● **RESEARCH ARTICLE**

Regional volume changes of the brain in migraine chronification

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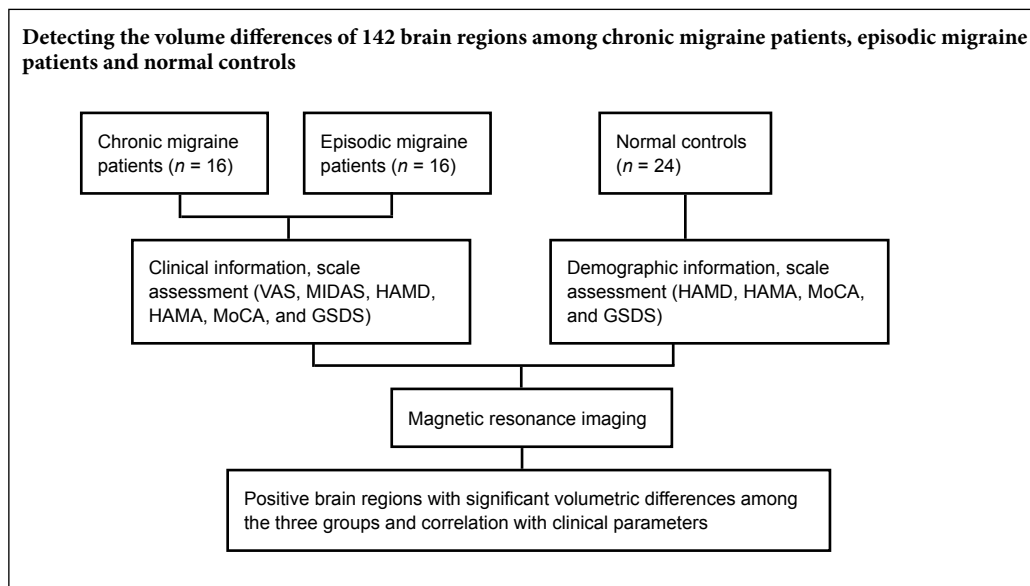
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Graphical Abstract

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Detecting the volume differences of 142 brain regions among chronic migraine patients, episodic migraine patients and normal controls

Abstract

The pathophysiology of migraine is complex. Neuroimaging studies reveal functional and structural changes in the brains of migraine patients. We sought to explore regional volume differences in intracranial structures in patients with episodic and chronic migraine. Sixteen episodic migraine patients, 16 chronic migraine patients, and 24 normal controls were recruited and underwent 3.0 T MRI scanning. The volumes of 142 brain regions were calculated by an automatic volumetric algorithm and compared with clinical variables. Results demonstrated that the volumes of specific regions in the frontal and occipital lobes, and the right putamen, were increased and the volume of the fourth ventricle was decreased in the episodic migraine patients compared with controls. The volumes of the left basal forebrain, optic chiasm, and, the fourth ventricle were decreased in the chronic migraine patients, while the occipital cortex and the right putamen were larger. Compared to episodic migraine patients, chronic migraine patients displayed larger left thalamus and smaller frontal regions. Correlation analysis showed that headache frequency was negatively correlated with the volume of the right frontal pole, right lateral orbital gyrus, and medial frontal lobes and positively correlated with the volume of the left thalamus. The sleep disturbance score was negatively correlated with the volume of the left basal forebrain. This suggests that migraine patients have structural changes in regions associated with pain processing and modulation, affective and cognitive processing, and visual perception. The remodeling of selective intracranial structures may be involved in migraine attacks. This study was approved by the Ethics Committee of Chinese PLA General Hospital (approval No. S2018-027-02) on May 31, 2018.

Key Words: brain volume; chronic migraine; frontal lobe; magnetic resonance imaging; migraine; remodeling; thalamus; visual processing system

Chinese Library Classification No. R445.2; R747.2; R321.81

Introduction

Migraine is a common neurological disorder which can cause significant disability (GBD 2016 Neurology Collaborators, 2019). Episodic migraine (EM) refers to fewer than 15 headache days per month, while chronic migraine (CM) implies headache occurring ≥ 15 days per month for at least 3 months with migraine features on ≥ 8 days every month (No authors listed, 2018). About 3% of patients may transform from EM to CM within a year (Lipton et al., 2015; Scher et al., 2017; Borkum, 2018). The prevalence of CM was reported to be 0.6–1.7% in Asia-Pacific region (Stark et al., 2013) and 1–2% in the global population (Burch et al., 2019). A number of risk factors, such as increased headache frequency, acute medication overuse, and depression are related to the transition from EM to CM, termed "chronification" (Buse et al., 2019). CM associated with medication overuse, also called "medication overuse headache" (Goudarzi et al., 2016), returns to episodic form after medication withdrawal, and may not actually be CM (No authors listed, 2018).

