Brain Regions Involved in Fractional Amplitude of Low-Frequency Fluctuation in Cluster Headache Patients: A Resting-State Functional MRI Study

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Abstract

Background:

A limited number of studies have reported on fractional amplitude of low-frequency fluctuation (fALFF) in cluster headache (CH). We used resting-state functional magnetic resonance imaging (RS-fMRI) to assess the possible pathogenic role of fALFF in CH.

Methods:

RS-fMRI scans of 23 patients with CH were obtained (11 with left-sided headache and 12 with right-sided headache), along with scans of 23 age- and sex-matched normal controls. The RS-fMRI data were analyzed to explore abnormal brain activity in the left CH and right CH patients during the non-painful state of cluster period. fALFF was compared between patients and controls, and correlation analysis between the regional mean fALFF values and clinical characteristics was performed.

Results:

A decrease in fALFF was detected in the left cerebellum, left lentiform nucleus, left frontal lobe, left anterior cingulate, and right postcentral gyrus in the left CH group compared to the controls, while a decrease of fALFF was detected in the right cerebellum, right cingulate gyrus, right superior parietal lobule, right inferior parietal lobule, right postcentral gyrus, and left precuneus in the right CH group. No patient had a region with increased fALFF. A moderate correlation was observed between some regional mean fALFF values and the clinical characteristics.

Conclusions:

We deduced that dysfunction in multiple brain areas is involved in the non-painful state of CH during cluster period. Several functional networks are involved, such as the default-mode, cerebellar, and somatomotor networks, suggesting that CH is the result of abnormal functioning in multiple brain functional networks.

Background

Cluster headache (CH) is a male-predominant [1], excruciating and strictly one-sided pain syndrome characterized by attacks accompanied by marked ipsilateral cranial autonomic symptoms, such as lacrimation and conjunctival injection [2]. CH affects about 0.12% of the population [3]. Single attacks last 15–180 min and the frequency of attacks ranges from once every day to eight times per day. CH is considered a chronobiological disorder, where seasonal and circadian rhythmicity affect the likelihood of an attack [4]. Approximately 80–90% of CH patients suffer from episodic headaches [5]. These clinical

features indicate that CH is a central disease, activated by the posterior hypothalamus [6] and regulated by the trigemino-parasympathetic reflex [7]. Several intracranial cortical brain regions are also involved, but the pathogenesis of CH remains unclear [8]. Functional neuroimaging of headache patients has revolutionized our understanding of the pathophysiology of CH and provided unique insight into this syndrome [9].

As a resting-state functional magnetic resonance imaging (RS-fMRI) signal, fractional amplitude of low-frequency fluctuation (fALFF), which covers the low-frequency power spectrum (0.01–0.08 Hz), reflects the intensity of local spontaneous activity in brain areas [10, 11]. fALFF is minimally affected by the cerebrospinal fluid, veins, and physiological noise, and improves the cortical activity detection rate. fALFF is sensitive and specific to spontaneous neuronal activity of the resting brain [12]. fALFF is a powerful marker of group differences in spontaneous brain activity, and brain areas with increased fALFF are associated with the default mode network (DMN) in the resting state [13, 14]. fALFF is now considered reliable for measuring regional coherence in spontaneous activity, and for revealing the pathophysiology of neuropsychiatric disorders including Alzheimer's disease [15], post-stroke depression [16], anxiety, depression [17], and migraine [18, 19].

However, few studies have detected spontaneous brain activity in patients with CH using fALFF during the resting state. We performed RS-fMRI during the non-painful period of CH, calculated the fALFF value, and compared brain activity between CH patients and normal controls.

Methods

Participants

All procedures were approved by the Chinese Ministry of Health and the Ethics Committee of the Chinese PLA General hospital, Beijing, china and were conducted according to the ethical principles of the Declaration of Helsinki. Participants admitted to the International Headache Center of PLA General Hospital between January 2017 and January 2018 were enrolled in the study after providing written informed consent.

