Research Paper

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Changes in functional connectivity of pain modulatory systems in women with primary dysmenorrhea

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Abstract

Menstrual pain is the most prevalent gynecological complaint, and is usually without organic cause (termed primary dysmenorrhea, PDM). The high comorbidity in the later life of PDM with many functional pain disorders (associated with central dysfunction of pain inhibition, eg, fibromyalgia) suggests possible maladaptive functionality of pain modulatory systems already occurred in young PDM women, making them vulnerable to functional pain disorders. Periaqueductal gray (PAG) matter functions as a critical hub in the neuraxis of pain modulatory systems; therefore, we investigated the functional connectivity of PAG in PDM. Forty-six PDM subjects and 49 controls received resting-state functional magnetic resonance imaging during menstruation and periovulatory phases. The PAG of PDM subjects exhibited adaptive/reactive hyperconnectivity with the sensorimotor cortex during painful menstruation, whereas it exhibited maladaptive hypoconnectivity with the dorsolateral prefrontal cortex and default mode network (involving the ventromedial prefrontal cortex, posterior cingulate cortex, or posterior parietal cortex) during menstruation or periovulatory phase. We propose that the maladaptive descending pain modulatory systems in PDM may underpin the central susceptibility to subsequent development of various functional disorders later in life. This hypothesis is corroborated by the growing body of evidence that hypoconnectivity between PAG and default mode network is a coterminal to many functional pain disorders.

Keywords: Default mode network, Functional connectivity, Magnetic resonance imaging, Pain modulatory systems, Periaqueductal gray

1. Introduction

Primary dysmenorrhea (PDM), menstrual pain without organic causes, is a prevailing problem in women of reproductive age. As many as 90% of adolescent girls and more than 50% of menstruating women worldwide report suffering from PDM, with 10% to 20% of them describing their suffering as so severe and distressing that it requires absence from school or work, which in turn results in tremendous socioeconomic loss.[7,21] Notably, it has recently been reported that otherwise healthy patients with PDM are associated with a much higher prevalence of incidental brain findings, particularly normal variants, compared with controls.[41] There may even be genetic factors, eg, the *BDNF* Val66Met polymorphism, underlying the susceptibility to PDM.[39] Despite its high prevalence rate[56] and the resulting significant reduction in quality of life,[34] PDM has been neglected, receiving surprisingly slight scientific and clinical attention.[7]

Later in life, dysmenorrhea often co-occurs with many functional disorders and chronic pain conditions, including painful bladder syndrome,[17] irritable bowel syndrome,[1] fibromyalgia,[29] temporomandibular joint disease, chronic fatigue syndrome, chronic headache, low back pain, and many others.[7] Notably, all these functional pain disorders have pronounced female predominance,[49] and their highest prevalence rates usually occur after age of 30[46] (cf., the prevalence of PDM peaks much younger in age[64]). The high comorbidity in the later life of PDM with many functional pain disorders (associated with central dysfunction of pain inhibition[9,13,60,62]) suggests possible maladaptive functionality of pain modulatory systems already occurred in young women with PDM, making them vulnerable to functional pain disorders. This point is of particular importance because pain and stress early in life can predict a reduced quality of life and severe or chronic pain later in life.[7]

Periaqueductal gray (PAG) is one of the most important neural substrates of the descending pain modulatory systems because it functions as a critical hub in the neuraxis of the systems.[15] Given PAG as a key structure of dysfunction in many functional pain conditions[62] and an important neural substrate structurally altered in our previous report of PDM,[65] we set out in this functional connectivity (FC) study of resting state functional

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magnetic resonance imaging (fMRI) to address the functional dynamics of the PAG-seeded FCs in the pain modulatory systems of the PDM brain on the network level. Using FC, studies have also revealed abnormal brain networking in various chronic pain conditions, shedding light on the pathophysiological mechanisms underlying the different facets of chronification and the neural bases for neurocognitive conditions of chronic pain.[5,18,32,37,47,51]

We specifically examined neural networking between the PAG and related brain regions (prefrontal cortex [PFC], sensorimotor cortex, posterior parietal cortex, amygdala, etc; Supplementary Table 1, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154) based on documented brain anatomy[15] and the information obtained from fMRI[36] and diffusion tensor imaging studies.[43] We demonstrated that the various experiential dimensions and the pathoneurophysiological underpinnings of PDM could be represented by functional alterations in discrete PAG-seeded networks, which in turn might be relevant to adaptive or maladaptive brain resilience in PDM.

2. Methods

2.1. Subjects

The subjects of this study were a subset of the participants from our previous genetic association and behavioral studies of PDM who were eligible for neuroimaging studies.[39] In brief, 46 otherwise healthy patients with PDM and 49 healthy female controls (CON), matched for both calendar age and gynecological age, participated in this study (**Table 1**). All participants, recruited from Internet advertisements, were screened through telephone and in-person structured interviews (C-.Y.C.). They were blind regardless of case or control status. All participants were double screened and diagnosed in the gynecology clinic by a gynecologist (H-.T.C.). The following were the inclusion criteria for the PDM: (1) a regular menstrual cycle of approximately 27 to 32 days; (2) a history of menstrual pain longer than 6 months; (3) averaged menstrual pain under regular treatment with a rating at least higher than 4 on a verbal numerical scale (0 = not at all, 10 = worst imaginable pain) in the past 6 months; and (4) right-handedness, as confirmed by the Edinburgh Handedness Inventory.[53] The inclusion criteria for the healthy female controls were similar to those for the PDM, except that the controls had no pain whatsoever during menses (verbal numerical scale = 0). The following were the exclusion criteria for all the participants: (1) using oral contraceptives, hormonal supplements, Chinese medicine, or any central-acting medication (eg, opioid, antiepileptics) within 6 months before the study; (2) pathological pituitary gland disease; (3) organic pelvic disease; (4) any psychiatric or neurological disorders, particularly premenstrual dysphoric disorder; (5) head injury with loss of consciousness; (6) immediate plans for pregnancy or a positive pregnancy test; (7) a history of childbirth; and (8) having a metal or pacemaker implant, claustrophobia, or any contraindications to MRI. No analgesics were taken within 24 hours before the study. All the patients with PDM underwent pelvic ultrasonography to exclude secondary dysmenorrhea caused by organic pelvic diseases, such as endometriosis or adenomyosis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital. All participants gave their written informed consent.

