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Structural and functional abnormalities in migraine patients without aura

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Migraine is a primary headache disorder characterized by recurrent attacks of throbbing pain associated with neurological, gastrointestinal and autonomic symptoms. Previous studies have detected structural deficits and functional impairments in migraine patients. However, researchers have failed to investigate the functional connectivity alterations of regions with structural deficits during the resting state. Twenty-one migraine patients without aura and 21 age- and gender-matched healthy controls participated in our study. Voxel-based morphometric (VBM) analysis and functional connectivity were employed to investigate the abnormal structural and resting-state properties, respectively, in migraine patients without aura. Relative to healthy comparison subjects, migraine patients showed significantly decreased gray matter volume in five brain regions: the left medial prefrontal cortex (MPFC), dorsal anterior cingulate cortex (dACC), right occipital lobe, cerebellum and brainstem. The gray matter volume of the dACC was correlated with the duration of disease in migraine patients, and thus we chose this region as the seeding area for resting-state analysis. We found that migraine patients showed increased functional connectivity between several regions and the left dACC, i.e. the bilateral middle temporal lobe, orbitofrontal cortex (OFC) and left dorsolateral prefrontal cortex (DLPFC). Furthermore, the functional connectivity between the dACC and two regions (i.e. DLPFC and OFC) was correlated with the duration of disease in migraine patients. We suggest that frequent nociceptive input has modified the structural and functional patterns of the frontal cortex, and these changes may explain the functional impairments in migraine patients. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: migraine; voxel-based morphometric (VBM); resting state; functional connectivity

INTRODUCTION

As an idiopathic headache disorder, migraine is characterized by moderate to severe pain, which consists of unilateral and pulsating headache attacks that are typically aggravated by physical activity (1). Migraine headaches cause significant individual and societal burdens as a result of pain, such as environmental sensitivity, disability and even lost productivity (2). Recently, advanced neuroimaging has led to an evolution in our perception of migraine pathophysiology. No longer should migraine be considered as a vascular or neurovascular disorder, but a disease mediated by the central nervous system (1,2). Numerous neuroimaging studies have detected alterations in brain structure (3–7) and function (8–10) in patients with migraine, such as the

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Abbreviations used: *ACC, anterior cingulate cortex; BET, brain extracting tool; CSD, cortical spreading depression; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FAST, FMRIB's automated segmentation tool; fMRI, functional MRI; FNIRT, FMRIB's nonlinear image registration tool; FSL, FMRIB Software Library; MCFLIRT, FMRIB's Linear Motion Correction; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; ReHo, regional homogeneity; VBM, voxel-based morphometric.*

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anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), insula, temporal gyrus, posterior cingulate cortex, supplementary motor area, cerebellum and thalamus. Repeated migraine attacks over time may lead to selective damage to several brain regions involved in central pain processing (11,12). Furthermore, migraine may have cumulative effects on brain structure and function, because some alterations are possibly associated with longer migraine duration and increased migraine frequency (3–6).

Resting-state functional MRI (fMRI) is a noninvasive imaging technique which measures spontaneous brain activity as low-frequency fluctuations in blood oxygen level-dependent signals (13). During the resting state, correlated spontaneous fluctuations occur within spatially distinct and functionally related groups of cortical and subcortical regions, consisting of the human brain's intrinsic functional networks (14). The variations in intrinsic functional networks may influence task performance in real life (15–17). Furthermore, the resting-state method has been used extensively to reveal the intrinsic typical and atypical functional architecture of the brain (13,18). The changed features during the resting state may serve as a marker to reflect the progress of multiple diseases, such as heroin addiction (19–21), schizophrenia (22), Alzheimer's disease (23), Parkinson's disease (24) and treatment-refractory depression (25). However, until recently, few studies had evaluated the abnormalities of the resting state in migraine patients. Recently, Yu *et al.* (26) employed the regional homogeneity (ReHo) method, and found that patients with migraine without aura showed a significant decrease in ReHo values in the right ACC, prefrontal cortex (PFC), OFC and supplementary motor area. In addition, the ReHo values were negatively correlated with the duration of disease in the right ACC and PFC. Unfortunately, they failed to investigate the functional connectivity changes in the resting-state networks of the brain regions with structural deficits. No study, to our knowledge, has determined whether the symptoms of migraine are associated with functional connectivity in brain areas with gray matter deficits.

