Original Article

Revealing the mechanism of central pain hypersensitivity in primary dysmenorrhea: evidence from neuroimaging

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Background: Primary dysmenorrhea (PDM) is the most common problem in menstruating women. A number of functional magnetic resonance imaging (fMRI) study have revealed that the brain plays a crucial role in the pathophysiology of PDM. However, these results have been inconsistent, and there is a lack of a comprehensive fMRI study to clarify the onset and long-term effects of PDM. The aim of this study was thus to investigate the onset and long-term effects of PDM in a cohort of patients with PDM.

Methods: This study employed a cross-sectional design with prospective data collection, in which 25 patients with PDM and 20 healthy controls (HCs) were recruited. The patients with PDM underwent fMRI scans both during the PDM during the pain phase (PDM-P) and nonpain phase (PDM-NP). The long-term effects of PDM on the brain was assessed by comparing PDM-NP findings with those of HCs, and the central mechanism of PDM was assessed by comparing the PDM-P findings with those of PDM-NP. To identify changes in brain function, the amplitude of low-frequency fluctuations and the regional homogeneity (ReHo) were measured. To assess changes in brain structure, voxel-based morphometry (VBM) was applied. The periaqueductal gray (PAG) was set as a region of for conducting seed-based whole-brain functional connectivity (FC) analysis. Subsequently, Pearson correlation analyses were employed to evaluate the associations between the abnormal brain region and the clinical information of the patients.

Results: There were neither functional nor structural differences between patients in the PDM-NP and HCs. Compared with those in PDM-NP, those in PDM-P showed increased ReHo in the left dorsolateral prefrontal cortex (DLPFC) but decreased FC between PAG and right superior parietal gyrus, bilateral inferior parietal gyrus, right calcarine gyrus, left superior occipital gyrus, left precentral gyrus, right DLPFC, and left crus I of the cerebellar hemisphere.

Conclusions: The results from this study suggest that the mechanism of central pain hypersensitivity of PDM may be related to the disorder of the FC between the PAG and descending pain modulation system, default mode network (DMN), and occipital lobe. These findings could help us better understand the pathophysiology of PDM from a neuroimaging perspective.

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Keywords: Functional magnetic resonance imaging (fMRI); primary dysmenorrhea (PDM); regional homogeneity (ReHo); functional connectivity (FC); pain modulatory system

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Introduction

Primary dysmenorrhea (PDM) is defined as menstrual pain without pelvic primary disease and is characterized by the pain in the lower abdomen radiating to the lower back or inner thighs, occasionally accompanied by dizziness, nausea, diarrhea, and other discomfort (1,2). PDM is the most common issue in menstruating women (3), with the prevalence of PDM ranging between 50% and 90% among adolescent women in studies with different populations and age groups (4,5). The exact causes of PDM are not fully understood. Related research has identified a variety of factors, including prostaglandins, anomalous uterine contractions, and psychological influences as the primary drivers of PDM (5-7). However, recent studies indicate that the brain plays a crucial role in the pathophysiology of PDM, with its involvement encompassing central sensitization, altered pain processing, regulation of neuroendocrine factors, and interactions with psychological factors (8-11).

Advancements in magnetic resonance technology, especially functional magnetic resonance imaging (fMRI), has enabled researchers to investigate the underlying central mechanism of PDM. Several studies have used fMRI to investigate the alterations of brain function and structure in patients with PDM but have yielded inconsistent results, which may be due to the variability in study groups and the different scan times in the menstrual cycle [i.e., patients with PDM being compared with healthy controls (HCs) during different time points in the menstrual cycle, lack of accounting for the interaction between the phase and group, and lack of clarity concerning the menstrual cycle].

