Disrupted effective connectivity of the periaqueductal gray in migraine without aura patients

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Abstract

Background: The periaqueductal gray (PAG) is a key region in the descending pain modulatory system. We applied a Granger causality analysis (GCA) based approach to examine resting-state effective connectivity (RSEC) of the bilateral PAG regions in migraine patients without aura (MwoA).

Methods: Resting-state fMRI data were obtained from 28 MwoA patients and 17 well-matched healthy controls (HCs). The RSEC of the bilateral PAG was characterized using a voxel-wised GCA method. The resulting RSEC measurements were assessed for correlations with other clinical features.

Results: Compared with the HCs, MwoA patients showed increased EC from left PAG to left anterior cingulate gyrus and right postcentral gyrus. Meanwhile, MwoA patients also showed increased EC from right PAG to left precentral gyrus and increased RSEC from left caudate and right middle occipital gyrus to right PAG.

Conclusions: Disturbances of RSEC between PAG and limbic system, primary sensorimotor cortex, and visual cortex may play a key role in neuropathological features, perception, and affection of MwoA. The current study provides further insights into the complex scenario of MwoA mechanisms.

1. Background

Migraine is the most common type of primary headache in clinical practice. It is a common recurrent headache disorder. Migraine without aura is the most common type of migraine, accounting for approximately 80% of cases [1]. It presents with recurrent episodes of pulsating headache on one or both sides of the frontotemporal region lasting 4–72 hours and may be accompanied by nausea, vomiting, photophobia, and vocal aversion. Migraine without aura (MwoA) has a high prevalence and high frequency of attacks, which affects the work, study, and life of patients [2].

The periaqueductal gray (PAG) is an important node of the descending pain modulatory system and the main hub for the upstream and downstream channels of nociceptive information. Tassorelli et al. [3] found that stimulation of the ventral lateral region of the PAG led to migraine-like symptoms. Raskin et al. [4] implanted stimulating electrodes into the periaqueductal gray matter of non-migraine patients, resulting in migraine-like attacks. It is hypothesized that PAG may be the source center of migraine pain perception.

With the development of neuroimaging techniques, different functional magnetic resonance imaging (fMRI) methods have been used to study the mechanisms of PAG in clinical migraine patients. Foci can be found on T2 structural images of PAG in most migraine patients [5]. A study based on diffusion kurtosis imaging showed that the Mean kurtosis (MK) and mean diffusivity values of the PAG were significantly increased in the migraine patients compared with the controls. The MK values of the PAG were significantly positively correlated with both age and the untreated period in the patient group [6]. Compared with healthy controls (HCs), migraine patients showed a significantly decreased resting-state functional connectivity (RSFC) between the PAG and prefrontal cortex, anterior cingulate, amygdala, and brain regions with a predominant role in pain modulation [7]. MwoA patients also showed reduced RSFC between the PAG and rostral anterior cingulate cortex/medial prefrontal cortex (rACC/mPFC). The reduced RSFC between the PAG and rACC/mPFC was associated with increased migraine headache intensity at the baseline. After treatments, RSFC between the PAG and the rACC in MwoA patients significantly increased. The changes in RSFC among the PAG, rACC, and ventral striatum were significantly associated with headache intensity improvement [8].

However, the PAG, as an important node in the upstream and downstream of the nociceptive pathway, RSFC cannot detect the directional information of the PAG brain network [9]. Effective connectivity (EC) reflects the direct causal effect of one brain region on another, which contributes to a detailed understanding of the neuropathological mechanisms of functional architecture. Granger causal analysis (GCA) provides a feasible approach to achieving this goal by identifying directional functional interactions from time-series data [10].

In the current study, we hypothesized that MwoA subjects would exhibit altered the resting state EC (RSEC) of the bilateral PAG regions in emotional, cognitive, and sensory-related brain areas. We utilized rsfMRI and voxel-wised GCA to investigate alterations in RSEC in MwoA patients, compared with HC.

2. Methods

2.1 Participants

28 MwoA patients and 17 HCs were recruited in this study between March 2014 and October 2014. All MwoA subjects meet the diagnostic criteria of the International Classification of Headache Disorders, Third Edition (beta version) (ICHD-3beta) [11]: no headache attacks within 3 days before the scan, on the day of the scan, and within 3 days after the scan; No history of substance abuse or prophylactic drug use; No contraindications to MRI scanning; Female subjects not pregnant or in menstruation. The age-, sex-, and years of education-matched healthy subjects were recruited as healthy controls (HCs). The inclusion criteria were having no history of migraine or other headache disorders, and no family history of migraine. To minimize hormonal influences on cortical excitability, all female participants were included at mid-cycle and excluded if pregnant or breastfeeding. This study was approved by the Institutional Review Board of our university. All participants provided written informed consent before undergoing.