The pathogenesis of migraine chronification has been only partially revealed. Neuroimaging studies of CM have found functional and microstructural alterations in the brainstem, hypothalamus, basal ganglia, and cortex, sites that are involved in pain processing. Some of the changes correlate with headache frequency and/or duration, while others may be associated with mood and emotion, cognitive dysfunction and insomnia (Coppola et al., 2017; Neeb et al., 2017; Schulte et al., 2017; Androulakis et al., 2018; Domínguezet al., 2019; Lee et al., 2019; Woldeamanuel et al., 2019). These functional and structural alterations reflect central plasticity of CM, but whether the changes were the etiology or the effects of migraine chronification has yet to be revealed. Neuroimaging findings were variable across different studies, probably due to the diversities of patients' background, clinical aspects, imaging processing methods, and statistical power. Previous structural imaging studies have investigated alterations in gray matter volume or thickness (Coppola et al., 2017; Neeb et al., 2017; Woldeamanuel et al., 2019), iron deposition (Domínguez et al., 2019), white matter lesions (Zheng et al., 2014; Neeb et al., 2015) and textural features of gray matter (Chen et al., 2017). Among those morphometric studies, volumetric analysis was most widely performed, and may well reflect brain remodeling in migraine. We intended to assess for the intracranial volume changes in EM and CM by calculating the volume of 142 brain regions according to a commercial template (Neuromorphometrics, Somerville, MA, USA) using an automatic morphometric algorithm over the whole brain. Compared to previous volumetric studies that usually investigated the cortical voxelwise microstructural changes (Coppola et al., 2017; Neeb et al., 2017; Palm-Meinders et al., 2017), this study directly calculated the volume differences not only in the cortex, but also in the white matter and the ventricles in a more macroscopic view using the automatic morphometric algorithm.

This study investigated the global and regional brain volume changes in EM and CM patients compared with normal controls (NCs), the global and regional brain volume differences between EM and CM patients, and the correlation of altered brain-region volumes with headache duration, frequency, and intensity and the scores for anxiety, depression, cognition, and sleep quality in all migraine patients.

Subjects and Methods

Fifty-six subjects were included in this prospective cross-sectional study, comprising 16 EM patients, 16 CM patients and 24 NCs. Migraine patients were consecutively recruited from the Outpatient Headache Clinic of the Department of Neurology of the First Medical Center of Chinese PLA General Hospital. Diagnosis of EM and CM fulfilled the criteria of ICHD-3 (No authors listed, 2018) and only migraine patients without aura were included, aura being relatively uncommon in the Chinese population. Inclusion criteria were age 18–60 years old, right-handed, willing to engage in the study, and not taking prophylactic medication or acute headache medications for more than 10 days per month during the last 3 months. Patients with chronic somatic or psychiatric disorders such as hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular diseases, brain trauma, neoplasm, infection, connective tissue diseases, other subtypes of headache, chronic somatic pain, severe anxiety or depression before the onset of headache, or substance addiction were also excluded Inclusion and exclusion criteria of NCs were similar to those of the patients, except for the diagnosis of migraine.

Demographic information and general headache data were collected. All the patients completed a Visual Analogue Scale (VAS) (Aicher et al., 2012) for pain and a Migraine Disability Assessment (MIDAS) questionnaire (Hung et al., 2006) for assessing the impact of headache. The ten-point VAS was structured with a score greater than 6 corresponding to severe pain, a score of 4–6 indicating moderate pain, and a score lower than 4 indicating mild pain. The MIDAS score is derived from five questions about missed time from work, household work, and missed days of nonwork activities. The higher the MIDAS score, the more severe the disability caused by migraine. Both patients and NCs underwent Hamilton Anxiety Scale (HAMA) (Matza et al., 2010, Nair et al., 2015), Hamilton Depression Scale (HAMD) (Zimmerman et al., 2013), Montreal Cognitive Assessment (MoCA) Beijing Version (www.mocatest.org), and General Sleep Disturbance Scale (GSDS) (Lee, 2007) assessment for evaluating anxiety, depression, cognition and sleep quality, respectively. A HAMA score 8–14 indicates mild anxiety; 15–23 indicates moderate anxiety; and ≥ 24 indicates severe anxiety (Matza et al., 2010). A HAMD score of 8–16 indicates mild depression; 17–23 indicates moderate depression; and ≥ 24 indicates severe depression (Zimmerman et al., 2013). The total score of MoCA is 30 and when the score falls below 26, cognitive impairment is present. The lower the MoCA score is, the worse the cognitive function. GSDS is a self-rated, 8-point scale arranged from 0 (never) to 7 (every day); and higher GSDS scores indicate more severely disturbed sleep (Lee, 2007). The above scales were evaluated by trained doctors. This study was approved by the Ethics Committee of Chinese PLA General Hospital (approval No. S2018-027-02) on May 31, 2018 (**Additional file 1**). All the participants signed informed consents (**Additional file 2**) which complied with the *Declaration of Helsinki* before participating in the study.

