Aberrant brain functional connectome in migrainures revealed by resting-state fMRI

*[1]Yingying Huang MD, *[2]Jinming Cheng MD, [1]Mei Huang MS, [3]Xi Zhang MD, [2]Xiaoyuan Wu MD, [4]Zhihong Wang MD PhD, [2]Hebo Wang MD, [1]Xiaozheng Liu PhD
*YY Huang and JM Cheng contributed equaly to this work and are co-first authors

[1]Department of Radiology of the Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou, Zhejiang China; [2]Department of Neurology of the Hebei General Hospital, Shijiazhuang, Hebei, China; [3]Department of Neurology of Xingtai people's Hospital, Xingtai, Hebei, China; [4]Department of Neurology of the Second Affiliated hospital, Hebei Medical University, Shijiazhuang, Hebei, China*

Abstract

Previous studies have shown abnormalities in brain functional networks in different brain regions in migraineures, but the neural mechanisms underlying the whole brain functional connectome in migraineures remain unclear. We used resting-state functional magnetic resonance imaging (rsfMRI) to study abnormalities in the functional connectome of migraineures. In this study, we collected rsfMRI data from 39 migraineures and 17 healthy controls. The network-based statistic method was used to evaluate functional connectome differences between the two groups. We used Pearson correlation analysis to explore the relationship between abnormal functional connectivity and clinical characterisation. After network-based statistic analysis ($p < 0.01$, permutation = 500), compared to healthy controls, migraineurs showed an abnormal subnetwork of 76 nodes and 179 edges. The nodes were mainly located in the basal ganglia and sensorimotor areas. Functional connectivities between the caudate nucleus and occipital lobe and sensorimotor areas were significant positive correlated with visual analogue scale ($p < 0.02$). Abnormalities in the functional connectivity of the basal ganglia and sensorimotor areas are involved in the pathological mechanisms of migraine, while the caudate nucleus is a potential imaging marker for migraine.

Keywords: migrainure; network-based statistic; functional connectome.

INTRODUCTION

Migraine is a neurological disorder characterized by paroxysmal one-sided throbbing headaches and dysfunction of the autonomic nervous system. Migraine affects between 10-15% of the population and is a significant personal and social burden.[1] Prolonged migraines can lead to memory loss, which may lead to anxiety and depression over time, affecting daily life and work.[2] However, the pathological mechanisms of migraine are still unclear.

Neuroimaging techniques have been used to explore the pathological mechanisms of migraine.[3-5] Structural magnetic resonance imaging (MRI) showed greater total volume of the caudate nucleus and thalamus in migraineurs compared with healthy controls.[3] Meta-analysis showed a persistent and strong decrease in spontaneous brain activity in the angular gyrus, visual cortex and cerebellum, and an increase in activity in the caudate, thalamus and prefrontal cortex in migrainures.[4] Acute transcutaneous vagus nerve stimulation (taVNS) modulates functional connectivity (FC) between vagal pathway brainstem regions and brain regions associated with the limbic system (bilateral hippocampus), pain processing and modulation (bilateral postcentral gyrus, thalamus, and middle frontal gyrus), and the basal ganglia (nucleus accumbens/caudate nucleus) to ameliorate the clinical symptoms of migrainures.[5]

Functional connectomics is able to describe the functional connectivity and topological organization of the human brain, which is

essential for understanding normal brain function and the neurobiological mechanisms of brain disease.[6-8] Silvestro *et al*. investigated the topological characteristics of the white matter structural connectivity network in migrainures based on diffusion tensor imaging.[7] Functional connectivity between cortical nodes involved in pain perception and regulation and cognitive and affective attribution of pain experience in migraine patients was enhanced compared to healthy controls.[7] Michels *et al*. used a graph theory analysis framework and network-based statistic (NBS) to analyze the topological characteristics of structural magnetic resonance images of migrainures.[6,8] Compared with healthy controls, migrainures had significantly lower functional connectivity between the frontotemporal, parietal lobe, and visual regions.[8]

However, there is still a lack of research on the use of resting-state functional magnetic resonance imaging (rsfMRI) and connectomics to explore the functional connectivity network characteristics of migrainures. In this study, we used functional connectome and NBS methods to explore abnormal sub-networks in migrainures and look for biomarkers in imaging related to migraine.