Therefore, the purposes of this study were as follows: (i) to identify brain regions with gray matter volume reduction in migraine patients employing voxel-based morphometric (VBM) analysis; and (ii) to investigate the abnormal functional connectivity of these structural deficits. By combining structural and functional data, we aimed to explore the relationship between the structural deficits and functional impairment in migraine patients.

MATERIALS AND METHODS

The protocol was approved by the Ethical Committee of Xi'an Jiaotong University. All participants gave their written informed consent after the experimental procedure had been explained fully.

Subjects

The diagnostic criteria for migraine without aura of the International Headache Society consist of the occurrence of at least five headache attacks that fulfill the following criteria: (i) headache attacks lasting 4–72 h (untreated or unsuccessfully treated); (ii) headache with at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe pain intensity and aggravation by causing avoidance of routine physical activity (e.g. walking or climbing stairs); (iii) during the headache, the sufferer must have at least one of the following: nausea and/or vomiting, photophobia and phonophobia; and (iv) headache cannot be attributed to another disease. According to the International Headache Society criteria, migraine patients without aura were screened in our hospital (27). Twenty-one migraine patients without aura (16 females, aged 21–53 years, 31.2 ± 11.3 years) were enrolled in our hospital. In addition, 21 age- and gender-matched healthy controls (16 females, aged 22–54 years, 30.7 ± 10.5 years) participated in our study. The controls either had no headache days per year or had family members who suffered regularly from a migraine or had other headaches. All of the participants were right-handed. Exclusion criteria for both groups were as follows: (i) the existence of a neurological disease; (ii) alcohol, nicotine or drug abuse; (iii) pregnancy or menstrual period in women; (iv) any physical illness, such as a brain tumor, hepatitis or epilepsy, assessed according to clinical evaluations and medical records; and (v) claustrophobia. Patients could not have suffered a migraine attack at least 72 h prior to testing, and no patient had a migraine precipitated during or on the day following the scan. Migraine patients rated the average pain intensity as 5.6 ± 1.2 on a 0–10 scale derived from attacks in the past 4 weeks, with 10 being the most intense pain imaginable. The clinical characteristics of migraine patients without aura are shown in Table 1.

Data acquisitions

This experiment was carried out in a 3-T GE scanner with an eight-channel phase-array head coil at the Mental Health Center, the First Affiliated Hospital of the Medical College, Xi'an Jiaotong University. For each subject, a high-resolution structural image was acquired using a three-dimensional MRI sequence with a voxel size of 1 mm^3 employing an axial fast spoiled gradient recalled sequence with the following parameters: TR = 1900 ms; TE = 2.26 ms; data matrix, 256 × 256; field of view, 256 mm × 256 mm. The resting-state functional images were obtained with echo planar imaging with the following parameters: 30 contiguous slices with a slice thickness of 5 mm; TR = 2000 ms; TE = 30 ms; flip angle, 90°; field of view, 240 mm × 240 mm; data matrix, 64 × 64; total volumes, 180. During the 6-min functional scan, subjects were instructed to keep their eyes closed, not to think about anything and to stay awake during the entire session. After the scan, the subjects were asked whether or not they remained awake during the whole procedure.

Table 1. Clinical information of migraine patients without aura and healthy controls (mean ± standard deviation)

	Migraine patients	Healthy controls
	($n = 21$)	($n = 21$)
Age (years)	31.2 ± 11.3	30.7 ± 10.5
Gender (female/male)	16/5	16/5
Duration of disease (years)	10.6 ± 6.6	N/A
Attack frequency(times)	4.7 ± 2.0	N/A
Average duration of a migraine attack (h)	14.1 ± 6.6	N/A
Average pain intensity(0–10)	5.6 ± 1.2	N/A

N/A, not applicable.

