Altered local and distant functional connectivity density relate to headache frequency in migraine without aura

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Abstract

Background

Episodic migraine (EM) is associated with alterations in functional connectivity of several regions or resting-state networks, but it is not well known how large-scale functional connectivity pattern of the whole brain is affected in chronic migraine (CM).

Methods

Fifty-six migraineurs without aura (39 with EM, 17 with CM) and 35 healthy controls (HC) underwent clinical assessment and resting-state functional MRI. Functional connectivity density (FCD) was calculated in a voxel-wise way to examine large-scale brain network property over the whole brain.

Results

Compared with HC, both migraine groups showed increased local FCD in the left orbital frontal gyrus (OFG), right hippocampus/parahippocampal gyrus (HP/PHG), cerebellum, and decreased local FCD in the bilateral dorsolateral prefrontal cortex. Local FCD of the left OFG increased in CM compared to EM. In comparison with HC, EM showed increased local FCD in the left middle temporal gyrus, and CM exhibited decreased local FCD in the left sensorimotor cortex and bilateral precuneus. Furthermore, relative to HC, EM showed increased distant FCD in the right PHG while CM showed increased distant FCD in the right HP and OFG. Importantly, majority of the observed local and distant FCD alterations were associated with migraine frequency across all migraineurs.

Conclusion

Patients with higher migraine frequency present more extensive and pronounced functional connectivity dysfunctions in regions involved in pain processing and modulation. FCD, especially local FCD may be a sensitive biomarker for examining the neural mechanism of migraine.

Introduction

Migraine is a common and debilitating neurological condition manifesting with attacks of headache, sensory hypersensitivity, nausea and vomiting as well as cognitive dysfunction[1]. The prevalence of migraine is about 12% in the general population[2]. Migraine causes significant limitations in daily life and ranks as the seventh-highest specific cause of disability worldwide according to the World Health Organization[3]. A better understanding of the neurobiological basis may explain the pathogenesis of this disorder and aid in development of effective therapeutic approaches.

Brain functional imaging has provided important insight into the neural mechanisms of migraine during both interictal phase and ictal phase. Many studies examined task-related activation using different experiment paradigms, such as visual, olfactory, auditory, and somatosensory stimuli[4]. The most

common findings included atypical activation in the brainstem, hypothalamus, thalamus, limbic structures, sensorimotor cortex, prefrontal cortex, visual cortex in migraineurs, suggesting an imbalance of pain facilitation and inhibition[5]. In the past decade, resting-state functional MRI, a relatively novel approach independent of stimulation, has been widely utilized to investigate functional interactions of brain regions and functional networks implicated in migraine pathophysiology[6].

However, resting-state functional connectivity findings on migraine are less consistent and appear more complex. Although decreased functional connectivity within the default mode network and executive network has been repeatedly observed in migraine, opposite results have also been reported for these networks[7]. In addition, both increased and decreased functional connectivity between the periaqueductal gray matter (PAG) and precentral gyrus have been revealed in the literature[8, 9]. The small sample size, patients' clinical heterogeneity and different methodological approach may contributed to the conflicting findings[6]. Some researchers examined functional connectivity using seed-based method with varied regions of interest, such as the PAG and insula, while others utilized independent component analysis, making it difficult to compare results across studies. It is worth noting that most functional connectivity study focused on selected regions or resting-state networks, thus not capable of evaluating the large-scale functional connectivity of the whole brain.

Recently, a voxel-wise data-driven method, namely functional connectivity density (FCD) mapping, has been proposed to examine large-scale brain network property over the whole brain[10]. This technique is independent of seed or network selection and allows identification of functional hubs of brain network (nodes with high functional connectivity), which may be dysfunctional in neuropsychiatric disorders. To date, two functional imaging studies have investigated FCD patterns of patients with episodic migraine (EM) compared with healthy controls (HC), and implicated altered intrinsic functional connectivity architecture in the migraine brain[11, 12]. However, whether FCD alterations progress in chronic migraine (CM) remains to be determined.

In the current study, we analyzed FCD in patients with EM and CM without aura in the interictal period, as well as its association with clinical feature. Based on previous findings, we hypothesized that migraineurs would exhibit altered FCD in regions of the pain matrix, such as the PAG, hippocampus, and prefrontal cortex. Furthermore, there may be more pronounced FCD abnormalities in CM than EM, given greater headache-related impact on quality of life reported in the former group[13]. We also expected altered FCD to be associated with migraineurs' sympotomatology.

Materials And Methods

Participants and clinical assessment

Fifty-six right-handed patients with migraine without aura (39 with EM, 17 with CM) and 35 age- and sex-matched right-handed HC subjects were recruited for this study. Migraine patients were enrolled from the department of neurology of the first affiliated hospital of Soochow university between December 2016

and September 2017. Diagnoses of migraine were made by an experienced neurologist based on the international classification of headache disorders, 3rd edition (beta version) (ICHD-3 beta)[3]. All migraineurs were free of migraine for at least 3 days at the time of MRI scan. HC subjects were recruited by advertisement and had no history of any primary headache disorders or other types of headache. No family history of migraine and psychiatric disorders was also required for the HC group.