This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (**Additional file 3**).

MRI acquisition

Nicotine, alcohol, and caffeine were prohibited at least 12 hours prior to MRI scanning. For EM patients, MRI examinations were performed at least 3 days after the last migraine attack. Headache status was recorded for CM patients at MRI examination. All the MRI examinations were carried out on a GE 3.0 Tesla MRI scanner (DISCOVERY MR750, GE Healthcare, Milwaukee, WI, USA) with a conventional 8-channel quadrature head coil. High-resolution structural images were collected by a three-dimensional T1-weighted fast spoiled gradient recalled echo sequence with the parameters as follows: repetition time = 6.3 ms, echo time = 2.8 ms, flip angle = 15 degrees, field of view (Bilgiç, Kocaman et al., 2016) = 25.6 × 25.6 cm^2, matrix size = 256 × 256, number of acquisition = 1180 contiguous axial slices, slice thickness = 1 mm. Subjects with obvious structural abnormalities and lesions in the brain, as assessed by a radiologist and neurologist, unless they were a few white matter lesions which may be related to migraine, were excluded from the study.

Data processing

All the MRI structural images were processed using computational Anatomy plugins (CAT, http://www.neuro.uni-jena. de/cat/) implemented within MATLAB 7.6 (The Mathworks, Natick, MA, USA) based on Statistical Parametric Mapping 12 (SPM 12, http://www.fil.ion.ucl.ac.uk/spm/). The volumes of 142 brain regions were automatically extracted from gray matter, white matter and cerebrospinal fluid according to the software as in our previous methods (Chen et al., 2018) composed of several procedures: spatial registration of individual brain images to an International Consortium for Brain Mapping (ICBM) space template (East Asian brains) (Mazziotta et al., 2001) to obtain normalized images, segmentation of normalized tissue into gray matter, white matter and cerebrospinal fluid, and volume extraction of 142 brain regions according to the Neuromorphometrics template.

Statistical analysis

The sample size was calculated by PASS 11 power analysis software (NCSS, Kaysville, UT, USA) based on our preliminary data with type 1 error rate of 0.5 and power of 90% in the one-way analysis of variance power analysis. Sample sizes of 14, 14, and 21 were obtained from the three groups whose means were to be compared. The total sample of 49 had 91% power to find means to be different among the groups using an F test with significance level of 0.05. The common standard deviation was assumed to be 0.21 in the means and 0.40 within a group.

Statistical analysis was performed with IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA). The continuous data in demographics and clinical profiles were presented as the mean ± standard deviation. The differences in age, HAMA, HAMD, MoCA, sleep disturbance scale, total volume of gray matter, white matter, cerebrospinal fluid, and total intracranial volume were compared among the three groups using

a one-way analysis of variance test followed by pairwise comparison using the Bonferroni method. Sex ratios of CM and EM were compared with the chi-squared test. Headache duration, headache frequency, VAS, number of doses of each medication per month, and MIDAS were compared between the EM and CM groups with an independent samples *t*-test. The differences in brain-region volume among EM, CM and NCs were calculated with a general linear model using age, sex and total intracranial volume as covariates followed by pairwise comparison corrected by the Bonferroni method. Partial correlation analyses were performed between the volumes of altered brain regions and the clinical parameters in EM and CM patients compared with controls for age, sex, and total intracranial volume. A value of *P* < 0.05 was considered statistically significant.

