The brain function state in different phase and relation with clinical symptoms in migraine: an fMRI study based on ReHo

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Research Article

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Abstract

Objective

Through regional homogeneity (ReHo) to analyze the activation of brain regions at different phase in migraineurs and to explore its relationship with clinical symptoms.

Methods

we analyzed resting-state Resting brain functional magnetic resonance in 19 patients with episodes and 22 patients with interictal phase, 22 healthy controls. Using regional homogeneity (ReHo) method to do post-processing. All subjects were evaluated by Montreal cognitive assessment scale (MoCA), simple mental state examination (MMSE), Hamilton anxiety scale (HAMA), Hamilton depression scale (HAMD). Subjects' clinical indicators (such as frequency of attack, course of disease, duration of each headache, and severity of headache) were correlated with ReHo values of brain regions. This study was approved by the ethics committee of Yangtze river shipping general hospital.

Results

the episodes group compared with the interictal group, Montreal Neurological Institute (MNI) (-9,42,15) is that the ReHo value of bilateral anterior cingulate cortex was lower active than the interictal group; and Montreal Neurological Institute (MN) (-3,24,66), the ReHo value of bilateral paracentral lobule was stronger active than the interictal group ($P < 0.01$). Compared with the control group, patients in interictal phase had lower activation in bilateral cuneus and bilateral lingual gyrus, MNI of the two are (9, -84, 36) and (0, -72, 6). No significant different brain area was found between the episodes group and the control group. In episodes group, significant correlation was found between attack frequency and ReHo value of the bilateral paracentral lobule ($r = 0.492$; $p = 0.038$).

Conclusion

We need to observe the course of migraine as a whole. Even in the interictal, it may affect the development of the disease through the cuneus and lingual gyrus. ACC regulates different states of migraine by inducing anti-injury sensation regulation function. Paracentric lobule is not only associated with migraine attacks, but also with the frequency. it may have an effect with the outcome of subsequent migraines, whether become chronic, and the remodeling of the brain.

1. Introduction

Migraine is a severe and disabling brain condition, listed as the sixth most disabling disorder globally by the World Health Organization, and the most disabling of all neurological disorders (Todd J Schwedt et al.

2015). It is an episodic, recurrent, and genetically related brain excitatory disorder characterized by attacks of unilateral, throbbing head pain, with sensitivity to movement, visual, auditory, and other afferents inputs (Santangelo et al. 2016). Other symptoms such as tiredness, irritability, reduced concentration. The mechanism of migraine is still unclear, and the diagnosis mainly based on the analysis of clinical characteristics, without objective diagnostic methods (Russo et al. 2018).

ReHo is a method for processing fMRI images, which was first proposed by Chinese researcher Zang et al (Zang et al. 2004) and has been gradually applied to the field of medicine. According to ReHo theory, (1) when the functional brain area is under certain conditions, there is time consistency between the voxel and peripheral voxel in this brain area.(2) if ReHo is increased, the local connections of neurons in the local brain region are enhanced;(3) if ReHo is decreased, it indicates that the local connections of local neurons are weakened. Therefore, it can be concluded that there is a significant correlation between abnormal ReHo and the changes of neuron activity in the local brain functional areas. In other words, when abnormal ReHo occurs, the synchronous activity of local neurons changes.

Therefore, the use of brain functional imaging as a noninvasive examination method is helpful to observe the pathophysiological changes of migraine during episodes and interictal phase, the relationship between region of interest with clinical symptoms, providing objective basis for understanding the course of migraine and prevention.

2. Materials And Methods

2.1 Study population

41 migraine patients from the department of neurology Wuhan Yangtze river shipping general hospital, collected between April 2018-December 2018, include 19 patients with episodes phase (male/female ratio is 5/19, the average age is 35.53 ± 10.67), 22 patients with interictal phase (male/female ratio is 5/22, the average age is 33.32 ± 10.27), all are right-handed, all migraine sufferers are conformed to the migraine criteria from international headache society international classification of headache disorders version 3 (ICHD-3). All the patients diagnosed by neurology specialist, excluding other neurological diseases. Montreal cognitive assessment scale MoCA, simple mental state examination (MMSE), Hamilton anxiety scale (HAMA), Hamilton depression scale (HAMD), headache impact questionnaire (HIT-6), visual analogue scale (VAS) were used to evaluate the basic situation of patients. The control group was a healthy population with age and gender matching, include 22 cases (male/female ratio is 6/22, the average age is 34.59 ± 7.99).