General exclusion criteria included age < 18 years or > 65 years; migraine with aura; a headache attack during MRI scan or within 24 h after scanning; any other neurological or psychiatric disease; other pain conditions; drug or alcohol abuse; a history of taking any prophylactic headache medicine in the last 3months; MRI contraindications; and excessive movement during MRI scanning (translation > 1.5 mm or rotation > 1.5° at any direction). The demographic data, including age, gender, and years of education, were recorded for all participants. The assessed clinical characteristics of patients comprised migraine attack frequency (number of migraine days per month), headache degree. A 10-point visual analog scale (VAS) from 0 (none) to 10 (very severe) was used to rate headache degree. The study was carried out in accordance with the declaration of Helsinki, and was approved by the ethics committee of the first affiliated hospital of Soochow university. Written informed consent was acquired from all participants.

MRI Data Acquisition

MRI scan was performed using a 3.0 T scanning system (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) at the department of radiology, the first affiliated hospital of Soochow university. Earplugs and tight padded clamps were used to minimize noise exposure and head motion. Scanning was terminated if the participant complained of any discomfort. Resting-state functional images were collected using an echo-planar imaging sequence with the following parameters: TR/TE = 2000/30 ms, flip angle = 90°, FOV = 256 × 256 mm^2, matrix = 64 × 64, slice number = 33, slice thickness = 4 mm, no intersection gap, total volume number = 240. The axial sections were placed approximately parallel to anterior commissure-posterior commissure line. High-resolution T1-weighted images were obtained using a sagittal fast spoiled gradient recalled echo sequence using the following parameters: TR/TE = 2300/2.98 ms, matrix = 256 × 256, FOV = 256 × 256 mm^2, slice thickness = 1 mm. During the functional MRI scanning, all subjects were instructed to remain still, keep their eyes closed, not to fall asleep or think about anything in particular.

Data Preprocessing

The functional images were preprocessed using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl. ac.uk/spm/). The first 10 volumes were discarded to allow for signal equilibrium. The remaining functional images were slice-time corrected, realigned, and co-registered with the T1-weighted images. The co-registered anatomical images were then segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and spatially normalized into standard Montreal

Neurological Institute (MNI) space with a final size of $3 \times 3 \times 3$ mm^3. The resulting normalization matrix was then applied to the functional images. After that, the functional data were detrended to correct for general signal drift, and band-pass filtered (0.01–0.08 Hz) to reduce low frequency drift and high-frequency noise utilizing Resting-State fMRI Data Analysis Toolkit (REST, http://www. restfmri.net). Finally, nine nuisance covariates, including six movement parameters obtained during realignment, and time series predictors for global signal, WM signal, and CSF signal were sequentially regressed from the time series.

FCD Analysis

FCD was computed by using an in-house script written based on Linux platform according to a previously reported approach[14]. Specifically, voxel-based whole brain correlation analysis was conducted for each voxel within the gray matter mask[12]. The FCD was calculated as the sum of weights (r values) of significant functional connections ($r > 0.25$) for each voxel[14], in a manner analogous to weighted density centrality in the graph theory of the brain. Local FCD (lFCD) and distant FCD (dFCD) were defined based on a neighborhood strategy. Voxels within a 12-mm sphere around each voxel were included for lFCD, while voxels outside the 12-mm sphere were exclusively considered for dFCD. Notably, global FCD (gFCD) is the union of lFCD and dFCD, and dFCD and gFCD maps are highly correlated given that the lFCD has a small contribution to the total counts compared with the dFCD[14]. For further statistic analyses, the individual lFCD and dFCD maps were converted in to Z-score maps. Subsequently, spatial smoothing was conducted with a 8-mm full width at half-maximum Gaussian kernel.

Statistic Analysis

Chi-squared test was used to analyze gender distribution, and one-way analysis of variance (ANOVA) was conducted for age and education level. When the ANOVA analysis revealed any significant difference, post-hoc analyses were employed for inter-group comparisons. For clinical data, independent t test was used to detect differences between migraine subgroups. The above analyses of demographic and clinical data were accomplished with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA), with a significance threshold of $P < 0.05$.

For FCD maps, random-effect one-sample t-tests were performed in SPM8 to depict the distribution pattern of each group, with a false discovery rate corrected threshold of $P < 0.05$. lFCD and dFCD differences among the three groups were then assessed by performing ANOVA in SPM8 with sex, age and education level as covariates, followed by post hoc t tests to detect between-group differences. A threshold adjustment based on Monte Carlo simulations (using the REST' program Alphasim) was applied to correct for multiple comparison. Significant clusters were identified with a combined height-extent threshold (voxel-wise $P < 0.005$ and cluster size > 42), corresponding to a false-positive rate of $P < 0.05$. In addition, we also performed an exploratory analysis using an uncorrected threshold of $P < 0.001$ with minimum cluster extents of 10 voxels.

Finally, to examine the association between the brain measures and migraine symptom severity, mean lFCD and dFCD values of clusters with significant difference were extracted and the correlated against the clinical measures (migraine frequency, VAS) by using Spearman correlation analysis. The correlation analysis was performed with SPSS, with a significant threshold of $P < 0.05$ (not corrected).

Results

Demographic and clinical characteristics

The demographic and clinical characteristics were summarized in Table 1. The two migraine subgroups and HC group were similar in terms of education level ($F = 1.663$, $P = 0.195$) and gender distribution ($P = 0.06$). There was significant difference in age among the three groups ($F = 8.627$, $P < 0.001$). The mean age was significantly larger in the CM group than the other two groups. The CM group had increased migraine frequency compared with the EM group ($P < 0.001$). The two migraine subgroups did not differ with respect to VAS ($P = 0.635$).