2.2MRI scan

All subjects underwent a functional fMRI scan with a 3 T MRI scanner (Achieva X-series, Philips Medical, Best, the Netherlands) with an 8-channel head coil. For functional scan, $T2^*$-weighted echo-planar images were acquired with the following parameters: 35 axial slices, thickness/gap = 4/0 mm, in-plane resolution = 80 × 80, repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle = 90°, and field of view (FOV)

= 240 × 240 mm^2. Each functional imaging consisted of 240 volumes. We instructed patients to remain still and close their eyes during image acquisition.

2.3Data processing

Data preprocessing was carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit plus V1.25 (RESTplus V1.25) (http://www.restfmri.net). The preprocessing steps were as follows: the discarding of the first 10 volumes, correction for slice-timing and head motion, spatial normalization to Montreal Neurological Institute (MNI) space with a resampling resolution of 3 × 3 × 3 mm^3, spatial smoothing with a 6-mm Gaussian kernel along all three directions, linear trend removal and temporal bandpass filter (0.01–0.08 Hz). Finally, the nuisances were further removed from the resulting images by regressing out head motion parameters, the cerebral spinal fluid signal, and the white-matter signal. Subjects with a head motion greater than 2.0 mm translation or a 2.0° rotation in any direction were excluded.

2.4 resting-state effective connectivity analysis

A voxel-wise GCA analysis was performed on each subject with RESTplus V1.25. For each participant, two PAG seeds (3-mm radius), centered at MNI coordinates [− 4, − 26, −14] and [4, − 26, −14], were identified according to the published literature [12]. The average time series of seed regions are defined as the seed time series X, while the time series Y represents the time series of remaining voxel in the whole brain. The linear direct effect of X on Y (information flow from X to Y) and the linear direct effect of Y on X (information flow from Y to X) are evaluated voxel by voxel throughout the brain. Regarding directionality, a positive coefficient from X to Y suggests that activity in area X has a causal influence on activity in area Y in the same direction. On the other hand, a negative coefficient from X to Y indicates that the activity in area X has an opposite directional influence on the activity in area Y. The results for each subject are presented as a GCA map from the PAG to the whole brain (x2y) and a GCA map from the whole brain to the PAG (y2x). Each individual-level RSFC map obtained was then converted to a z-map using Fisher r-to-z transformation for second-level group analyses, respectively.

2.5 Statistical analysis

We performed Statistical analysis using REST. A two-sample t-test was conducted on the individual normalized RSEC maps in a voxel-by-voxel manner between the two groups. To reduce the effect of confounding variables in the statistical analysis, we regress out the mean relative displacements of head motion, age, and gender as covariates in a two-sample t-tests analysis. For multiple comparisons, the resulting statistical map was set at $p < 0.05$ (AlphaSim corrected for multiple comparisons, with a combined individual voxel p-value < 0.005 with a cluster size > 25 voxels). To investigate the association between the RSEC values and clinical scores in MwoA patients, a Spearman's rank correlation was performed between the Z value of the abnormal brain regions and the clinical scores of MwoA patients in a voxel-wise manner. The statistical threshold was set at $P < 0.05$.

3. Results

3.1 Neuropsychological results

There was no significant difference between the two groups with regard to age (t = − 0.332, *P* = 0.7406), sex distribution (χ^2 = 2, *P* = 0.1573), or years of education (t = 0.973, *P* = 0.2030). Details of the demographic data and corresponding tests are presented in Table 1.

3.2 Altered EC in MwoA Patients

Compared with HCs, MwoA patients showed increased RSEC from left PAG to left anterior cingulate gyrus and right postcentral gyrus. MwoA patients also showed increased RSEC from right PAG to left precentral gyrus, and increased RSEC from left caudate nucleus and right middle occipital gyrus to right PAG (Figs. 1 and 2; Tables 2 and 3).

3.3 Relationships between Network Parameters and MMSE

No correlations were found between clinical scores and RSEC values.

Table 1
Demographics and neuropsychological data.

	MwoA	HCs	t/χ^2	*p*
Gender, n (M/F)	28(21/6)	17(11/6)	2	0.1573
Age, years	35.6 ± 9.9	36.5 ± 8.9	-0.332	0.7406
Education(years)	13 ± 4	15 ± 4	0.973	0.2030
Duration(years)	9 ± 7	-	12.773	0.000
Frequence(d/m)	5.9 ± 9.4	-	13.044	0.000
VAS score	6.85 ± 1.3	-	17.701	0.000

Data represent mean ± SD. Data were analyzed using independent-samples t-tests. MwoA: Migraine without aura; HCs: Healthy controls; d/m: day per month; VAS: visual analogue scale.