Regardless, these studies have reported that compared with HC, patients with PDM show increased amplitude of low-frequency fluctuation (ALFF) in the medial prefrontal cortex, inferior temporal gyrus, anterior cingulate cortex, and precuneus but decreased ALFF in the thalamus, cerebellum, middle temporal gyrus, hippocampus, brainstem, postcentral gyrus, and middle frontal gyrus (12-14); increased regional homogeneity (ReHo) in the hippocampus, anterior cingulate cortex, and secondary somatosensory cortices but decreased ReHo in the cerebellum, temporal gyrus, and dorsolateral prefrontal cortex (DLPFC) (14,15); increased cerebral blood flow in the inferior frontal gyrus, precentral gyrus, posterior cingulate cortex, and superior temporal gyrus and precuneus (13,16); increased gray matter volume (GMV) in the hippocampus, anterior cingulate cortex, periaqueductal gray (PAG), hypothalamus, precuneus, and cerebellum but decreased volume in the medial prefrontal cortex, precuneus, secondary somatosensory cortices, postcentral gyrus, and superior occipital gyrus (17,18); and hypoconnectivity between the PAG and default mode network (DMN) (19).

Therefore, to comprehensively understand the mechanism of PDM, we used ALFF and ReHo to characterize the brain function change associated with PDM and voxel-based morphometry (VBM) to assess the brain structure associated with PDM. Furthermore, as the PAG is the key region of the pain modulation system and may serve a crucial role in the pathophysiology of PDM (17,19-22), we used the PAG as a region of interest to conduct seed-based whole-brain functional connectivity (FC) analysis. The aim of this study was to (I) clarify the long-term effects of PDM on the brain by comparing the patients with PDM during the nonpain phase (PDM-NP) with HCs and (II) to identify the mechanism of central pain hypersensitivity in individuals with PDM experiencing menstrual pain by comparing the patients with PDM during the pain phase (PDM-P) with those during the PDM-NP. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1687/rc).

Methods

Participants

This study employed a cross-sectional design with prospective data collection. Patients with PDM who had undergone two fMRI scans during the PDM-P and the PDM-NP were recruited in this study. The patients with

PDM were screened by a gynecologist with the help of a sonographer conducting pelvic ultrasound to detect pelvic organ disease. The inclusion criteria for patients were as follows: (I) diagnosed as PDM according to the Primary Dysmenorrhea Consensus Guideline (6), (II) visual analogue scale (VAS) ≥4 in the past 6 months, (III) in the pain-free phase of the menstrual cycle, (IV) nulliparous status, and (V) aged 18–35 years with right-handedness. Meanwhile, the exclusion criteria were the following: (I) contraindications to MRI scanning; (II) participation in other clinical trials during the same period, (III) intake of analgesics or sedatives within 1 week before MRI examination; and (IV) combined with relevant medical history and other examinations, accompaniment of life-threatening primary diseases, mental disorders, or other suspected diseases that could not be excluded. The demographic and clinical characteristics, including age, years of education, smoking status, drinking status, past medical history, body mass index (BMI), visual analog scale (VAS), Cox Menstruation Symptom Scale-severity subscale (CMSS-s), self-rating depression scale (SDS), and self-rating anxiety scale (SAS) were all recorded. In the nonpain phase, patients with PDM were asked to record the average VAS and CMSS-s scores for the previous 6 months. In the pain phase, patients with PDM were asked to record the current VAS and CMSS-s scores. HCs without a history of PDM were also recruited in this study.

The study was carried out in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University (No. 2022ky079). Written informed consent was obtained from each participant.

MRI acquisition

All scans were conducted on the 3.0 Tesla MR scanner (Discovery MR750 scanner, GE HealthCare) equipped with a 32-channel head coil. All participants were wearing earplugs and were instructed to lie on the scanning bed supine, with their head in the head coil. Cushioned pads were used to fix the head to reduce the motion artifact. All participants were asked to keep their eyes closed and to think of nothing but to stay awake during the scan. First, the conventional MRI session including T1-weighted imaging (T1WI), T2-weighted image, T2- and fluid-attenuated inversion recovery (T2-FLAIR), and diffusion-weighted imaging (DWI) to ensure that participants had no intracranial lesions. High-resolution T1W structural images were acquired with the Sagittal three-dimensional (3D) T1-weighted brain volume imaging (BRAVO) sequence [repetition time (TR) =8.2 ms, echo time (TE) =3.2 ms, flip angle =12, matrix =256×256, slice thickness =1.2 mm with no gaps]. Functional images were obtained with the gradient-echo echo-planar imaging (EPI) sequence [TR =2,000 ms, TE =35 ms, matrix =64×64, field of view (FOV)=240×240 mm, FA =90°, slice thickness =5 mm with no gaps, number of slices =30].