Table 1
Demographic and clinical characteristics of patients and healthy controls.

	EM (n = 39)	CM (n = 17)	HC (n = 35)	P value
Gender (males/females)	9/30	9/8	15/20	0.060[c]
Age (year)	39.74 (11.59)	49.59 (14.64)	34.91 (10.89)	0.000[d]
Education (year)	10.33 (4.02)	9.71 (3.94)	11.80 (4.92)	0.195[d]
Days with headache[a]	3.75 (2.64)	19.56 (4.17)		0.000[e]
VAS[b]	6.22 (1.77)	7.24 (1.89)		0.635[e]

[a] Migraine days per month; [b] Visual analog scale, grading pain severity on a scale of 1 to10; [c]P value obtained with Chi-square test; [d]P value obtained with one-way analysis of variance; [e]P value obtained with independent t test; Continuous variables are given as mean (standard deviation). EM, episodic migraine; CM, chronic migraine; HC, healthy control.

Within-group And Between-group FCD Analyses

Within each group, brain regions with relatively high lFCD values were bilaterally distributed within several medial and lateral brain regions, including the precuneus, posterior cingulate cortex, medial and dorsolateral prefrontal cortex (dlPFC), lateral parietal lobe, and visual cortex (Fig. 1), which were previously identified as functional hubs of healthy human brain. The dFCD patterns were similar in the HC group and two migraine subgroups, with regions with relatively high dFCD values mainly located in

the precuneus, medial prefrontal cortex, lateral parietal and temporal lobe, and visual cortex (Fig. 1). As mentioned above, the gFCD map resembled the corresponding dFCD map within each group (Fig. 1).

Compared with the HC group, the EM group showed increased lFCD in the left orbital frontal gyrus (OFG), middle temporal gyrus (MTG), right cerebellum, and decreased lFCD in the bilateral dlPFC (Fig. 2 and Table 2). With an uncorrected threshold of $P < 0.001$, an increase of lFCD was additionally observed in the right hippocampus/parahippocampal gyrus (HP/PHG) (Additional file 1). Relative to the HC group, the CM group exhibited increased lFCD in the bilateral OFG, right HP/PHG, temporal pole (TP), cerebellum, as well as deceased lFCD in the left sensorimotor cortex (SMC), bilateral dlPFC and precuneus (Fig. 2 and Table 2). Increased lFCD in the left OFG was revealed in the CM group compared to the EM group (Fig. 2 and Table 2).

Table 2

Brain regions with significant difference in local FCD between groups.

Brain region	Voxel	MNI coordinate (x, y, z)	Peak T value
EM VS HC			
SFG	113	-15,66,21	-5.19
MFG	76	-33,54,9	-3.75
MFG	149	45,48,15	-4.08
OFG	41	-6,42,-21	2.88
MTG	64	-51,-45,-6	4.24
Cerebellum	50	18,-69,-57	2.95
CM VS HC			
SFG	69	15,63,27	-3.45
MFG	91	-36,60,9	-4.41
MFG	67	39,60,15	-3.46
SMC	81	-39,-30,72	-4.14
Precuneus	97	3,-72,60	-3.86
HP/PHG	139	36,-6,-21	4.85
TP	57	36,6,-33	3.72
OFG	227	-9,27,-24	4.09
Cerebellum	192	30,-66,-51	3.62
CM VS EM			
OFG	59	-18,24,-21	3.08

EM, episodic migraine; CM, chronic migraine; HC, healthy control; MNI, Montreal Neurological Institute; SFG, superior frontal gyrus; MFG, middle frontal gyrus; OFG, orbital frontal gyrus; MTG, middle temporal gyrus; SMC, sensorimotor cortex; HP, hippocampus; PHG, parahippocampal gyrus; TP, temporal pole.

In the analysis corrected for multiple comparisons, we did not detect any regions with significant dFCD differences among the three groups. With an uncorrected threshold of $P < 0.001$, increased dFCD in the right PHG was observed in the EM group compared with the HC group, while increased dFCD in the right HP, PHG/TP, and OFG were detected in the CM versus HC comparison (Fig. 3 and Table 3). Differences in dFCD were not found when comparing the CM group to EM group. Group comparison results of the gFCD were very similar to those of the dFCD analysis (Additional file 2 and Table 4).

Table 3

Brain regions with significant difference in distant FCD between groups.

Brain region	Voxel	MNI coordinate (x, y, z)	Peak T value
EM VS HC			
PHG	16	36,-33,-15	4.22
CM VS HC			
OFG	18	9,45,-24	3.91
HP	16	36,-9,-18	3.90
PHG/TP	71	27,3,-30	3.71

EM, episodic migraine; CM, chronic migraine; HC, healthy control; MNI, Montreal Neurological Institute; PHG, parahippocampal gyrus; OFG, orbital frontal gyrus; HP, hippocampus; TP, temporal pole.

Table 4

Brain regions with significant difference in global FCD between groups.

Brain region	Voxel	MNI coordinate (x, y, z)	Peak T value
EM VS HC			
PHG	16	36,-33,-15	4.20
CM VS HC			
OFG	25	9,45,-24	3.96
HP	20	36,-9,-18	3.97
PHG/TP	77	33,9,-36	3.71

EM, episodic migraine; CM, chronic migraine; HC, healthy control; MNI, Montreal Neurological Institute; PHG, parahippocampal gyrus; OFG, orbital frontal gyrus; HP, hippocampus; TP, temporal pole.

