

Regional homogeneity abnormalities in patients with interictal migraine without aura: a resting-state study

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Previous studies have provided evidence of structural and task-related functional changes in the brains of patients with migraine without aura. Resting-state brain activity in patients with migraine provides clues to the pathophysiology of the disease. However, few studies have focused on the resting-state abnormalities in patients with migraine without aura. In the current study, we employed a data-driven method, regional homogeneity (ReHo), to analyze the local features of spontaneous brain activity in patients with migraine without aura during the resting state. Twenty-six patients with migraine without aura and 26 age-, education- and gender-matched healthy volunteers participated in this study. Compared with healthy controls, patients with migraine without aura showed a significant decrease in ReHo values in the right rostral anterior cingulate cortex (rACC), the prefrontal cortex (PFC), the orbitofrontal cortex (OFC) and the supplementary motor area (SMA). In addition, we found that ReHo values were negatively correlated with the duration of disease in the right rACC and PFC. Our results suggest that the resting-state abnormalities of these regions may be associated with functional impairments in pain processing in patients with migraine without aura. We hope that our results will improve the understanding of migraine. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: migraine without aura; regional homogeneity (ReHo); resting state; functional MRI (fMRI); supplementary motor area (SMA); prefrontal cortex (PFC); rostral anterior cingulate cortex (rACC); orbitofrontal cortex (OFC)

INTRODUCTION

Migraine is an idiopathic headache disorder and causes a significant individual and social burden. Frequent migraine attacks may produce pain, sensitivity and productivity loss, and even increase the risk of subtle lesions in certain brain regions (1–3). With the help of neuroimaging technology, our perception of migraine has transformed from a vascular to a neurovascular and, most recently, to a central nervous system disorder (4). Advanced neuroimaging approaches have been employed to investigate structural and functional brain changes in patients with migraine (4,5). Voxel-based morphometric studies of migraine have reported significant gray matter reduction in the cingulate cortex, insula, superior temporal gyrus, orbitofrontal cortex (OFC), inferior frontal gyrus and precentral gyrus in patients with migraine (6–9). Furthermore, gray matter reduction is correlated with both attack frequency and headache duration in patients with migraine (6,9). Facilitated by the diffusion tensor imaging technique, DaSilva *et al.* (10) reported lower fractional anisotropy in the ventroposterior medial thalamus and the corona radiata of the trigeminal somatosensory and modulatory pain systems in patients with migraine with and without aura and in the periaqueductal gray matter in patients with migraine without aura. Moreover, task-related functional MRI (fMRI) studies have also revealed abnormal activation of some brain regions associated with pain-related information processing in patients with migraine, such as the anterior cingulate cortex

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Abbreviations used: ACC, anterior cingulate cortex; fMRI, functional MRI; FWE, family-wise error; KCC, Kendall's coefficient of concordance; OFC, orbitofrontal cortex; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; ReHo, regional homogeneity; SMA, supplementary motor area; SPMS, Statistical Parametric Mapping 5.

(ACC), prefrontal cortex (PFC), OFC, insula and supplementary motor area (SMA) (11–13). All of these findings strongly support the assertion that migraine is a progressive disease and that repeated migraine attacks over time may result in selective damage to several brain regions involved in central pain processing (14,15).

By focusing on the neural responses under task conditions, resting-state analysis has been utilized to investigate the integration level of neural systems when no explicit task is engaged (16). It is worthwhile to note that the different neuronal activity at the baseline state should be considered when explaining findings in the task-performing state. The changed features with respect to the resting state may serve as an adequate marker to reflect the progress of disease (17). Such resting-state studies have been employed in several brain diseases, such as heroin addiction (18–20), schizophrenia (21), Alzheimer's disease (22), Parkinson's disease (23) and treatment-refractory depression (17). Together with providing potential diagnostic information and treatment strategies, these findings have revealed a reduction in integrity and efficiency of disease-relevant networks and may be beneficial for the understanding of disease states. All of these studies suggest that resting-state fMRI may be appropriate for studying migraine. However, until recently, few studies have evaluated the abnormalities of the resting state in subjects with migraine.