Data processing

A similar data processing approach was used as in our previous studies (23,24), with functional and structural images being preprocessed using the Data Processing & Analysis of Brain Imaging (DPABI) tool (http://rfmri.org/dpabi) (25). The steps were as follows: (I) conversion of Digital Imaging and Communications in Medicine (DICOM) format to Neuroimaging Informatics Technology Initiative (NIfTI) format; (II) removal of the first 10 time points; (III) slice timing correction; (IV) segmentation; (V) head motion correction; (VI) normalization; (VII) calculation of ALFF; (VIII) filtering; (IX) calculation of ReHo ; (X) seed-based FC analysis, in which seeds were defined as bilateral ventrolateral PAG (±4, –26, –14) based on a previous study (26); and (XI) smoothing. For details, see *Figure 1*.

Statistical analysis

For demographic and clinical characteristics data, statistical analyses were performed using SPSS software 25.0 (IMB Corp.). For the data conforming to normal distribution, paired *t*-tests were used for intragroup comparisons, while two-sample *t*-tests were used for intergroup comparisons. Pearson correlation coefficient was used to evaluate the associations between the abnormal brain regions and the clinical information of the patients. Meanwhile, the rank-sum test and Spearman rank correlation coefficient were used for nonnormally distributed data. The significance level was set at a threshold of a two-tailed P value <0.05.

For fMRI data, statistical analyses were performed using DPABI software. Two-sample *t*-tests were performed to determine the differences between patients in the PDM-NP and HCs. A paired *t*-test was performed to explore the differences between patients in the PDM-P and those in the PDM-NP. Multiple comparison correction was performed using the Gaussian random field (GRF) with

