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Limbic system abnormalities in episodic cluster headache: a 7T MRI multimodal study



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Abstract

Background Although the limbic system has long been thought to be involved in the pathophysiology of cluster headache, inconsistencies in imaging studies of episodic cluster headache (eCH) patients and limited understanding of the specific regions within the limbic system have prevented a full explanation of its involvement in the disease. Therefore, we performed multimodal imaging analysis using 7 T MRI with the aim of exploring structural–functional abnormalities in subregions of the limbic system and their relationship with clinical features.

Methods In this cross-sectional study, we employed 7T MRI to investigate structural (volumetric) and functional (fractional amplitude of low-frequency fluctuations (fALFF), regional homogeneity (ReHo)) alterations in limbic subregions (hypothalamus, thalamus, amygdala, hippocampus) among 69 in-bout but outside the attacks eCH patients and 63 healthy controls (HCs). Automated volumetry and resting-state functional MRI analyses were performed after adjusting for age, Generalized Anxiety Disorder scale, sex (and intracranial volume when evaluating volumetric measures). Then functional-structural coupling indices were computed to assess network-level relationships.

Results In eCH patients, volumes in right anterior inferior and right posterior of hypothalamus, left molecular_layer_ hippocampal-head, left lateral-nucleus and left Central-nucleus on the headache side, as well as left tuberal inferior and left tuberal superior of hypothalamus, and right parasubiculum on the contralateral side were significantly altered compared with HCs (P < 0.05). Additionally, the volume of the right anterior inferior was positively correlated with the duration of last headache episode. After false discovery rate correction, widespread alterations in fALFF and ReHo values were observed among hypothalamic, thalamic, hippocampal, and amygdalar subregions, some of which correlated with clinical measures. Furthermore, the structure–function coupling indices in the right anterior inferior and the left lateral geniculate nucleus on the headache side differed significantly between eCH patients and HCs.

Conclusions Our findings demonstrate that in-bout but outside the attacks eCH patients present anatomical and functional maladaptation of the limbic system. Moreover, the observed dissociation between localized abnormalities and largely preserved network coupling—except in the hypothalamus and thalamus—suggests that these two regions may be particularly susceptible to eCH-related dysfunction, while broader brain networks retain

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compensatory capacity in pathological states. These findings refine potential neuromodulation targets and highlight the value of ultrahigh-field imaging in eCH research.

Keywords Episodic cluster headache, Hypothalamus, Thalamus, Amygdala, Hippocampus, 7T MRI, Structure-function coupling

Introduction

Episodic cluster headache (eCH) is a rare but debilitating primary headache disorder, affecting approximately 0.1% of the general population [1]. Clinically, it is characterized by severe, unilateral periorbital pain accompanied by ipsilateral autonomic symptoms and is often considered one of the most excruciating pain states, surpassing childbirth and bone fractures [2]. These disorders typically occur in multiple daily episodes lasting for weeks or months, followed by extended periods of remission [3, 4].

Although the neural mechanisms of eCH have not been fully elucidated, the limbic system [5, 6] (hypothalamus, amygdala, hippocampus, and thalamus), as a neural hub integrating nociception, emotion, and autoregulation, has become a focal point of research. For example, Ferraro et al. demonstrated functional impairments in the posterior hypothalamic network of chronic cluster headache (cCH) patients. This network, which includes regions at the diencephalon-midbrain junction and belongs to the mesolimbic dopamine system [7], has been implicated in cross-disorder pain research. Specifically, corticostriatal-limbic neuroplasticity has been proposed as a potential mechanism underlying the transition from acute to chronic pain states [8, 9]. Additionally, it has been shown that the hypothalamus plays a central role in CH pathogenesis [10]. Deep brain stimulation (DBS) targeting the hypothalamus and ventral tegmental area (VTA) can reduce attack frequency by 50-70% in refractory cases [11, 12], while subsequent studies have further demonstrated spontaneous hypothalamic activation during acute attacks [13, 14]. Other limbic regions also appear to be involved. The amygdala mediates emotional and autonomic aspects of pain, exhibits overactivation during in-bout and outside attacks, and contains injurysensitive neurons responsive to painful stimuli [15]. As a key relay station for nociceptive signals, the thalamus demonstrates volume loss in some CH patients [16, 17]. Meanwhile, the hippocampus is implicated in pain modulation through connections to the prefrontal cortex and hypothalamus, with altered hippocampal volumes noted in chronic pain syndromes and possibly contributing to cognitive and emotional dimensions of eCH [18].

