Original Article

Increased effective connectivity from the hypothalamus to the left superior frontal gyrus and its association with visual analogue scale in persons with migraines

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Background: In recent years, several functional imaging studies have shown that the hypothalamus is closely associated with migraine and have suggested that the hypothalamus may be a potential site of migraine generation. Studying the characteristics of the functional network of the hypothalamus in persons with migraines may help to understand the neural mechanisms of migraine. We thus used resting-state functional magnetic resonance imaging (rsfMRI) and Granger causal analysis to investigate the effective connectivity (EC) of the hypothalamus in persons with migraines.

Methods: The study included 17 healthy volunteers and 39 persons with migraines. The EC calculation was based on rsfMRI data from a 3-T magnetic resonance imaging scanner. The brain networks of the hypothalamus were compared using a general linear model to determine if there were any differences between the two groups. We used Pearson correlation analysis to examine the correlation between EC values in abnormal brain regions and clinical variables.

Results: Compared with healthy controls, those with migraines showed decreased EC from the hypothalamus to the left fusiform and increased EC from the hypothalamus to the medial frontal gyrus/orbital part, right lingual gyrus, left superior frontal gyrus, and right middle frontal gyrus ($P<0.05$). Meanwhile, persons with migraines also showed decreased EC from the left middle frontal gyrus and right medial frontal gyrus/orbital part to the hypothalamus ($P<0.05$). EC from the hypothalamus to the left superior frontal gyrus correlated significantly and positively with the visual analogue scale in those with migraines ($r=-0.3820$; $P=0.0164$).

Conclusions: Disturbances in the EC between the hypothalamus and the prefrontal gyrus and visual cortex may play a key role in the neuropathological features of persons with migraines. The current study

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adds to our understanding of the complexity of migraine mechanisms.

Keywords: Persons with migraines; hypothalamus; effective connectivity (EC)

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Introduction

Migraine is a neurological disorder characterized by paroxysmal unilateral throbbing headache and autonomic nervous system dysfunction. Migraine affects 10–15% of the population and is a significant personal and social burden (1). Headaches can be accompanied by nausea, vomiting, scalp tenderness, and other negative symptoms, and frequent attacks can seriously disrupt daily life and work (1).

A growing body of research suggests that the hypothalamus is involved in the pathogenesis of migraine (2,3). Many of the symptoms of the prodromal phase of migraine, such as fatigue, irritability, mood changes, and disruption in circadian rhythm, are closely linked to hypothalamic function (2,3). Other imaging studies have also demonstrated the early activation of hypothalamic function in persons with migraines (4-7).

During the headache phase of a migraine attack, blood flow to the limbic system is higher and hypothalamic connections to the limbic system are reduced as compared to the interictal phase (4,5). Migraine attacks are preceded by a decrease in blood flow to the hypothalamus in persons with migraines (6). During headache, there is a significant activation of the hypothalamus in those with migraines, which persists even after the headache is relieved by sumatriptan (7).

Research has also identified the presence of abnormalities in the functional network of the hypothalamus (8,9). A longitudinal follow-up study showed reduced functional connectivity between the hypothalamus and the parahippocampal gyrus, temporal lobe, lingual gyrus, and orbitofrontal gyrus in persons with migraines at baseline compared to healthy controls (HCs). Functional connectivity between the hypothalamus and bilateral orbitofrontal gyrus was increased in persons with migraines compared with baseline. Those with migraines also had reduced functional connectivity between the hypothalamus and the lingual gyrus. The higher the frequency of migraine attacks was, the lower the functional connectivity between the hypothalamus and the lingual gyrus at baseline, while the greater the impact of headaches at follow-up was, the lower the functional connectivity between the hypothalamus and the orbitofrontal gyrus at baseline. At follow-up, lower migraine attack frequency was associated with higher functional connectivity between the hypothalamus and the orbitofrontal gyrus (8). Another cross-sectional analysis of resting-state functional connectivity showed significantly increased functional connectivity between the hypothalamus and brain regions of the default mode network (DMN) and the dorsal visual network in persons with migraines compared with HCs. Migraine severity was positively correlated with the strength of connections in the hypothalamus and negatively correlated with the strength of connections in the medial prefrontal cortex, which is part of the DMN (9).