METHODS

Participants

In this study, 39 migraineurs and 17 healthy controls (HC) were enrolled between March and October 2014. The group of 39 migraine patients comprised 28 patients with migraine without aura and 11 patients with migraine with aura. All migraineurs met the diagnostic criteria of the International Classification of Headache Disorders, Third Edition (ICHD-3)[9]: no headache attacks 3 days prior to, on the day of, and 3 days after the scan; no epilepsy or psychiatric conditions; no history of substance abuse or prophylactic medication; no contraindications to MRI and no abnormal signals on routine brain scans; female subjects who were not pregnant; and no contraindications; no MRI-related contraindications, no aberrant brain scan signals, and female patients who were neither pregnant or menstrual. A high signal on FLAIR imaging led to the exclusion of two migraineurs.[10] HC were selected from healthy subjects who were matched for age, sex, and years of schooling. No prior history of migraine or other headache disorders, as well as no migraine in the family, were requirements for inclusion. All female subjects were enrolled mid-cycle and were disqualified if they were pregnant or nursing in order to minimize the impact of hormones on cortical excitability. The institutional review board at our university gave its approval to this project. Prior to the procedure, all participants signed written informed consent forms.

MRI scan

A 3.0 Tesla magnetic resonance imaging scanner (Achieva X-series, Philips Medical, Best, the Netherlands) was used to capture the images. Using a gradient-echo planar imaging sequence, functional images were acquired axially with the following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; slice = 35; thickness = 4 mm; gap = 0 mm; field of view (FOV) = 240 mm × 240 mm; acquisition matrix = 80 × 80; flip angle (FA) = 90°. Sequences for fMRI took 8 minutes. Patients were told to close their eyes and stay still while the images were being taken.

Data processing

SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and the Resting State fMRI Data Analysis Toolkit+V1.25 (RESTplus V1.25) (http://www.restfmri.net) were used for data preprocessing. The first ten volumes were discarded before being corrected for slice time and head motion, spatially normalised to Montreal Neurological Institute (MNI) space, and resampled to a resolution of $3 \times 3 \times 3$ mm^3, smoothed with an isotropic Gaussian kernel (full width at half maximum = 6 mm), linear trend removal, and temporal bandpass filtering (0.01-0.08 Hz). Finally, interference in the resulting images was removed by regressing head motion parameters, CSF signal, and white matter signal. Subjects who moved their heads more than 2.0 mm translationally or 2.0° rotationally in any direction were excluded.

Functional connectome construction

Based on the preprocessed fMRI data, we used Gretna2.0 to construct the functional connectivity matrix.[11] The brain regions were divided using the AAL90 template.[12] Each subject got a 90x90 functional connectivity matrix (i.e., a functional connectome) (Figure 1).

Network-based statistic

We performed NBS analysis using the NBS-predict toolbox Version 1.0.0-beta.10.[13] NBS-
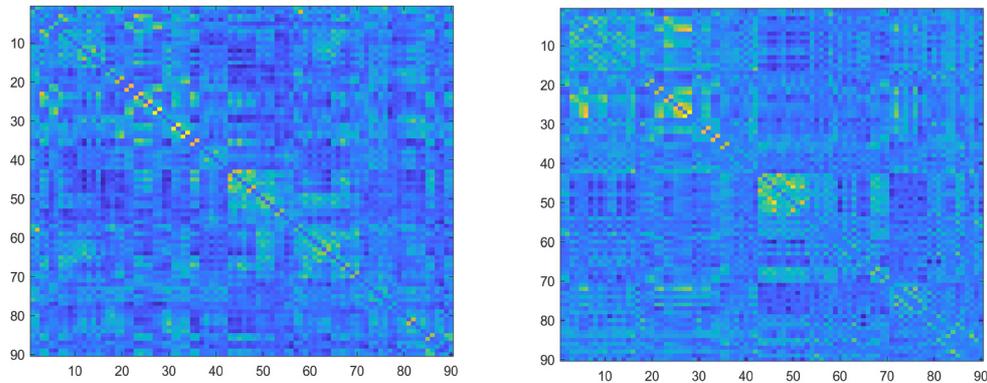
Figure 1. Schematic diagram of the functional connectome. Left image: functional connectome for healthy subjects; right image: functional connectome for migrainures. Coordinates 1-90 correspond to the 90 brain regions of the AAL atlas.