Results

Demographics and clinical data of EM, CM, and NCs

A total of 56 participants (16 EM patients, 16 CM patients and 24 NCs) were enrolled in this study. Only two patients in the CM group were headache-free during MRI scanning. **Table 1** shows the demographics and clinical data. There were no statistical differences in age and sex among the three groups. Years with headache, headache intensity, and number of acute analgesics taken per month were not significantly different between EM and CM groups. Both EM and CM patients were significantly more anxious, depressed, and had worse sleep disturbance than NCs (*P* < 0.001). CM patients were more depressed and had more severe sleep disturbance than EM patients (*P* < 0.05). Cognitive function as measured by MoCA was much lower in CM patients than in EM patients and NCs (*P* = 0.001). CM patients endured a much higher burden of migraine disability than EM patients (*P* < 0.001).

Volume differences in intracranial structures among EM patients, CM patients and NCs

The total intracranial volume and total volume of gray matter, white matter, and cerebrospinal fluid yielded no statistical differences among EM patients, CM patients, and NCs (*P* > 0.05; **Table 2**). The results did not change after adjusted by age and using the Bonferroni correction for multiple group comparison.

Region-volume analyses with multiple comparisons found significantly larger volumes of several regions in the frontal lobe, occipital lobe, right putamen and lower volume of the 4th ventricle of EM patients compared with NCs (*P* < 0.05; **Table 3** and **Figure 1**).

Compared with NCs, greater volume was detected in the left lingual gyrus, left fusiform gyrus, and right putamen, while the optic chiasm, the 4th ventricle, and basal forebrain in CM patients (**Table 3** and **Figure 2**) were lower in volume compared with NCs.

Compared with EM patients, the frontal lobe volume was smaller and the left thalamus volume was larger in CM patients (**Table 3** and **Figure 3**).

Correlation of clinical parameters and the volume of different brain regions

Headache frequency (headache days per month) was nega-

tively correlated with the volume of the right frontal pole (r = –0.571, P = 0.001), right lateral orbital gyrus (r = –0.395, P = 0.034), and left and right medial frontal lobes (r = –0.501, P = 0.006; r = –0.493, P = 0.007, respectively). Headache frequency was positively correlated with the volume of the left thalamus (r = 0.583, P = 0.001). The sleep disturbance scale was negatively correlated with the volume of the left basal forebrain (r = –0.410, P = 0.024; **Figure 4**). No significant correlation was found between other clinical parameters and the volume of brain regions.

Discussion

This structural MRI study analyzed volume alterations of regions in the gray matter, the white matter, and the ventricles in migraine patients. In this study, the altered volume in several regions of prefrontal cortex, occipital lobe, right putamen, the 4th ventricle, the optic chiasm, and thalamus of migraine patients may indicate a central plasticity in migraine pathogenesis and chronification.

The prefrontal cortex has a key role in cognitive processing and pain modulation by wide connections with other brain areas, including the parietal cortex, insula, hippocampus, amygdala, thalamus, basal nuclei and periaqueductal gray matter (Ong et al., 2019). Previous studies have reported impaired prefrontal cortical function in migraine patients as shown by neuropsychological testing (Lev et al., 2010, 2013). Voxel-based morphometry studies generally demonstrated volume or density reduction of the frontal cortex in migraine patients (Kim et al., 2008; Schmitz et al., 2008; Valfrè et al., 2008; Jin et al., 2013; Coppola et al., 2017). Different from most voxel-based morphometry studies, EM patients in our study showed volume expansion of the frontal and occipital lobes. Those selected areas have been reported in previous studies to demonstrate volume alteration in migraine patients (Kim et al., 2008; Schmitz et al., 2008; Valfrè et al., 2008; Jin et al., 2013; Bilgiç et al., 2016; Yu et al., 2016; Coppola et al., 2017; Palm-Meinders et al., 2017). Therefore, we speculated that those regions indeed had alteration in EM patients.

Similar to our results, one study using whole-brain vertex-by-vertex analysis also found thickened prefrontal cortex in migraine patients without aura (Kim et al., 2014). More surface-based morphometry studies reported increased thickness in the somatosensory cortex (DaSilva et al., 2007) and motion-processing visual areas (Granziera et al., 2006) in EM patients. However, other surface-based morphometry studies reported thinner cortex in the frontal lobe, occipital lobe (Yu et al., 2016) and basal ganglia (Yuan et al., 2013) in migraine patients. The results from structural MRI studies are influenced by several factors, such as the patients' ethnicity, migraine duration and/or frequency (Maleki et al., 2012), MRI parameters, morphometric methods, statistical efficacy, and ictal or interictal state (Coppola et al., 2015). In our study, those enlarged frontal areas in EM patients were no more larger in CM patients compared with NCs and the volume of some frontal regions was negatively correlated with headache frequency. The increased prefrontal cortex in EM patients may indicate adaptation of the central nervous system, which would enhance descending pain modulation at