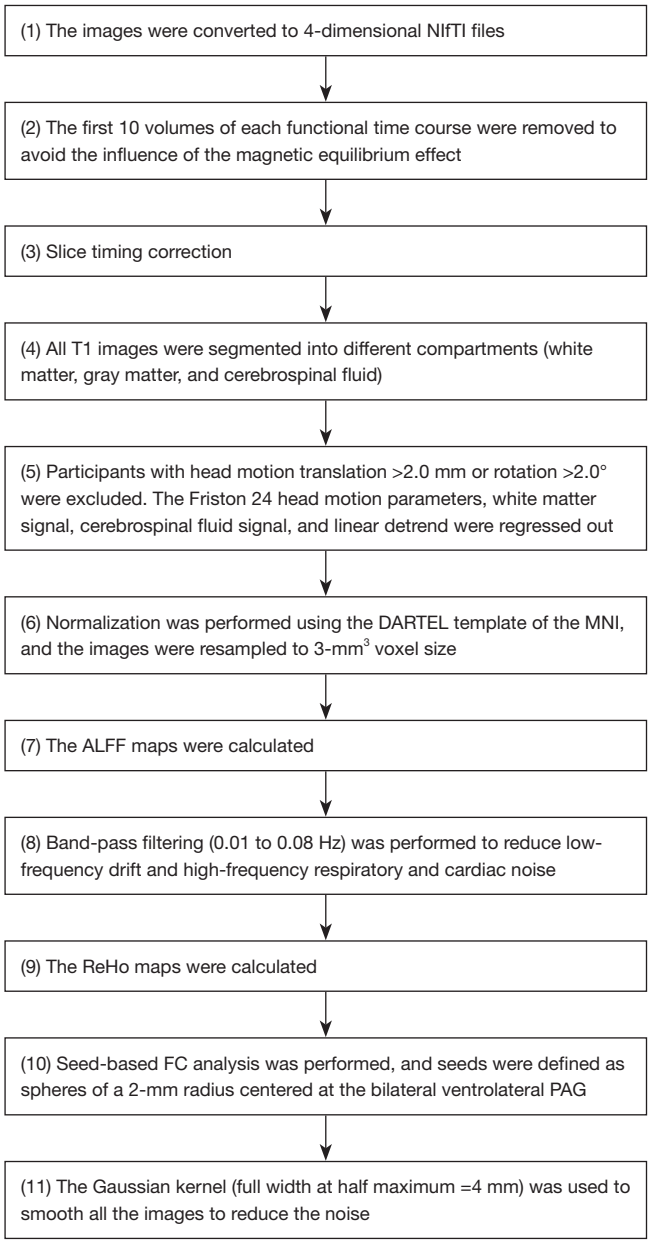

Figure 1 The steps of data processing. NIfTI, Neuroimaging Informatics Technology Initiative; DARTEL, diffeomorphic anatomical registration through the exponentiated lie algebra; MNI, Montreal Neurological Institute; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity; FC, functional connectivity; PAG, periaqueductal gray.

associated Bonferroni correction being performed with a voxel-wise P value <0.0005 and a cluster-wise P value <0.05, which is a strict threshold and has high test-retest reliability and replicability (27). Pearson correlation analyses were

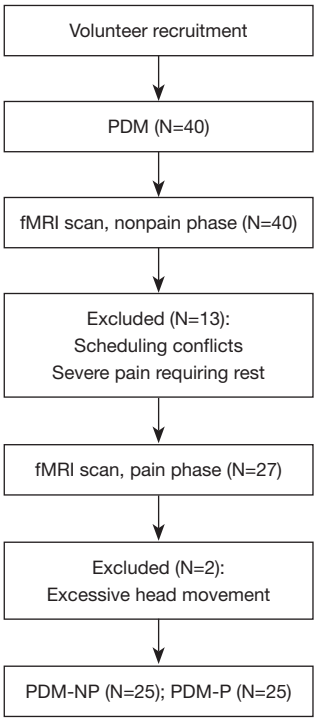

Figure 2 Patient selection flowchart. PDM, primary dysmenorrhea; fMRI, functional magnetic resonance imaging; PDM-NP, PDM during the nonpain phase; PDM-P, PDM during the pain phase.

employed to evaluate the associations between the z-scores of the cluster and the clinical information of the patients.

Results

Demographic and clinical characteristics

Initially, 40 patients with PDM and 20 HCs were recruited in the study, with complete fMRI scan during the nonpain phase. Thirteen patients dropped out due to scheduling conflicts and severe pain during the pain phase, in that they needed to rest at home and were unable to come to the hospital to complete the fMRI scan. Therefore, 27 patients with PDM underwent the fMRI scans during the pain phase. Additionally, two patients with PDM during the pain phase were excluded due to excessive head motion. Finally, 25 patients with PDM and 20 HCs were included in the final analyses (*Figure 2*).

The demographic and clinical characteristics of the patients with PDM and HCs are shown in *Table 1*. None of the patients with PDM or HCs engaged in smoking or the drinking of alcohol. The menstrual phase of patients with

Table 1 Demographic and clinical data between the PDM and HC groups (mean ± SD)

Characteristics	PDM (n=25)	HC (n=20)	P value	Cohen's d
Age (years)	24.40±2.06	25.30±2.22	0.16	–0.421
Education (years)	17.96±1.56	18.25±1.51	0.53	–0.188
Body mass index (kg/m^2)	19.93±1.71	20.04±1.94	0.84	–0.061
Onset age of menophania (years)	13.28±1.02	13.30±1.26	0.95	–0.018
Menstrual cycle (days)	32.52±4.81	31.65±4.59	0.54	0.184
Menstrual phase (days)	6.56±0.96	5.85±1.22	0.03	0.654
History of PDM (years)	6.92±3.16	–	–	–
SAS scores	32.00±7.03	28.50±4.00	0.05	0.594
SDS scores	31.84±7.58	29.15±7.16	0.23	0.363

PDM, primary dysmenorrhea; HC, healthy control; SD, standard deviation; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