Correlation Between FCD And Clinical Indices

Spearman correlation analyses revealed that migraine frequency positively correlated with lFCD in the right HP, and negatively correlated with lFCD in the left precentral gyrus (PreCG), MTG, and precuneus (Fig. 4A). The migraine frequency also showed positive correlation with dFCD in the right HP and OFG (Fig. 4B). Similarly, migraine frequency positively correlated with gFCD in the right HP and OFG (Additional file 3). No significant correlation was observed between FCD and headache degree (VAS).

Discussion

This study investigated the large-scale resting-state functional connectivity of the whole brain in migraine without aura during interictal phase by using FCD analysis. Migraineurs showed altered lFCD or dFCD in the dlPFC, OFG, HP, PHG, MTG, precuneus, SMC, and cerebellum, some of which were more apparent in CM compared with EM. The FCD values in the HP, OFG, MTG, SMC, and precuneus correlated with migraine frequency, indicating that abnormal functional interactions may reflect migraine symptom severity. Consistent with a previous FCD study on EM, more widespread group-differences were observed in lFCD than dFCD. Although the exact biological mechanism of lFCD remains unclear, it is analogous to regional homogeneity (ReHo), a measure thought to reflect the efficiency of coordinated neuronal activity and used to assess local brain functional alterations[15].

Compared with HC, both EM and CM showed reduced lFCD in the bilateral dlPFC. In support of our results, multiple migraine studies consistently reported decreased ReHo in the dlPFC in EM compared with HC[11, 16, 17]. However, the current study extended previous findings of altered brain function in the dlPFC to CM. The dlPFC is involved in cognitive evaluation[18], working memory[19], opioid analgesia[20], and play a critical role in mediation attenuation of pain perception via cognitive control mechanisms[21]. Therefore, our finding of lFCD reduction in the dlPFC may suggest disrupted pain modulation in different subtypes of migraine without aura. We also found increased lFCD in the right cerebellum in both migraine groups compared to HC. The cerebellum plays an important role in human nociception and modulating of pain perception[22–24]. Previous studies have found an increased prevalence of ischemic lesions in the cerebellar posterior lobe[25]. In addition, relatively consistent findings of reduced gray matter volume were reported in the cerebellum in EM and CM [26–28]. Collectively, increased lFCD in the cerebellum in our study may indicate common ineffective inhibition of pain perception in EM and CM.

Our data revealed that lFCD of the OFG in EM was higher than that in HC, but was lower than that in EM. Additionally, in the CM versus HC comparison, we found increased dFCD in the right OFG which positively associated with migraine frequency across all patients. Therefore, the results indicated both local and distant functional connectivity abnormalities in this region and the alterations may progress with repeated migraine attacks. Supporting our results, a MRI study on EM reported increased ReHo in patients compared to HC[17]. Zhao et al. also found increased ReHo in EM without aura, which was more profound in patients with long-term disease duration than those with short-term disease duration[29]. Concerning remote functional connection, Tian et al. reported enhanced OFG connectivity with the right nucleus accumbens in EM relative to HC[30]. The OFG also showed increased functional connectivity with the hypothalamus and amygdala in CM compared with EM or HC [31, 32]. The OFG is proposed to participate in sensory integration, decision making, expected reward and punishment, especially response inhibition[33, 34]. Stimulation, both pain and pleasure, has been reported to elicit opioid release in the OFG[35]. A recent resting-state MRI study found increased regional brain activity in the OFG in migraineurs after verum acupuncture[36]. Furthermore, persistent orbitofrontal hypofunction was reported to be associated with medication overuse headache[37], and decreased gray matter of this region was predictive of poor response to treatment[38]. We speculated that higher FCD in the OFG may be adaptive mechanism associated with affective and cognitive response in migraine.

In this study, EM showed increased and decreased lFCD in the HP/PHG as compared with HC and CM, respectively. Furthermore, compared with HC, EM had higher dFCD in the right PHG while CM showed higher dFCD in the right HP and PHG/TP. Interestingly, both lFCD and dFCD in the right HP positively correlated with migraine frequency. The current findings were partially supported by two prior studies reporting increased ReHo in the HP/PHG in EM compared to HC[17, 29]. However, in contrast to our results, Gao et al. found lower lFCD in bilateral HP in the EM versus HC comparison[11]. The discrepancy may result from different option regarding global-signal regression in data preprocessing. With respect to interregional functional connectivity, increased PHG connectivity with multiple regions have been repeatedly observed in EM relative to HC[30, 39]. By contrast, migraineurs showed both increased and decreased HP connectivity compared to HC. Nevertheless, our findings was supported by a DTI study based on graph theory approaches by showing that excessive network integration of the HP in migraineurs predicted poor placebo effect and may contribute to the development and maintenance of persistent migraine[40]. We recently found that migraine frequency negatively associated with gray matter volume in the right HP/PHG[41]. The HP is involved in learning and memory formation, as well as pain-related attention and anxiety, and stress response[42, 43]. The PHG is closely functionally related to HP, and plays a role in memory and emotional response[44]. Overall, our finding of greater FCD in the HP/PHG in patients with higher headache frequency may be compensatory changes for structural atrophy, reflecting insufficient inhibitory feed back to HPA axis, delayed shutdown and overactivation of stress responses[45].