Table 2
Brain regions with significantly different EC values with left PAG in the MwoA group compared with the HCs group

	Brain regions	**Voxels**	**BA**	**MNI coordinates**			***T* value**
				x	**y**	**z**	
from left PAG to the rest of the brain (X2y)							
Cingulate_Ant_L	25	24	0	33	30	3.4586	
Postcentral_R	67	4	30	-27	51	4.1977	
MwoA: Migraine without aura; HCs: Healthy controls; MNI: Montreal Neurological Institute; BA: Brodmann area.							

Table 3
Brain regions with significantly different EC values with right PAG in the MwoA group compared with the HCs group

	Brain regions	**Voxels**	**BA**	**MNI coordinates**			***T* value**
				x	**y**	**z**	
from right PAG to the rest of the brain (X2y)							
Precentral_L	30		-45	-6	48	4.0603	
from the rest of the brain to right PAG (y2x)							
Caudate_L	36		-12	24	-3	4.3089	
Occipital_Mid_R	30	4	35	-66	25	3.9030	
MwoA: Migraine without aura; HCs: Healthy controls; MNI: Montreal Neurological Institute; BA: Brodmann area.							

4. Discussion

In the current study, we examined alterations of RSEC in direction brain networks in MwoA patients. Compared with HCs, MwoA patients showed increased RSEC from left PAG to left anterior cingulate gyrus and right postcentral gyrus. MwoA patients also showed increased RSEC from right PAG to left precentral gyrus and increased RSEC from left caudate nucleus and right middle occipital gyrus to right PAG. Abnormal brain regions are located primarily in the limbic system and sensorimotor areas.

Our results show an unusually RSEC between the PAG and the left anterior cingulate and gyrus left caudate nucleus, which belong to the limbic system [13]. The limbic system is the center of nociceptive-emotional processing and is closely related to migraine. Migraines have extensive functional brain abnormalities in the limbic system, including local brain activity, functional connectivity, and effective connectivity [14–16]. Both the PAG and the limbic system are major nodes of the nociceptive modulation pathway. Our study suggests that alternation of RSEC between the PAG and limbic system are the main pathological mechanisms of MwoA.

Our results show an unusually RSEC between the PAG and right postcentral gyrus and left precentral gyrus, which belong to the primary sensorimotor cortex [17]. The primary sensorimotor cortex plays a key role in the processing and integration of somatosensory information and is involved in the development and maintenance of migraines [17]. Compared with controls, patients with migraine and insomnia showed regional gray matter volume changes in the precentral, and postcentral gyrus [19]. MwoA patients also exhibited increased fractional amplitude of low-frequency fluctuation in the left thalamus, left inferior parietal gyrus, bilateral precentral gyrus, right postcentral gyrus, and bilateral supplementary motor areas [19]. Central sensory processing and sensorimotor integration are affected in migraines, which may reflect increased excitability to headache attacks.

The middle occipital gyrus located within the visual ventral stream subserves visual processing of relative spatial relationships with objects [20]. The occipital lobe is an important brain region for the cortical spreading depressing (CSD) hypothesis of migraine. Various noxious stimuli induce an inhibitory zone of neuroelectrical activity originating in the posterior cerebral cortex (occipital lobe), which extends to the adjacent cortex and is accompanied by an extended blood volume reduction [21]. Various studies have previously illustrated structural and functional alterations of the occipital cortex in patients with migraine, which are generally thought to be associated with the aura phenomenon, especially visual aura [22]. The occipital cortex has been shown to be a potential target of acupuncture treatment for migraine, and the feasibility of predicting the clinical efficacy of acupuncture treatment for MwoA using the spontaneous activity patterns of the middle occipital gyrus [23].

Several limitations should be considered when interpreting the current results. First, a relatively small sample size reduces the reliability of the statistics. Second, the current study had a cross-sectional design, and therefore cannot address whether these observations are a consequence of MwoA. Future longitudinal studies should be performed to address this question. Third, Subregions of the PAG in migraine patients have shown abnormal RSFC, and further studies should explore the RSEC patterns of PAG subregions in migraine patients [24].

5. Conclusions

We explored the RSEC of the PAG region in MwoA patients using resting-state functional MRI and GCA analysis. Compared with the HC, MwoA patients' differential brain regions are located primarily in the limbic system, primary sensorimotor cortex, and visual cortex. The current study provides further insights into the complex scenario of MwoA mechanisms.

Abbreviations

RSEC: Resting-state effective connectivity

RSFC: Resting-state functional connectivity

PAG: periaqueductal gray

MwoA: migraine without aura

GCA: Granger causality analysis

HCs: healthy controls

fMRI: functional magnetic resonance imaging.