Table 2 Clinical data of patients with PDM during the pain and nonpain phases (mean ± SD)

Characteristics	Pain (n=25)	Nonpain (n=25)	P value	Cohen's d
SAS scores	33.64±8.92	32.00±7.03	0.15	0.291
SDS scores	34.64±9.42	31.84±7.58	0.04	0.414
VAS scores	4.96±1.09	5.68±1.60	0.04	–0.425
CMSS-s scores	13.56±7.98	14.40±7.31	0.45	–0.153

PDM, primary dysmenorrhea; SD, standard deviation; SAS, self-rating anxiety scale; SDS, self-rating depression scale; VAS, visual analog scale; CMSS-s, Cox Menstruation Symptom Scale-severity subscale.

PDM was longer than that of the HCs (P=0.03; *Table 1*). There were no statistically significant differences in the age, education, BMI, menstrual cycle, onset age of menophania, SAS, or SDS scores between patients with PDMs and HCs (P>0.05; *Table 1*).

The differences in clinical characteristics between patients in the PDM-P and those in the PDM-NP are shown in *Table 2*. The SDS score during pain phase was higher than that in the nonpain phase (P=0.04; *Table 2*); moreover, the VAS score during pain phase was lower than the average score reported in the previous 6 months (P=0.04; *Table 2*).

GMV, ALFF, ReHo, and FC results

There were no statistically significant differences between patients in the PDM-NP and HCs. Compared with patients in the PDM-NP, those in the PDM-P showed increased ReHo in the left DLPFC (*Table 3* and *Figure 3*) but decreased FC between the PAG and several regions, including the right superior parietal gyrus, bilateral inferior parietal gyrus, right calcarine gyrus, left superior occipital gyrus, left precentral gyrus, right DLPFC. and left crus I of cerebellar hemisphere (*Table 3* and *Figure 4*). In addition, the FC between left PAG and left crus I of the cerebellar hemisphere was negatively correlated with VAS score during the pain phase (r=–0.478; P=0.016) (*Figure 5*).

Discussion

This study employed ReHo, ALFF, FC. and VBM to explore the mechanism of central pain hypersensitivity of PDM during menstrual pain by comparing patients in the PDM-P with those in the PDM-NP. In addition, the long-term effects of PDM were investigated by comparing patients in the PDM-NP with HCs. The findings revealed that there were no functional or structural differences between patients in the PDM-NP and HCs. However, there

Table 3 Regions showing differences in the ReHo and FC in patients with PDM during the pain and nonpain phases

Contrast	Voxels	Brain region	MNI coordinate			*t* value
			X	Y	Z	
ReHo						
Pain > nonpain	11	L dorsolateral prefrontal cortex	−12	51	42	6.2622
Fc_l_pag						
Pain < nonpain	34	R superior parietal gyrus	21	−57	51	−4.7103
Pain < nonpain	28	L inferior parietal gyrus	−24	−54	51	−5.4097
Pain < nonpain	28	R calcarine gyrus	27	−72	12	−5.5317
Pain < nonpain	42	L superior occipital gyrus	−15	−84	12	−5.4554
Pain < nonpain	40	L crus I of cerebellar hemisphere	−30	−87	−21	−5.2779
Fc_r_pag						
Pain < nonpain	20	L precentral gyrus	−42	−3	54	−5.7316
Pain < nonpain	31	R inferior parietal gyrus	42	−39	45	−5.3688
Pain < nonpain	69	R dorsolateral prefrontal cortex	42	51	−6	−5.7665
Pain < nonpain	21	L crus I of cerebellar hemisphere	−30	−84	−21	−5.3087

ReHo, regional homogeneity; FC, functional connectivity; PDM, primary dysmenorrhea; MNI, Montreal Neurological Institute; L, left; R, right; Fc_l_pag, brain regions with altered functional connectivity to the left periaqueductal gray; Fc_r_pag, brain regions with altered functional connectivity to the right periaqueductal gray.