Continuing with this line of inquiry, investigating these intracranial changes from both volumetric and functional perspectives may provide a more comprehensive view of eCH pathophysiology, and accumulating evidence indicates that the use of 7T MRI substantially enhances sensitivity to subtle alterations in small subregions of these brain areas, resulting in better detection of disorders. T1-weighted threedimensional magnetization-prepared rapid acquisition gradient echo (3D-T1WI-MP-RAGE) sequences, employing 180° inversion pulses and small-angle excitations, offers unparalleled spatial resolution and rapid acquisition times, enabling detailed 3D visualization of small limbic subregions. For example, patients with chronic headache often manifest changes in pain-related areas-including the ventral diencephalon, nucleus accumbens, frontal pole, hippocampus, and amygdala [19, 20]-with these changes correlating with headache severity. Additionally, advances in resting-state functional MRI (rs-fMRI) have significantly improved our understanding of functional brain changes. By analyzing blood oxygen level-dependent (BOLD) signal correlations, this noninvasive imaging technique has revealed unique functional and connectivity patterns in patients with eCH, providing important insights into neural networks potentially associated with clinical symptom exacerbation [7]. Therefore, through using structural and functional neuroimaging techniques, we aim to make progress in our understanding of the neural basis of eCH, which can better understand some of the clinical symptoms of CH and its severity like the previous literature [7, 19, 20].

Based on this context, we recruited 69 in-bout but outside the attacks eCH patients and 63 healthy controls (HCs), acquiring 7 T 3D-T1 and rs-fMRI data to characterize structural and functional brain changes and hypothesize that 7T MRI's enhanced spatial resolution will elucidate previously undetected abnormalities in limbic subregions of eCH patients. Specifically, we propose that: (1) Subregion-specific volumetric changes will be observed in crucial limbic structures (e.g., hypothalamus, amygdala, hippocampus, and thalamic nuclei). (2) Functional alterations in these limbic subregions will correlate with clinical indicators of eCH severity and progression. (3) Preserved functional-structural coupling at the network level, despite focal disruptions, reflecting the compensatory capacity of the brain in acute-phase eCH. These findings are expected to provide novel mechanistic insights into eCH pathophysiology and inform precision medicine approaches for this debilitating disorder.

Materials and methods

Participants

This study belongs to a Chinese Cluster Headache Register Individual Study (CHRIS) [21] and was approved by the Ethics Committee of the Chinese PLA General Hospital (S2022-202–01) (Beijing, China). All study procedures adhered to the latest revision of the Helsinki Declaration. Participants were recruited from the Chinese PLA General Hospital and provided written informed consent following a comprehensive explanation of the study protocols.

In this cross-sectional study, we enrolled 90 patients with CH and 85 HCs to investigate the differences in brain structure and function. Participants included in the study were newly diagnosed or had discontinued previously ineffective treatments. They did not take preventive medications prior to the scans (After completing the MRI, appropriate preventive treatment was administered based on the patient's condition). Each participant completed standardized neuropsychological assessments and underwent 7 T 3D-T1 and rs-fMRI scans (All MRI procedures were performed during a bout but outside the acute attack period). In addition, diagnostic information and detailed medication histories were acquired through structured interviews conducted by two neurologists. All participants were right-handed and of Chinese Han descent.

The inclusion criteria for eCH patients were based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) [22] and included the followings: (1) age 18-80 years; (2) a diagnosis of eCH under ICHD-3 (A-E); (3) a clearly defined cyclical headache pattern (typical bout lasting 7 days to 1 year, with ≥ 3 months of headache-free remission between bouts); (4) no comorbid neurological or psychiatric disorders (including other primary headaches or pain conditions); and (5) no notable structural lesions detected by routine MRI. Exclusion criteria were (1) the presence of other neurological disorders (e.g., epilepsy, stroke, traumatic brain injury); (2) meeting the diagnostic criteria for other primary or secondary headaches; (3) any history of caffeine, nicotine, or alcohol abuse; and (4) MRI contraindications. Clinical variables, such as the duration of last headache episode and headache intensity, were recorded. For the HC group, participants were 18-80 years old, with no past neurological (including primary headache or other chronic pain) or psychiatric conditions, and no contraindications for MRI.

Ultimately, MRI scans confirmed that none of the included participants had visible intracranial abnormalities. A total of 21 patients and 22 HCs were excluded for meeting criteria for cCH, exhibiting excessive head motion artifacts (>2 mm or 2°), or having incomplete scanning sequences or center point misalignment. The final sample comprised 69 in-bout but outside the attacks eCH patients and 63 HCs.

Image acquisition

All MRI scans were performed using a whole-body 7T scanner (MAGNETOM Terra, Siemens Healthcare, Erlangen, Germany) equipped with an 8-channel transmit and 32-channel receive coil. During the scanning process, subjects lay supine within the scanner bore and foam padding was used to minimize motion artifacts. The sequences were as follows: A rs-fMRI scan was performed with echo-planar imaging (EPI) as follows: voxel = $1.8 \times 1.8 \times 1.8$ mm³, repetition time (TR) = 2000 ms, echo time (TE) = 24 ms, flip angle = 90°, FOV=216 * 216 mm, matrix=120×120, slice thickness=1.8 mm, and interleaved slices=80. The MRI protocol included a volumetric high-resolution structural 3D-T1 image (voxel= $0.7 \times 0.7 \times 0.8 \text{ mm}^3$, TR=6000 ms, TE=2.21 ms, flip angle $1=4.0^\circ$, flip angle $2=5.0^\circ$, FOV=224 * 224 mm, slice thickness=0.75 mm, 240 sagittal slices). Participants were instructed to remain relaxed with their eyes closed throughout the scanning process. Participants' level of vigilance was confirmed post-scan to ensure that they remained awake.