The inclusion criteria were as follows: met the diagnostic criteria for CH of the International Classification of Headache Disorders 3rd Edition (ICHD-3) [20]; severe unilateral headache; aged 20–60 years; right-handed; no chronic diseases, including diabetes, hypertension, hypercholesterolemia, cardiovascular and cerebrovascular diseases, or tumors, epilepsy, infectious diseases, connective tissue diseases, other types of chronic pain, or severe anxiety and depression; and no history of alcohol, nicotine, or other substance abuse. The control group was healthy people recruited from the staff of the PLA General Hospital and their relatives. The normal controls (NC) were age- and gender-matched with the CH patients and had no history of primary headache or any other type of headache in the past year. This study was reviewed and approved by the Chinese Ministry of Health and the Ethics Committee of the Chinese PLA General hospital, Beijing, china and all participants signed an informed consent form.

RS-fMRI data collection

All subjects were advised to keep their eyes closed, but to remain awake and think of nothing in particular during the scan. The scans were taken with the Sigma 3.0 T magnetic resonance imaging system (Siemens, Munich, Germany), and the functional images were acquired using an echo plane pulse sequence. The scanning parameters were as follows: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, layer thickness = 3.0 mm, interval = 0.6 mm, matrix = 64×64 , field of view = 200×200 mm, flip angle = 90° , scan duration = 4 min 14 s. There were 33 layers, from the foramen magnum to the top of the head (240 time points and 7,920 image frames). Subsequently, a sagittal 3D T1-weighted image of the whole brain was acquired in 128 layers (TR = 2,500 ms, TE = 3.5 ms, layer thickness = 1.0 mm, interval = 0.6 mm, matrix = 256×256 , field of view = 256×256 mm, flip angle = 8°).

Image data preprocessing

MATLAB 2013b software (MathWorks, Natick, MA, USA) was used for data processing, and the fMRI data were processed using DPARSF software (<http://www.rfmri.org>). The fMRI data preprocessing method employed herein is well-established [17] and includes eight steps. First, DICOM format data were converted into the NIFTI format (Neuroimaging Informatics Technology Initiative). Second, the first 10 time points were removed to reduce the effect of maladjustments at the beginning of the scan. Then, data from all layers were calibrated to a specific time point using a time correction process, and the functional time series was realigned to correct for head motion across the time series. The brain images of each subject were then transferred to standard space for normalization, to reduce differences between individuals for the next step, i.e., smoothing, in which the effect of spatial noise and differences in brain structure between subjects was reduced using a $4 \times 4 \times 4$ mm smoothing kernel. Finally, after detrending, the low-frequency band wave was used to remove the effect of high frequency signals from respiratory heartbeats, and high frequency noise, to obtain the low-frequency (0.01–0.10 Hz) fluctuations in the resting brain (filtering). After calculating the fALFF value, the Gaussian kernel function was applied for spatial smoothing, and a standardized fALFF diagram was acquired of each participant over the range of 0.01–0.08 Hz. Then, Statistical Parametric Mapping 8 (SPM8) (<http://www.fil.ion.ucl.ac.uk/spm>) and RESTplus V1.21 (<http://www.restfmri.net/forum/REST>) software were used for statistical analyses of the fALFF data, and to integrate the fALFF value with the image and determine changes in local brain function. The abnormal brain area of CH patients was defined as the mask, and RESTplus was used to extract the corresponding index values from the center of the region of interest (radius = 6 mm), to derive the mean fALFF value.

Statistical analysis

Headache pain was evaluated using a visual analog scale (VAS). The chi-square test or Fisher's exact test, performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA), was used to analyze the demographic and clinical characteristics of the patients. Independent sample tests were performed using Matlab (R2013b) to compare fALFF values between the case and control groups. RESTplus software was used to extract the corresponding index values. A P -value < 0.01 for a minimum volume of $1,458 \text{ mm}^3$

was taken to indicate a significant difference. Pearson's correlation analysis was performed to assess the relationship between the mean fALFF value across all voxels (in brain regions with abnormal fALFF values) and clinical characteristics of the CH patients.