VBM analysis

The structural images of all participants were examined to exclude the possibility of clinically silent lesions by two professional radiologists. Structural data were processed with an FSL-VBM protocol (28,29) with FMRIB Software Library (FSL) 4.1 software (http://www.fmrib.ax.ac.uk/fsl) (30). First, all T_1 images were brain extracted using the brain extracting tool (BET) (31). Next, tissue-type segmentation was carried out using FMRIB's automated segmentation tool (FAST) V4.1 (32). The resulting gray matter partial volume images were then aligned to MNI152 standard space using FMRIB's linear image registration tool (FLIRT) (33,34), followed optionally by nonlinear registration using FMRIB's nonlinear image registration tool (FNIRT) (35,36), which employs a *b*-spline representation of the registration warp field (37). The resulting images were averaged to create a study-specific template, to which the native gray matter images were nonlinearly re-registered. The optimized protocol introduced a modulation for the contraction/enlargement caused by the nonlinear component of the transformation: each value of the voxel in the registered gray matter image was divided by the Jacobian of the warp field. Finally, in order to choose the best smoothing kernel, all modulated, normalized gray matter volume images were smoothed with isotropic Gaussian kernels increasing in size ($\sigma = 2.5$, 3, 3.5 and 4 mm, corresponding to full widths at half-maximum of 6, 7, 8 and 9.2 mm, respectively). Regional changes in gray matter were assessed using permutation-based nonparametric testing with 5000 random permutations (38). Analysis of covariance was employed with age, gender effects and total intracranial volume as covariates. Total intracranial volume was calculated as the sum of gray matter, white matter and cerebrospinal fluid volumes from FSL BET segmentations. Correction for multiple comparisons was carried out using a cluster-based thresholding method, with an initial cluster forming a threshold at $t = 2.0$. Results were considered to be significant for $p < 0.05$. For the regions in which migraine patients showed significantly different gray matter volume than controls, the gray matter volumes were extracted, averaged and regressed against the duration of migraine.

Resting-state functional connectivity analysis

The first five volumes were discarded to eliminate nonequilibrium effects of magnetization and to allow subjects to get used to the scanning environment. The preprocessing steps for single-subject resting-state fMRI data were performed using FSL software (http://www.fmrib.ax.ac.uk/fsl). For each subject's resting-state fMRI dataset, the following preprocessing steps were taken: (i) motion correction using FMRIB's Linear Motion Correction (MCFLIRT); (ii) skull-stripping using BET; (iii) spatial smoothing with a 5-mm full width at half-maximum spatial filter; and (iv) co-registration and transformation of the resting-state fMRI dataset to the MNI152 standard template using FLIRT. A band-pass filter was employed to retain the signal between 0.01 and 0.1 Hz by removing linear drift artifacts and high-frequency noise (39). Functional connectivity was examined using a method based on a seeding voxel correlation approach (21,22). The regions with structural deficits were defined as our seeding areas in the functional connectivity analysis. The reference time series for each seeding area was obtained by averaging the fMRI time series for all voxels within each of the regions with anatomic deficits. Correlation analysis was conducted between the seeding reference and the rest of the whole brain in a voxel-wise manner using the preprocessed images. The resultant r value maps were subsequently transformed to approximate Gaussian distribution using Fisher's z transformation (40). For between-group comparison, two-sample t-tests were used to compare z value maps between migraine patients and healthy comparison subjects (family-wise error correction at $p < 0.05$).

RESULTS

VBM results

Relative to healthy comparison subjects, migraine patients showed significantly decreased gray matter volume in the following five brain regions: left medial prefrontal cortex (MPFC), dorsal ACC (dACC), right occipital lobe, cerebellum and brainstem (Fig. 1). Only the gray matter volume of the left dACC showed a significant negative correlation with the duration of disease in migraine patients ($r = -0.6193$; $p < 0.003$). No significant increased gray matter volume was detected.