Table 1

Demographic data and baseline information.

	PDM (n = 46)	CON (n = 49)	P (2-tailed)
Age, y	23.33 ± 2.42	23.80 ± 2.47	0.351
Age at menarche	11.93 ± 1.32	12.31 ± 1.08	0.140
Years of menstruating	11.39 ± 2.84	11.49 ± 2.86	0.867
Days of 1 menstrual cycle	29.50 ± 1.28	29.52 ± 1.19	0.936
Menstrual pain experience			
Pain history, y	9.22 ± 2.85	—	—
Absenteeism, %	65.2	—	—
Drug taken, %	41.3	—	—
Recalled PRI scores	34.48 ± 12.50	—	—
Edinburgh Handedness Inventory	82.96 ± 16.05	80.20 ± 20.44	0.467
SF-36*			
Mental component summary	46.80 ± 7.43	53.65 ± 5.30	0.000†
Physical component summary	47.22 ± 9.02	54.99 ± 4.22	0.000†

* Three control subjects without the SF-36 were excluded from the calculations.
† Significant differences between 2 groups at $P < 0.001$.
Data are presented as mean ± SD.
CON, controls; PDM, primary dysmenorrhea; PRI, pain rating index; SF-36, Short Form Health Survey.

2.2. Experimental design

MRI scanning was individually scheduled according to each subject's first day of menstruation. Psychological assessments, blood samples for gonadal hormone assays, and MRI images (T1 and resting-state fMRI images) were obtained at 2 time points in the menstrual cycle: menstruation phase (MENS phase, days 1-3 of the menstrual cycle) and periovulatory phase (POV phase, days 12-16 of the menstrual cycle). Ovulation was confirmed using a urinary luteinizing hormone test (Han Chiun Proper LH Rapid Test).

2.3. Psychological and quality-of-life assessments for pain experience

All participants in the 2 groups completed the Short-Form Health Survey (SF-36)[69] during the initial examination to assess the quality of life. The patients with PDM completed the McGill Pain Questionnaire during the initial examination and during the MENS phase to assess the recalled overall and present experiences of menstrual pain, respectively. All participants in the 2 groups completed the Pain Catastrophizing Scale (PCS)[72] during the MENS and POV phases to assess pain-maladaptive psychological status.

2.4. Serum gonadal hormone measurements

The sera extracted from the blood samples drawn during the MENS and POV phases were stored for batch analysis using commercialized assays (UniCel DxC 800 Synchron Clinical Systems, Beckman Coulter, Inc, Brea, CA). The total serum concentrations were assayed using a chemiluminescence immunoassay technique for estradiol and progesterone, and a radioimmunoassay technique for testosterone. The patients with PDM had lower progesterone but higher testosterone compared with the controls. There were phase differences in estradiol and testosterone. No interaction between them was noted for any measured thresholds (Supplementary Table 2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154). As gonadal hormones may affect resting-state FC,[6,54,68] the hormone fluctuations were regressed out as covariates of noninterest in the subsequent image processing.

2.5. Image acquisition

Resting-state fMRI images were acquired using a 3.0 Tesla MRI scanner (Magnetom Trio Tim; Siemens, Erlangen, Germany) with a 12-channel head coil at the National Yang-Ming University. High-resolution T1-weighted 3-dimensional structural images using a magnetization-prepared rapid-acquired gradient echo sequence ([TR]/[TE] = 2530 ms/3.03 ms, flip angle = 70°, field-of-view = 224 × 256 × 192 mm^3, in-plant matrix size = 224 × 256 × 192, slice thickness = 1 mm) and T2*-weighted gradient echo sequence ([TR]/[TE] = 2500 ms/30 ms, flip angle = 90°, field-of-view = 220 × 220 × 136 mm^3, in-plant matrix size = 64 × 64 × 40, slice thickness = 3.4 mm and 204 volumes per run) were conducted for high-resolution anatomical T1 images and fMRI images. The first 4 EPI scans of each resting-state fMRI series were discarded for signal saturation and magnetic-field stabilization. The participants remained awake during the scan (eyes open, heads still but relaxed, without thinking about anything in particular). Head cushions and earplugs were provided to reduce head motion and noise, respectively.