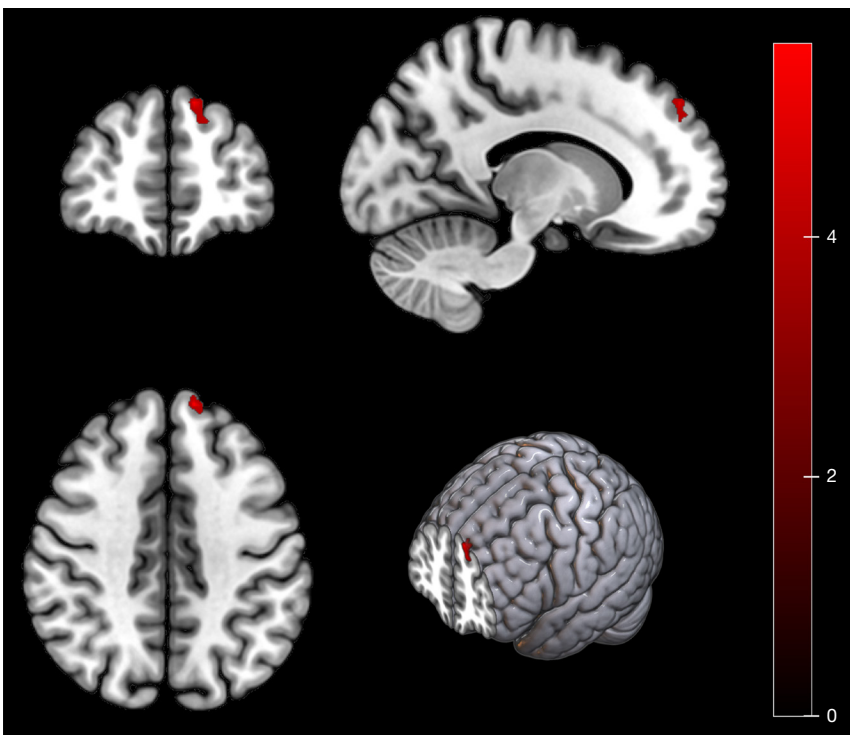

Figure 3 Brain regions showing increased ReHo (red) in the left dorsolateral prefrontal cortex in PDM-P compared with PDM-NP. ReHo, regional homogeneity; PDM-P, PDM during the pain phase; PDM-NP, PDM during the nonpain phase; PDM, primary dysmenorrhea.