Data preprocessing

[23] (Version: freesurfer-linux-FreeSurfer v7.4.1 ubuntu22_x86_64-7.4.1-20,230,614-7eb8460) was used for preprocessing of 3D-T1 data and for volumetric calculations of subregional brain structures (e.g., bilateral thalami, amygdalae, hippocampi). The standard Free-Surfer pipeline includes skull stripping, spatial normalization, segmentation of cortical and subcortical gray matter, cortical thickness estimation, and other procedures [24-37]. Briefly, the following steps were performed: 1. Data preparation: The original DICOM images were converted to NIfTI format, and the 3D-T1 data were denoised using DenoiseImage (given the higher noise in 7 T imaging). 2. Reconstruction: The FreeSurfer "reconall" command was then run to automatically process each participant's MRI data, including skull stripping, Talairach transformation, cortical and subcortical segmentation, cortical thickness measurement, and surface reconstruction. 3. Quality control: The results of segmentation were inspected using Freeview to ensure accuracy. 4. Volumetric extraction: The volumes of specified structures were extracted.

Rs-fMRI data were preprocessed using the DPABI toolbox [38] in MATLAB R2022b. Standard procedures were followed to ensure data quality and reproducibility: 1. Conversion of DICOM images to NIfTI and removal of the first five time points to avoid magnetic saturation



Fig. 1 Sagittal, coronal, and axial ROIs used to calculate functional and structural indices are indicated: light blue for the thalamus, yellow and red for the hypothalamus, dark blue for the left hippocampus and amygdala, and green for the right hippocampus and amygdala. L, left; R, right

effects. 2. Preprocessing of 235-time points, including slice timing correction, head motion correction (reoriented to the anterior commissure-posterior commissure plane), realignment, and coregistration with the T1-weighted structural image (the structural image was segmented using DARTEL [39]). 3. Spatial normalization to the Montreal Neurological Institute (MNI) template and spatial smoothing (6-mm full width at half maximum (FWHM) Gaussian kernel for amplitude of low-frequency fluctuations (ALFF); regional homogeneity (ReHo) analyses were performed without smoothing to preserve local features). 4. ALFF was calculated using a fast Fourier transform (FFT) in the 0.01-0.08 Hz range and converted to z scores to yield mALFF (mean amplitude of the low-frequency fluctuation) data; ReHo was computed based on Kendall's W, measuring the local consistency of each voxel with its 27 neighbors and converted to z scores. 5. Regressing out nuisance covariates, including white matter signal, cerebrospinal fluid signal, and head motion parameters (using Friston's 24-parameter model), followed by linear detrending and bandpass filtering (0.01-0.08 Hz). Two experienced radiologists performed visual inspections of all preprocessed data to guarantee data quality. 6. The resulting fALFF (fractional amplitude of low-frequency fluctuations) and ReHo maps were then in NIfTI format.

Because the standard FreeSurfer atlas does not include hypothalamic subregions, we utilized a previously published hypothalamic subregion atlas and implemented H-SynEx methods to extract hypothalamic subregion volumes [40]. However, due to insufficient co-registration between images and masks in certain patients after applying the H-SynEx method, two eCH patients were excluded from our hypothalamic analysis (Left-sided headaches and right-sided headaches, respectively).

The region-specific masks of the hypothalamus, thalamus, amygdala, and hippocampus (Fig. 1) – core limbic structures known to be involved in autonomic and nociceptive processing [41-43] – were spatially transformed onto individual functional maps (fALFF and ReHo) using the transformation matrix derived from T1-weighted to fALFF space normalization. This approach ensured precise spatial correspondence between structural definitions and functional metrics while accounting for individual neuroanatomical variability. Subregions that were too small and lost during mask registration were excluded from subsequent region-of-interest (ROI) analyses.

Statistical analysis

The Shapiro–Wilk test was used to assess normality in continuous variables. Clinical characteristics between in-bout but outside the attacks eCH patients and HCs were compared as follows: normally distributed continuous variables were analyzed with independent two-sample *t*-tests, non-normally distributed variables with Mann–Whitney *U* tests, and categorical variables with chi-square tests. Statistical significance was set at P < 0.05.