2.2 Exclusion criteria

Other types of headaches; Combined with other organic brain diseases, cardiovascular and cerebrovascular diseases and other internal diseases; A history of drug abuse or alcohol addiction; Patients with contraindications to MRI. Remove data that incomplete magnetic resonance sequence, inconsistent parameters or head movement of $> 3\text{mm}$.

Imaging protocol MRI was conducted by using Siemens Magnetom Verio 3T superconducting MRI system, which was provided by the Radiology Department of Yangtze river shipping general hospital, Wuhan, China. The parameters of the T1- weighted 3D magnetization applied as follows: repetition time (TR): 2300 ms, time inversion (TI) : 1200 ms, echo time (TE) : 3.28ms, flip angle (FA): 9°, matrix size : 256×256, slice thickness: 1 mm, number of slices: 256, inter-slice gap: 0.5 mm. The blood oxygenation level-dependent (BOLD) rs-fMRI was conducted in axial plane by utilizing the EPI (echo-planar imaging) sequence of a few associated parameters, including TE: 30 ms, TR : 2300 ms, field of view: 256×256 mm², FA = 90°, NEX: 1, matrix size: 64×64, inter-slice gap: 0.5 mm, slice thickness: 3.7 mm, number of slices: 31, acquisition time: 480s (Wang et al. 2019). All of the patients were instructed to stay awake, relax and close their eyes. Meanwhile, during the resting fMRI scan, the participants were instructed to remain as motionless as possible. The noise was also reduced by using rubber earplugs, and the participant's head was also fixed to minimize the potential motion artifacts by employing the foam cushions.

2.3 Data processing of rs-fMRI image

MRICro software (www.mricro.com) was used to check data integrity and exclude incomplete data. Preprocessing data analyzed by SPM8 package (website: <http://www.fil.ion.ucl.ac.uk/spm>). Slice-timing realignment and adjustment for the correction of the head-motion were also conducted. One patient was excluded because of the excessive head movement. The criterion for excessive head movement was that the head motion exceeded 3° rotation or 1.0 mm translocation in any direction throughout the course of the scan (Gordon 1972). The images were normalized spatially to the stereotaxic coordinates for standard MNI (Montreal Neurological Institute) template and re-sampled into a 3×3×3 mm³ voxel size. Then, they were smoothed by convoluting with an isotropic Gaussian kernel of 6 mm to reduce the spatial noise. In order to remove the higher frequency noise and the lower frequency drift, we band-filtered the residual-time series within the frequency range from 0.01 Hz to 0.08 Hz (Song et al. 2011). Using the REST software (www.restfmri.net) (Song et al. 2011) analyzed and calculated the ReHo values. In the window of ReHo analysis of the REST software, selected the frequency band between 0.01 Hz to 0.08 Hz. Two-sample t tests were conducted to illustrate where in brain the standardized ReHo values were significantly different from other one, GRF correction, $P < 0.01$. In the statistical parameter diagram, yellow color represents positive activation and blue color represents negative activation.

Table 1
Basic data of three groups

Index	Epi_group	Int_group	Con_group	P values
Gender(male/female)	5/19	5/22	6/22	0.936
Age(year)	35.53 ± 10.67	33.32 ± 10.27	34.59 ± 7.99	0.268
Education(year)	12.42 ± 2.63	12.41 ± 3.65	16.36 ± 2.63	0.991*1<0.01*2<0.01*3
HAMDA	8.68 ± 3.33	8.50 ± 3.11	2.86 ± 3.03	0.606*1<0.01*2<0.01*3
HAMDD	8.63 ± 3.40	8.73 ± 3.07	2.86 ± 3.06	0.924*1<0.01*2<0.01*3
MoCA	26.61 ± 1.81	27.55 ± 1.57	28.27 ± 1.72	0.044*10.352*2 0.038*3
MMSE	28.89 ± 1.15	28.56 ± 1.29	29.00 ± 1.22	0.254*10.784*20.143*3
Epi_group: group of patients in episode Int_group: group of patients ininterictal				
Con_group: control group				
*1: Epi_group VS Int_group *2Epi_group VS Con_group				
*3: Int_group VS Con_group				