Resting-state results

Compared with healthy controls, migraine patients showed increased functional connectivity between several regions and the left dACC. The regions consisted of the bilateral middle temporal lobe, OFC and left dorsolateral prefrontal cortex (DLPFC) (Fig. 2). No regions showed significant decreased functional connectivity with dACC in migraine patients. The functional connectivity between the dACC and left DLPFC ($r = 0.6629$; $p < 0.001$) and right OFC ($r = 0.5941$; $p < 0.005$) was positively correlated with the duration of disease in migraine patients.

In addition, our results demonstrated that the right occipital lobe showed increased functional connectivity with the left DLPFC and right MCC, the left MPFC showed increased functional connectivity with the bilateral DLPFC and the right cerebellum showed increased functional connectivity with the right MPFC in migraine patients without aura (Fig. 3). However, no brain regions were detected with abnormal resting-state functional connectivity with the brainstem. The correlation analysis failed to find any significant correlation between the functional connectivity changes and the duration of disease or the attack frequency in migraine patients without aura.

DISCUSSION

Migraine is a primary headache disorder characterized by recurrent attacks of throbbing pain associated with neurological, gastrointestinal and autonomic symptoms. Patients with migraine demonstrate remarkable impairment in their daily activities and are severely burdened by their headache syndrome. With the help of advanced neuroimaging techniques, our perception of migraine has improved in the last decade (2). Previous studies have detected structural deficits and functional impairments in migraine patients (1,4–6,9). However, researchers have failed to investigate the functional connectivity alterations of the regions with structural deficits during the resting state. In this study, we made a connection between the structural (gray matter volume) and functional (resting state connectivity) brain alterations in migraine patients without aura by combining

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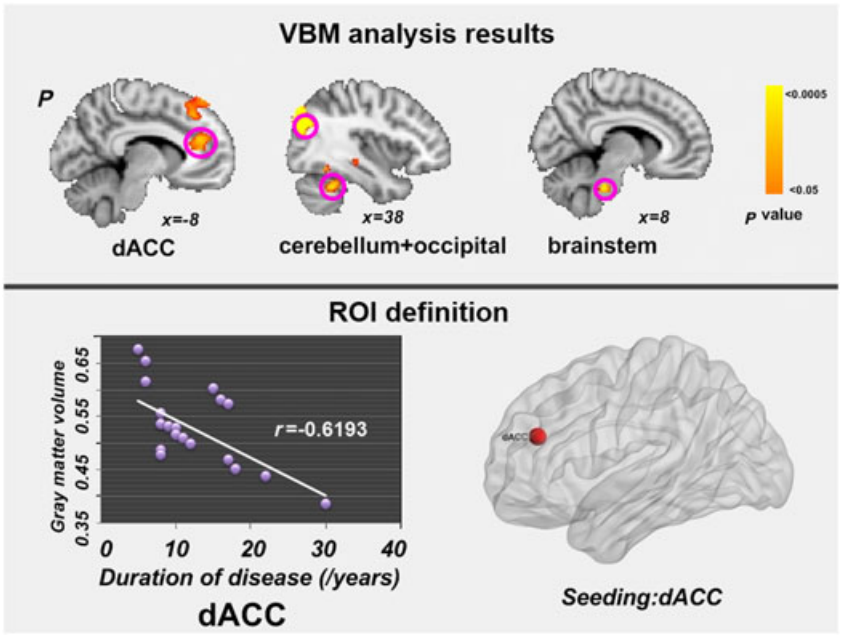

Figure 1. Structural analysis results of migraine patients without aura and healthy controls ($p < 0.05$, family-wise error corrected). The gray matter volume of the left dorsal anterior cingulate cortex (dACC) was negatively correlated with the duration of disease; therefore, we chose the left dACC as the 'seeding' area for the functional connectivity analysis. VBM, voxel-based morphometric.