Declarations

Authors' contributions

KL and ZHW designed the study. YL, YGC, KYC, XW, JMC, LPD and XZL performed the experiments. XZL and JMC analyzed the data and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Ethical approval and consent to participate

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. All participants gave their informed, written consent.

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Figures

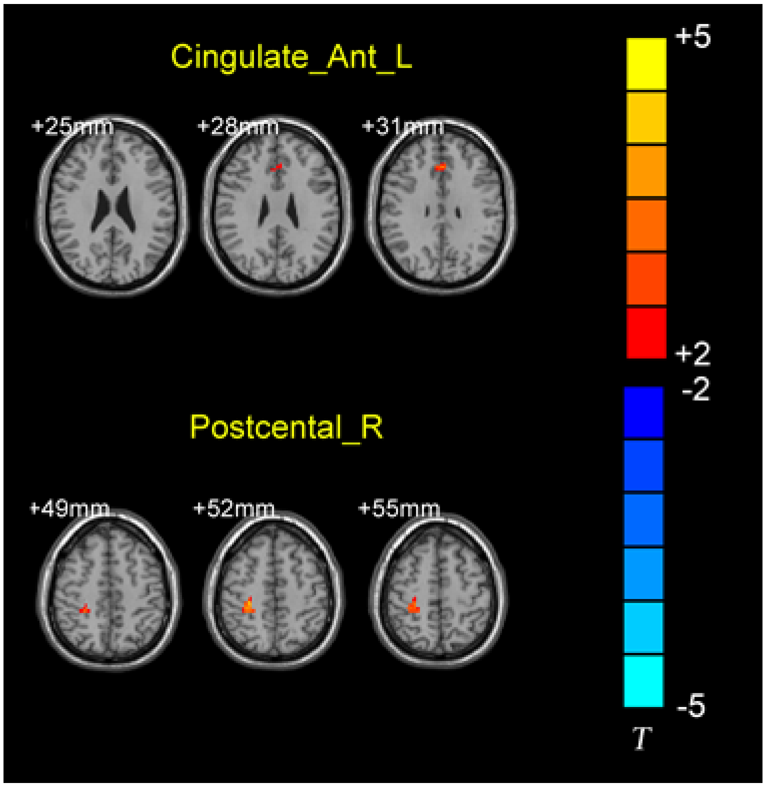

Figure 1

Brain regions with significantly different EC values with left PAG in the MwoA group compared with the HCs group.

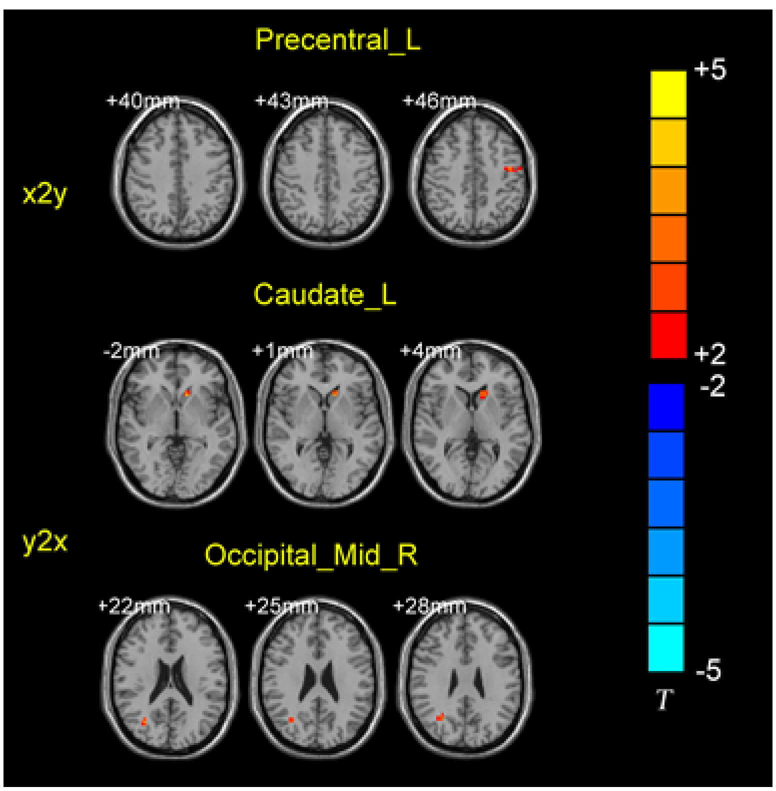

Figure 2

Brain regions with significantly different EC values with right PAG in the MwoA group compared with the HCs group.