Functional connectivity describes the correlation of activity between different brain regions but does not provide information regarding the direction of action between brain regions. In contrast, effective connectivity (EC), obtained using Granger causal analysis (GCA), can provide both correlations and directions of action between different brain regions (10). GCA has been used to investigate the EC of the thalamus and amygdala in persons with migraines (11,12).

In our study, we investigated the characteristics of EC of the hypothalamus in persons with migraines using resting-state functional magnetic resonance imaging (fMRI) and GCA methods. Based on previous studies, we hypothesized that there would be differences in EC between the hypothalamus and visual-, cognitive-, and emotion-related brain regions in persons with migraines as compared to HCs. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-588/rc).

Methods

Participants

Between March 2014 and October 2014, 41 persons with migraines and 17 HCs were recruited for this cross-sectional study conducted at the Second Affiliated Hospital of Hebei Medical University. All persons with migraines fulfilled the diagnostic criteria of the International Classification of Headache Disorders, Second Edition (ICHD-2) (13). Two neurologists specializing in headache disorders who were blinded to the magnetic resonance imaging (MRI) and neuropsychological results clinically assessed the participants. Demographic data and the following clinical characteristics were obtained from those with migraines: age of onset, duration of disease, frequency of migraine attacks (days/months), and mean pain intensity. The average pain intensity of migraine attacks was assessed using the visual analogue scale (VAS). The VAS score is marked by the patient according to their feelings. A scale about 10 cm long is used, with 0 and 10 at opposite end, with 0 indicating no pain and 10 indicating the most unbearable pain. A score of 4 or more indicates significant pain. The inclusion criteria were no headache attacks 3 days before, on the day of, and 3 days after the scan; no history of substance abuse or prophylactic medication; no contraindications to MRI and no abnormal signals on routine brain scans; and not in a state of pregnancy or menstruation. Patients were required to be pain free throughout the fMRI recording and to have not taken any acute migraine medication for at least 3 days prior to the scan in order to prevent any potential interference from attacks or treatments. To avoid the effects of other brain diseases, two persons with migraines were excluded due to high signal on fluid-attenuated inversion recovery images. HCs were matched in terms age, sex, and years of education. The exclusion criteria for this study included a family history of migraine or any other type of headache disorder. To minimize the effect of hormones on cortical excitability, all female participants were enrolled midcycle and could not be pregnant or lactating.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of Second Affiliated Hospital of Hebei Medical University (No. 2017-R006). All participants provided their written informed consent before undergoing any procedures.

MRI scans

Images were acquired on a 3.0-Tesla Achieva X-series MRI scanner (Philips, Amsterdam, the Netherlands). All participants were told to lie in the supine position, keep their heads still, remain awake, and close their eyes during the MRI scan. Gradient-recalled echo-planar imaging was used to acquire resting-state fMRI images. The following parameters were used: repetition time =2,000 ms, echo time =30 ms, slice =35, thickness =4 mm, gap =0 mm, field of view =240 mm × 240 mm, acquisition matrix =80×80, and flip angle =90°. The fMRI sequences were completed in 8 minutes.

Data processing

Preprocessing of the functional images was performed using the SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and the Resting State fMRI Data Analysis Toolkit+ (RESTPlus) v. 1.25 (http://www.restfmri.net). In order to guarantee a steady-state condition, the first 10 volumes were discarded. Slice timing and head motion were adjusted for the remaining images. Excluded from the study were participants exhibiting head movements greater than 2.0 mm in translation or 2.0° in rotation in any direction. The subsequent procedures involved resampling with a 3×3×3 mm^3 resolution, spatial normalization in the Montreal Neurological Institute (MNI) space, and spatial smoothing using a Gaussian kernel of 6 mm at full width at half-maximum. In order to minimize high-frequency noise and low-frequency drift, the resulting fMRI data were band-pass (0.01–0.08 Hz) filtered and purged of linear trends. Several sources of spurious variance were eliminated, including signals from the entire brain, the ventricular system, and white matter, as well as head motion parameters.