predict uses NBS to determine the connection values for the presence of suprathreshold edges of the functional connectome. Specifically, suprathreshold edge selection consists of the following steps: (i) each edge is fitted to a general linear model based on a given contrast and the corresponding p-value is computed; (ii) edges with p-values lower than a predefined p-value are then initially selected; (iv) a breath-first search algorithm is then used to identify suprathreshold edges that may exist in the in the set of connected components. p-value=0.01, permutation=500, hyperparameter optimization steps=5, grid search are the main parameters.

Statistical analysis

The Mann-Whitney U-test was used to compare the age and education of the two groups in order to determine whether or not there was a significant difference. To match the gender composition of the two groups, the chi-square was used.

Between-group differences in whole-brain correlation matrices between migraineurs and controls were examined using NBS. After generalised linear regression of the functional connectivity boundaries between each of two brain regions, the NBS uses alignment tests to identify significant components or 'clusters' of neighbouring region-to-region connections and corrects for multiple comparisons (p-value=0.01, permutation=500), which can be more powerful than large-scale single-variable tests in cases where brain connectivity features of interest are correlated with each other. This can provide a more robust control of family error rates than large-scale univariate tests. To investigate the association between FC value and clinical

outcome in migraineurs, a Pearson correlation between the Z value of abnormal brain regions and clinical outcome of migraineurs was performed in a voxel system. The statistical threshold was set at $p < 0.02$ (FDR correction).

RESULTS

Neuropsychological results

Age ($z = -0.749$, $P = 0.4533$), gender distribution ($\chi^2 = 2$, $P = 0.1573$), and years of education ($z = -1.430$, $P = 0.1527$) did not differ significantly between groups. The demographic data and associated tests are detailed in Table 1.

Abnormal functional connectivity in the migraineurs

In contrast to HC, migraineurs shows an anomalous subnetwork with increased connectivity, consisting of 179 nodes and 76 edges (Figure 2 and Table 2). Nodes are primarily located in the basal ganglia and sensorimotor areas.

Relationships between functional connectivity values and clinical variables

The functional connectivity (FC) values between left caudate nucleus and right precentral gyrus, right supplementary motor area, right superior occipital gyrus and right middle occipital gyrus are significant positive correlated with visual analogue scale ($r = 0.6110$, $p = 0.0016$; $r = 0.5867$, $p = 0.0016$; $r = 0.5853$, $p = 0.0016$; $r = 0.5923$, $p = 0.0016$) (Figure 3). The FC values between right caudate nucleus and right precentral gyrus, left supplementary motor area, right superior

Table 1: Demographics and neuropsychological data

	migraineurs	HC	z/χ²	p
Gender, n (M/F)	39(30/9)	17(11/6)	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	-	-	-
Frequence(d/m)	4.0±6.5	-	-	-
VAS score	6.64±1.4	-	-	-

Data represent mean ± SD. Data were analyzed using independent-samples t-tests. HC: Healthy controls; d/m: day per month; VAS: visual analogue scale.

occipital gyrus and right middle occipital gyrus are significant positive correlated with visual analogue scale (r = 0.5104, p = 0.0115; r = 0.5551, p = 0.0116; r = 0.5200, p = 0.0115; r = 0.5375, p = 0.0115) (Figure 4).

DISCUSSION

In the current study, we examined alterations of functional connectome in migraineurs. In contrast to HC, migraineurs shows an anomalous subnetwork with increased connectivity, consisting of 179 nodes and 76 edges. Nodes were primarily located in the basal ganglia and sensorimotor areas. Functional connectivity between the caudate nucleus and the sensorimotor area, occipital lobe were significantly positively correlated with visual analogue scale.