eCH (<i>N</i> =69)	HC (<i>N</i> =63)	U/t/x ²	Р
33(28,37)	31(26,40)	2109.0	0.770
58/11	31/32	18.21	<0.001*
29/35/5	NA	NA	NA
10(5,14)	NA	NA	NA
29	NA	NA	NA
24	NA	NA	NA
16	NA	NA	NA
30(20,52.5)	NA	NA	NA
10	NA	NA	NA
23	NA	NA	NA
36	NA	NA	NA
60(38.75,120)	NA	NA	NA
8(8,8)	NA	NA	NA
14(11,18)	8(7,11)	3742.5	<0.001*
11(7,15)	11(9,14)	2044.5	0.556
	eCH (N=69) 33(28,37) 58/11 29/35/5 10(5,14) 29 24 16 30(20,52.5) 10 23 36 60(38.75,120) 8(8,8) 14(11,18) 11(7,15)	eCH (N=69) HC (N=63) 33(28,37) 31(26,40) 58/11 31/32 29/35/5 NA 10(5,14) NA 29 NA 24 NA 16 NA 30(20,52.5) NA 10 NA 36 NA 60(38.75,120) NA 8(8,8) NA 14(11,18) 8(7,11) 11(7,15) 11(9,14)	eCH (N=69) HC (N=63) U/t/x² 33(28,37) 31(26,40) 2109.0 58/11 31/32 18.21 29/35/5 NA NA 10(5,14) NA NA 29 NA NA 24 NA NA 16 NA NA 30(20,52.5) NA NA 10 NA NA 36 NA NA 60(38.75,120) NA NA 8(8,8) NA NA 14(11,18) 8(7,11) 3742.5 11(7,15) 11(9,14) 2044.5

Abbreviations: eCH Episodic cluster headache, HC Healthy control, VAS Visual Analogue Scale, GAD-7 Generalized Anxiety Disorder-7, PHQ-9 Patient Health Questionnaire-9

^a significant difference from the HC (*P* < 0.05). Data following a normal distribution were expressed as mean ± SD, whereas data not meeting the normal distribution criteria were expressed as median and interquartile range (IQR)

The DPABI toolbox was used to extract the mean signal of each subregion, and group differences in fALFF and ReHo for these subregions were tested by controlling for age, sex and Generalized Anxiety Disorder (GAD-7) (the results were considered significant for P < 0.05false discovery rate (FDR)-corrected). The covariate TIV (Intracranial volume) was additionally controlled for when comparing volumes (with a significance threshold of P < 0.05). Specifically, normally distributed variables were assessed using the Linear Model (LM), while nonnormally distributed data were evaluated using the Generalized Linear Mode (GLM). To investigate relationships between alterations in structure and function and clinical or neuropsychological variables, partial correlation analyses were conducted, controlling for age, sex, and GAD-7 (and TIV when evaluating volumetric measures). Statistical significance was determined at P < 0.05.

Additionally, we computed the structure–function coupling index, which quantitatively measures the interrelationship between anatomical structure and functional activity in the brain. This index characterizes how structural connectivity influences functional interactions across brain regions during task execution [44]. Following the approach described by Min et al. [45], who calculated surface-based correlations between ReHo and cortical thickness as coupling indices, we similarly derived functional-structural coupling indices by correlating subregional volume with fALFF/ReHo metrics. Subsequently, we performed Fisher's Z-transformation on these correlation coefficients to normalize their distributions, and the Fisher's Z-transformed coupling coefficients were then statistically compared between the two groups, the results were considered significant for P < 0.05.

Results

Demographics and clinical data

A total of 69 patients were included in this study, consisting of 35 with right-sided headache, 29 with left-sided headache, and 5 with alternating headache sides. When comparing headache-side brain regions between patients and HCs, these 5 patients with alternating headaches were categorized as left- and right-sided headache. However, when comparing the non-headache (contralateral) side between patients and HCs, those 5 patients were excluded from analysis. Table 1 presents the baseline characteristics of the participants, with *p*-values reflecting group comparisons between in-bout but outside the attacks eCH patients and HCs. There were no significant differences in age between the groups (P > 0.05), whereas sex distribution significantly differed between groups (P < 0.05). The eCH group reported higher GAD-7 scores compared to the HC group (P < 0.001). However, there

Marker	eCH group volume	HC group volume	Z/t values	Р
Headache side				
R-anterior inferior	27.12 ± 21.85	22.51 ± 4.75	-2.378	0.019*
R-posterior	45.29±28.03	36.00 ± 6.79	-2.422	0.017*
L-molecular_layer_HP-head	321.53 ± 36.36	323.38±38.00	2.081	0.040*
L-lateral-nucleus	661.09±71.14	656.01±69.33	2.025	0.046*
L-Central-nucleus	38.48 (34.80, 42.98)	41.81 (36.25, 43.91)	2.494	0.013*
Contralateral side				
L-tuberal inferior	72.50 ± 32.23	63.63 ± 10.17	-2.154	0.034*
L-tuberal superior	44.57 ± 14.81	37.18±9.13	-2.413	0.018*
R-parasubiculum	54.88 (48.09, 59.71)	57.35 (52.00, 65.37)	2.418	0.016*

 Table 2
 Brain regions displaying significant between-group differences in volume

Abbreviations: L left, R right, eCH episodic cluster headache, HC healthy control, HP hippocampal

^a significant difference from the HC (*P* < 0.05). Data following a normal distribution were expressed as mean ± SD, whereas data not meeting the normal distribution criteria were expressed as median and interquartile range (IQR)

was no significant difference in Patient Health Questionnaire-9 (PHQ-9) scores between the two groups (P > 0.05).