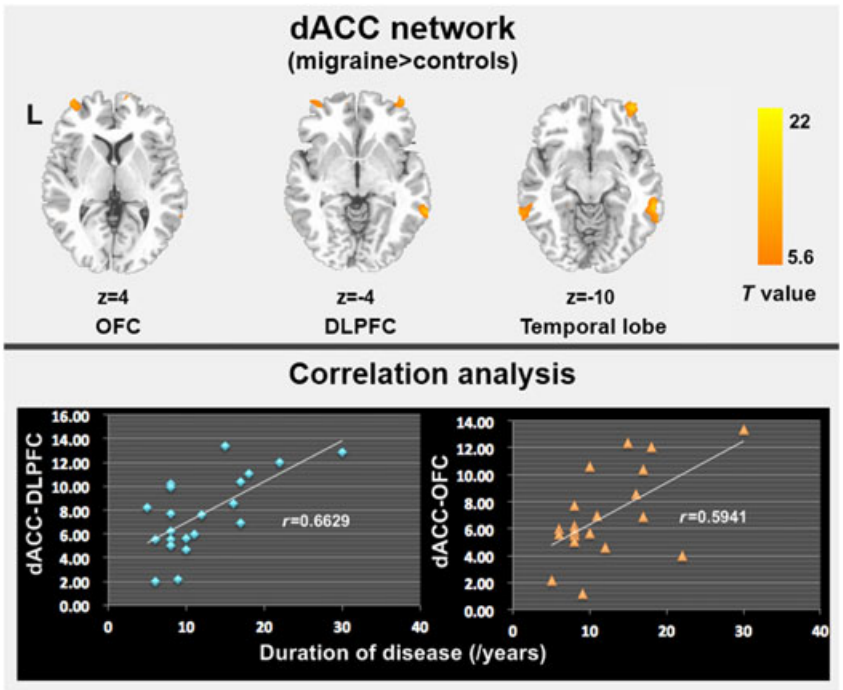

Figure 2. Functional analysis results of the left dorsal anterior cingulate cortex (dACC) during the resting state of migraine patients without aura and healthy controls ($p < 0.05$, corrected). The functional connectivity between the left dACC, right orbitofrontal cortex (OFC) and left dorsolateral prefrontal cortex (DLPFC) was positively correlated with the duration of disease in migraine patients without aura.

VBM and functional connectivity methods. Recently, there has been a significant advance in our knowledge with regard to the neural circuitry involved in nociceptive processing within the brain. Several brain regions that have generally been shown to be activated by pain in different experimental conditions, including the frontal and prefrontal cortices, primary and secondary somatosensory cortices, ACC, thalamus, insula, basal ganglia, cerebellum, amygdala, hippocampus and regions within the parietal and temporal cortices, are known as the pain matrix (2,11). Consistent with previous VBM findings in migraine patients (3,5,6), decreased gray matter volume was found in several brain regions associated with pain processing, such as

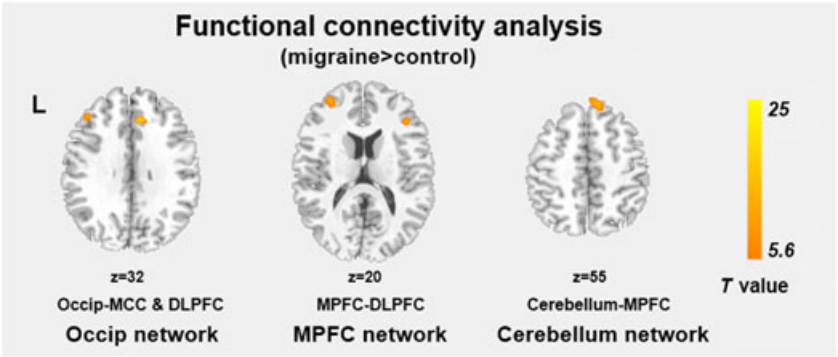

Figure 3. We also detected increased functional connectivity between the right occipital and left dorsolateral prefrontal cortex (DLPFC), left medial prefrontal cortex (MPFC) and bilateral DLPFC, and right cerebellum and right MPFC in migraine patients without aura. However, no brain regions showed abnormal resting-state functional connectivity with the brainstem.

the left MPFC, dACC, right occipital lobe, cerebellum and brainstem (Fig. 1). Our results of reduced gray matter volume validated the previous findings.