In the current study, we employed a data-driven method, regional homogeneity (ReHo), to analyze the blood oxygen level-dependent signals of the brains of patients with migraine without aura during the resting state (24). This has been shown to advance the understanding of the complexity of brain function and to complement task-related analysis in disease-related fMRI studies (24). Given that previous migraine studies have reported abnormal structural and functional properties of the brain regions involved in pain processing caused by frequent attacks, we hypothesized that the ReHo values of these brain regions would be different from those of healthy controls. In addition, to investigate the relationship between ReHo values of brain regions showing abnormal resting-state properties and the duration of migraine, a correlation analysis was carried out between these two factors.

EXPERIMENTAL DETAILS

Subjects

This study was approved by the Medical Ethics Committee of the West China Hospital of Sichuan University. All participants gave written informed consent after the experimental procedure had been fully explained. The patients with migraine without aura were screened following the International Headache Society criteria (25). The diagnostic criteria of the International Headache Society for migraine without aura include 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) featuring 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 headache at least one of the following: nausea and/or vomiting, photophobia and phonophobia; and (iv) not attributed to another disease. Seventy-three patients with migraine without aura fitting the above-mentioned criteria were included. In

addition, 29 age- and gender-matched healthy controls were enrolled. The controls either had no headache days per year or had family members who suffered regularly from a migraine or other headaches. Exclusion criteria for both groups were: (i) 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 as assessed according to clinical evaluations and medical records; and (v) claustrophobia. Finally, 26 patients with migraine without aura (20 females; age, 20–53 years; mean age, 32.2 ± 10.7 years) and 26 healthy controls (20 females; age, 23–55 years; mean age, 31.1 ± 11.7 years) were recruited in our study. Patients had not suffered from a migraine attack at least 72 h prior to testing (12). In addition, no patient had a migraine precipitated during or on the day following the scan. Subjects rated the average pain intensity as 5.5 ± 1.4 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 patients with migraine without aura are shown in Table 1. All of the participants were right-handed. In addition, prior to scanning, urine drug screening was performed on all subjects to exclude the possibility of substance abuse.

Data acquisitions

The experiment was carried out on a 3-T GE scanner (EXCITE, GE Signa, Milwaukee, WI, USA) with an eight-channel phase-array head coil at the Huaxi MR Research Center. The heads of the subjects were positioned carefully with comfortable support, and ear plugs were used to reduce scanner noise. Prior to the functional run, a high-resolution structural image for each subject was acquired using a three-dimensional MRI sequence with a voxel size of 1 mm^3 employing an axial fast spoiled gradient recalled sequence (TR = 1900 ms; TE = 2.26 ms; data matrix, 256×256 ; field of view, $256 \times 256 \text{ mm}^2$). The structural images were examined to exclude the possibility of clinically silent lesions for all of the participants by two expert radiologists. The resting-state functional images were obtained with echo-planar imaging (30 contiguous slices with a slice thickness of 5 mm; TR = 2000 ms; TE = 30 ms; flip angle, 90° ; field of view, $240 \times 240 \text{ mm}^2$; 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 they remained awake during the whole procedure.

Table 1. Clinical details of patients with migraine without aura and healthy controls (mean \pm standard deviation)

Clinical details	Patients with migraine without aura (n = 26)	Healthy controls (n = 26)
Age (years)	32.2 ± 10.7	31.1 ± 11.7
Sex (F, female; M, male)	20 F, 6 M	20 F, 6 M
Disease duration (years)	10.6 ± 6.6	—
Information on migraine attacks during the past 4 weeks		
Attack frequency (times)	4.7 ± 2.0	—
Duration of migraine attack (h)	14.1 ± 6.6	—
Pain intensity (0–10)	5.5 ± 1.4	—

Data preprocessing

The first five volumes were discarded to eliminate nonequilibrium effects of magnetization and to allow subjects to become familiar with the scanning environment. All of the data preprocessing procedures were performed using Statistical Parametric Mapping 5 (SPM5) (<http://www.fil.ion.ucl.ac.uk/spm>). The images were corrected for the acquisition delay between slices, aligned to the first image of each session for motion correction and spatially normalized to the standard MNI template in SPM5. No subjects had head motions exceeding 1 mm of movement or 1° rotation in any direction. Finally, a band-pass filter ($0.01 \text{ Hz} < f < 0.08 \text{ Hz}$) was applied to remove physiological and high-frequency noise (26).