Volumetric changes in hypothalamic, thalamic, amygdalar, and hippocampal subregions in eCH and association with clinical variables

By comparing the results of volumetric analysis, after controlling for age, sex, GAD-7 and TIV, we found that in patients with eCH, the volumes of right anterior inferior and right posterior of hypothalamus, left molecular_layer_ HP-head of hippocampus, left lateral-nucleus and left Central-nucleus of amygdala on the headache side, as well as left tuberal inferior and left tuberal superior of hypothalamus, right parasubiculum of hippocampus on the contralateral side were significantly altered compared with HCs (P<0.05) (Table 2), with no statistical differences between the remaining brain regions (Data from other regions can be found in Table S2 and Table S3). As presented in Fig. 2, partial correlation analysis showed that the volume of the right anterior inferior hypothalamus on the headache side was positively correlated with the duration of last headache episode (r=0.339, P=0.046). However, there was no



the volume of the right anterior interior

Fig. 2 The volume of the right anterior inferior hypothalamus on the headache side was positively correlated with the duration of the last headache episode

significant correlation between the other subregions with volumetric alterations and clinical parameters.

Group differences in functional values and association with clinical variables

The results indicated that eCH patients demonstrated higher fALFF values in hippocampal (left-parasubiculum, bilateral-hippocampal-fissure, right-presubiculum-head, bilateral-subiculum-head, bilateral-Cornu Ammonis (CA) 1-head, left-CA3-head, bilateral-CA4-head, left-CA4body, bilateral-Granule Cell and Molecular Layer of the Dentate Gyrus (GC-ML-DG)-head, left-GC-ML-DGbody, bilateral-molecular layer hippocampus (HP)-head, left-molecular_layer_HP-body) and amygdalar subregions (bilateral-Lateral-nucleus, left-Basal-nucleus and right-Paralaminar-nucleus) on the headache side. Elevated fALFF values were also observed in hippocampal (leftparasubiculum, left-hippocampal-fissure, left-presubiculum-head, left-presubiculum-body, left-subiculum-head, left-CA1-head, left-CA3-head, left-CA4-head, left-CA4body, left-GC-ML-DG-head, left-GC-ML-DG-body, left-molecular_layer_HP-head, left-molecular_layer_HPbody) and amygdalar subregions (left-Lateral-nucleus, left-Basal-nucleus, left-Anterior-amygdaloid-area-AAA and left-Paralaminar-nucleus), in addition to a decreased fALFF value in left-CA3-body on the contralateral side, compared to HCs ($P_{FDR} < 0.05$). Further details are presented in Table S4 and Table S5.

Inversely, ReHo analysis showed that patients with eCH had significantly lower ReHo values than HCs $(P_{FDR} < 0.05)$ in hypothalamus (left-anterior inferior, leftposterior, left-tuberal inferior, left-tuberal superior, leftanterior superior), thalamus (left-Anteroventral Thalamic Nucleus (AV), left-Lateral Posterior Thalamic Nucleus (LP), left-Lateral Pulvinar Nucleus (PuL), left-Ventral Anterior Nucleus (VA), left-Ventral Lateral Anterior Nucleus (VLa), left-Ventral Lateral Posterior Nucleus (VLp)), and amygdala (left-Central-nucleus, left-Accessory Basal nucleus) on the headache side, as well as in hypothalamus (right-anterior inferior, right-tuberal inferior, right-anterior superior), thalamus (right-AV, right-LP, right-VLa, right-VLp), hippocampal (right-Hippocampal tail), and amygdala (right-Central-nucleus) on the contralateral side. The comparison results can be seen in Table S6 and Table S7.

Further partial correlation analyses showed that the fALFF value in left-subiculum-head on the headache side was negatively correlated with cluster period duration (r=-0.356, P=0.049). Moreover, on the headache side, the ReHo values in left-tuberal superior, left-LP, left-PuL, left-VLp were positively correlated with cluster period duration (r=0.370, P=0.044; r=0.447, P=0.012; r=0.532, P=0.002; r=0.401, P=0.025), whereas the

ReHo value in left-anterior superior was negatively correlated with headache intensity (r=-0.606, P<0.001), and the ReHo value in left-Central-nucleus was positively correlated with PHQ-9 (r=-0.405, P=0.024). On the contralateral side, the ReHo value in the right VLp was positively correlated with cluster period duration (r=0.413, P=0.036), and the ReHo values in the right anterior superior and right central nucleus were positively correlated with PHQ-9 (r=0.420, P=0.037; r=0.570, P=0.002) (Fig. 3). The rest data can be seen in Table S1.

Correlation analysis of functional and structural coupling across limbic subregions

To further investigate how structural and functional abnormalities interact within the limbic system in eCH, we first identified regions that showed concurrent structural and functional alterations (e.g., left molecular layer HP-head, left-Central-nucleus), yielding no significant association. We then computed functional-structural coupling indices (i.e., correlation coefficients between volume and fALFF/ReHo) for each subregion and transformed these indices with Fisher's z. Group comparisons showed that coupling indices in the right anterior inferior (Z_{diff} = -2.093, P=0.036) and the left LGN (Z_{diff} = -2.067, P=0.039) on the headache side differed significantly between eCH patients and HCs. No other brain regions demonstrated statistically significant group differences (P > 0.05). The correlation coefficients and coupling indices are presented in Table S8 and Table S9.