Results

Demographic characteristics

Forty-six volunteers were enrolled in the study, including 23 CH patients and 23 healthy sex- and age-matched controls. The healthy controls did not have any primary or secondary head or face pain. More male than female CH patients suffered from CH, in both the left and right CH groups (81.8% and 75.0% male, respectively). The average age and age at onset of the patients in the left and right CH groups were 33.8 and 33.2 years, and 26.7 and 23.5 years, respectively. The majority of the patients experienced severe pain (VAS score > 8), lasting for more than 30 min and accompanied by conjunctive ingestion and lacrimation at the time of onset. No significant differences in gender, age, age at onset, duration of headache attack, number of attacks per day, cluster bout duration, pain duration, degree of pain at onset, or accompanying symptoms including nausea, vomiting, photophobia, phonophobia, conjunctive ingestion, lacrimation, nasal congestion, and rhinorrhea were observed between the left and right CH groups (Table 1).

Table 1
Comparison of the general characteristics of the left and right cluster headache groups

Characteristic		Left (n = 11)	Right (n = 12)	<i>p</i>
Age (years)	Mean $\pm$ SD	33.8 $\pm$ 12.8	33.2 $\pm$ 9.1	0.275
	Onset age	26.7 $\pm$ 10.1	23.5 $\pm$ 7.1	0.085
Sex	Female	2	3	1
	Male	9	9	
Headache attack duration	$\leq$ 30 min	1	2	1
	> 30 min	10	10	
Frequency of attacks	$\leq$ 1 time/day	8	10	0.640
	> 1 time/day	3	2	
Cluster bout duration	$\leq$ 4 weeks	5	7	0.537
	> 4 weeks	6	5	
Disease duration	$\leq$ 10 years	7	5	0.292
	> 10 years	4	7	
Visual analogue scale score	$\leq$ 8	5	2	0.193
	> 8	6	10	
Nausea	Yes	8	6	0.400
	No	3	6	
Vomiting	Yes	6	3	0.214
	No	5	9	
Photophobia	Yes	5	3	0.400
	No	6	9	
Phonophobia	Yes	4	3	0.667
	No	7	9	
Conjunctive ingestion	Yes	10	11	1
	No	1	1	
Lacrimation	Yes	9	12	0.217

Characteristic		Left (n = 11)	Right (n = 12)	<i>p</i>
Nasal congestion	No	2	0	0.146
	Yes	4	8	
Rhinorrhea	No	7	4	0.214
	Yes	5	9	
	No	6	3	

fALFF results

fALFF values of the left cerebellum, left lentiform nucleus, left frontal lobe, left anterior cingulate, and right postcentral gyrus were significantly lower in the left headache than NC group, while fALFF values of the right cerebellum, right cingulate gyrus, right superior parietal lobule, right inferior parietal lobule, right postcentral gyrus, and left precuneus were significantly lower in the right headache than NC group ($P < 0.01$). No fALFF value in the left CH or right CH groups was higher than the corresponding value in the NC group (Tables 2 and 3).

Table 2
The fALFF brain area was decreased in the left CH compared to the normal control

Brain regions	Hemisphere	BA	No. of voxels	Talairach coordinates (mm)			T-score (peak)
				x	y	z	
Left cerebellum	L	—	17	-27	-51	-33	-3.473
Lentiform nucleus	L	—	47	-24	3	-6	-4.4634
Frontal lobe	L	10	29	-24	33	6	-3.6416
Anterior cingulate	L	24	44	-18	36	18	-4.3421
Postcentral_R (aal)	R	3	16	27	-33	51	-4.5212
Brain regions with greater fALFF changes in left CH patients during the non-painful period vs. normal controls. Threshold: $P < 0.01$; R: right; L: left; BA: Brodmann's area.							