2.6. Image preprocessing

Preprocessing was performed using the DPARSF toolbox (State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China) with Statistical Parametrical Mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm) in MATLAB. All functional images were subjected to slice timing, realignment for head motion correction, co-registration to each individual's anatomical image, and normalization to the Montreal Neurological Institute (MNI-152) template. Subjects having head motion of any volume more than 2 mm or 2° were excluded from further processing.[16] The images were resampled to an isotropic 2 mm^3 voxel size in the normalization step and then spatially smoothed using a 3D Gaussian kernel of 8 mm full-width at half maximum. Linear trends were then removed from the resulting time series, and the time series was temporally bandpass filtered (0.01-0.08 Hz) to extract the low-frequency oscillations for spontaneous neuronal activity.[44]

2.7. Removal of physiological/scanner-related noise

Averaged time courses of the following nuisance variables or confounding artifacts were regressed out: (1) the 6 head movement parameters computed based on rigid body translation and rotation during the realignment in SPM8, (2) the global mean signal (global signal regression), (3) the mean signal within the lateral ventricles, and (4) the mean signal within a deep white matter region (centrum ovale). The cerebrospinal fluid and the white matter signals are thought to reflect fluctuations in nonspecific regional correlations. We performed global signal regression because it has been shown to maximize the specificity of positive resting-state correlations in real and simulated data.[70] The neuroscientific interpretation of anticorrelation has been challenged,[11] and global signal regression may cause a negative shift in the distribution of correlations[25,50]; therefore, we implemented a mask to address positive connectivity only.

2.8. Definition of PAG seed(s) and PAG-seeded FC maps

Two PAG seeds (3-mm radius), centered at MNI coordinates ([−4, −26, −14] and 4, −26, −14), were identified according to the published literature.[36,42] The mean time-series activities in the seed regions of each subject were extracted. PAG-seeded FC maps were then generated.[16] Each individual-level FC map obtained was then converted to a z-map using Fisher *r*-to-*z* transformation for second-level group analyses.

2.9. Statistical analyses

2.9.1. Demographic information and psychophysiological measurements

SPSS Statistics 20.0 (SPSS Inc, Chicago, IL) was used for all analyses. The data are presented as mean ± SD. The results were considered significant at $P < 0.05$ (2-tailed). We did not apply multiple corrections for all the inventories because they assess different sensory, affective, cognitive, and physiological dimensions of pain, as well as the distinct physical and mental impacts of social life. A 2-sample *t* test was conducted for the between-group (PDM vs CON) differences in demographic characteristics, Edinburgh Handedness Inventory scores, and SF-36 scores. A paired *t* test was conducted for the between-stage (inception stage vs painful stage during MENS phase) differences and correlations in the McGill Pain Questionnaire scores. To assess the PCS scores and serum hormone levels during the 2 phases, a general linear model with a repeated-measures design was applied to examine the possible effects of group (PDM vs CON), menstrual cycle phase (MENS vs POV), and the interactions between these factors.

2.9.2. Image analyses

2.9.2.1. Between-group differences in PAG-seeded FC

A mixed-effects model of factorial design (3 factors: subjects, phase, and group) was used for the FC maps in SPM8 (Wellcome Trust Centre for Neuroimaging). Gonadal hormones were regressed out as covariates of noninterest. Statistical maps were computed to identify changes in PAG-seeded FC in the following contrasts: (1) between-group comparisons for each phase, (2) between-phase comparisons for each group, and (3) second-level between-group comparisons of between-phase differences ($PDM_{\Delta(MENS\ -\ POV)}$ − $CON_{\Delta(MENS\ -\ POV)}$). PAG-seeded FC changes during the MENS phase (painful stage) in the between-group comparisons were regarded as *state* changes, whereas changes during the POV phase (pain-free stage) or throughout the menstrual cycle were regarded as *trait* changes. Significance was set at the uncorrected voxel level $P < 0.005$, followed by the family-wise error rate (FWE)-corrected cluster level $P < 0.05$.

2.9.2.2. Correlation analyses between functional connectivity and questionnaire data

2.9.2.2.1. McGill Pain Questionnaire and left PAG-seeded FC

A 1-sample *t* test was conducted to examine the correlation between the present or recalled overall experience of menstrual pain and the *state* or *trait* PAG-seeded FC in PDM, respectively. We first entered the demeaned (in SPM) pain rating index (PRI) and present pain intensity values from the present or recalled McGill Pain Questionnaire as regressors to identify brain regions with either positive or negative correlations with PAG-seeded FC in the MENS or POV phase. Present pain correlations during the MENS phase were regarded as *state* relationships, whereas recalled pain correlations during the POV phase were regarded as *trait* relationships. To further determine whether different dimensions of pain experience were associated with different brain regions, we used

subscales of the PRI as regressors. Significance was set at the uncorrected voxel level $P < 0.005$, followed by the FWE-corrected cluster level $P < 0.05$.

2.9.2.2.2. PCS and left PAG-seeded FC

A 2-sample *t* test was conducted to determine the correlation between pain-related maladaptive psychological status (ie, rumination, helplessness, and magnification of pain) and the *state* or *trait* PAG-seeded FCs in both groups for the MENS or POV phase, respectively. We entered different demeaned (in SPM) subscales scores of PCS as different regressors to identify brain regions with either positive or negative correlations with PAG-seeded FC in PDM. PDM>CON contrasts were performed to identify regions where the correlation between PAG FCs and the psychological assessments was greater in the between-group comparison. Correlations during the MENS phase (painful stage) were regarded as *state* relationships, whereas correlations during the POV phase (pain-free stage) or throughout the menstrual cycle were regarded as *trait* relationships. Significance was set at the uncorrected voxel level $P < 0.005$, followed by the FWE-corrected cluster level $P < 0.05$.

2.9.2.2.3. SF-36 and left PAG-seeded FC

A 2-sample *t* test was conducted to examine the correlation between the physical and mental discontent and the *trait* PAG-seeded FCs in both groups. We entered the demeaned (in SPM) physical and mental component summary separately as a regressor to identify brain regions with either positive or negative *trait* correlations with PAG-seeded FCs in the POV phase for PDM. PDM>CON contrasts were performed to identify regions where the correlation between PAG FCs and the psychological assessments was greater in the between-group comparison. Significance was set at the uncorrected voxel level $P < 0.005$, followed by the FWE-corrected cluster level $P < 0.05$.

