figure 4

The mean PerAF values of altered brain regions. Notes: Compared with the HCs, the perAF values of the following regions were changed in various extents: 1- Right Putamen (BA 74, t = 7.894), 2- Left Inferior Temporal (BA 89, t = -5.8829), 3- Right Precentral (BA 2, t = 5.0579). Abbreviations: HCs, healthy controls; BA, Brodmann's area.

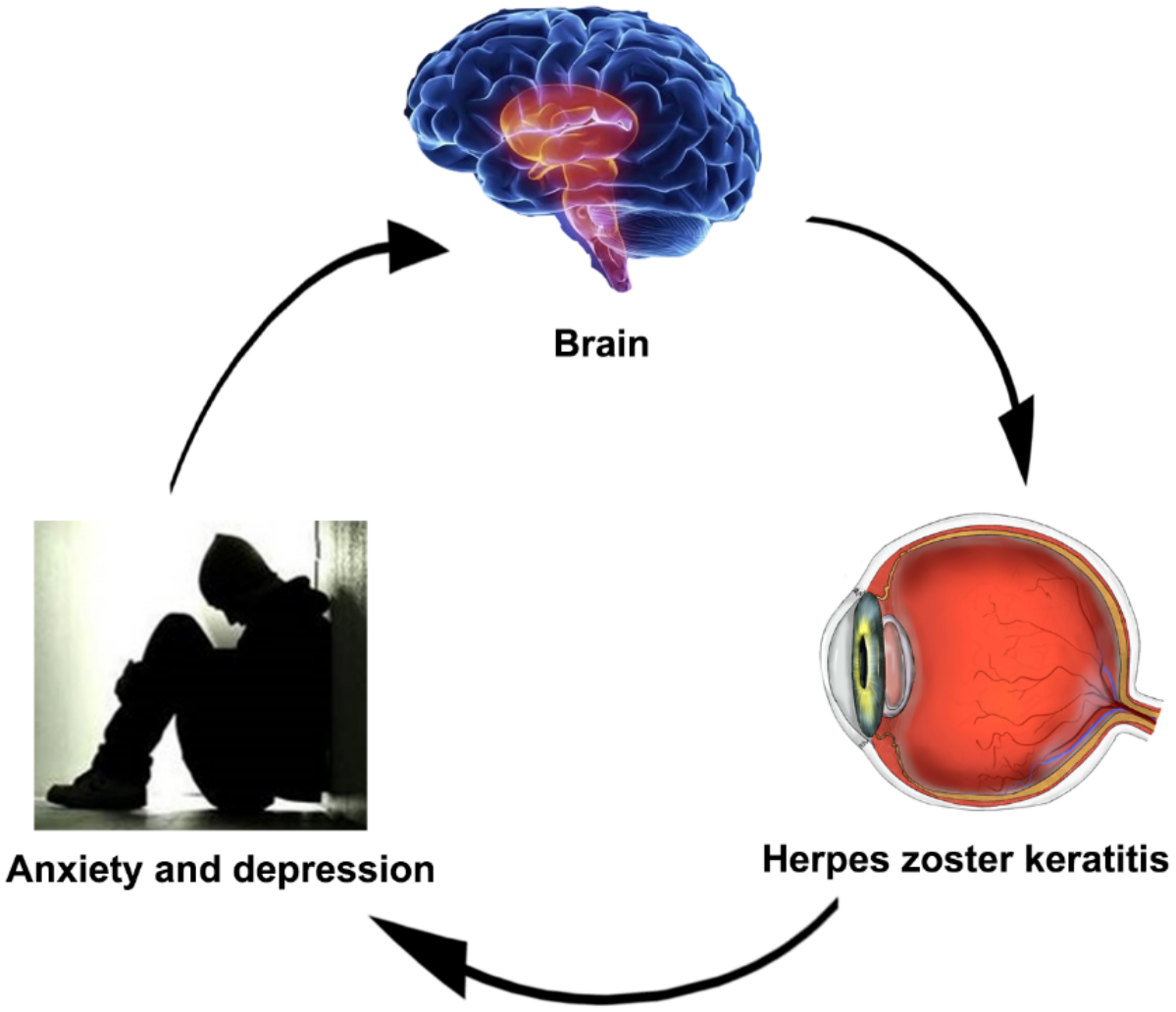

Figure 5

The relationship between herpes zoster keratitis, brain activity, and mood changes.