Discussion

Based on a strong prior hypothesis, we conducted a multimodal investigation of structural (volumetric) and functional (fALFF/ReHo) alterations in 7T MRI across limbic subregions in eCH patients, while simultaneously evaluating functional-structural coupling indices to uncover mechanistic underpinnings. We report three main robust findings. First, we observed significant volumetric alterations in the hypothalamus, hippocampus, and amygdala on the headache side, alongside subregional hypothalamic and hippocampal changes on the contralateral side. Importantly, the volume of the right anterior inferior hypothalamus (on the headache side) was associated with the duration of the last headache episode. Second, widespread functional reorganization, characterized by elevated fALFF and reduced ReHo across most of these altered subregions, with clinically relevant correlations involving cluster period duration, headache intensity, and PHQ-9 scores. Third, altered coupling indices in the right anterior inferior hypothalamus and the left LGN. These three findings suggest that acute eCH pathophysiology involves subregion-specific changes within



Fig. 3 Correlation between functional values and clinical parameters. A A significant negative correlation between the fALFF values in left-subiculum-head on the headache side and cluster period duration; B A significant correlation between the ReHo values of different brain regions on the headache side and cluster period duration; C A significant negative correlation between ReHo values of left-anterior superior on the headache side and headache intensity; D A significant positive correlation between the ReHo values of left-Central-nucleus on the headache side and PHQ_9; E A significant positive correlation between the ReHo values of right_VLP on the contralateral side and cluster period duration; F A significant correlation between the ReHo values of different brain regions on the contralateral side and PHQ_9

hypothalamic-limbic circuits, while most network-level coupling remains resilient—a phenomenon potentially attributable to compensatory mechanisms.

Although volumetric studies of cCH often report significant alterations in limbic regions [46-48], eCH studies remain scarce [49–51], likely due to methodological limitations in detecting subtle subregional changes. Through stringent in-bout but outside the attacks patient selection and 7 T MRI's enhanced resolution, we identified a hypothalamic volumetric increase-a region associated with autonomic/neuroendocrine functions [52]. This finding aligns with sporadic reports of hypothalamic hypertrophy in CH [48] and emphasizes the important roles of the hypothalamus in the pathophysiology of CH [53, 54] in terms of macroscopic-level evidence. The correlation between right anterior inferior hypothalamic volume and the duration of the last headache episode implies a state-dependent plasticity that may underlie the pathophysiological heterogeneity of eCH, reflecting activity-dependent or neuroplastic changes previously described in headache disorders [1, 55–57].

In agreement, the seminal positron emission tomography (PET) /fMRI work by May et al. [10] demonstrated posterior hypothalamic activation during eCH attacks and laid the foundation for investigating this region's dual role in pain modulation and circadian regulation. Based on this background, Goadsby et al. [52] further established the hypothalamus as the nexus of CH's circadian features (e.g., nocturnal attack predominance) and autonomic manifestations (e.g., tearing, rhinorrhea), mediated through its connections to the suprachiasmatic nucleus (SCN) and brainstem autonomic centers. These clinical phenomena concur with the SCN's master regulatory role in circadian rhythms [58, 59] and the thalamic involvement in nociceptive signal integration and affective processing [60]. We propose that during headache attacks, these networks may become abnormally hyperactive, potentially resulting in localized metabolic changes and subsequent microstructural alterations (e.g., in neurons, glial cells, or vasculature) [61], manifesting as detectable volumetric alterations on high-resolution MRI [62].

Notably, we also detected volumetric alterations in the hippocampus (e.g., left-molecular layer HP-head, right-parasubiculum) and amygdala (left-lateral nucleus, left-central nucleus), underscoring that hypothalamic

changes do not occur in isolation. The hippocampus is very sensitive to chronic stress and pain, and repeated severe pain and sleep disruption (CH often nocturnal) can trigger activation of the stress axis, and excessive glucocorticoids and excitotoxicity may lead to hippocampal atrophy or inhibit neuroplasticity [17]. Established migraine studies have shown that the higher the frequency of headache, the smaller the hippocampal volume, indicating that chronic headache can bring about structural plasticity changes in the hippocampus [63]. The amygdala is a central structure for the modulation of nociceptive emotions and autonomic responses, and its central nucleus is connected to downstream nociceptive modulation and autonomic centers in the brainstem. We observed abnormal volume of the central nucleus of the amygdala, suggesting that extreme pain stress in CH may trigger neural loop remodeling in the amygdala, which has also been reported in patients with chronic migraine combined with depression [64]. Therefore, the altered volume of the hypothalamus may be the underlying alteration in the pathogenesis of CH, whereas the abnormalities in the hippocampus and amygdala reflect the cumulative effects of recurrent episodes on the limbic system, which together form part of the complex pathophysiology of CH: both the mechanisms of pain onset, and the modulation of pain, memory, and emotional response. Whether these volumetric changes persist beyond the active period of eCH remains an open question, emphasizing the need for longitudinal designs to discern trait markers from state-dependent responses.