Resting-state EC analysis

Each participant's hypothalamus was seeded in an *in vivo* anatomical atlas of subcortical nuclei using an atlas-based methodology (14) (*Figure 1*). RESTPlus v. 1.25 was used to perform voxel-wise GCA analysis on each participant. The causal effects of the region of interest on other regions (the X to Y effect and the Y to X effect) were evaluated using Granger causality estimation. For each participant, the results were displayed as a GCA map from the hypothalamus to the entire brain (x2y) and as a GCA map from the entire brain to the hypothalamus (y2x). Fisher r-to-z transformation was then used to convert each individual-level EC map into a z-map for second-level group analyses.

Statistical analysis

To determine if there were statistically significant

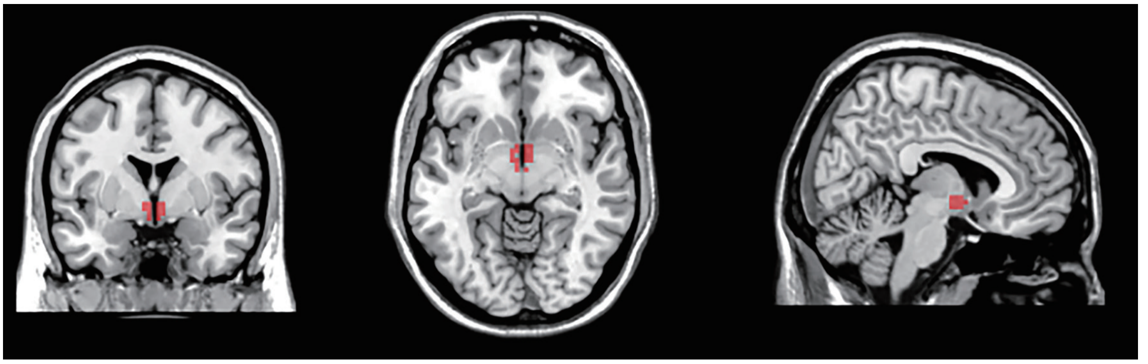

Figure 1 Schematic representation of the positioning of the hypothalamus, superimposed on the Colin27 template (15). The Colin27 template is published with open access under the following copyright: 1993–2009 Louis Collins, McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University. We were not required to obtain permission for its use.

Table 1 Demographics and neuropsychological data

	Persons with migraines	HC	z/χ^2	P
Gender, n (M/F)	39 (9/30)	17 (6/11)	2	0.1573
Age (years)	34.5±9.6	36.5±8.9	−0.749	0.4533
Education (years)	14±4	15±4	−1.430	0.1527
Duration (years)	9±7	–	–	–
Frequency (d/m)	4.0±6.5	–	–	–
VAS score	6.64±1.4	–	–	–

Data are the mean ± SD. Data were analyzed using independent-samples *t*-tests. HC, healthy control; M, male; F, female; d/m, days per month; VAS, visual analogue scale; SD, standard deviation.

differences in clinical information between the two groups, the Chi-squared test was used to compare group differences in gender while the Mann-Whitney test was used to compare age and educational level between the two groups.

Restplus (www.restfmri.net) was used for statistical analysis. Individual functional connectivity maps, normalized between the two groups on a voxel-by-voxel basis, were subjected to a general linear model. We regressed the mean relative change in head movement, age, and sex as covariates in a two-sample *t*-test analysis to minimize the effect of confounding variables in the statistical analysis. AlphaSim was used to correct for multiple comparisons, with individual combined P values for voxels <0.005 with cluster size >25 voxels resulting in a statistical map with P<0.05 (for multiple comparisons). A Pearson correlation between the Z-value of abnormal brain regions and clinical outcomes (VAS, frequency, duration of illness) in persons with migraines was performed to investigate the relationship between EC value and clinical outcomes in those with migraines. The cutoff for statistical significance was set at P<0.05.

Results

Neuropsychological results

The two groups were not significantly different in terms of age (z=−0.749; P=0.4533), sex distribution (χ^2=2; P=0.1573), or years of education (z=−1.430; P=0.1527). *Table 1* shows details of the demographics data and associated tests.