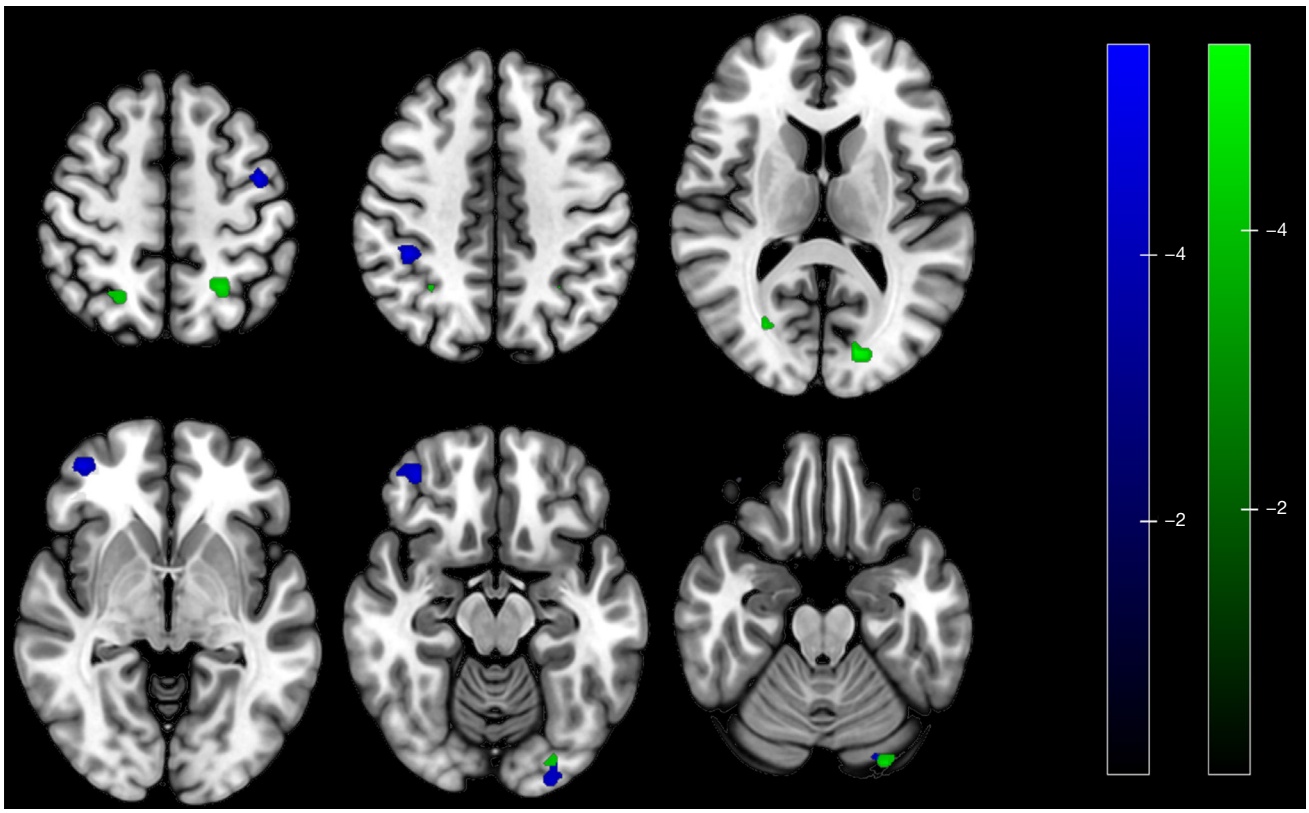

Figure 4 Brain regions showing differences in FC changes of patients with PDM. Decreased FC between right (blue) and left (green) PAG and right superior parietal gyrus, bilateral inferior parietal gyrus, right calcarine gyrus, left superior occipital gyrus, left precentral gyrus, right DLPFC, and left crus I of cerebellar hemisphere in patients in the PDM-P compared with those in the PDM-NP. FC, functional connectivity; PDM, primary dysmenorrhea; PAG, periaqueductal gray; DLPFC, dorsolateral prefrontal cortex; PDM-P, PDM during the pain phase; PDM-NP, PDM during the nonpain phase.

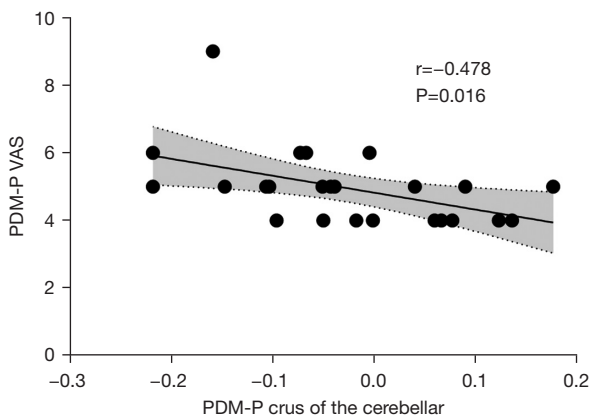

Figure 5 The FC between the left PAG and left crus I of the cerebellar hemisphere was negatively correlated with the VAS score during pain phase. PDM-P, patients with primary dysmenorrhea during pain phase; VAS, visual analog scale; FC, functional connectivity; PAG, periaqueductal gray.

was evidence of altered brain function and FC patterns of the PAG during the pain phase.