the stage of migraine attack. The volume decrease in prefrontal cortex in patients with higher headache frequency may reflect maladaptive volume reduction (Liu et al., 2017) and dysfunction of pain inhibition, which would facilitate migraine attacks and promote migraine chronification (Krummenacher et al., 2010; Bräscher et al., 2016). The mechanism of remodeling of migraine brain is unclear, but is considered to be related to the number and size of neuronal or glial cells and their synapses, and altered interstitial fluids or blood flow (May, 2011) probably resulting from neural excitability, neuroinflammation, vascular constriction or dilation, and neural degeneration.

Interestingly, our study detected decreased basal forebrain size in CM patients compared with NCs, which was not reported in previous structural MRI studies. The basal forebrain contains at least three distinct populations of neurons (cholinergic, glutamatergic, and GABAergic), which have extensive projections to cortical and subcortical areas to regulate arousal, motivation, and other behaviors (Agostinelli et al., 2019). An animal study found increased pain sensitivity after destruction of basal forebrain cholinergic neurons in rats, revealing that cholinergic transmission of basal forebrain may be involved in pain processing (Vierck et al., 2016). A quantitative electroencephalogram study found that migraine patients suffered from highly asymmetric values in anterior δ power and posterior α and θ waves, suggesting altered activity patterns in the cholinergic brainstem or basal forebrain nuclei and thalamocortical connections prior to migraine attack (Bjørk and Sand, 2008). Further, the basal forebrain is considered to play a role in regulating the sleep–wake cycle in animals (Hermanstyne et al., 2013). In our study, the volume of basal forebrain was negatively correlated with the sleep disturbance scale, which further supported that altered basal forebrain may be associated with poorer sleep in migraine patients.

The visual processing pathway is strongly associated with migraine pathophysiology and clinical manifestations (Marzoli and Criscuoli, 2017). Light stimulation is a possible trigger of migraine attack. Visual aura is the most frequent form of migraine aura. Photophobia is a common accompanying symptom of migraine. Light hypersensitivity in migraine has been considered to be associated with light transmission from the retina to the trigeminovascular thalamocortical pathway (Noseda et al., 2010). Several studies reported a thinner retinal nerve fiber layer (Reggio et al., 2017; Tak et al., 2018) and/or retinal ganglion cell layer (Reggio et al., 2017; Gunes et al., 2018) in migraine patients, and the thickness may be negatively correlated with headache frequency (Reggio et al., 2017). Our study demonstrated volume reduction of the optic chiasm in CM patients, which further supports the structural alteration of the visual processing pathway. Similar to a previous surface-based morphometry study which reported thickened motion-processing visual regions (MTt and V3A) in migraine patients (Granziera et al., 2006), our study found thickened occipital regions in EM and CM patients, indicating the remodeling of central visual system in migraine patients.

The deep gray matter basal ganglia are important in integrating sensory, motor, motivation, cognitive and pro-
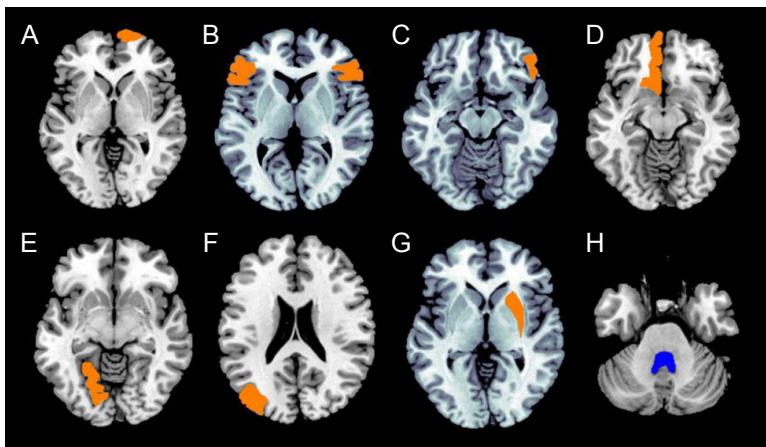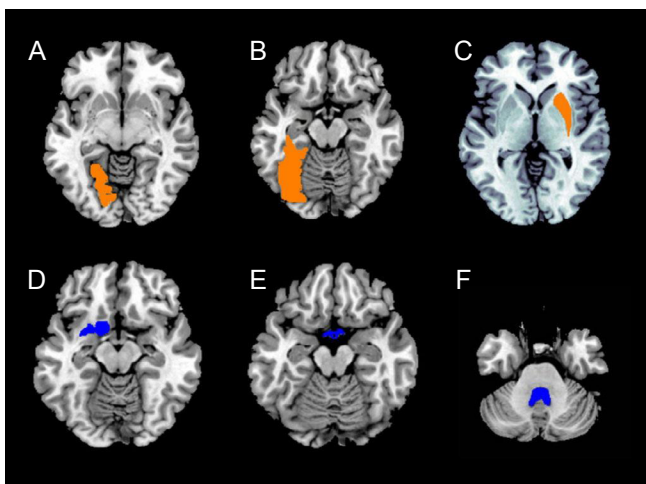
Figure 1 Brain regions positive for volume alteration in episodic migraine compared with normal controls ($P <$ 0.05, Bonferroni corrected).
(A–G) Orange color represents larger brain regions in the right frontal pole ($P = 0.015$), bilateral inferior frontal angular gyrus ($P = 0.008$), right lateral orbital gyrus ($P = 0.004$), left medial frontal cerebrum ($P = 0.005$), left lingual gyrus ($P = 0.039$), left middle occipital gyrus ($P = 0.01$) and right putamen ($P = 0.013$). (H) Blue color represents smaller brain regions in the 4th ventricle ($P = 0.005$).