3. Results

3.1. Demographic data and baseline information

There were no significant differences between the PDM and the controls with regard to age, age at menarche, years of menstruation, average days of 1 menstrual cycle, or Edinburgh Handedness Inventory scores ($P > 0.05$). All 46 patients with PDM in this neuroimaging study had a long history of menstrual pain (mean ± SD = 9.22 ± 2.85 years), with duration of pain of approximately 1 to 3 days in 1 menstrual cycle (mean ± SD = 1.92 ± 0.76 days). Thirty patients with PDM (65.2%) reported absences from school or work because of debilitating menstrual pain, and 19 patients with PDM (41.3%) used over-the-counter analgesics on occasion (**Table 1**).

3.2. Psychological measurements

3.2.1. Inception stage

The recalled overall pain experience, as assessed by scores on the McGill Pain Questionnaire (mean ± SD = 34.48 ± 12.50), confirmed that patients with PDM experienced moderate to severe menstrual pain, which was equivalent to labor pain.[48] No menstrual pain or discomfort was reported in the age, menstrual years, and menstrual duration-matched controls. The SF-36 for measuring the quality of life revealed that the patients with PDM exhibited lower mental (PDM: 46.80 ± 7.43, CON: 53.65 ± 5.30, $P = 0.000$) and physical (PDM: 47.22 ± 9.02, CON: 54.99 ± 4.22, $P = 0.000$) well-being compared with the controls (**Table 1**).

3.2.2. Painful (state) stage during MENS phase

The pain experience, as assessed by McGill Pain Questionnaire scores (mean ± SD = 30.11 ± 11.86), confirmed that the PDM patients experienced moderate menstrual pain (**Table 2**). Notably, the pain experience correlated significantly with the recalled overall menstrual pain based on assessment with the McGill Pain Questionnaire; however, the former was significantly lower than the latter (Supplementary Table 3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154). In the subscale analyses of the McGill Pain Questionnaire, the recalled overall pain experience was significantly correlated with the present pain experience in the subscales of sensory, affective, and miscellaneous dimensions of pain. The evaluation and miscellaneous dimensions of the recalled overall pain experience were significantly higher than those of the present pain experience.

The rumination (PDM: 8.26 ± 4.17, CON: 2.08 ± 2.66, $P = 0.000$), magnification (PDM: 3.41 ± 2.46, CON: 1.00 ± 1.56, $P = -0.000$), helplessness (PDM: 10.22 ± 5.80, CON: 2.22 ± 2.84, $P = 0.000$), and total scores (PDM: 21.89 ± 11.52, CON: 5.31 ± 6.44, $P = 0.000$) of the PCS were significantly higher in the patients with PDM compared with the controls.

3.2.3. Pain-free (trait) stage during POV phase

The patients with PDM had significantly higher scores on the PCS regarding the subscales of rumination (PDM: 7.41 ± 4.26, CON: 1.98 ± 3.00, $P = 0.000$), magnification (PDM: 3.07 ± 2.49, CON: 1.16 ± 1.70, $P = 0.000$), and helplessness (PDM: 8.22 ± 5.06, CON: 2.63 ± 3.72, $P = 0.000$), and they had higher total PCS scores (PDM: 18.70 ± 10.60, CON: 5.78 ± 7.80, $P = 0.000$).

Table 2

Psychological and behavioral assessments.

	PDM ($n = 46$)	CON ($n = 49$)	*P* (2-tailed)
PCS total scores (range, 0-52)			
MENS phase	21.89 ± 11.52*	5.31 ± 6.44	0.000†
POV phase	18.70 ± 10.60*	5.78 ± 7.80	0.000†
Pain rumination (range, 0-16)			
MENS phase	8.26 ± 4.17	2.08 ± 2.66	0.000†
POV phase	7.41 ± 4.26	1.98 ± 3.00	0.000†
Pain helplessness (range, 0-24)			
MENS phase	10.22 ± 5.80*	2.22 ± 2.84	0.000†
POV phase	8.22 ± 5.06*	2.63 ± 3.72	0.000†
Pain magnification (range, 0-12)			
MENS phase	3.41 ± 2.46	1.00 ± 1.56	0.000†
POV phase	3.07 ± 2.49	1.16 ± 1.70	0.000†
Present PRI scores (range, 0-78)	30.11 ± 11.99	—	—
Sensory (range, 0-42)	16.54 ± 6.01	—	—
Affective (range, 0-14)	3.91 ± 2.85	—	—
Evaluation (range, 0-5)	2.54 ± 2.02	—	—
Miscellaneous (range, 0-17)	7.11 ± 3.62	—	—
Present PPI scores (range, 0-5)	2.72 ± 0.96	—	—

* Significant differences in group–phase interaction at $P < 0.05$.
† Significant differences between 2 groups at $P < 0.001$.
Data are presented as mean ± SD.
MENS phase, menstruation phase; PCS, Pain Catastrophizing Scale; PDM, primary dysmenorrhea; PPI, present pain intensity; PRI, pain rating index; POV phase, periovulatory phase.

In PDM, the helplessness and total scores were significantly higher in the MENS phase than in the POV phase (pain helplessness: $P = 0.012$; total scores: $P = 0.018$). No phase difference was noted in the controls (**Table 2**).

