A resting-state functional MRI study in patients with vestibular migraine during interictal period

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Abstract
To evaluate the spontaneous neuronal activities and the changes of brain functional network in patients with vestibular migraine (VM). Three groups including 18 patients with VM, 21 patients with migraine without aura (MWOA) and 21 healthy controls (HCs) underwent the scanning of the resting-state fMRI. Covariance analysis and bonferroni multiple comparisons were used to obtain brain regions with significant differences in amplitude of low-frequency fluctuation (ALFF) values. Furthermore, the brain regions with the most significant differences of ALFF values were recognized as a region of interest (ROI) and functional connectivity (FC) analysis was performed in these regions. (1) ALFF: Compared with HCs, patients with VM showed significantly lower ALFF in the right putamen (P < 0.05), and significantly higher ALFF in the right lingual gyrus (P < 0.05). In addition, compared with MWOA patients, patients with VM showed significantly higher ALFF in the right lingual gyrus (P < 0.05). (2) Compared with HCs, VM patients showed significantly higher FC among the cerebellum, the left dorsolateral superior frontal gyrus and the right putamen (P < 0.05) but significantly lower FC among the left median cingulate, paracingulate gyri and the right putamen (P < 0.05). Compared with MWOA patients, VM patients showed significantly higher FC between the cerebellum and the right putamen (P < 0.05) but significantly lower FC among the left median cingulate, paracingulate gyri and the right putamen (P < 0.05). There are functional abnormalities in nociceptive, vestibular and visual cortex regions in patients with VM during the interictal period.

Keywords Vestibular migraine · Resting-state functional magnetic resonance imaging · Vestibular processing · Cerebellum

Introduction
Vestibular migraine (VM) is a vestibular disease that has a causal relationship with migraine [1], which was included in the appendix of the third edition of the International Classification of Headache Disorders (ICHD-3) in 2018 [2]. Neuroimaging techniques are helpful to explore the pathogenesis of VM [3–6]. Resting-state functional MRI (fMRI) which is a noninvasive imaging technique measures low-frequency fluctuations in BOLD signals [7]. FMRI mainly uses two methods: functional connectivity analysis (FC) and low-frequency amplitude fluctuation (ALFF) [8]. The former studies the temporal relationship of internal fluctuations observed in spatially different brain regions, and the latter measures the spontaneous neuronal activity in the region, which is mainly used in fMRI research. The characteristic changes of resting state can be used as indicators of disease progression, such as heroin addiction [9–11], Alzheimer’s disease [12] and schizophrenia [13].

In this exploratory study, we evaluated the patterns of regional brain spontaneous neuronal activity alterations and corresponding brain circuit changes in VM patients without any stimulation during the interictal period in comparison to migraine patients without aura and healthy controls (HCs). We also investigated the correlation between functional abnormalities and patients’ clinical characteristics.
Materials and methods

Subjects

Written informed consent was obtained from all participants according to the approval of the ethics committee of the local institutional review board. 39 right-handed patients (18 VM, of which 3 had a past history of migraine with vestibular aura and 21 migraine without aura (MWoA) patients) were recruited from the outpatient clinic of the neurology department of the affiliated hospital of Qingdao University from September 2018 to May 2019. All patients were enrolled according to the diagnostic criteria of ICHD-3. The enrolled patients with MWoA had no vestibular symptoms and patients with VM were enrolled according to the definite criteria for VM. The subjects ranged in age from 18 to 60. All patients were in attack-free state for three days before, on and after MRI scan [14]. In addition, they were not taking any medications to prevent migraine, vertigo or dizziness. The control group consisted of 21 healthy right-handed subjects with no significant differences in gender, age, or educational level from the enrolled patients. The HCs had no pathologic pain, including chronic pain, and no family history of migraine. None of the research subjects reported any other neurological, psychiatric, endocrine, cardio-cerebrovascular diseases and other major system diseases. All subjects did not have peripheral vestibular dysfunction according to videonystagmography (VNG) recordings with caloric testing. In addition, participants who abused substances (such as alcohol, nicotine) that affected test results were excluded.

No brain structural abnormalities, such as T2 hyperintensities in deep white matter, were found in the enrolled subjects through conventional MRI scanning.

MRI acquisition

All subjects whose heads were fixed with sponge pads were supine on a 3.0 T GE scanner, and a conventional eight-channel quadrature head coil was used for MRI scanning to obtain images. To avoid the adverse effect of machine noise on the results, subjects needed to insert earplugs in their ears. Besides, subjects were required to stay awake and close their eyes without systematic thinking.