2.4 Statistical analysis

The data were analyzed by the spss19(SPSS Inc, Chicago, IL,USA).Chi-square test was used for gender comparison in three groups, and one-way ANOVA test was used for comparison age, years of education, and scale scores. Correlation between ReHo value of different brain regions and clinical observation indexes (headache duration, interval time between attacks, course of disease, Hamilton anxiety score and Hamilton depression score) was analyzed by Pearson correlation analysis, and P value < 0.05 was considered statistically significant.

Table 2
significant brain area

ROIs	Regions	Voxel size	T	MNI coordinate		
				X	Y	Z
Epi VS Int						
1	bilateral paracentral lobule	117	3.29	-3	-24	66
2	bilateral anterior cingulate	109	-3.77	-9	42	15
Int VS con						
3	bilateral cuneus	190	-3.64	9	-84	36
4	bilateral lingual gyrus	163	-3.53	0	-72	6
MNI-Montreal Neurological Institute Coordinate System						

3. Results

3.1 General data

Age, gender, education years, Hamilton anxiety score, Hamilton depression score, MoCA, MMSE score of patients with episode and interictal not statistically significant ($P > 0.05$). The education years in the control group was shorter than that in the two migraine groups, possibly because the control group was mainly from our hospital staff. Compared with the control group, the score of Hamilton anxiety and depression was lower than that of the migraine group (Table 1).

3.2 ReHo analysis

Compared with the ReHo value of the Epi-group and Int-group, the MNI coordinate of the decreased ReHo were (-9, 42, 15), Voxel size = 109, include bilateral anterior cingulate cortex (ACC), $T = -3.77$; and Montreal Neurological Institute (MNI) [-3, -24, 66], Voxel size = 117, $T = 3.29$, the ReHo value of bilateral paracentral lobule was stronger active than the interictal group ($P < 0.01$), As shown in Table 2 and Fig. 1. Compared with the control group, patients in interictal phase had stronger activation in bilateral cuneus (Voxel size = 190, $T = -3.64$) and bilateral lingual gyrus (Voxel size = 163, $T = -3.53$)—MNI of the two are (9, -84, 36) and (0, -72, 6), As shown in Table 2 and Fig. 2. No significant different brain area was found between the episodes group and the control group. In episodes group, significant correlation was found between attack frequency and ReHo value of the bilateral paracentral lobule ($r = 0.492$; $p = 0.038$), As shown in Fig. 3. All the results through GRF correction.

4. Discussion And Conclusion

The resting state functional magnetic resonance imaging (rs-fMRI) technique is a noninvasive and advanced neuroimaging measurement that has been recently used to investigate the pathophysiology of several disorders. By identifying imaging findings of imaging biomarkers, the shift from laboratory research to clinical understanding has provided migraine patients with key information for diagnosis, prognosis, disease outcome and development of reasonable treatment and nursing approaches (Fleming and Carlsson 2014). ReHo analysis is an analysis method to examine the features of functional integration. Its advantages are as follows: no specific requirements on the sample distribution, strong applicability. The ReHo analysis method can infer the function of the corresponding brain region by analyzing the consistency of spontaneous nerve activity in the local brain region, which reflects the synchronization of neuronal activity in the local brain region in time, rather than the intensity of neuronal activity. The higher the ReHo value, the better the synchronization of activity in this brain region (Mainero et al. 2011).