The frontal cortex is one of the most prominent areas associated with brain abnormalities in migraine patients (2,6). Previous studies have suggested that the MPFC may play a specific role in mediating the attenuation of pain perception via cognitive control mechanisms (41,42), which are associated with pain modulation (43,44). Schmitz *et al.* (45) reported that migraine patients showed decreased gray matter density in the MPFC and a slower response time to the set-shifting task. In addition, the delayed response time was correlated significantly with reduced gray matter density of MPFC in migraine patients. The dACC, lying on the medial surface of the frontal lobe, maintains strong connections with the DLPFC, parietal cortex and striatum. The dACC is believed to play a critical role in complex cognitive processing, target detection, response selection and inhibition, error detection, performance monitoring and motivation (11,46). Numerous studies have provided scientific evidence that the dACC is engaged with a cognitive–attentional response to pain (11) and the unpleasant emotional experience from pain (47). In addition to the frontal cortex, the brainstem, cerebellum and occipital cortex also showed structural deficits in migraine patients (Fig. 1). Afridi *et al.* (48,49) and others (50) have reported functional, pain-related activation changes in the brainstem during migraine attacks. Cerebellar abnormalities are thought to be the underlying cause for functional and metabolic disturbances in migraine (51–53), although the relationships between the observed morphological, metabolic and functional changes have yet to be established. Cortical spreading depression (CSD) has long been thought to be the physiological substrate of migraine aura (2). During CSD, an initial neuronal depolarization occurs, followed by hyperpolarization and relative neuronal silence that spreads contiguously from the occipital lobe forwards. CSD had been suggested to activate trigeminal sensory afferents and cause the pain of a migraine headache (54). The reduced gray matter volume of the occipital lobe may be associated with repetitive CSD in migraine patients.

In addition to the anatomical deficits of the brain regions in migraine patients without aura, the resting-state functional connectivity changes were investigated in our study. By comparing the resting-state dACC functional connectivity patterns in healthy controls and migraine patients, increased functional connectivity between several brain regions and the dACC was found, i.e. the bilateral middle temporal lobe, OFC and left DLPFC (Fig. 2). We also detected increased functional connectivity between the right occipital and left DLPFC, left MPFC and bilateral DLPFC, and right cerebellum and right MPFC in migraine patients without aura (Fig. 3). However, no brain regions showed abnormal resting-state functional connectivity with the brainstem. The DLPFC has been shown to mediate part of the cognitive dimension of pain processing associated with the localization and encoding of the attended stimulus (55). The OFC is also thought to contribute to cognitive control of goal-directed behavior through the assessment of the motivational significance of stimuli and the selection of behavior to obtain desired outcomes (56). The OFC has extensive connections with the striatum and limbic regions (such as the amygdala). As a result, the OFC is well situated to integrate the activity of several limbic and subcortical areas associated with motivational behavior and reward processing (57). The increased functional connectivity between the dACC and DLPFC, and between the dACC and OFC, may explain the abnormal pain processing (9,10,58) and executive function in migraine patients (45). We suggest that frequent nociceptive input modifies the frontal cortex resting-state connectivity patterns and these changes may explain the functional impairments in migraine patients.

The correlation between the neuroimaging findings (i.e. structural and functional changes) and the duration of disease in migraine patients was investigated. Our results demonstrated that the gray matter volume of the left dACC showed a significant negative correlation with the duration of disease (Fig. 1). The functional connectivity between the dACC, left DLPFC and right OFC were positively correlated with the duration of disease in migraine patients (Fig. 2). According to previous findings and our correlation analysis results, we conclude that our study confirms that migraine is a progressive disorder and may have cumulative effects on the brain in terms of both structure and function. Yu *et al.* (26) revealed abnormal resting-state properties of certain brain regions in patients with migraine without aura by employing the ReHo method. The Reho method provides local features, measured by the similarities of intra-regional time series, but yields little information on the similarities of inter-regional time series. We investigated the resting-state changes of the brain regions with structural deficits in patients with migraine without aura using the functional connectivity method, which focused on inter-region synchronization. Our multimodal methods provide scientific evidence for functional connectivity changes in resting-state networks of the brain regions with structural deficits in migraine patients without aura.

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