Our results show that the caudate nucleus is a major node in the abnormal subnetwork of migraineurs. The caudate nucleus is associated with visual function and control of sensorimotor.[14] Wistar rat studies showed that cortical spreading depression (CSD) affects caudate nucleus neuronal activity.[15] Low-frequency amplitudes were increased in the left caudate nucleus, left insula, and right parahippocampal gyrus in migraineurs compared with HC.[16] Migraineurs had increased functional connectivity between the right caudate nucleus and brain regions primarily involved in emotion, cognition, and sensation-related brain regions compared to HC.[17] Enhanced functional connectivity in the caudate nucleus may be a complementary mechanism after the onset of CSD in migraineurs.

Anodal transcranial direct current stimulation of the left motor cortex has a significant prophylactic effect on resistance to intractable chronic migraine.[18] The FC between supplementary motor area I and the postcentral gyrus was reduced in migraineurs after taVNS compared with before taVNS.[19] Meta-analysis showed that activation within the motor system plays a key role in suppressing pain symptoms in sensory altered processing patients and inhibiting activity in key pain regions of the brain in motor altered
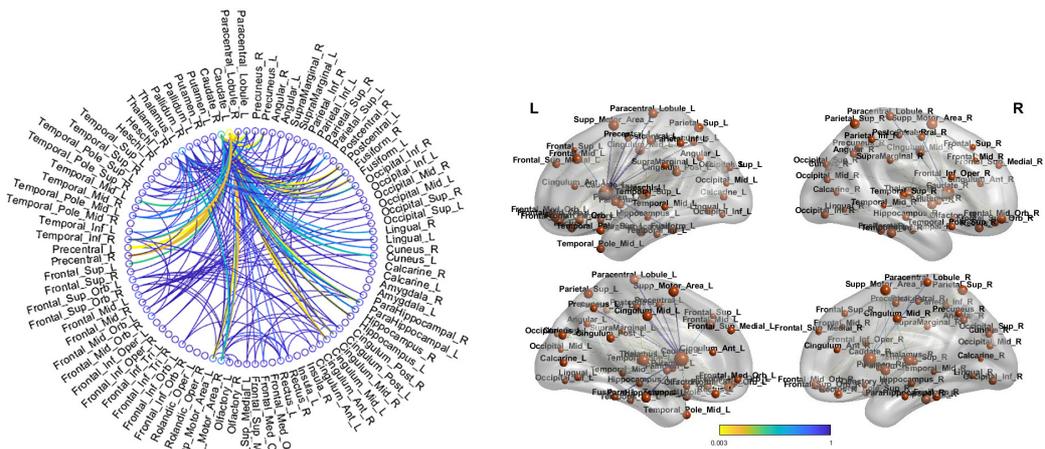

Figure 2. Compared to HC, migraineurs shows subnetworks with increased connectivity. Nodes are primarily located in the basal ganglia and sensorimotor areas.

Table 2: Nodes with increased connections and their degree in the migraineurs, compared with healthy controls. (Degree > 6)

Node	Degree
Caudate_L	54
Caudate_R	30
Thalamus_L	15
Supp_Motor_Area_R	14
Supp_Motor_Area_L	11
Thalamus_R	11
Frontal_Mid_R	8
Cingulum_Mid_L	8
Parietal_Sup_R	8
Frontal_Mid_Orb_R	7
ParaHippocampal_L	7
Pallidum_R	7
Temporal_Inf_R	7
Frontal_Mid_Orb_L	6
Cingulum_Mid_R	6
Parietal_Sup_L	6

processing patients.[20]

When interpreting the current results, several limitations should be considered. For starters, the small sample size limits the generalizability of the findings. Second, because the current study used a cross-sectional design, it is impossible to say whether the findings are due to migraine. Future longitudinal surveys should address this issue. Third, multi-site and large sample data are required to validate the reliability of the study's results.