Migraine is not only an important health problem, a worldwide burden in terms of patient suffering, but also a topic of enduring interest. Although migraine is not a fatal disease, it has many comorbidities that can seriously affect everyday life. In our study, compare the basic data of three group, we found that mood disorders were more common in migraine group, It is consistent with previous studies (Walters et al. 2014, Vetvik and Mac Gregor 2017). But whether it's comorbid or cause-and-effect is unclear, It is not clear how and from which area of the brain the migraine pain starts and which brain areas are active in the different stages of migraine.

In our study, the episodes group compared with the interictal group, Montreal Neurological Institute(MNI) $-3, -24, -66$, the ReHo value of bilateral paracentrallobule was stronger active than the interictal group ($P < 0.01$). Paracentral lobule(PCL) is a part of sensorimotor network (SMN), located on the medial face of the parietal cortex. Precuneus occipital cortex also around it. This associative cortex is well-placed to play an important role in multisensory integration, specific aspects of which participate to bodily awareness (Guillaume Herbet et al. 2019). In another clinical study, abnormal ICN connectivity of the OFC and IPL within the DAN and of the PCL within the SMN normalized in chronic pain patients after CBT treatment (Yoshino et al. 2018). A significant increase in PCL activity in chronic pain patients. The PCL is associated mainly with the action-execution or processing and perception of pain (Smith et al. 2009). Patients with chronic pain show distorted recognition or sensory pain assessment accompanied by abnormal activities of the PCL (Catley et al. 2014), and PCL activity has also been associated with pain chronicity (Chou et al. 2016). Migraine is a neurological disorder involving multiple sensory. PCL is activated in the episode period also explain the symptoms that accompany the headache, such as fatigue, yawning, photophobia, and so on.

And the Montreal Neurological Institute(MNI) $-9, 42, 15$ is that the ReHo value of bilateral anterior cingulate cortex was lower active than the interictal group. In migraines, the most relevant functions with ACC are those related to pain control and involved emotional aspects. Recent studies using H-MRS measurements have shown that ACC metabolites in migraine patients during the onset are "complex" and hyper excitatory even during interictal (Becerra et al. 2016). Consistent with these studies, our results

indicate that the ReHo of ACC varies from different phases for migraine. Possible mechanism: it may mediate the analgesic effect of motor cortex stimulation to some extent. Previous studies have confirmed the anatomical connection between cortex and brain stem pain processing region. These connections enable the top-down adjustment of pain sensation from cortical region through brain stem opioids (Hadjipavlou et al. 2006). ACC is rich in opioid receptors and selectively activates opioids, playing a key role in the analgesic control of central opioids. In addition, ACC is connected to the periaqueductal gray of the midbrain, which is also a key area of migraine pathogenesis (Denuelle et al. 2007). All the above conditions are mediated by activation of descending anti-injury sensation pathway.

In addition, the activation of excitatory synaptic in ACC will promote pain perception and increase sensitivity about pain discomfort (Bliss et al. 2016). Specifically, glutamate from ACC project and enhance sensory transmission in the spinal cord, which will aggravate pain. This excitatory neurotransmission in ACC is regulated by serotonin(5-HT), which inhibits the release of glutamate (Tian et al. 2017). We consider it related with the functional state of the brain, the adaptive and remodeling functions of the brain. Migraine sufferers are in different periods, have different attack frequency and pain duration. With the extension of time, the chronic development of migraine all these factors may have complex effects on ACC.