Altered EC of the hypothalamus in persons with migraines

Compared with HCs, those with migraines showed decreased EC from the hypothalamus to the left fusiform and increased EC from the hypothalamus to the medial frontal gyrus/orbital part, right lingual gyrus, left superior frontal gyrus, and right middle frontal gyrus. Moreover, this

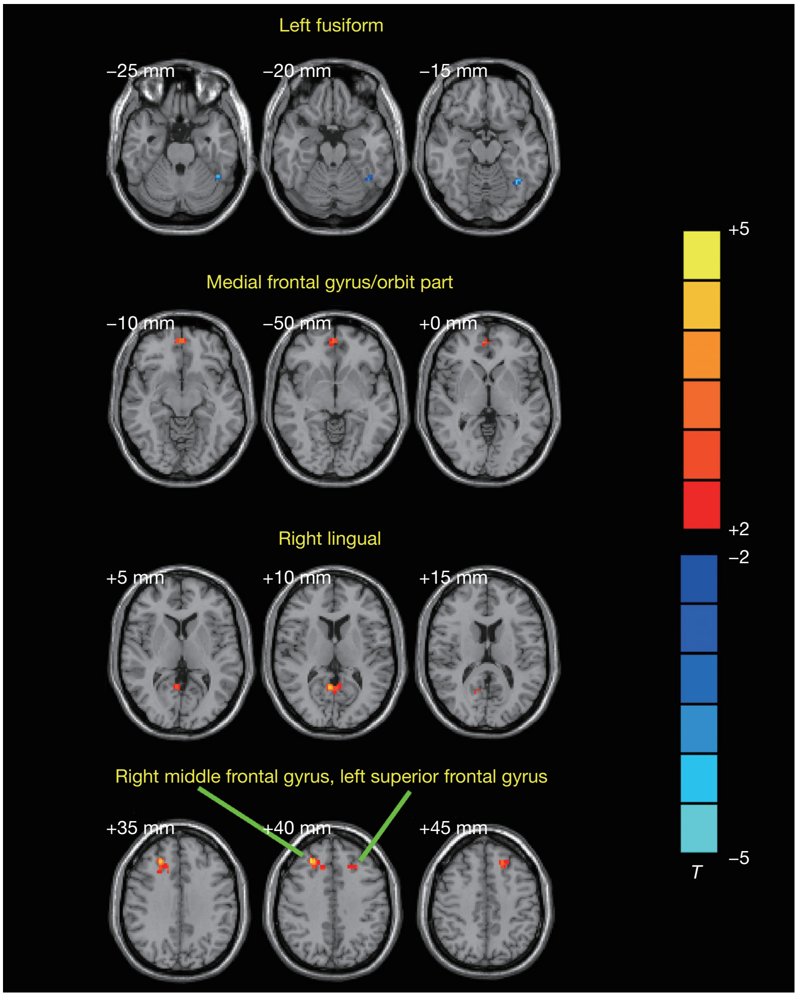

Figure 2 Brain regions with significantly different EC values from the hypothalamus to these brain regions in the persons with migraines group compared with the HC group. The *t* values for the peak points of the differential brain regions are depicted in *Table 2*. EC, effective connectivity; HC, healthy control.

group showed decreased EC from the left middle frontal gyrus and right medial frontal gyrus/orbital part to the hypothalamus (*Figures 2,3*, *Table 2*).

Relationships between EC values and clinical variables

EC values from the hypothalamus to the left superior frontal gyrus were significantly negatively correlated with the VAS (r=−0.3820; P=0.0164) (*Figure 4*).

Discussion

In this study, we investigated changes in hypothalamic EC in persons with migraines. EC from the hypothalamus to the left fusiform was lower in those with migraines compared with HCs, while the EC with the medial frontal gyrus/orbital part, right lingual, left superior frontal gyrus, and right middle frontal gyrus was higher. Meanwhile, persons with migraines also showed reduced EC from the right medial frontal gyrus/orbital part to the hypothalamus and left middle frontal gyrus. Abnormal brain regions were found particularly in the prefrontal cortex and visual cortex.