Figure 2 Brain regions with volume alteration in chronic migraine compared with normal controls ($P < 0.05$, Bonferroni corrected).
(A–C) Orange color represents larger brain regions in left lingual gyrus ($P = 0.001$), left occipital fusiform gyrus ($P = 0.034$) and right putamen ($P = 0.004$). (D–F) Blue color represents smaller brain regions in left basal forebrain ($P = 0.002$), optic chiasm ($P = 0.007$) and the 4th ventricle ($P = 0.002$).
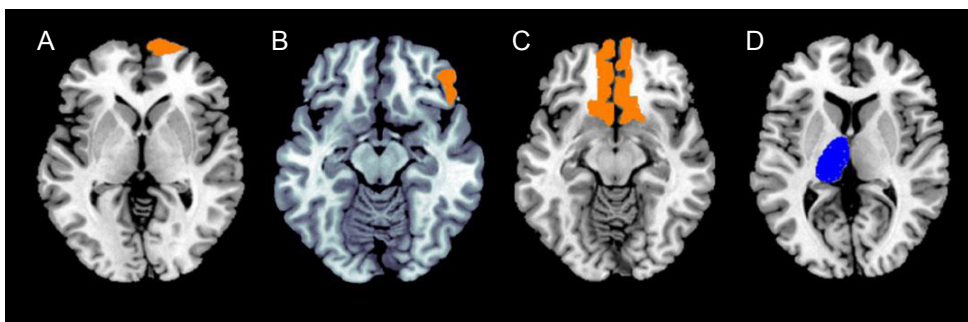

Figure 3 Brain regions positive for volume alteration in episodic migraine compared with chronic migraine ($P < 0.05$, Bonferroni corrected).
(A–C) Orange color represents larger regions in the right frontal pole ($P = 0.021$), right lateral orbital gyrus ($P = 0.035$), and bilateral medial frontal cerebrum ($P = 0.002$). (D) Blue color represents smaller brain regions in the left thalamus ($P = 0.009$).
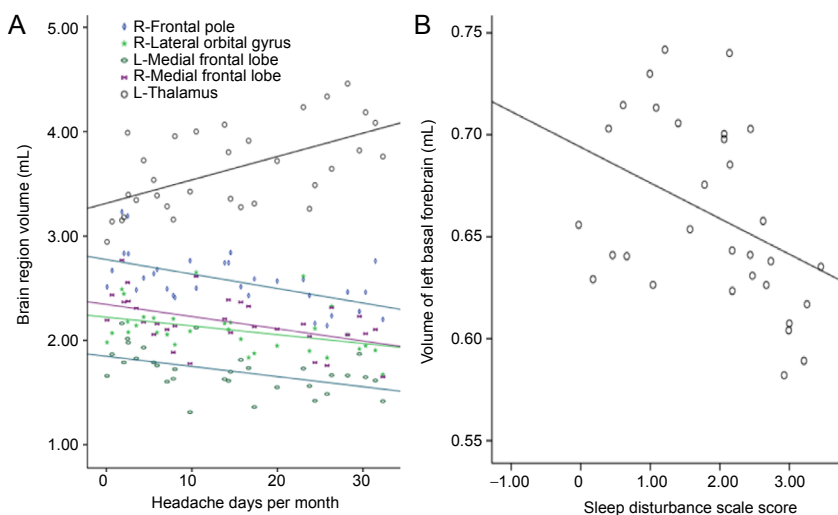