Before the functional running, the brain structural images of each subject were generated by a three-dimensional T1-weighted magnetization prepared rapid gradient echo (3D T1-MPRAGE) sequence with the following parameters: repetition time (TR) = 5.5 ms, echo time (TE) = 1.8 ms, flip angle = 9°, slice thickness = 1.0 mm, 256 slices, matrix size = 256×256, voxel size = 0.9 × 0.9 mm × 0.9 mm, field of view (FOV) = 256 × 256 mm. Two experienced radiologists examined all participants’ brain structure information to rule out the possibility of subclinical lesions.

Then, functional blood-oxygen level-dependent (BOLD) signals were obtained by using the echo-planar imaging sequence with the following parameters: TR = 2000 ms, TE = 35 ms, flip angle = 90°, slice thickness = 3.5 mm, FOV = 256 mm × 256 mm, matrix size = 64×64, 64slices.

Data preprocessing

Statistical Parametric Mapping 12 (SPM12) software was used for data preprocessing and statistical analyses. The first 10 volumes of each subject’s scanned image were discarded for subjects’ adaptation to the scanning environment and scanner calibration [15]. Then, the remaining volumes were corrected for acquisition delay between slices and aligned to the first image of each session for motion correction [16]. The functional image data of subjects was imported into DARTEL standard spatial template for spatial normalization with a resampling voxel size of 3×3×3 mm. The subjects’ heads should not move more than 1 mm or rotate 1°in any direction. Next, the 6-mm full-width at half-maximum Gaussian kernel was used to spatially smooth the images to improve the signal to noise ratio of the functional images and reduce the influence of noise.

Finally, imaging data were temporally filtered (band pass, 0.01–0.08 Hz) to obtain the low-frequency resting-state functional magnetic resonance signal.

ALFF analysis

Amplitude of low-frequency fluctuation (ALFF) analysis was performed by using RESTplus V1.22 software. Fast Fourier transform (FFT) was used to transform the preprocessed filtered time series into the frequency domain to obtain the power spectrum. The average square root of each voxel in the range of 0.01–0.08 Hz was taken as the ALFF value. For standardization, the ALFF of each voxel was divided by the global average of the ALFF value [16].

ROI-based FC analysis

Before performing functional connectivity (FC) analysis, multiple sources of false variance were removed from the preprocessed data by linear regression, including head motion parameters, global average BOLD signals and average BOLD signals of ventricular and white matter regions. Region of interest (ROI) method was adopted for FC analysis. The brain region with the largest differenita in ALFF comparison was selected as ROI to calculate the whole
brain and its FC, and fisher-z transformation was conducted to obtain the FC map of each subject. Finally, covariance analysis was used to quantitatively compare the FC of brain regions in the three groups.

Statistics

The data of demographics and clinical characteristics were expressed by \( \bar{x} \pm s \) and percentage. Fisher exact test was used to analyze the difference among the categorical data, and meanwhile, student’s t-test and analysis of variance were used to analyze the difference of the continuous variables. These data were analyzed using SPSS 22.0.

The comparisons of ALFF and FC maps which had smoothed among three groups were assessed using analysis of covariance in SPM12, including age and gender as covariates. At the same time, ALFF survived with FDR correction. Then, the Bonferroni method was used for multiple comparisons, and the \( p \) value threshold was less than 0.05 (double tails). Finally, the results were displayed with xjView and MRlcron software.

The ALFF values of the VM group corresponding to the ROI were extracted and correlated with the clinical characteristics of patients with VM. \( p < 0.05 \) was considered statistically significant.

Results

Demographics and clinical characteristics are summarized in Table 1. There was no difference in age \((p = 0.915)\), gender \((p = 0.922)\), and education level \((p = 0.954)\) among the three groups.

The results of ALFF analysis among the three groups by analysis of covariance are summarized in Table 2 and shown in Fig. 1. The ALFF values of the right putamen and right lingual gyrus were not completely equal \((p < 0.05, \) FDR corrected, cluster extent \( = 10 \) voxels). The results of the Bonferroni multiple comparisons are shown in Table 3. Compared with healthy control subjects, the VM patients and the MWoA patients showed significantly lower ALFF in the right putamen \((P < 0.05)\), and significantly higher ALFF in the right lingual gyrus \((P < 0.05)\). Compared with MWoA patients, VM patients showed significantly higher ALFF in the right lingual gyrus \((P < 0.05)\). In addition, we found that ALFF values in the right putamen were negatively correlated with the duration of migraine and the frequency of migraine attacks \((P < 0.05)\). The results are shown in Table 4.