Data processing

Kendall's coefficient of concordance (KCC) (27) was used to evaluate ReHo (24), which was performed using the Resting-State fMRI Data Analysis Toolkit (X.-W. Song *et al.*, Beijing Normal University, Beijing, China, <http://www.restfmri.net>). Individual ReHo maps were generated by assigning each voxel a value corresponding to the KCC of its time series with its nearest 26 neighboring voxels (24). A whole brain mask was used to remove nonbrain tissues. Only the voxels within the mask were further analyzed. The individual ReHo maps were standardized by their own mean KCC within the mask (28,29). Then, a Gaussian kernel with a full width at half-maximum of 4 mm (21–23) was used to smooth the images in order to reduce noise and residual differences.

Statistical analysis

Statistical analysis was performed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). For patients with migraine without aura and the control group, a one-sample *t*-test [$p < 0.05$, family-wise error (FWE) correction] was performed to extract the ReHo results across the subjects within each group. Then, a two-sample *t*-test was applied to compare the ReHo results between the two groups ($p < 0.05$, FWE corrected). Finally, for the regions of interest in which patients with migraine without aura showed abnormal resting-state properties, the ReHo values of these regions were extracted, averaged and regressed against the duration of the migraine.

RESULTS

The ReHo results for patients with migraine without aura and healthy controls are shown in Fig. 1 ($p < 0.05$, FWE corrected). The major regions of the default mode network exhibited significantly higher ReHo values than other brain regions during the resting state (Fig. 1a, b), i.e. the medial temporal lobe, posterior cingulate cortex, precuneus, medial prefrontal cortex and inferior parietal lobe. As illustrated in Fig. 2, the results of the two-sample *t*-test revealed that patients with migraine without aura showed significant decreases in ReHo values in the right rostral ACC (rACC), PFC, OFC and SMA ($p < 0.05$, FWE corrected). No brain regions with increased ReHo values were found. Furthermore, correlation analysis results demonstrated that there were significant negative correlations between the average ReHo values of the right PFC ($r = -0.5032$, $p = 0.0088$), rACC ($r = -0.4306$, $p = 0.0281$) and duration of migraine (Fig. 2). The relationships between these resting-state properties and

the average pain intensity and attack frequency were also checked. No results exceeded the threshold.

DISCUSSION

Typical task-related fMRI studies focus on brain activation defined as the comparison of blood oxygen level-dependent signals between the task and baseline resting state (30). In contrast with the traditional task-based approach, resting-state fMRI studies observe the blood oxygen level-dependent signal in the absence of an overt task or stimulation. During the resting state, correlated spontaneous fluctuations occur within spatially distinct, functionally related groups of cortical and subcortical regions, consisting of the human brain's intrinsic functional networks (31). The variations in the intrinsic functional networks may influence task performance in real life (32–34). Most resting-state fMRI studies adopt functional connectivity to investigate temporal relations between the intrinsic fluctuations observed in spatially distinct brain regions. However, functional connectivity provides few local features of spontaneous brain activity observed in specific regions. As a complement to the functional connectivity method, ReHo has been shown to be sufficient to detect ReHo abnormalities in the brain during the resting state. ReHo hypothesizes that voxels within a specific functional brain region are more temporally homogeneous when subjects are engaged in a specific condition (24). Previous resting-state studies have reported that several brain diseases result in abnormal ReHo values in related brain regions, and suggest that this method may be an important technique to improve the understanding of the neuromechanism of diseases (17,21–23).

Functional imaging studies have revealed that certain brain regions consistently show greater activity during the resting state than during tasks (35). These regions constitute a network supporting a default mode of brain function. The default mode network is a set of brain regions that exhibits synchronized low-frequency oscillations in the resting state, and involves the retrieval and manipulation of past events, both personal and general, in an effort to solve problems and develop future plans (16,36). Consistent with previous findings (17,21–23), we identified the major regions of the default mode network exhibiting significantly higher ReHo values than other brain regions during the resting state (Fig. 1a, b), i.e. the medial temporal lobe, posterior cingulate cortex, precuneus, medial prefrontal cortex and inferior parietal lobe. These results demonstrate that the ReHo method is helpful for understanding the probable organization of the brain.