In conclusion, we explored the functional connectome alternations in migraineurs using resting-state functional MRI and NBS method. Compared with the HC, migraineurs shows an anomalous subnetwork with increased connectivity, consisting of 179 nodes and 76 edges. Nodes were primarily located in the basal ganglia and sensorimotor areas. Our study suggests that the caudate nucleus may be an imaging marker and therapeutic target for migraine.

DISCLOSURE

Ethics: The institutional review board at our university gave its approval to this project. All participants gave their informed, written consent.
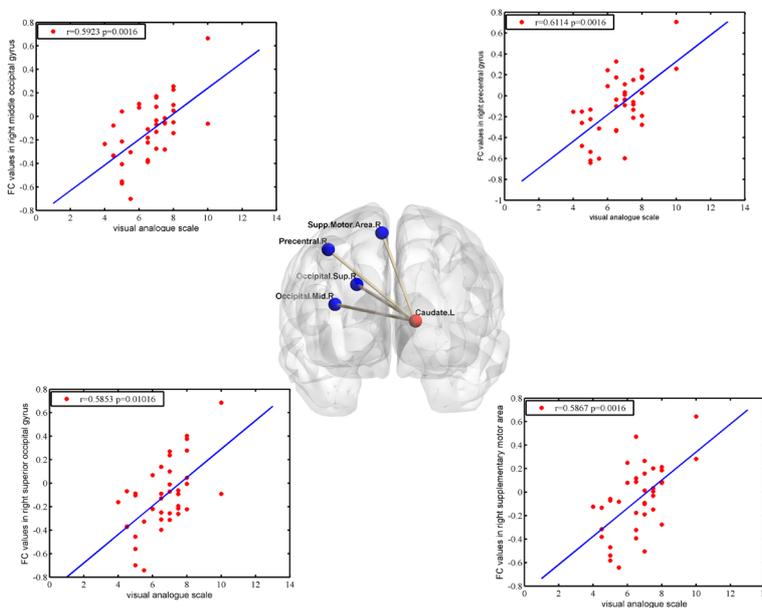

Figure 3. The FC values between left caudate nucleus and right precentral gyrus, right supplementary motor area, right superior occipital gyrus and right middle occipital gyrus are significant positive correlated with visual analogue scale (p < 0.02, FDR correction).
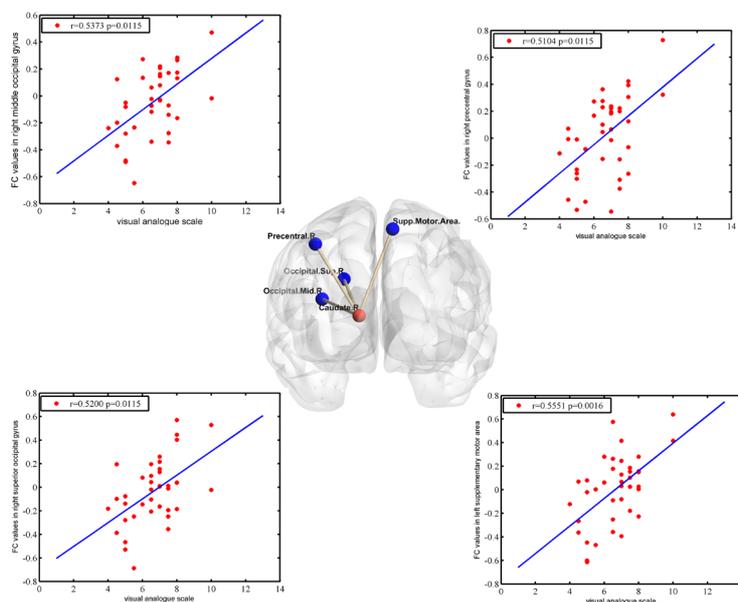
Figure 4. The FC values between right caudate nucleus and right precentral gyrus, left supplementary motor area, right superior occipital gyrus and right middle occipital gyrus are significant positive correlated with visual analogue scale (p < 0.02, FDR correction).

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