We also found increased lFCD in the left MTG in the EM versus HC comparison, and decreased lFCD in the left SMC and bilateral precuneus in the CM versus HC comparison. Moreover, migraine frequency negatively associated with lFCD in the MTG, PreCG, and precuneus across all patients, indicating that patients with higher migraine frequency had lower lFCD in these regions. Supporting our results, Zhang et al. reported decreased ReHo and degree centrality in the primary somatosensory cortex and premotror cortex in migraine without aura[46]. Reduced ReHo in the precuneus was also observed in female EM patients relative to HC[17]. Interestingly, another resting-state MR study revealed ReHo reduction in the precuneus only in migraineurs with long-term disease duration[29]. The authors also found higher ReHo in the MTG in patients with short-term disease duration but lower ReHo in this region in patients with long-term disease duration. Thus, it was possible that distinct functional plasticity may exist in the MTG in migraineurs with different disease burden. More studies are needed to verify this hypothesis, though it was partially in accordance with our findings of increased lFCD in EM but a negative relationship between migraine frequency and lFCD in this region. The postcentral gyrus predominantly participates in sensory-discriminative pain processing. The precuneus is involved in spatial orientation and sensory information processing and interpretation[47]. The MTG is related to language and semantic memory processing as well as multimodal sensory integration[48]. Motor cortex stimulation has been reported to be a potential tool to centrally modulate chronic pain[49], although its role in pain is not completely understood. Collectively, altered lFCD in the MTG, precuneus and SMC may be associated with disrupted mutlisensory integration, nociceptive information processing, and pain modulation in migraine.

Conclusion

In summary, this study revealed lFCD and dFCD alterations in regions involved in sensory-discriminative processing of pain, affective and cognitive processing and pain modulation in migraineurs, indicating that FCD may provide new insight into the neural mechanism of migraine. The lFCD appeared to be a more sensitive biomarker of migraine compared to dFCD. Patients with CM and EM share some common abnormalities in pain processing and inhibitory network. However, CM present more extensive and pronounced dysfunctions, which may be associated with migraine frequency.

Abbreviations

PAG: Periaqueductal gray matter; FCD: Functional connectivity density; EM: Episodic migraine; CM: Chronic migraine; HC: Healthy controls; VAS: Visual analog scale; GM: Gray matter; WM: White matter; CSF: Cerebrospinal fluid; MNI: Montreal Neurological Institute; lFCD: Local functional connectivity density; dFCD: Distant functional connectivity density; gFCD: Global functional connectivity density; ANOVA: Analysis of variance; OFG: Orbital frontal gyrus; MTG: Middle temporal gyrus; HP: Hippocampus; PHG: Parahippocampal gyrus; TP: Temporal pole; SMC: Sensorimotor cortex; ReHo: Regional homogeneity.

Declarations

Ethics approval and consent to participate

The study protocol was in accordance with the declaration of Helsinki, and were approved by the ethics committee of the first affiliated hospital of Soochow university. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

Jun Ke, Yang Yu, Xiaodong Zhang, Yunyan Su, Ximing Wang, Su Hu, Hui Dai, Chunhong Hu, Hongru Zhao, Lingling Dai declare that they have no conflicts of interest.

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Authors' contributions

DL and ZH made substantial contributions to interpretation of data as well as in drafting the manuscript. KJ and YY conducted data processing and statistical analysis, and wrote the first draft of the manuscript. ZX, SY made a contribution to the interpretation of data. WX and HS were implied in recording data. DH and HC gave critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Additional Files

Additional file 1 Local FCD differences between groups. Statistical parametric maps show local FCD alterations with a uncorrected threshold of $P < 0.001$ superimposed on a standard T1 image. Warm color indicates increased local FCD and cool color indicates decreased local FCD. FCD, functional connectivity density; CM, chronic migraine; EM, episodic migraine; HC, healthy control.

Additional file 2 Global FCD differences between groups. Statistical parametric maps show global FCD alterations with an uncorrected threshold of $P < 0.001$ superimposed on a standard T1 image. Warm color indicates increased global FCD. FCD, functional connectivity density; CM, chronic migraine; EM, episodic migraine; HC, healthy control.

Additional file 3 Correlation of global FCD and migraine frequency (days per month). Across all patients, migraine frequency positively associates with global FCD in the right HP and OFG ($P < 0.05$, not corrected). FCD, functional connectivity density; HP, hippocampus, OFG, orbital frontal gyrus.