While structural neuroimaging provides valuable insights, it does not give a complete picture of eCH pathophysiology. Emerging evidence suggests functional metrics may better reflect dynamic pathological processes. Diverging from conventional whole-region analyses [54, 65], our subregion-based paradigm uncovered more extensive functional disturbances than structural anomalies. eCH, as a primary subtype of trigeminal autonomic cephalalgias (TACs), involves complex interactions within the trigeminal nerve, its associated brainstem nuclei (e.g., the spinal trigeminal nucleus), and their connections to the hypothalamus, thalamus, and amygdala. These structures form intricate, bidirectional neural networks [14]. These systems can become hyperactive during eCH attacks, causing abnormal sympathetic/ parasympathetic activity (manifesting as tearing, rhinorrhea, etc.), while simultaneously engaging emotion- and memory-related structures (e.g., hippocampus and amygdala) and provoking fear/anxiety circuitry in the amygdala. This may leads to amplified emotional reactivity and autonomic dysregulation, ultimately causing widespread functional disturbances, Furthermore, when the SCN and neighboring hypothalamic regions are placed under

high stress or hyperactivation, dysregulated neurochemical release (e.g., glutamate, serotonin, and orexin) may ensue [1, 57], disrupting network-level integration and manifesting as altered fALFF/ReHo metrics [54]. Our data support this hypothesis, demonstrating the limbic system's alterations in both fALFF and ReHo among eCH cohorts.

The apparent paradox of concurrent fALFF elevation and ReHo reduction resolves when considering their distinct neurophysiological correlates [66], increased nociceptive drive and autonomic dysregulation may collectively amplify neuronal excitability while impairing local temporal coherence in eCH pathophysiology-a dual mechanism potentially underlying aberrant painemotion integration, as observed in other chronic pain disorders [10, 67]. Notably, the correlation of fALFF and ReHo measures with key clinical features highlights the clinical significance of these neuroimaging findings. For example, reduced ReHo in the ipsilateral anterior superior hypothalamus was negatively associated with headache intensity, indicating that more severe headaches coincide with greater local desynchronization. Conversely, decreased ReHo in the central nucleus of the amygdala was positively correlated with PHQ-9 scores, suggesting that limbic system disruption may link mood dysregulation to the chronic pain experience [68]. These findings collectively support that functional reorganization of the brain in CH patients is not an accidental phenomenon, but a dynamic process closely related to disease severity (e.g., headache frequency and intensity) and psychological state. The brain adapts to repeated severe pain stimuli by adjusting the strength and synchronization of local neural activity, but this adjustment may also mediate symptom exacerbation (e.g., increased pain and co-morbid mood disorders), reflecting a complex maladaptive mechanism.

Interestingly, despite noticeable local abnormalities, our subregion-level coupling analyses indicated most hypothalamic-limbic networks maintained stable structure-function relationships. This "preserved network coupling" phenomenon implies that within the relatively short time duration of acute eCH attacks, local functional and structural changes may not have a sufficient impact on global structure-function relationships to produce statistically detectable differences. Function-structure coupling might act as a more stable or slowly adapting index, only deviating from normal under prolonged or more severe pathological stress [69]. Nevertheless, one of the study's more novel findings is altered coupling indices in the right anterior inferior hypothalamus and left LGN. As a key node in the CH, abnormalities in the structurefunction coupling of the right anterior inferior imply that anatomical alterations are not translated into functional

outputs in a normal ratio, which echoes previous studies that gray matter increased while metabolically active in the hypothalamus during headache attacks [70]. And because the LGN relays visual signals to the suprachiasmatic nucleus, alterations in this region may implicate circadian misalignment in nocturnal eCH attacks [71]. Overall, our results may not only represent a pathological reorganization of neural circuits, but also prove hypothalamic and thalamic susceptibility in the pathogenesis of eCH. Additionally, as our analysis focused on coupling within the same subregion, prior research indicates that function-structure coupling may also occur across different regions [72], underscoring brain may have compensatory function and the importance of whole-brain network analyses. It is also important to recognize that insufficient statistical power and methodological limitations are significant reasons for obtaining negative results.

Our study has several strengths that enhance the robustness and reliability of the study: First, we included a total of 69 patients with eCH, which is a larger sample size than previous studies. Second, unprecedented 7T MRI resolution enables submillimeter detection of subtle neurodynamic changes typically obscured at lower field strengths; Finally, multimodal integration of structural, functional, and coupling metrics provides triangulated pathophysiological insights. Clinically, our high-precision mapping of hypothalamic-thalamic-hippocampal anomalies could inform targeted neuromodulation strategies, potentially optimizing DBS electrode placement or combining hypothalamic stimulation with hippocampal-directed interventions [73].