The orbitofrontal lobe is part of the limbic system, which, through its connection to the hypothalamus, is involved in mediating instinctive and affective behavior (16). Migraine is strongly associated with comorbid depression, anxiety, posttraumatic stress disorder, and sleep disturbance (17). Cross-sectional studies using low-frequency amplitude

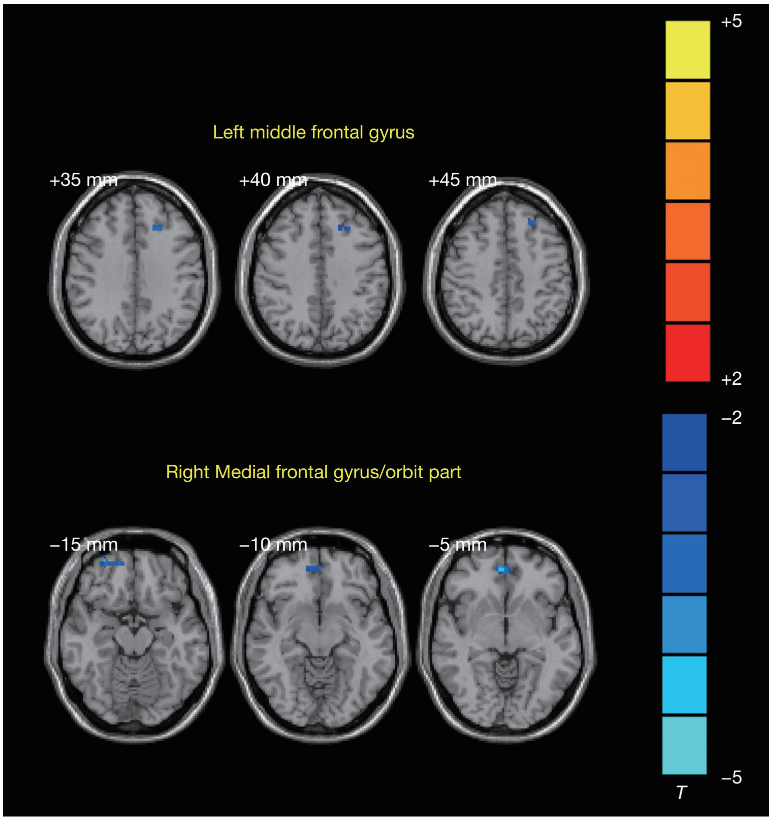

Figure 3 Brain regions with significantly different EC from these brain regions to the hypothalamus in persons with migraines group compared with the HC group. The *t* values for the peak points of the differential brain regions are depicted in *Table 2*. EC, effective connectivity; HC, healthy control.

Table 2 Brain regions with significantly different EC values with hypothalamus in the persons with migraines compared with HCs

Brain region	Voxels	BA	MNI coordinates			*t* value	P value
			x	y	z		
X2y							
Left fusiform	36	37	−39	−54	−18	−3.9895	<0.005
Medial frontal/orbit part	37	10	3	54	−6	3.6211	<0.005
Right lingual	53	17	6	−57	9	3.9725	<0.005
Left superior frontal gyrus	46	32	−18	30	45	3.6277	<0.005
Right middle frontal gyrus	59	9	27	33	39	4.3677	<0.005
Y2x							
Medial frontal/orbit part	57	10	3	51	−6	−4.1195	<0.005
Left middle frontal gyrus	34	9	−22	30	36	−4.4365	<0.005

EC, effective connectivity; HC, healthy control; BA, Brodmann area; MNI, Montreal Neurological Institute; X2y, from the hypothalamus to the other brain regions; Y2x, from the other brain regions to the hypothalamus.

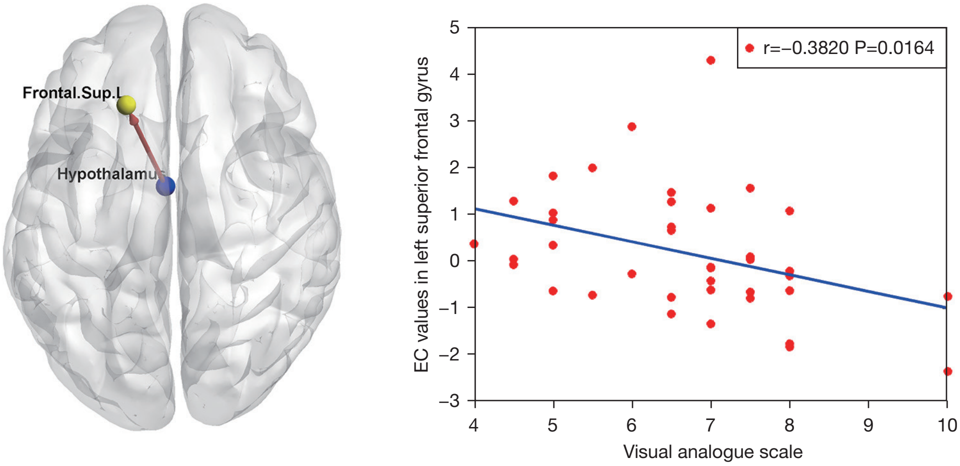

Figure 4 Values of EC from the hypothalamus to the left superior frontal gyrus were significantly negatively correlated with the visual analogue scale in persons with migraines. Sup, superior; EC, effective connectivity.