Table 3
The fALFF brain area was decreased in the right CH compared to the normal control

Brain regions	Hemisphere	BA	NO. of voxels	Talairach coordinates (mm)			T-score (peak)
				x	y	z	
Right cerebellum	R	—	68	45	-66	-42	-4.7791
Cingulate gyrus	R	31	109	3	-30	39	-5.6906
Superior parietal lobule	R	7	66	36	-60	51	-4.7168
Inferior parietal lobule	R	40	81	48	-45	48	-4.697
Precuneus_L (aal)	L	7	96	-9	-60	54	-4.3352
Postcentral gyrus	R	3	54	15	-60	72	-4.4526
Brain regions with greater fALFF changes in right CH patients during non-painful period vs. normal controls. Threshold: $P < 0.01$, BA: Brodmann's area.							

Correlation analysis of clinical characteristics and mean fALFF values

No significant correlations were observed between the regional fALFF values and the clinical characteristics. However, some regional fALFF values and clinical characteristics were moderately correlated. For example, a moderate negative correlation was observed between the left lenticular nucleus fALFF values and VAS score in the left CH group ($r = -0.691$, $P = 0.019$). The right superior parietal lobule fALFF values were moderately correlated with the number of attacks per day in the right CH group ($r = -0.665$, $P = 0.018$), and the right inferior parietal lobule fALFF values were moderately correlated with patient age ($r = 0.620$, $P = 0.032$). Additionally, a moderate correlation was detected between the right postcentral gyrus fALFF values and typical duration of the bout (in weeks) ($r = 0.602$, $P = 0.038$) (Fig. 3).

Discussion

To the best of our knowledge, this is the first RS-fMRI investigation of patients with CH to use fALFF values. We found a decrease in fALFF values in certain brain areas, such as the cerebellum, lentiform nucleus, frontal lobe, and right postcentral gyrus, indicating that the intensity of local functional activity was lowered in several brain networks, such as the DMN, cerebellar network (CEN), and somatomotor network (SEN). Our results suggest that the function of multiple brain networks in the non-painful CH period is impaired.

Because CH attacks are usually unilateral, we divided the patients into left and right headache groups. Patients in the left headache group showed only left headache during the attack, while only right pain

was observed in the right group. The abnormally active brain areas were not the same between the left and right headache groups. This may be due to differences in structure [21] and function [22] between the bilateral cerebral hemispheres. However, fMRI research has demonstrated that cerebral asymmetries are never absolute; even for strongly left-lateralized functions such as language, the right hemisphere makes a significant contribution [23]. Second, brain network functions in bilateral hemispheres are not completely symmetrical. Imaging, clinical, and behavioral data demonstrate hemispheric asymmetries in attentional networks, as revealed by the lateralized attention network test [24]. The orienting and alerting networks show left hemisphere dominance [25], while the executive control network is right hemisphere-dominant [26]. The allocation of spatial attention is balanced through the regulatory action of the corpus callosum. An impairment in the lateralization of brain function is seen in many diseases; for example, the visuospatial attention network may be disrupted after stroke and rehabilitated by non-invasive brain stimulation [27]. Therefore, we believe that studies of CH should group participants according to headache side.

Based on regional homogeneity, we previously showed that activity in brain regions such as the bilateral middle prefrontal cortex, right posterior cingulate cortex, and left dorsolateral prefrontal cortex decreases during a cluster period [28]. Another study reported greater hypometabolism in the perigenual anterior cingulate, prefrontal and orbitofrontal cortices, as revealed by positron emission tomography, in CH patients compared to healthy volunteers [29], which supported our results. Notably, the cingulate gyrus, superior parietal lobule, inferior parietal lobule, precuneus, and frontal lobe constitute the hub region of the DMN, which is the most studied brain network, was shown to be active in the resting state (i.e., in the absence of thinking), but was dormant in the task state [30]. In our study, activity of the default network in CH patients decreased rather than increased, suggesting that the activity of the DMN in CH patients is reduced on the same side as the headache during the resting state.