Figures

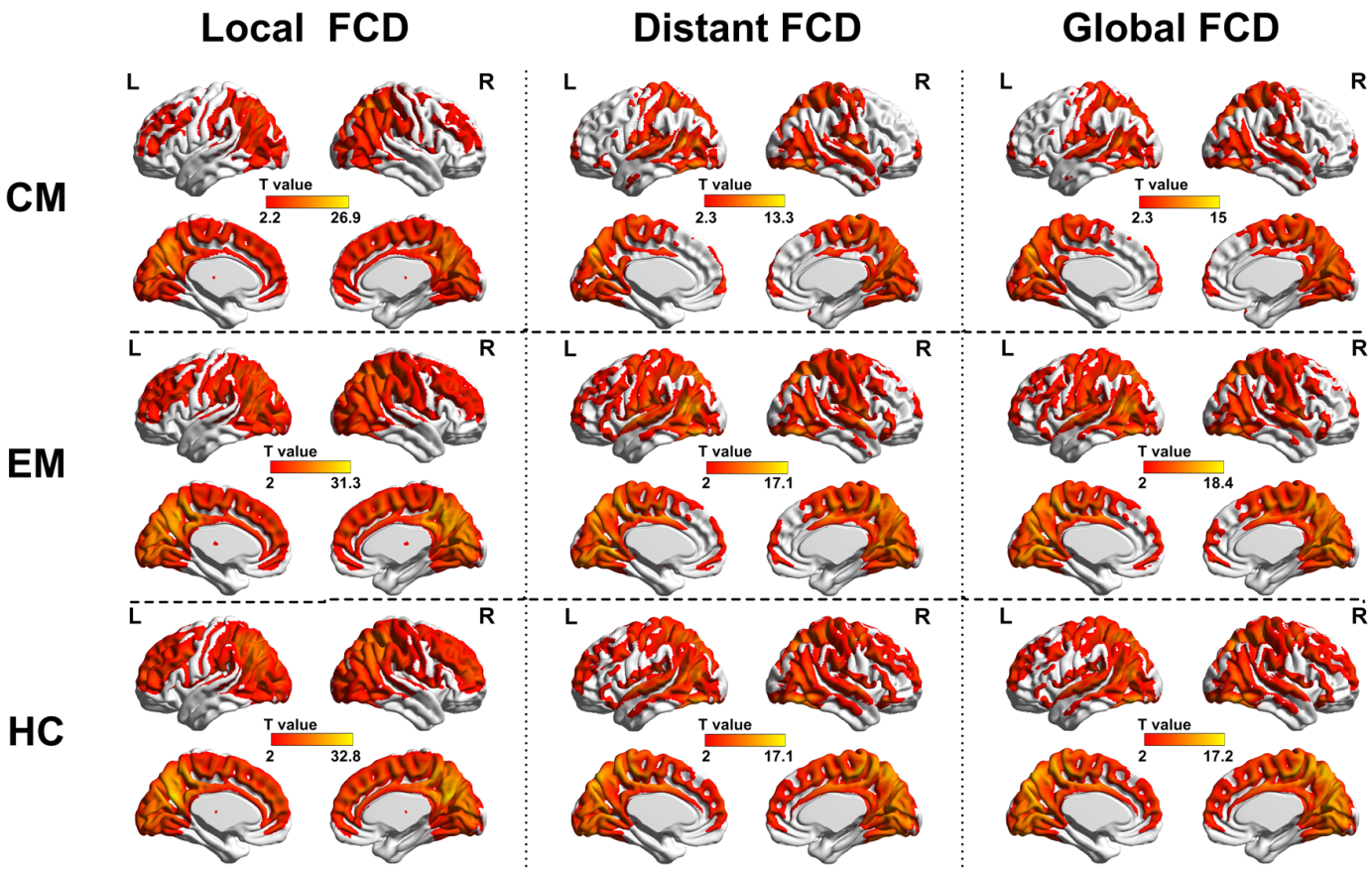

Figure 1

FCD maps of the CM, EM and HC groups. Local FCD, distant FCD, and global FCD maps are shown in the left, middle, and right column, respectively. Within each group, brain regions with high FCD value include the precuneus, medial prefrontal cortex, lateral parietal lobe, and visual cortex ($P < 0.05$, FDR corrected). FCD, functional connectivity density; CM, chronic migraine; EM, episodic migraine; HC, healthy control; FDR, false discovery rate.