methods have shown that persons with migraines have local spontaneous activity abnormalities in the orbitofrontal lobe (18). A longitudinal fMRI study showed that blood flow to the limbic system is increased during a migraine attack. Compared with that in the preictal interictal period, functional connectivity of the hypothalamus to the limbic system is reduced (4). Consistent with previous findings (4), we also identified abnormal EC from the hypothalamus to the limbic system in persons with migraines using Granger causality analysis.

Our results showed increased EC from the hypothalamus to the middle and superior frontal gyrus in persons with migraines. The middle and superior frontal gyrus are part of the DMN, a large-scale distributed brain network that plays a key role in cognition, including episodic memory formation and the monitoring of internal thoughts (19). Cognitive dysfunction is a common manifestation of migraine attacks (20). One meta-analysis reported abnormalities in the functional connectivity within the DMN in persons with migraines. Moreover, it found that persons with migraines have increased connections in the right parahippocampal gyrus and right cingulate gyrus and decreased connections in the left superior frontal gyrus, left middle frontal gyrus, and right orbitofrontal lobe (21). Transcutaneous vagal nerve stimulation (taVNS) can improve clinical symptoms in those with migraines, and an fMRI study demonstrated there to be increased connectivity between the inferior temporal gyrus and the DMN in those with migraines after taVNS intervention (22). This research indicates that there are different degrees of variation in DMN function in persons with migraines (21,22). However, the above-mentioned studies used a functional connectivity method, whereas our study used an EC method with the hypothalamus used as the seed point.

The lingual gyrus and fusiform gyrus are part of the visual cortex and are mainly responsible for recognizing faces and the secondary classification of objects (23,24). Individuals with migraine often have cognitive symptoms at different stages of the migraine. These include visuospatial ability, processing speed, attention, and executive function. Messina *et al.* performed fMRI visuospatial assessment, including angle and color discrimination tests, in persons with migraines. About 20% of persons with migraines have deficits on the visuospatial cognitive test (25). In one study, it was found that compared with HCs, persons with migraines had a reduction in low-frequency amplitude in the right lingual gyrus and left posterior cingulate gyrus (26). This study suggested abnormal spontaneous brain activity in the lingual gyrus in those with migraines (26). Studies of the relationship between brain glucose uptake (^{18}F-fluorodeoxyglucose) and age in HCs and persons with episodic migraines have shown a positive correlation between age and fusiform gyrus metabolism in those with migraines (27). The above-mentioned studies indicate abnormal function of the lingual gyrus and fusiform gyrus in persons with migraines from the perspective of local brain activity, while our results showed abnormal effective connections between the brain regions involved in visual cognition and the hypothalamus from the perspective of the brain network in those with migraines.

Our findings should be interpreted with several limitations in mind. First, multisite and large-sample data are needed to validate the reliability of the results of this study. Second, we employed a cross-sectional design that could only clarify the abnormal EC of the hypothalamus in persons with migraines but could not determine whether functional changes in the hypothalamus are involved in the development of migraine disease or their correlation with clinical manifestations. This should be investigated in future longitudinal studies. Third, we examined the characteristics of the hypothalamic EC in persons with migraines, but whether there is also abnormal fiber connectivity in the white matter between these brain regions and the hypothalamus needs to be investigated using diffusion tensor imaging.

Conclusions

We investigated the EC of the hypothalamus in persons with migraines using resting-state fMRI and the GCA method. Compared to that in HCs, the EC in persons with migraines is mainly located in the limbic system, the DMN, and the visual cortex. This study extends our understanding of brain network patterns in the hypothalamus of persons with migraines and helps us to better understand the underlying neural mechanisms related to this condition.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-588/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-588/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of Second Affiliated Hospital of Hebei Medical University (No. 2017-R006). All participants provided their written informed consent.

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