3.3. Neuroimaging studies

3.3.1. Painful (state) condition during MENS phase

3.3.1.1. Between-group differences in left PAG-seeded FC

The patients with PDM had significantly increased left PAG-seeded FC (hyperconnectivity) in the primary somatosensory cortex (S1; BA 1, 3), primary motor cortex (M1; BA 4), and supplementary motor area (SMA; BA 6) compared with the controls (**Fig. 1** and **Table 3**). These hyperconnectivity regions survived the second-level between-group comparisons of between-phase differences ($PDM_{\Delta(MENS\ -\ POV)} - CON_{\Delta(MENS\ -\ POV)}$). In contrast, patients with PDM had significantly decreased left PAG-seeded FC (hypoconnectivity) in the anterior cingulate cortex (ACC; BA 24), dorsomedial prefrontal cortex (dmPFC; BA 9), and dorsolateral prefrontal cortex (dlPFC; lateral sections of BA 10) compared with the controls. None of these hypoconnectivity regions survived the second-level between-group comparisons of between-phase differences ($PDM_{\Delta(MENS\ -\ POV)} - CON_{\Delta(MENS\ -\ POV)}$), indicating that the decreased FC in the group differences did not significantly vary across phases. Notably, no significant difference was found in PAG FC between the MENS and POV phases in either group, ie, the *state* (PDM, painful stage) during MENS does not alter FC connectivity relative to the pain-free stage. This suggests that the group differences could be attributed to neither the fluctuating pain across phases nor the fluctuating gonadal hormones (the hormone fluctuations had been regressed out as covariates of noninterest in the image processing), but to the chronicity of PDM. It would be heuristic to study young adolescents of initial PDM to explore the effects of fluctuating pain across phases.

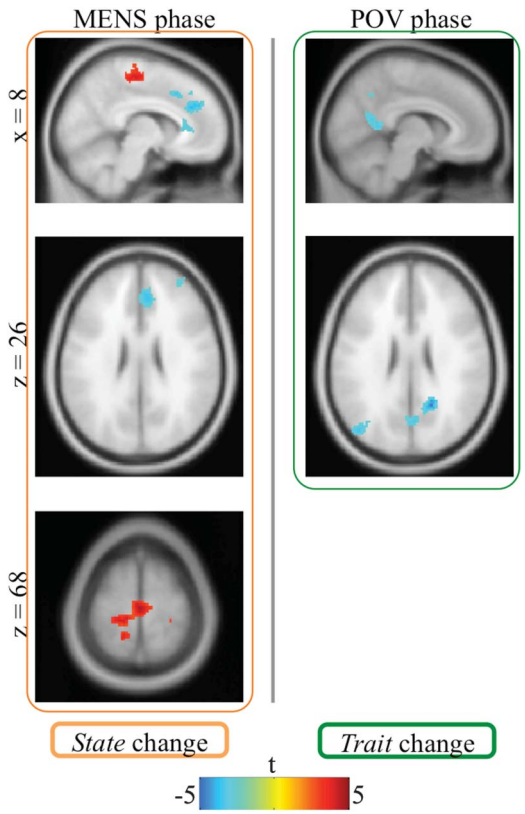

Figure 1. Regions exhibiting significant resting-state functional connectivity with left periaqueductal gray (PAG) in the contrast of primary dysmenorrhea (PDM) vs control groups. The between-group comparison showed significantly enhanced PAG functional connectivity (FC) with the primary somatosensory cortex, primary motor cortex, and supplementary motor area only in the menstruation phase (MENS phase) in patients with PDM. Decreased PAG FCs were found in the anterior cingulate cortex, the dorsomedial prefrontal cortex (dmPFC), and the dorsolateral prefrontal cortex (dlPFC) in the MENS phase, and in the posterior parietal cortex (PPC), the precuneus/posterior cingulate cortex, and the retrosplenial cortex in the periovulatory phase (POV phase). All statistical images are thresholded at the uncorrected voxel level $P < 0.005$, followed by the family-wise error rate (FWE)-corrected cluster level $P < 0.05$. The results are superimposed on the Statistical Parametrical Mapping T1 template, and warm or cold colors represent increased or decreased PAG FC, respectively. The color bar represents the *t* scores. All figures depict neurological orientation (left = left).

3.3.1.2. Correlation analyses between functional connectivity and questionnaire data

Because the right PAG-seeded FC analyses yielded similar results to the left PAG-seeded analyses (Supplementary Fig. 1 and Supplementary Table 4, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154), we presented only the left PAG-seeded FC maps in the following correlation analyses.

3.3.1.2.1. MENS-McGill Pain Questionnaire and left PAG-seeded FC

The patients with PDM demonstrated negative correlations between the PRI and the sensory subscale of the PRI of the MENS-McGill Pain Questionnaire with left PAG-seeded FC in the dmPFC (BA 9, superior sections of BA 10) (**Fig. 2** and **Table 4**). A negative correlation between the miscellaneous subscale of the PRI and left PAG-seeded FC was found in the dmPFC (BA 9, superior sections of BA 10) and dlPFC (BA 9).

A positive correlation between the PRI and left PAG-seeded FC was found in the cuneus and lingual gyri. These 2 regions and the retrosplenial cortex (BA 30) also demonstrated positive correlations between the evaluation subscale of the PRI and present pain intensity with left PAG-seeded FC. A positive correlation between the affective subscale of the present PRI and left PAG-seeded FC was found in the ventrolateral prefrontal cortex (vlPFC; BA 45, pars triangularis of the inferior frontal gyrus), posterior parietal cortex (PPC; BA 40) and lingual gyrus.