We all know that migraine is now defined as a neurological disorder. So that in addition to changes in brain functions in episodes, what happens between migraines? With the course of the disease, the frequency of attacks, the level of pain, and other accompanying symptoms, does the brain function change in remission? Although migraine is an episodic disorder, we should study the entire course of the disease as a whole. In our study, compared with the control group, patients in interictal phase had lower activation in bilateral cuneus and bilateral lingual gyrus. PET scans were performed using regional cerebral blood flow (rCBF) as a marker of neuronal activity. There were significant changes in rCBF in cuneus, correlated to painscores, and in the ACC, correlated to stimulation-induced paraesthesia scores. ACC and cuneus is probably involved in the affective dimension of pain (Matharu et al. 2004). Another finding was that changes in rCBF in the cuneus that were directly correlated to paraesthesia scores and inversely correlated to pain scores. A functional MRI study investigating the affective dimension of pain reported right cuneus activation, which the authors attributed to the anticipation and subjective experience of pain (Fulbright et al. 2001). The cuneus and lingual gyrus belong to the visual center. Photophobia is an abnormal sensitivity to light experienced by migraineurs and is perhaps caused by cortical hyper excitability. Photophobia accompanying migraine headaches is a symptom of important diagnostic value, and as one of the diagnostic criteria of migraine without aura by the International Headache Society (IHS) (Aygul et al. 2004). Its prevalence is about 85% of patients during attacks, and it can also be present between attacks (Main et al. 1997). Even reported that bright or flickering lights as a trigger for their attacks. When no concomitant pain stimulation was applied, luminous stimulations activated the visual cortex bilaterally in migraineurs (specifically in the cuneus, lingual gyrus and posterior cingulate cortex) but not in controls (Boulloche et al. 2010). Negative affective pictures elicited stronger activation than neutral affective pictures in migraineurs, which included the bilateral cerebellum anterior lobe, the bilateral lingual gyri, the bilateral precuneus and cuneus (Wang et al. 2017). These data

indicated that migraine patients were hypersensitive to negative stimuli, which might provide clues to aid in the understanding of the pathophysiology and psychiatric comorbidities of migraines. Combined with our research, although in remission, the visual cortex is still damaged. Such long-term, insidious changes gradually affect changes in brain function, leading migraine sufferers to develop visual symptoms. And with the basic data, the two groups of migraineurs got higher scores about HAMDA and HAMDD than the control group. So the effects of migraines are persistent and tend to increase negative emotion. Whether the two are comorbid disorders or caused by a single disease is unknown. Therefore, large sample longitudinal studies are needed to continue to look for subtle changes in these abnormal brain regions. And through imaging findings to find targeted receptor therapy and prevention.

To observe the relationship between ReHo values in different brain regions and clinical symptoms in migraine patients, we found that frequency and ReHo value of the bilateral paracentral lobule has a positive correlation ($r = 0.492$; $p = 0.038$). Paracentral lobule (PCL) is a part of sensorimotor network, located on the medial face of the parietal cortex. Compared with interictal group, Paracentral lobule is stronger activation in episode group. This suggests that the paracentric lobule is not only associated with migraine attacks, but also with the frequency. Through activation of the paracentral lobule, the connections between sensorimotor networks and even other networks are affected. So it may have an effect with the outcome of subsequent migraines, whether they become chronic or not, and the remodeling of the brain.

5. Conclusion

Although migraine is an episodic disease, the disease is not static, and we need to observe the course of the disease as a whole. Even in the interictal, it may affect the development of the disease through the visual centers (the cuneus and lingual gyrus). ACC regulates different states of migraine by inducing anti-injury sensation regulation function. paracentric lobule is not only associated with migraine attacks, but also with the frequency. it may have an effect with the outcome of subsequent migraines, whether they become chronic or not, and the remodeling of the brain.

Declarations

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Ethics approval:

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Code availability: Not applicable

Authors' contributions

JJZ agreed on the content of the study. JJZ, ML and DMW collected all the data for analysis. JJZ agreed on the methodology. JJZ, ML and DMW completed the analysis based on agreed steps. Results and conclusions are discussed and written together. The author read and approved the final manuscript.

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Figures

Figure 1

GRF correction (Epi-group vs Int-group), coordinate: (-3, -24, 66); $T=3.29$; voxel size=117, bilateral paracentral lobule; (-9, 42, 15); $T=-3.77$; voxel size=109, bilateral anterior cingulate.

Figure 2

GRF correction (Int-group vs Con-group), coordinate:(9, -84, 36), $T=-3.64$, voxel size=190, bilateral cuneus; (0, -72, 6), $T=-3.53$, voxel size=163, bilaterallingual gyrus.

Figure 3

frequency and ReHo value of the bilateral paracentrallobule has a positive correlation ($r=0.492$; $p=0.038$), The X axis is frequency, Y axis is the ReHo value of the Paracentral lobule.