In this study, we identified several brain regions showing differences between healthy controls and patients with migraine during the resting state. Specifically, ReHo values decreased in the right rACC, PFC, OFC and SMA in patients with migraine without aura compared with healthy controls. The brain regions that showed ReHo changes in patients with migraine without aura were similar to the brain regions reported in the structural (6–9) and task-related (11–13) studies, which were mainly involved in pain-related processing (Fig. 2) (4,5,37). We speculated that the resting-state abnormalities of these regions may be associated with structural and functional impairments in pain processing in patients with migraine without aura. Our findings provide local functional features in specific regions during the resting state and improve our understanding of task-related analysis. They may provide potential diagnostic information

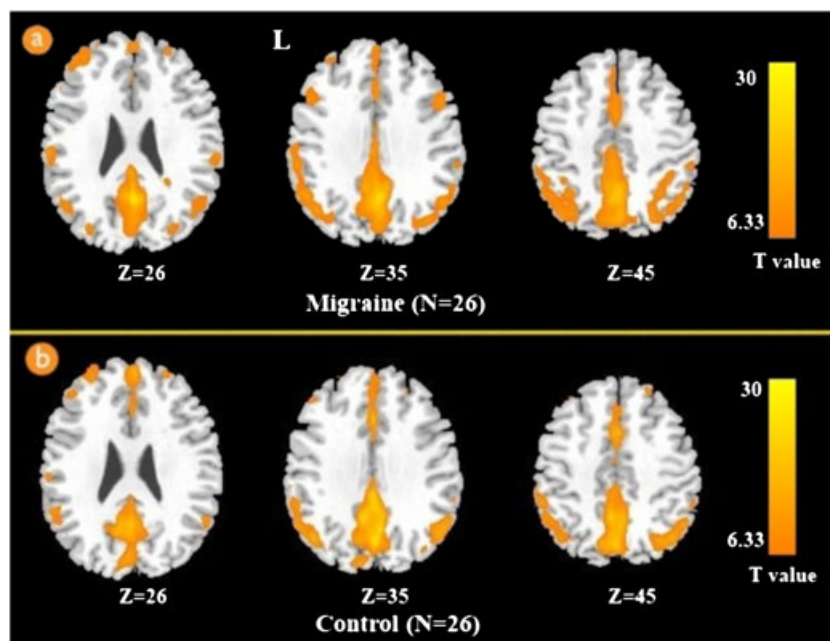


Figure 1. Results of regional homogeneity (ReHo) shown as a Kendall's coefficient of concordance (KCC) map across all patients with migraine without aura (a) and healthy control subjects (b) during the resting state [$p < 0.05$, family-wise error (FWE) corrected].

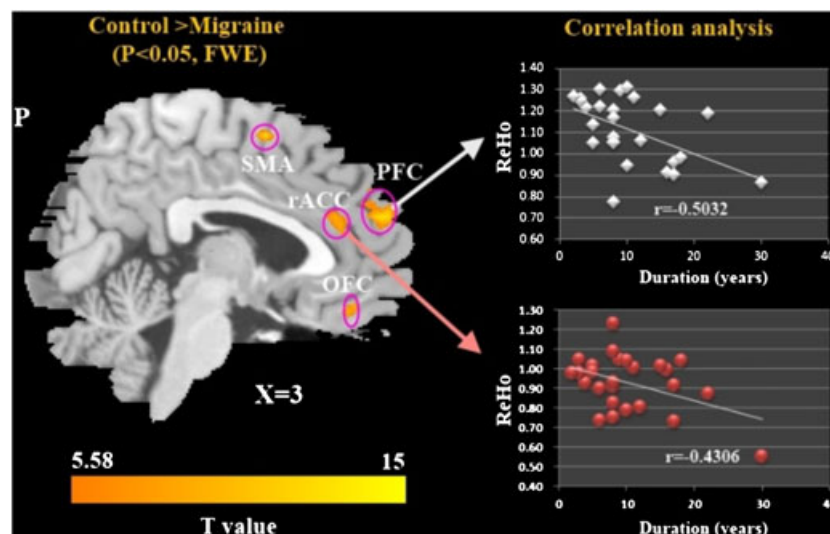


Figure 2. Left: migraine-related changes in regional homogeneity (ReHo) shown as a comparison of Kendall's coefficient of concordance (KCC) maps between patients with migraine without aura and controls [$p < 0.05$, family-wise error (FEW) corrected] during the resting state. T score bars are shown at the bottom. Warm colors indicate ReHo decreases in patients with migraine without aura. Right: correlation analysis results between the average ReHo values of the right prefrontal cortex (PFC) (top)/rostral anterior cingulate cortex (rACC) (bottom) and duration of the migraine. OFC, orbitofrontal cortex; SMA, supplementary motor area.

and treatment strategies in patients with migraine. In addition, the ReHo values of rACC and PFC were negatively correlated with the duration of the migraine. Our results suggest that migraine is a progressive disease and that ReHo changes may serve as a biomarker to reflect the progress of migraine (17).