Figure 4 Correlation analysis of clinical profiles and the volume of positive brain regions.
(A) Headache frequency was positively correlated with the volume of the left thalamus ($r = 0.583$, $P = 0.001$) and negatively correlated with the right frontal pole ($r = -0.571$, $P = 0.001$), right lateral orbital gyrus ($r = -0.395$, $P = 0.034$), left medial frontal lobe ($r = -0.501$, $P = 0.006$) and right medial frontal lobe ($r = -0.493$, $P = 0.007$). (B) Sleep disturbance scale was negatively correlated with the volume of left basal forebrain ($r = -0.410$, $P = 0.024$). L: Left; R: right.

Table 1 Demographic and clinical information of EM patients, CM patients and NCs

Item	EM patients (n=16)	CM patients (n=16)	NCs (n=24)	P-value
Age (yr)	35.75±9.14	43.13±8.96	41.83±11.96	0.103
Sex (female/male, n)	3/13	3/13	5/19	0.981
Headache duration (yr)	13.38±8.09	11.25±9.30		0.496
Headache frequency (d/mon)	3.66±2.82	25.06±5.87[#]		< 0.001
Headache side				0.083
Left	4	0		
Right	1	2		
Bilateral or middle	5	10		
Left or right	6	4		
VAS score	8.31±1.48	7.88±1.45		0.408
Number of medications per month	5.00±3.85	4.31±3.77		0.614
HAMA score	15.25±10.41[*]	21.63±10.98[*]	2.39±1.47	< 0.001
HAMD score	10.19±7.41[*]	16.31±10.52[*#]	1.13±1.06	< 0.001
GSDS score	1.31±1.14[*]	2.56±0.96[*#]	0.13±0.34	< 0.001
MoCA score	26.75±4.28	22.94±5.37[*#]	28.13±2.07	0.001
MIDAS score	16.88±18.73	101.81±53.96[#]		< 0.001

Data are expressed as the mean ± SD, except sex and headache side. Sex and headache side were computed with the chi-square test. Headache frequency, VAS, the number of medications per month, and MIDAS were compared between EM and CM groups with independent samples t-test. The differences in age, HAMA, HAMD, GSDS, and MoCA among three groups were compared using one-way analysis of variance test followed by pairwise comparison using Bonferroni method. *$P < 0.05$, *vs.* NCs; #$P < 0.05$, *vs.* EM patients. CM: Chronic migraine; EM: episodic migraine; GSDS: General sleep disturbance scale; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MIDAS: Migraine Disability Assessment questionnaire; MoCA: Montreal Cognitive Assessment; NCs: normal controls; VAS: Visual Analogue Scale.

Table 2 Total intracranial volume (mL) of intracranial structure in EM patients, CM patients and NCs

	EM patients (n = 16)	CM patients (n = 16)	NCs (n = 24)	P-value
Gray matter	681.67±48.85	657.89±65.18	660.53±56.46	0.064
White matter	493.25±41.38	480.18±46.69	493.74±39.59	0.346
Cerebrospinal fluid	287.97±32.45	276.92±38.75	282.04±31.71	0.666
Total intracranial volume	1462.89±113.84	1414.99±144.17	1436.71±122.73	0.233

Data are expressed as the mean ± SD (one-way analysis of variance). CM: Chronic migraine; EM: episodic migraine; NCs: normal controls.

Table 3 Regional volume differences of brain regions among EM patients, CM patients and NCs