FC of brain regions in the patients with VM and subjects in two other groups were calculated using the right putamen as the ROI. The results of FC analysis among the three groups by analysis of covariance are summarized in Table 5 and shown in Fig. 2. The FC values of the right cerebellum, the left dorsolateral superior frontal gyrus and the left median cingulate and paracingulate gyri were not completely equal \((p < 0.001, \) cluster extent \( = 5 \) voxels). The results of the Bonferroni multiple comparisons are shown.

| Table 1 Demographics and patient characteristics |
|-----------------------------------------------|
| VM   | MWoA | HCs  |
|------|------|------|
| Number of subjects | 18   | 21   | 21   |
| Age (years)        | 36.17 ± 8.65 | 36.81 ± 11.61 | 36.15 ± 12.11 |
| Gender (male/female) | 3/15 | 4/17 | 5/16 |
| education level (years) | 12.11 ± 2.47 | 11.86 ± 2.74 | 12.00 ± 2.51 |
| VM disease duration (years) | 6.56 ± 3.36 | NA   | NA   |
| Migraine disease duration (years) | 12.67 ± 7.62 | 11.57 ± 7.32 | NA   |
| Attack frequency per month | 2.72 ± 2.23 | 1.86 ± 1.20 | NA   |

NA not applicable, VM vestibular migraine, MWoA migraine without aura, HCs healthy controls

| Table 2 Regions showing significant ALFF differences among VM patients, MWoA patients, and HCs \((p < 0.05, \) FDR corrected, cluster extent \( = 10 \) voxels) |
|-----------------------------------------------|
| Brain regions (AAL) | Cluster extent (number of voxels) | Peak MNI coordinates (X Y Z) | F Peak intensity |
|---------------------|----------------------------------|-----------------------------|-----------------|
| Putamen_R           | 38                               | 12 − 9                      | 15.9024         |
| Lingual_R           | 11                               | − 54                        | 14.7124         |

AAL Anatomical Automatic Labeling, L left, R right, MNI Montreal Neurological Institute, Putamen_R right putamen, Lingual_R right lingual gyrus
Compared with healthy volunteers, VM patients showed significantly higher FC among the right cerebellum, the left dorsolateral superior frontal gyrus and the right putamen \((P < 0.05)\) but significantly lower FC among the left median cingulate, the paracingulate gyri, and the right putamen \((P < 0.05)\). Compared with MWoA patients, VM patients showed significantly higher FC in the right cerebellum and in the right putamen \((P < 0.05)\) but significantly lower FC among the left median cingulate, the paracingulate gyri, and the right putamen \((P < 0.05)\). Compared with HCs, MWoA patients only showed significantly higher FC in the left dorsolateral superior frontal gyrus and in the right putamen \((P < 0.05)\).

### Table 3

| Brain regions (AAL) | Group 1 | Group 2 | Mean Difference (Group 1–Group 2) | P value |
|---------------------|---------|---------|----------------------------------|---------|
| Putamen_R VM        | HCs     | -0.457417 | 0.000                           |         |
| Putamen_R MWoA      | HCs     | -0.353476 | 0.000                           |         |
| Lingual_R VM        | HCs     | 0.994779   | 0.000                           |         |
| Lingual_R MWoA      | HCs     | 0.496900   | 0.030                           |         |
| Lingual_R MWoA      | HCs     | 0.497879   | 0.023                           |         |

### Table 4

| Characteristics                               | Mean ± SD | Correlation coefficient \(\rho\) | P value |
|-----------------------------------------------|-----------|---------------------------------|---------|
| The frequency of migraine attacks             | 3.62 ± 3.48 | -0.529                          | 0.035   |
| The duration of migraine                      | 13.25 ± 8.31 | -0.517                          | 0.040   |

### Table 5

| Brain regions (AAL) | Cluster extent (number of voxels) | Peak MNI coordinates (X Y Z) | F Peak intensity |
|---------------------|-----------------------------------|-----------------------------|-----------------|
| Cerebelum_6_R       | 19                                | 9 – 60 – 24                 | 11.4059         |
| Frontal_Sup_L       | 7                                 | – 15 63 24                  | 10.2476         |
| Cingulum_Mid_L      | 5                                 | – 12 42 48                  | 9.4814          |

Cerebelum_6_R right cerebellum, Frontal_Sup_L left dorsolateral superior frontal gyrus, Cingulum_Mid_L left median cingulate and paracingulate gyri

### Discussion

#### ALFF

The ALFF values of the lingual gyrus are responsible for processing visual information [17, 18]. This study showed that the ALFF values in patients with VM were significantly
higher than that in patients with MWoA and HCs, which indicated that the spontaneous neuronal activity of lingual gyrus in patients with VM under resting state was enhanced and the excitability was increased. It may reflect the changes in the integration function of visual information in the brain of patients with VM, which is most likely an adaptive change in response to repeated vertigo. In this study, the function of basal ganglia was abnormal in most patients with VM and MWoA. This may be due to the damage of the basal ganglia caused by the patient’s recurrent headaches, which leads to a decrease of pain regulation ability.