3.3.1.2.2. PCS and left PAG-seeded FC

In patients with PDM, significant positive correlations were found between pain helplessness and left PAG-seeded FC in the S1 (BA 1), M1 (BA 4), and SMA (BA 6), whereas negative correlations were found in the cerebellum between left PAG-seeded FC and total PCS score and pain rumination (**Fig. 3A** and **Table 5**). In the between-group comparison, the patients with PDM had a lower correlation between pain helplessness and left PAG-seeded FC in the dorsal premotor cortex (BA 6).

3.3.2. Pain-free (trait) condition during the POV phase

3.3.2.1. Between-group differences in the left PAG-seeded FC

Patients with PDM demonstrated decreased left PAG-seeded FC in the inferior PPC (BA 39), ventral precuneus, posterior cingulate cortex (BA 23, 31), and retrosplenial cortex (**Fig. 1** and **Table 3**). No

Table 3

Peak MNI coordinates for regions exhibiting significant resting-state functional connectivity with the left periaqueductal gray in the contrast of PDM vs control groups.

Contrast	Region	BA	*t* score	Peak coordinate		
				x	*y*	*z*
First level						
State changes (MENS phase)	Precentral gyrus	4	4.24	−14	−32	70
PDM–CON	Supplementary motor area	6	4.06	6	−22	62
	Postcentral gyrus	1	3.41	−16	−40	74
	Lateral PFC	10	4.86	32	58	8
CON–PDM	Medial PFC, dorsal	9	4.25	6	44	30
	ACC	24	3.53	−8	38	6
Trait changes (POV phase)	Posterior parietal cortex	39	4.68	−38	−74	36
CON–PDM	PCC/precuneus	23	3.75	4	−62	18
	Retrosplenial cortex	23/30	3.55	14	−48	10
Second level						
$PDM_{\Delta(MENS\ -\ POV)} - CON_{\Delta(MENS\ -\ POV)}$	Supplementary motor area	6	3.52	−2	−20	60
	Precentral gyrus	4	3.52	−18	−28	68
	Postcentral gyrus	3	3.37	−14	−32	70

Peak coordinates refer to the MNI space. Significance was set at the uncorrected voxel level $P < 0.005$, followed by the family-wise error rate (FWE)-corrected cluster level $P < 0.05$.
ACC, anterior cingulate cortex; BA, Brodmann area; CON, control; MENS phase, menstruation phase; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; PDM, primary dysmenorrhea; PFC, prefrontal cortex; POV phase, periovulatory phase.

region of higher left PAG-seeded FC was found in a comparison of PDM vs control groups.

3.3.2.2. Correlation analyses between functional connectivity and questionnaire data

3.3.2.2.1. The recalled McGill Pain Questionnaire and left PAG-seeded FC

The patients with PDM demonstrated a significant positive correlation between the recalled overall PRI and left PAG-seeded FC in the superior PPC (BA 7) (Supplementary Table 5, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154). The patients with PDM also demonstrated a positive correlation between the sensory subscale of the recalled overall PRI and left PAG-seeded FC in the inferior PPC (BA 40).

A significant negative correlation between the evaluation subscale of the recalled overall PRI and left PAG-seeded FC was noted in the thalamus, hippocampus, insula, globus pallidus, superior temporal gyrus, and internal capsule. In addition, there was a significant negative correlation between the miscellaneous subscale of the recalled overall PRI and left PAG-seeded FC in the dlPFC (BA 9).

3.3.2.2.2. PCS and left PAG-seeded FC

In patients with PDM, there was a positive correlation between the pain magnification subscale and left PAG-seeded FC in the superior PPC (BA 7), dorsal premotor cortex (BA 6), and fusiform, and inferior temporal gyrus (**Fig. 3A** and **Table 5**). In the between-group comparison, the patients with PDM demonstrated significantly lower correlations between left PAG-seeded FC and total PCS score, pain rumination, and pain helplessness in the ventromedial prefrontal cortex (vmPFC; inferior sections of BA 10) and ACC (**Fig. 3B**).

3.3.2.2.3. SF-36 and left PAG-seeded FC

In PDM, there was a negative correlation between the physical component and left PAG-seeded FC in the inferior PPC (BA 40), S1 (BA 3), M1 (BA 4), SMA (BA 6), and superior temporal gyrus (BA 22) (Supplementary Table 6, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154). No significant correlation between the mental component and left PAG-seeded FC was found in any brain region in PDM. In the between-group comparison, no region exhibited a significant difference in the correlation between the physical or mental component and left PAG-seeded FC.

4. Discussion

Our findings of alterations in the PAG FC are in line with the results of our structural neuroimaging studies of PDM. We previously reported a *trait*-related decrease in the regional gray matter volume in the default mode network (DMN) (medial prefrontal cortex [mPFC] and precuneus) and PPC[65] and a *state*-related increase in the regional gray matter volume in S1 in PDM.[66] In this study, we observed a *trait*-related hypoconnectivity in PAG-DMN FC and PAG-PPC FC and a *state*-related hyperconnectivity in PAG-S1/M1 FC in PDM (**Fig. 1**). Structural changes may be coupled with alterations in the resting network organization in the corresponding regions. Furthermore, there were PAG FCs that demonstrated predictive values for the overall quality of life of women with PDM. The higher the correlation strength of the PAG-S1/M1 FC, PAG-vlPFC FC, and PAG-PPC FC, the less the physical well-being as measured by the SF-36 (Supplementary Table 6, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154).