Brain regions	CM patients (n = 16)	EM patients (n = 16)	NCs (n = 24)	P-value
R-putamen	3.249±0.445↑	3.365±0.439↑	2.947±0.393	0.001
R-frontal pole	2.396±0.239▼	2.754±0.285↑	2.444±0.318	0.009
R-lateral orbital gyrus	1.941±0.228▼	2.263±0.287↑	1.921±0.259	0.005
L-medial frontal cerebrum	1.552±0.135▼	1.864±0.223↑	1.613±0.229	0.001
R-medial frontal cerebrum	2.001±0.209▼	2.354±0.309	2.143±0.262	0.012
L-inferior frontal angular gyrus	2.939±0.349	3.301±0.477↑	2.855±0.437	0.05
R-inferior frontal angular gyrus	3.222±0.311	3.641±0.404↑	3.202±0.375	0.012
L-lingual gyrus	6.902±0.553↑	6.901±0.776↑	6.342±0.567	0.001
L-middle occipital gyrus	5.424±0.570	6.059±0.499↑	5.363±0.660	0.012
L-occipital fusiform gyrus	3.232±0.420↑	3.209±0.240	3.017±0.338	0.03
L-thalamus	3.809±0.432▲	3.463±0.348	3.582±0.463	0.011
L-4th ventricle	0.094±0.014↓	0.100±0.022↓	0.112±0.019	0.004
R-4th ventricle	0.060±0.014↓	0.059±0.010↓	0.069±0.012	0.008
Optic chiasm	0.003±0.001↓	0.007±0.005	0.009±0.006	0.003
L-basal forebrain	0.633±0.059↓	0.694±0.052	0.692±0.060	0.003

Data are expressed as the mean ± SD (general linear model using age, sex and total intracranial volume as covariates followed by pairwise comparison corrected by Bonferroni method). Positive brain regions were presented at a threshold of $P < 0.05$. ↑: Volume larger than NCs; ↓: volume smaller than NCs; ▲: volume larger than EM; ▼: volume smaller than EM. CM: Chronic migraine; EM: episodic migraine; L: left; NCs: normal controls; R: right.

cedural learning functions (Kreitzer and Malenka, 2008). Previous studies have found volume alteration, functional connectivity changes, and iron deposits (Kruit et al., 2009; Yuan et al., 2013; Rocca et al., 2014) in the basal ganglia of migraine patients. Similar to previous studies (Rocca et al., 2014; Neeb et al., 2017), our study demonstrated an enlarged right putamen in both EM and CM patients, supporting the role of the basal ganglia in migraine patients. Another essential deep gray matter structure in migraine is the thalamus, which is responsible for pain processing, sleep–wake cycle regulation, awareness, cognitive behaviors, and the modulation of visual information in migraine (Younis et al., 2019). The volume reduction of thalamic nuclei (Magon et al., 2015) or thalamic microstructural alteration (Granziera et al., 2014) in migraine has reported in previous studies. Our previous study found that the thalamic volume was increased in medication-overuse headache patients compared to NCs (Chen et al., 2017). In this study, neither EM nor CM patients showed volume difference from NCs in the thalamus, which was consistent with a previous study (Granziera et al., 2014). However, compared with EM patients, CM patients presented with thalamic enlargement on the left side ($P = 0.004$), and the volume was positively correlated with headache days per month, indicating the plasticity of the thalamus in migraine chronification.

The decreased volume of the 4th ventricle in EM and CM patients may reflect enlargement of the brainstem or cerebellum, although we did not find statistical differences in the size of those structures. The brainstem contains the ascending trigeminal pathway and descending pain modulatory system. The volume of brainstem conflicted with data from previous studies. Some studies showed that gray matter volume of the brainstem decreased in migraine patients (Marciszewski et al., 2018) and CM patients (Bilgiç et al., 2016). Others demonstrated larger brainstem and subnuclei in migraine with aura (Petrusic et al., 2019) and in medication-overuse headache (Chen et al., 2018). The volume of the cerebellum in migraine patients was generally decreased in several studies (Bilgiç et al., 2016; Demir et al., 2016; Messina et al., 2017).

Our study has some limitations. First, because most of the CM patients had headache on MRI scanning, it is not possible to exclude that the non-edematous volumetric alterations observed in CM patients might be influenced by the presence of headache (Coppola et al., 2015). Nevertheless, it is impossible to perform subgroup analysis according to patients with or without headache when taking MRI examinations, because the sample was too small to allow this. The sample was small since CM without medication overuse was less prevalent. Second, we only recruited migraine patients without aura. Whether the volume alteration in migraine with aura occurs in the same or different brain regions is unknown. Third, this was a cross-sectional study, and we could not prove that chronification caused volume alteration or that volume alteration caused chronification.

In conclusion, this study revealed regional volume changes in the brains of CM and EM patients. The volume alterations were mainly located in the frontal lobe, visual processing system, basal ganglia, and thalami, which are involved in pain modulation, affective/cognitive processing, visual processing and pain processing. The volume of some brain regions may dynamically change with different migraine frequencies. However, the underlying mechanism of the volume alteration needs further investigation.

Additional files:
Additional file 1: Hospital Ethics Approval.
Additional file 2: Informed Consent Form.
Additional file 3: STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist.

References

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-10

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion

Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.