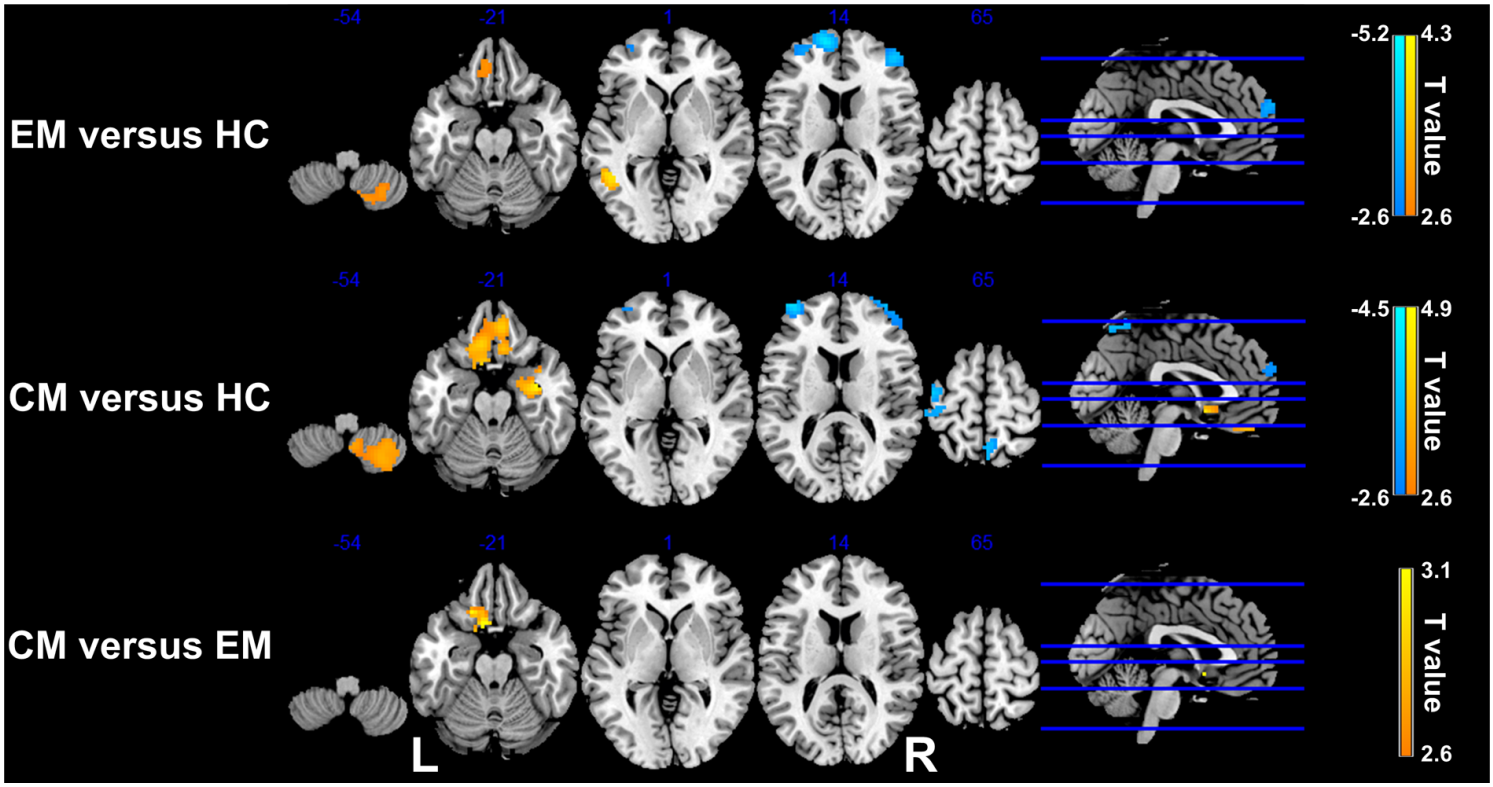

Figure 2

Local FCD differences between groups. Statistical parametric maps show local FCD alterations with a corrected threshold of $P < 0.05$ (determined by Monte Carlo simulation) superimposed on a standard T1 image. Warm color indicates increased local FCD and cool color indicates decreased local FCD. FCD, functional connectivity density; CM, chronic migraine; EM, episodic migraine; HC, healthy control.