4.1. State changes during the MENS stage

4.1.1. Engagement of the PAG-S1/M1 and PAG-SMA FCs (reactive and adaptive mode) mirroring the acute nature of menstrual pain

The targeting of PAG-S1/M1 (hyperconnectivity) only during the MENS stage may encode the acute nature of menstrual pain responses in an on-off manner, as PAG plays an important role in processing and mediating responses to somatic and visceral noxious inputs.[15] This finding is supported by the positive correlation (reactive mode) between PAG-S1/M1 FC and the pain helplessness subscale of the PCS in the MENS phase

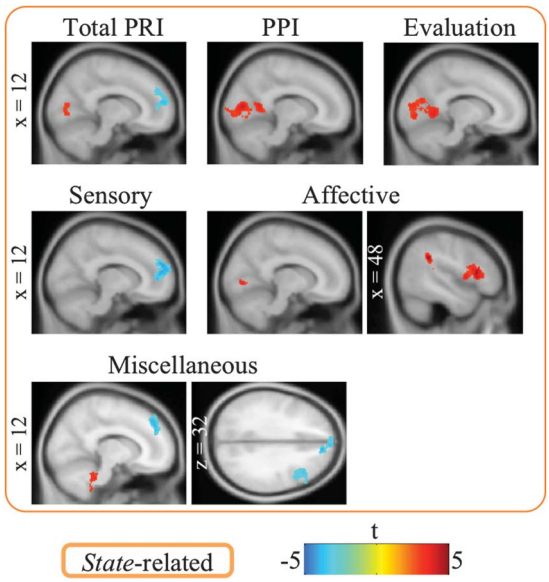

Figure 2. Periaqueductal gray (PAG) functional connectivity (FC) covaries with the present experience of menstrual pain in patients with primary dysmenorrhea (PDM). A positive correlation between the pain rating index (PRI) scores of the McGill Pain Questionnaire and PAG FC was found in the cuneus/lingual gyrus, and a negative correlation was found in the dorsomedial prefrontal cortex (dmPFC). The cuneus/lingual gyrus and the retrosplenial cortex exhibited positive correlations between PAG FC and the evaluation subscale of the present PRI and between PAG FC and the present pain intensity. The dmPFC exhibited negative correlations between PAG FC and the sensory and miscellaneous subscale of the present PRI. There were positive correlations between the affective subscale of the present PRI and PAG FC with the ventrolateral prefrontal cortex, posterior parietal cortex, and lingual gyrus. A positive correlation between the miscellaneous subscale of the present PRI and PAG FC was detected in the cerebellum, and negative correlations were found in the dorsolateral prefrontal cortex and dmPFC. All statistical images are thresholded at the uncorrected voxel level $P < 0.005$, followed by the family-wise error rate (FWE)-corrected cluster level $P < 0.05$. The results are superimposed on the Statistical Parametrical Mapping T1 template, and warm or cold colors represent positive or negative correlation, respectively. The color bar represents *t* scores. All figures depict neurological orientation (left = left).

Table 4

***State*-related (menstruation phase) periaqueductal gray functional connectivity covaries with present experience of menstrual pain* in the patients with primary dysmenorrhea.**

Region	BA	*t* score	Peak coordinate		
			x	*y*	*z*
PRI					
Positive					
Cuneus/lingual gyrus	17	3.56	−8	−88	12
Negative					
Medial PFC, dorsal	9	4.13	−2	62	28
PPI					
Positive					
Cuneus/lingual gyrus	17	4.36	−4	−86	6
Retrosplenial cortex	30	3.69	8	−54	6
Evaluation					
Positive					
Retrosplenial cortex	18/30	3.88	−14	−54	4
Cuneus/lingual gyrus	17	3.70	−16	−82	10
Affective					
Positive					
Posterior parietal cortex	40	5.21	48	−44	30
Lateral PFC, ventral	45	4.86	50	22	10
Lingual gyrus	18	3.47	10	−80	0
Sensory					
Negative					
Medial PFC, dorsal	9	4.84	14	56	26
Miscellaneous					
Positive					
Cerebellum	—	3.89	30	−50	−48
Negative					
Medial PFC, dorsal	9/10	3.90	−4	60	30
Lateral PFC, dorsal	9	3.69	42	18	36

Peak coordinates refer to the Montreal Neurological Institute space. Significance was set at the uncorrected voxel level $P < 0.005$, followed by the family-wise error rate (FWE)-corrected cluster level $P < 0.05$.
* Present experience of menstrual pain: PRI and PPI scores of the McGill Pain Questionnaire; evaluation, affective, sensory, and miscellaneous subscale of the present PRI.
BA, Brodmann area; PFC, prefrontal cortex; PPI, present pain intensity; PRI, pain rating index.

(**Fig. 3A**): the higher the helplessness rating, the stronger the FC. Our reasoning is corroborated by a recent study on painful bladder syndrome that reported higher PAG-S1/M1 FC when patients experienced pain during bladder filling.[35] Alternatively, the hyperconnectivity of the left-lateralized PAG-S1/M1 FC may also connote the possible spontaneous activation of a top-down modulation pathway as effected by the motor cortex and pyramidal tract. It has been reported that primary motor cortex stimulation can induce a top-down activation of the ventrolateral thalamus through corticothalamic projections, and can initiate a delayed but long-lasting activation in PAG for pain modulation.[27] Moreover, it is a common practice in recent exercises for pain modulation by transcranial direct current stimulation to place the active electrode on the M1 region contralateral to the dominant hand.[52] The hyperconnectivity of PAG-SMA FC during the MENS phase of PDM may have some relevance to automatic muscle contractions of pelvic floor muscles.[3,35,38] However, it remains elusive whether PDM is associated with altered motor function of pelvic floor muscles.