**FC**

In this study, the functional connection between the right cerebellum and right putamen significantly enhanced in VM patients. Combined with the previous study finding that bilateral cerebellar activation during VM attacks [19], it is indicated that cerebellar dysfunction may be involved in the pathogenesis of VM. And previous studies have found that the high sensitivity of VM patients to head movement and positional nystagmus is associated with cerebellar lesions [20–23]. Hyperactivity of cerebellum in VM patients during the onset and interictal stages was considered to be an adaptive mechanism to inhibit hyperactivity of the vestibular system [24]. While VM is closely linked to motion sickness [25], and even during the interictal stages, patients with VM are less tolerant of riding a carousel, a car, or even watching a 3D movie. As part of the pain matrix, the cerebellum is involved in pain processing and regulation [26]. The cerebellum also shows emotional processing functions [27]. Unfavorable emotions are important factors that can trigger

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**Table 6** Regions showing significant FC differences between patients and controls as well as between different groups of migraineurs using the Bonferroni multiple comparisons (p < 0.05)

| Brain regions (AAL)          | Group 1 | Group 2 | Mean Difference (Group 1–Group 2) | P value |
|-----------------------------|---------|---------|----------------------------------|---------|
| Cerebelum_6_R VM            | HCs     | 0.291095| 0.000                            |         |
| Cerebelum_6_R VM            | MWoA    | 0.240688| 0.001                            |         |
| Frontal_Sup_L MWoA HCs      | 0.237301| 0.000   |                                  |         |
| Frontal_Sup_L VM HCs        | 0.194002| 0.004   |                                  |         |
| Cingulum_Mid_L VM HCs       | −0.189849| 0.004  |                                  |         |
| Cingulum_Mid_L VM MWoA      | −0.249289| 0.000  |                                  |         |
VM. When the emotional function of cerebellum is abnormal, VM attacks may be induced. In this study, the change of cerebellar function in patients with VM during the interictal period suggested that VM is not a simple paroxysmal disease.

Dorsolateral superior frontal gyrus is an important part of the emotional pathway of pain perception. This study found that the FC was enhanced between the dorsolateral superior frontal gyrus and right putamen in patients with VM. It is suggested that the endogenous analgesic mechanism of VM patients is adjusted due to long-term pain stimulation, which can change the emotional response of pain, or reduce the pain perception and cognition, so as to reduce the input of pain signals.

The median cingulate and paracingulate gyri are not only involved in the attention and emotional response to pain, but also in the subjective perception of pain and its cognition and memory [28]. In a comparative study [29] of HCs and patients with chronic pain, a high concentration of opioid receptor binding sites was observed in the cingulate gyrus, which suggested that the median cingulate and paracingulate gyri played an important role in the formation and regulation of pain sensation. In this study, FC of the median cingulate and paracingulate gyri and ROI was weakened in patients with VM, which might be the result of nervous system adaptation. The attenuation of the nervous system itself can not only reduce the pain response and emotional response but also reduce the subjective perception of pain.

One limitation of the current work is that the number of participants in each group is small. Therefore, future work needs to analyze the data set with larger sample sizes.

To conclude, the functional in nociceptive, vestibular and visual cortex regions in patients with VM during the interictal period are abnormal, which are likely due to adaptive changes in the brain regions of patients with VM. The study not only indicates VM is not a simple paroxysmal disease but also supports the hypothesis that VM is a disease of the central nervous system, so as to a better understanding of the pathogenesis of VM.

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Authors’ contribution Study concept and design: HPW and SQW. Data acquisition: HPW, SQW, XJL, WJY, MHW and RLZ. Data analysis and interpretation: HPW, SQW, XJL, WJY, MHW and RLZ. Drafting of the manuscript: SQW. Revision of the manuscript: SQW, WJY and HPW. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was approved by the Institutional Ethical Committee of the Affiliated Hospital of Qingdao University. All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China.

Informed consent We have obtained written informed consent from all study participants.

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