Despite several strengths, some limitations need to be acknowledged. Firstly, our study exhibited a gender imbalance. Although we statistically controlled for gender as a covariate in the analyses, the uneven distribution may still limit the generalizability of our findings. Future studies should adopt stratified recruitment criteria or dedicated sex-balanced cohorts to validate these results and explore potential biological or behavioral differences across genders. Secondly, due to the present study's design precludes us from determining whether the structural and functional abnormalities are a cause or a consequence of the disease, or simply a status indicator. Future longitudinal investigations, ideally including remission imaging assessments, are crucial to confirm whether these alterations indeed represent state-dependent plasticity or serve as trait markers of eCH susceptibility. Additionally, although all participants were right-handed, and we controlled for age, sex, and TIV, medication effects could not be definitively excluded, despite some previous findings suggesting that observed volume changes may not be driven by treatments [48, 74-76]. Lastly, although we evaluated local morphological changes and spontaneous activity (fALFF, ReHo) and performed the corresponding coupling analysis, the neural circuits of pain are highly complex. The structural and functional connectivity patterns across the entire brain remain incompletely understood, and the brain regions within the limbic system have yet to be fully explored. Therefore, in future studies, we plan to integrate diffusion tensor imaging (DTI) and functional connectivity (FC) analyses to precisely characterize whole limbic system regions, aiming to better elucidate pain-related neural circuits.

Conclusions

Our results are a fundamental step further in the comprehension of the pathophysiology of eCH in relation to the possible involvement of the limbic system. Specifically, we identified marked volumetric and functional alterations in hypothalamic (right anterior inferior), hippocampal (subiculum-head, parasubiculum), and amygdalar (lateral and central nuclei) subregions, with clinically significant correlations. Most structure-function relationships appeared resilient under acute eCH conditions, but significant deviations in coupling indices at critical nodes (right anterior inferior hypothalamus, left LGN) highlight areas warranting further exploration. The limbic system abnormalities we documented hold promise as objective biomarkers to guide individualized interventions. For instance, hypothalamic DBS for intractable CH may be refined about the specifically atrophied subregions noted here, or possibly paired with other neuromodulation approaches [73]. However, longitudinal and multimodal imaging studies will clarify whether these anomalies persist across headache-free intervals and how they may inform targeted interventions to alleviate eCH burden.

Abbreviations

eCH	Episodic cluster headache
fALFF	Fractional Amplitude of Low-frequency Fluctuations
ALFF	Amplitude of low-frequency fluctuations
mALFF	Mean amplitude of the low-frequency fluctuation
ReHo	Regional homogeneity
HC	Healthy control
CH	Cluster headache
cCH	Chronic cluster headache
L	Left
R	Right
DBS	Deep brain stimulation
VTA	Ventral tegmental area
T1WI-3D-MP-RAGE	T1-weighted three-dimensional magnetization-pre- pared rapid acquisition gradient echo
rs- fMRI	Resting-state functional MRI
BOLD	Blood oxygen level-dependent
PHQ-9	Patient Health Questionnaire-9
GAD-7	Generalized Anxiety Disorder
ICHD-3	International Classification of Headache Disorders, 3rd edition
EPI	Echo-planar imaging
TR	Repetition time
TE	Echo time
MNI	Montreal Neurological Institute

FWHM	Full width at half maximum
FFT	Fast Fourier transform
ROI	Region-of-interest
TIV	Intracranial volume
LM	Linear Model
GLM	Generalized Linear Mode
FDR	False discovery rate
CA	Cornu Ammonis
GC-ML-DG	Granule Cell and Molecular Layer of the Dentate Gyrus
HP	Hippocampus
AV	Anteroventral Thalamic Nucleus
CM	Centromedian Nucleus
LGN	Lateral Geniculate Nucleus
LP	Lateral Posterior Thalamic Nucleus
MDm	Mediodorsal Medial Nucleus
MGN	Medial Geniculate Nucleus
Pf	Parafascicular Thalamic Nucleus
Pul	Inferior Pulvinar Nucleus
PuL	Lateral Pulvinar Nucleus
PuM	Medial Pulvinar Nucleus
VA	Ventral Anterior Nucleus
VLa	Ventral Lateral Anterior Nucleus
VLp	Ventral Lateral Posterior Nucleus
HATA	Hippocampus-Amygdala Transition Area
PET	Positron emission tomography
SCN	Suprachiasmatic nucleus
TACs	Trigeminal autonomic cephalalgias
DTI	Diffusion tensor imaging
IQR	Interquartile range
VAS	Visual Analogue Scale
CHRIS	Chinese Cluster Headache Register Individual Study
FC	Functional connectivity

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

XYW, LHZ, ZD, and XL. Acquisition of data: XYW, YQX, MMH, SHZ, CHD, SW, XYW, HXL, JYH, YL, ZXL. Data analysis and writing the manuscript: XYW and LHZ. Review and editing, funding acquisition, supervision: ZD and XL. All authors contributed intellectual content to the revised manuscript and read and approved the final manuscript. XYW and LHZ contributed equally to this article.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Chinese PLA General Hospital in accordance with the ethical principles of the Declaration of Helsinki. (S2023-459-01).

Consent for publication

All authors consent for the publication.

Competing interests

The authors declare no competing interests.

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