This study showed that both left- and right-sided CH were associated with decreased activity in the ipsilateral cerebellum. Although the specific mechanism underlying the involvement of the cerebellum in CH remains unclear, a previous structural and functional imaging study suggested that the cerebellum might be involved in the pathogenesis of CH [31]. Naegel et al. reported that the volume of cerebellar gray matter was greater in CH patients compared to NC [32]. This increase in gray matter may reflect increased regional cortical plasticity and promote chronic CH, as indicated by a structural imaging study of patients with paroxysmal and chronic CH [33]. A study of the macroscale functional neuroanatomy of the cerebellum revealed causal interactions of sub-lobular structures in the CEN with a large-scale cortical network and the DMN in a non-motor learning paradigm [34]. Morelli et al. were the first to study brain activation patterns in patients with episodic CH using RS-fMRI, and reported that the cerebellum, as an “unconventional” pain-related brain area, was abnormally activated [31]. Farago et al. used fMRI to study brain activation patterns and intensity in CH patients during the non-painful period. They also found that the ipsilateral cerebellum and CEN of headache patients were functionally connected, i.e., were activated simultaneously [35]. However, in this study, a decrease in cerebellar activation on the side ipsilateral to the pain was seen. There are several possible explanations for the abnormalities observed in our patients. First, we speculate that this may have been due to the research methods used. In the former study,

independent component analysis of functional integration was performed, while we used fALFF for functional differentiation. In addition, the acquisition range of the low-frequency blood oxygen signal was different: a “low-frequency” blood sample was collected (0.02–0.01 Hz) in the former study, while in this study the frequency range was 0.01–0.08 Hz. Furthermore, cerebellar activity occurs during the presence of acute and chronic pain [36], and the occurrence of headache in patients with CH is a dynamic process. We speculate that cerebellar activity is also dynamically changed. Therefore, we hypothesized that the CEN is involved in the painful period of CH.

The fALFF values in the right postcentral gyrus decreased in both of our groups. A moderate correlation was detected between the right postcentral gyrus fALFF value and headache attack duration in the right CH group. The central posterior gyrus is in the primary somatosensory area and somatosensory network, which is mainly involved in the localization and recognition of pain, and receives signals from the thalamus [37]. Both the current study and a previous one observed that postcentral gyrus activity decreased in chronic pain, which may be related to the suppression of pain perception under long-term stimulation [38].

The activity of the left lenticular nucleus decreased in our left CH headache group. In addition, a negative correlation was observed between the fALFF value in the left lenticular nucleus and VAS score; the lower the fALFF value, the higher the VAS score, and the more severe the pain. A study that utilized voxel-based morphometry to evaluate abnormal patterns of local gray and white matter in patients with CH reported that the volume of the lenticular nucleus was decreased in patients with CH [39]. Previous studies on the subcortical microstructure of right and left CH patients reported “higher” diffusion parameters of the lenticular nucleus [40], indicating microstructural disintegration and atrophy. The basal ganglia and subcortical structures have been proposed to play a central role in nociception. Furthermore, basal ganglia structures are activated during the application of painful stimuli [41]. Also, reduced fractional anisotropy was found in the corpus callosum and some frontal and parietal white matter tracts in CH patients, mainly on the contralateral side of the pain [42]. We speculate that the fALFF value of the lenticular nucleus may be useful when choosing the CH treatment during the non-painful CH period.

The activity of the parietal lobe was decreased in our right CH group, including the right superior parietal lobule, right inferior parietal lobule, right postcentral gyrus, and left precuneus lobe. A brain network study reported that the functional connections between the parietal lobe, insular lobe, and cerebellum were significantly stronger in CH than migraine patients, in both RS-fMRI and task-state fMRI analyses [43]. A study based on voxel-based morphometry reported that the grey matter volume of the left inferior parietal lobule was decreased, while the grey matter volume of the right cuneus was increased, in patients with CH [39]. The right superior parietal lobule fALFF value was moderately correlated with the frequency of attacks. The greater the frequency of attacks, the lower the right superior parietal lobule fALFF value. We speculate that the frequency of attacks in CH patients may not only affect the function of the superior parietal lobule, but also the structure of the brain.