Firstly, we found that ReHo values decreased in the right rACC in the patient group. As shown by experimental and clinical studies, the affective responses of pain, such as unpleasantness,

suffering and other negative effects, may be principally integrated in rACC (38–42). In addition, rACC is involved in endogenous pain control, which is mediated by the endogenous opioid systems (43,44). Therefore, we suggest that the resting-state abnormalities of rACC in patients with migraine without aura may be related to functional impairments in the long-term pain affective response and endogenous analgesia. Secondly, ReHo values decreased in the right PFC. The PFC is an important

region in opioid analgesia and in other forms of pain modulation (43,45). This brain region may play a specific role in mediating the attenuation of pain perception via cognitive control mechanisms (46,47). It is worthwhile noting that Aderjan *et al.* (11) studied the differences between healthy controls and patients with migraine without aura stimulated daily with a 20-min trigeminal pain paradigm for eight consecutive days, using functional MRI performed on days 1 and 8, and one follow-up measurement 3 months later. The results demonstrated that behavioral pain ratings were no different, but several brain regions known to be involved in endogenous pain control showed completely opposite behavior. In more detail, the activity level in PFC and rACC increased in healthy control subjects, whereas it decreased in patients with migraine (11). The opposite behavior during the input stimulation may be associated with abnormalities during the resting state. Decreased ReHo values in PFC, together with rACC, possibly suggest efficiency reduction in pain processing in patients with migraine without aura. In addition, we found that the ReHo values in rACC and PFC were both negatively correlated with the duration of disease, which is characterized by the duration of 'pain suffering'. Our findings suggest that the ReHo properties of rACC and PFC become abnormal as a function of time, which may reflect the progress of migraine.

Decreased ReHo values were also found in the right OFC. The OFC has been proposed to be involved in sensory integration, decision making, expectation and planning behavior associated with sensitivity to reward and punishment (48–50). Stimulation, both pain and pleasure, has been shown to elicit opioid release in the OFC (51–53). All received sensations are modulated and related affective responses are assigned accordingly by the OFC (54), which is involved in the learning of the affective and motivational value of stimulation (55). In particular, the OFC seems to be involved when responses based on the previous reward value need to be inhibited, i.e. response inhibition (56). The ReHo values of the right SMA also decreased, particularly in the pre-SMA. Most investigators proclaim that the SMA is far from 'supplementary' to requirements, but seems to be crucial for linking cognition to action (57–59). The pre-SMA is involved in executive control (60–63), pain anticipation (44,64–66) and the affective component of pain (67–69). Other tasks that require the inhibition of responses and switching between rules linking stimulation to responses also consistently activate the pre-SMA (70,71). In patients with migraine without aura, decreased ReHo values in the OFC and SMA may be related to deficits in affective pain modulation and affective pain response inhibition.

Contrary to our expectations, no significant changes in ReHo values were found in the insula for patients with migraine. Our results reveal that there is a trend for patients with migraine without aura to show smaller ReHo value decreases in the insula ($p < 0.005$, uncorrected), which do not survive FWE correction. The brain regions in which ReHo values were decreased were concentrated in the right hemisphere, which may be supported by the existence of a right hemispheric predominance for the affective and affective consequences of pain (72–74). It is suggested that this right hemispheric predominance corresponds to a right hemispheric predominance for homeostatic or autonomic control (75).

Although numerous studies have reported structural and functional changes in gray matter in patients with migraine, few have focused on the resting-state abnormalities. In the current study, we employed the ReHo method to investigate the

abnormal resting-state properties and to provide evidence for functional abnormalities in patients with migraine during the resting state. These changes in the right rACC and PFC may be associated with pain processing and may become more significant as the disease progresses. It is possible to argue that the ReHo abnormalities of these regions are a consequence of frequent nociceptive input. Our findings suggest that ReHo may be a potential tool to measure the severity and to monitor the progression of migraine. We hope that our results will improve the understanding of migraine mechanisms.

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