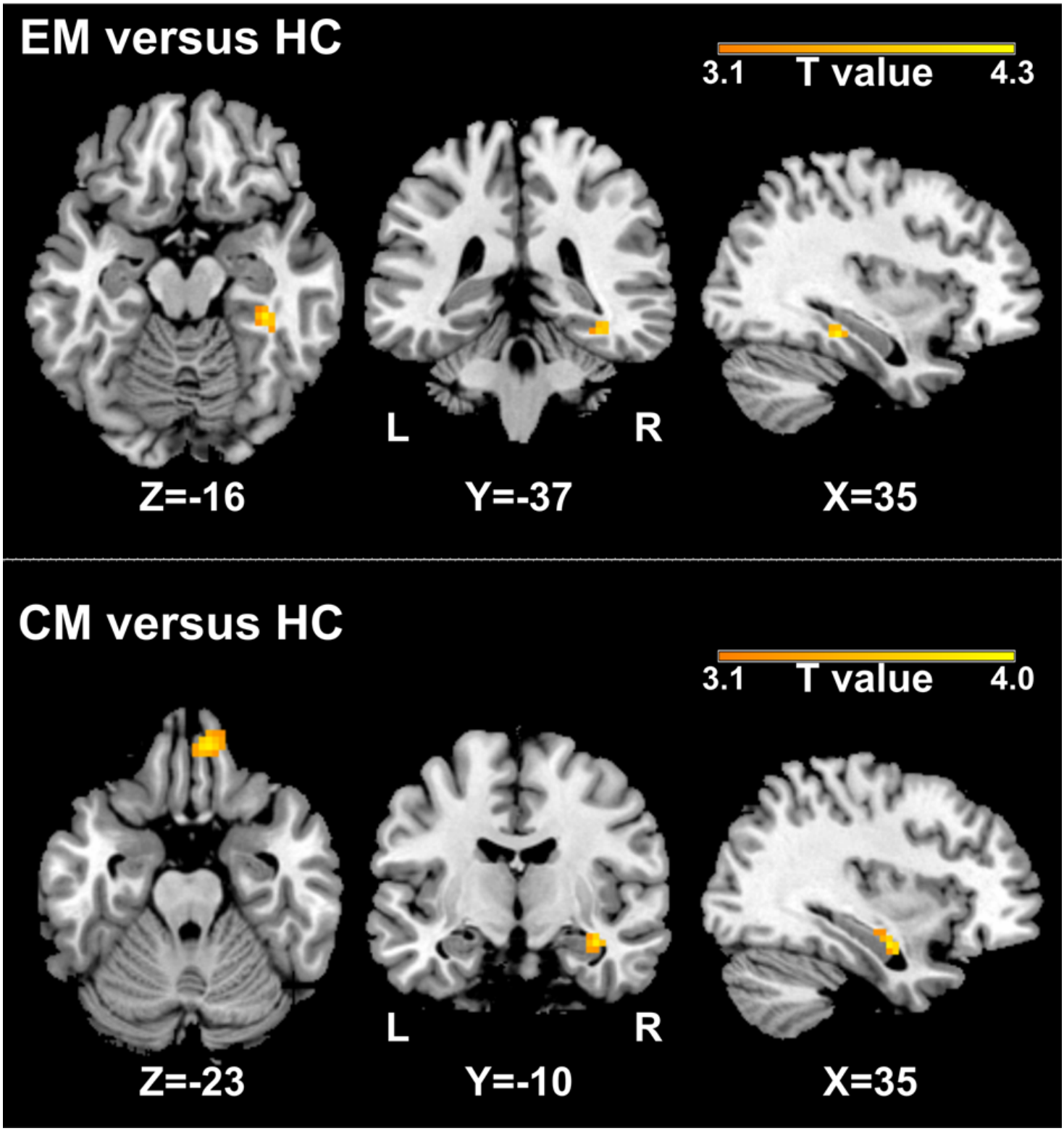

Figure 3

Distant FCD differences between groups. Relative to HC, EM shows increased distant FCD in right parahippocampal gyrus and CM shows increased distant FCD in the right hippocampus and orbital frontal gyrus. Statistical parametric maps show distant FCD alterations with an uncorrected threshold of $P < 0.001$ superimposed on a standard T1 image. Warm color indicates increased distant FCD. FCD, functional connectivity density; CM, chronic migraine; EM, episodic migraine; HC, healthy control.

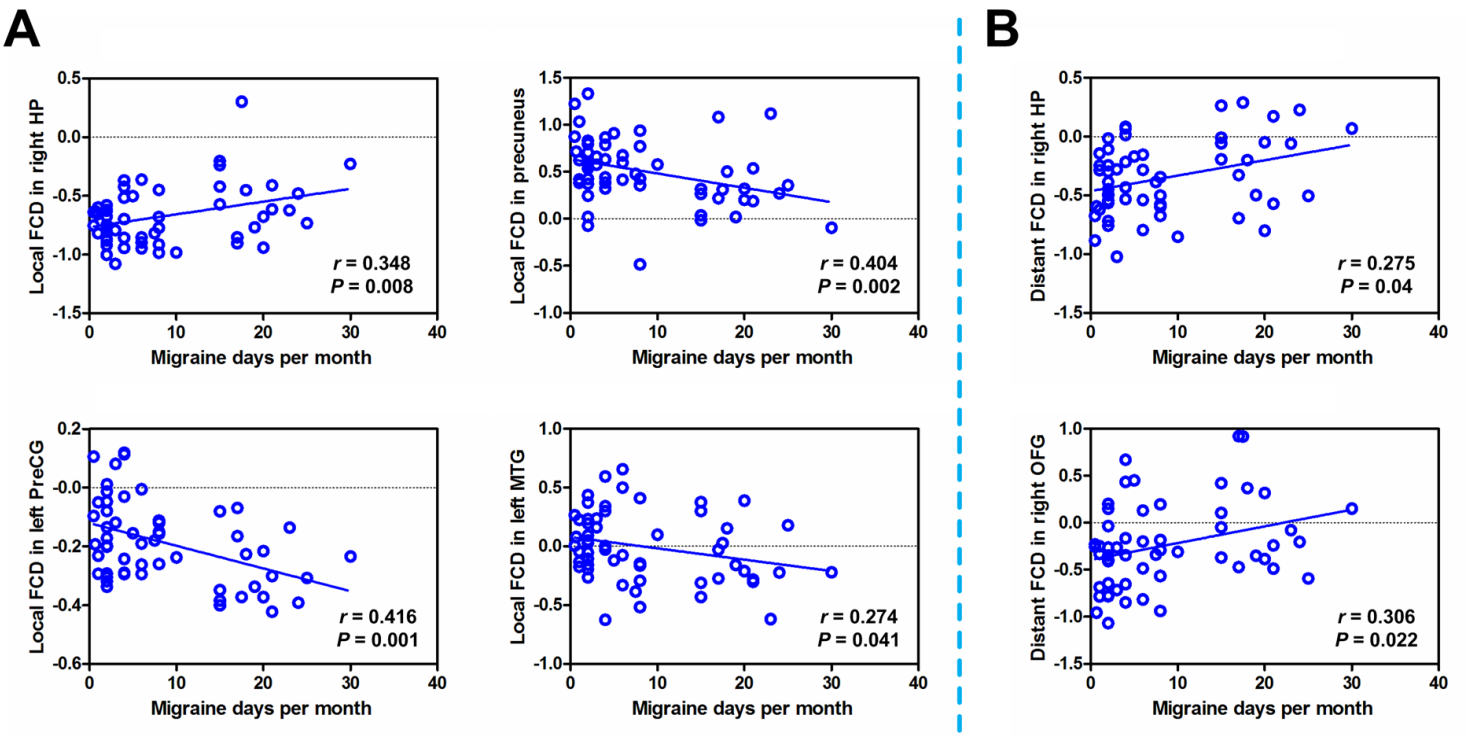

Figure 4

Correlation of local and distant FCD with migraine frequency (days per month). Higher migraine frequency is associated with increased local FCD in the right HP, decreased local FCD in the precuneus, left PreCG and MTG (A), as well as increased distant FCD in the right HP and OFG (B) across all migraine patients (P < 0.05, not corrected). FCD, functional connectivity density; HP, hippocampus; PreCG, precentral gyrus; MTG, middle temporal gyrus; OFG, orbital frontal gyrus.

Supplementary Files

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