Our findings have several potential implications for clinical treatment. Currently used analgesics, as well as oxygen, are not completely effective for CH. Given the hypofunctioning of the brain network on the side ipsilateral to the during period of CH, could non-invasive treatments be used? For example, meditation changes the activity of the DMN and improves the coupling of multiple brain networks by changing the functional connection between brain regions [44]. Transcranial magnetic stimulation (TMS) increases brain activity through single or repetitive pulses, which affect neuroplasticity and the functional connections among brain networks [45]. A naturalistic study reported that treating chronic CH with maintenance sessions of repetitive TMS (rTMS) of the motor cortex reduced the intensity of permanent and paroxysmal pain, as well as the daily number of painful attacks. However, there are few reports on the use of rTMS to treat CH [46]. Our results may lead to less-invasive treatments for CH.

Our study had several limitations. First, the sample size was small. The rarity of CH makes it difficult to conduct large, well-controlled studies. Second, our study was only concerned with the non-painful period of CH, as dynamic changes in fALFF during the onset of CH cannot be observed. Thus, a longitudinal follow-up study may be necessary; more evidence is needed to confirm that the changes in spontaneous brain activity observed herein were the result of CH.

Conclusion

Our results provide new insight into the pathogenesis of CH. Although the pathogenesis of CH is highly complex, dysfunction in multiple brain areas, such as the DMN, CEN, and SEN, was involved in the non-painful CH period. It is necessary to study CH according to the headache side, given the lateralization of brain function.

List Of Abbreviations

CH	cluster headache
fALFF	fractional amplitude of low-frequency fluctuation
RS-FMRI	resting-state functional magnetic resonance imaging
NC	The normal Controls
DMN	default-mode network
CEN	cerebellar network
SEN	somatomotor network
VAS	

visual analog scale
TMS
Transcranial magnetic stimulation
BA
Brodmann's area.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Chinese PLA General Hospital approved the research protocol, and the procedures conformed to the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

YC, XX, ZD, EQ and SY contributed the conception and design of the study. EQ, WD, ZD, YC, XX and LT contributed to MR data acquisition, and XX, YC contributed the clinical data acquisition. YC, EQ and LT contributed the image analysis and statistical analysis, YC, ZD and XX contributed to the interpretation and draft. YC, ZD, EQ, LT and SY contributed to the revision for important intellectual content. All authors read and approved the final manuscript.

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Figures

Figure 1

Regions showing significant differences in fALFF between L-CH patients during the non-painful period and normal controls, with a threshold of $P < 0.01$. The color bar indicates the t -score of brain regions with fALFF differences between CH patients during the non-painful period and normal controls, R: right; L: left. (A) The left cerebellum ($x = -27, y = -51, z = -33$). (B) The left lentiform nucleus ($x = -24, y = 3, z = -6$). (C) The left frontal lobe ($x = -24, y = 33, z = 6$). (D) The left anterior cingulate ($x = -18, y = 36, z = 18$). (E) The right postcentral gyrus ($x = 27, y = -33, z = 51$).

Figure 2

Regions showing significant differences in fALFF between R-CH patients during the non-painful period and normal controls, with a threshold of $P < 0.01$. The color bar indicates the t -score of brain regions with fALFF differences between CH patients during the non-painful period and normal controls, R: right; L: left. (A) The right cerebellum ($x = 45, y = -66, z = -42$). (B) The right cingulate gyrus ($x = 3, y = -30, z = 39$). (C) The right superior parietal lobule ($x = 36, y = -60, z = 51$). (D) The right inferior parietal lobule ($x = 48, y = -45, z = 48$). (E) The right postcentral gyrus ($x = -9, y = -60, z = 54$). (F) The left precuneus ($x = 15, y = -60, z = 72$).

Figure 3

Correlation analysis of clinical characteristics and mean fALFF values. The fALFF value was negatively correlated with the visual analog scale score (A) in the L-CH group and number of attacks per day (B) in the R-CH group, but positively correlated with patient age (C) and the typical duration of bout (in weeks) (D) in the R-CH group.