Patients in the PDM-P showed increased ReHo in the DLPFC compared with those in the PDM-NP. The ReHo measures the similarity of the time series of a given voxel to those of its nearest neighbors and reflects the coherence of spontaneous neuronal activity (28). The DLPFC is an important region in the pain modulatory system, is involved in cognitive control over pain, and acts as an interface between cognitive processing and pain regulation (29). Stimulation of the DLPFC can exert an immediate analgesic effect and reduce the unpleasantness of pain (30,31). A previous study demonstrated that stimulation of the DLPFC can improve anxiety and functionality in patients with PDM (32). Therefore, our study showed that increased coherence of spontaneous neuronal activity in the DLPFC may reflect defense or self-protection during the

pain phase. However, the PDM-P also showed decreased FC between the PAG and DLPFC. The PAG and DLPFC are considered to be important regions in the descending pain modulation system, and the DLPFC might play a role in pain suppression by regulating the subcortical pathway (30,33,34). Therefore, the disorder of descending pain the modulation system may contribute to the mechanisms of the central pain hypersensitivity of PDM.

This study found there to be decreased FC between the PAG and the inferior parietal gyrus and crus I of cerebellar hemisphere in patients in the PDM-P compared with those in the PDM-NP. These regions are considered to be the components of the DMN (35,36). The DMN is active in the resting state and has been implicated in the self-referential judgments, probing social cognition and communication, episodic memory operation, language comprehension, and semantic processing (37). It also participates in the pain process, and alterations in DMN function and the disrupted communication between the PAG and DMN have been reported in multiple pain conditions (38-41). Research also indicates there to be abnormal brain function and structural changes in the DMN in patients with PDM, and the maladaptive hypoconnectivity between the PAG and DMN has been identified as the central susceptibility to subsequent development of various functional disorders later in life in patients with PDM (12,15,17,19,42). Furthermore, our results showed that the FC between the PAG and cerebellum was negatively correlated with VAS in the PDM-P group. This suggests that the lower the FC between these two regions is, the more severe the symptoms of PDM. Therefore, our results provide evidence suggesting that the hypoconnectivity between the PAG and DMN may be one of the mechanisms of central pain hypersensitivity of PDM.

The superior parietal gyrus is part of the secondary sensory cortex, which is associated with the high-level integration function and is linked to the feeling of pain and painful emotions (43-46). It may be involved in analgesic effects, and its stimulation may lead to impaired judgment of pain intensity and reduce perceived pain intensity (47). The altered function and structure of the superior parietal gyrus has also been found in other pain disorders (48-50). Therefore, the hypoconnectivity between the PAG and the superior parietal gyrus in this study may suggest the disorder of the descending pain modulation system.

The calcarine gyrus and occipital gyrus are widely known as being associated with visual information processing. However, the occipital lobe has also been found to be involved in pain processing, the altered function and structure of which have been reported in other pain conditions (23,51). One study reported reduced thickness in the superior occipital gyrus in patients with PDM compared with HCs (18). There may be an integration of higher regions of the visual system and pain structure in pain processing (18). Therefore, the altered FC between the PAG and occipital lobe in patients with PDM needs to be further explored.

This study has some limitations which should be mentioned. First, the VAS score during the pain phase was lower than the average for the previous 6 months, which might have resulted from the patients with severe pain being excluded due to the inability to complete the fMRI scan. The potential effects of the different severity of the pain on the results cannot be ignored. Second, the SDS score during pain phase was higher than that in the nonpain phase. Thus, the possibility that emotions affected the results cannot be ruled out. Third, the family history of dysmenorrhea of patients with PDM was not recorded. The potential effects of this risk factor on the results should be noted. Fourth, we did not record laboratory indicators such as estrogen and progesterone. Future experiments on this subject should examine these factors.

Conclusions

The present study revealed that long-term PDM was not associated with functional or structural changes in the brain. However, the function of brain was changed during the pain phase, suggesting an important role for the brain in the pathophysiology of PDM. The mechanisms of central pain hypersensitivity of PDM may be related to the disorder of the FC between the PAG and various brain regions involved in descending pain modulation system, the DMN, and the occipital lobe. These findings could help us better understand the pathophysiology of PDM from a neuroimaging perspective, opening a new frontier in developing novel therapies for PDM treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1687/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1687/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was carried out in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University (No. 2022ky079). Written informed consent was obtained from each participant.

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