4.1.2. Maladaptive hypoconnectivity of PAG-dlPFC FC

The dlPFC subserves the cognitive modulation of pain,[28] as evidenced by the negative correlation between the PAG-dlPFC FC and the miscellaneous subscale of the present PRI (nonspecific components of the experience of menstrual pain) in the MENS phase in PDM (**Fig. 2**): the higher the functional coupling, the lower the rating. However, the hypoconnectivity of PAG-dlPFC FC (BA 10, *xyz* = 32,58,8; a top-down pain modulator[45,47,55]) may implicate a maladaptive brain response. PDM seem to inadvertently disengage this modulation pathway during the MENS stage.

4.1.3. PAG-vlPFC FC adaptively participates in the affective dimension of dysmenorrhea

The anterior lateral PFC (encompassing vlPFC) participates in the modulation of pain emotion, whereas the dlPFC subserves the modulation of pain attention.[28] vlPFC acts in behavioral control[40] and crucially connects with PAG for affective modulation of pain.[55,67] The positive correlation between the affective subscale of the present PRI and the PAG-vlPFC FC (pars triangularis) during the MENS stage (**Fig. 2**) suggests that this networking services the affective modulation of long-term menstrual pain. Although it remains elusive of the exact mechanisms and the unequivocal interpretations for the respective positive and negative direction of modulation by means of functional neuroimaging, our argument is in line with the previous report.[67] In addition, we did not observe any difference in the PAG-vlPFC (inferior frontal gyrus) FC between the PDM and control groups, connoting that the PAG-vlPFC functions reactively (adaptive or compensatory mode) for PDM during the MENS phase.

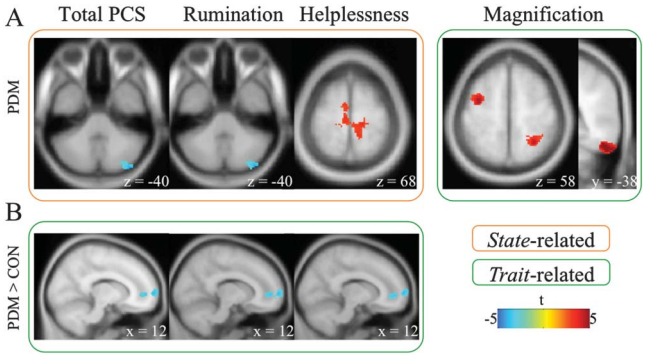

Figure 3. Periaqueductal gray (PAG) functional connectivity (FC) covaries with pain catastrophizing in the patients with primary dysmenorrhea (PDM) and the contrast of PDM vs control groups. (A) In the menstruation phase in patients with PDM, there were significant positive correlations between pain helplessness and PAG FC with the primary somatosensory cortex, primary motor cortex, and supplementary motor area, and there were negative correlations in the cerebellum between PAG FC and total Pain Catastrophizing Scale (PCS) score and pain rumination. In contrast, in the periovulatory phase (POV phase), there were significant positive correlations between pain magnification and PAG FC with the superior posterior parietal cortex (BA 7), dorsal premotor cortex, and fusiform/inferior temporal gyrus. (B) In the between-group comparison, there were weaker correlations between PAG FC and total PCS score, pain rumination and pain helplessness in the ventromedial prefrontal cortex in the POV phase. All statistical images are thresholded at the uncorrected voxel level $P < 0.005$, followed by family-wise error rate (FWE)-corrected cluster level $P < 0.05$. The results are superimposed on the Statistical Parametrical Mapping T1 template, and warm or cold colors represent positive or negative correlations, respectively. The color bar represents *t* scores. All figures depict neurological orientation (left = left).

4.1.4. Maladaptive hypoconnectivity of the PAG-mPFC FC

Our data demonstrate that PAG receives discrete streams of cognitive (dmPFC) and emotional (vmPFC) modulatory inputs for pain appraisal and experience, in line with the current understanding of functional specialization of different subregions of the mPFC.[2,14,59] The dmPFC acts in the cognitive appraisal or reappraisal of emotion, whereas the vmPFC serves a regulatory role in generating emotional responses.[12,22] In this study, PAG-dmPFC (BA 9) FC correlated negatively with the sensory subscale (pain quality) of the present PRI (**Fig. 2**), whereas PAG-vmPFC (BA 10) FC correlated weakly with the pain rumination and pain helplessness subscales of the PCS compared with the controls (**Fig. 3B**). The decreased *state*-related PAG-dmPFC FC in PDM (hypoconnectivity) during the MENS phase may denote maladaptive hypofunctioning in cognitive appraisal or reappraisal, which in turn can result in an enhanced experience of pain. This view is supported by a negative correlation between PAG-dmPFC FC and PRI (experience of menstrual pain; **Fig. 2**). Additional discussion about PAG-vmPFC is reported in the Supplementary Text (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154).

4.1.5. PAG-retrosplenium and PAG-cuneus/lingual cortex

The role of the retrosplenial and cuneus/lingual cortex in nociceptive processing is not fully understood despite many reports on the engagement of these structures in pain-imaging studies.[4,33,37,71] It has been suggested that these 2 regions may have connections to the PAG[57] because stimulation of the retrosplenial cortex and visual areas in the rat leads to descending pain modulation for pain alleviation.[58] In this context, the positive correlations between the present pain intensity and PAG-retrosplenium and PAG-occipital area FCs (**Fig. 2**) may implicate a possible similar mechanism in human beings.

Table 5

***State*-related (MENS phase) and *trait*-related (POV phase) periaqueductal gray functional connectivity covaries with pain catastrophizing* in the PDM patients and the contrast of PDM vs control groups.**

Region	BA	*t* score	Peak coordinate		
			x	*y*	*z*
State-related FC (MENS phase)					
Helplessness					
PDM					
Positive					
Precentral gyrus	4	4.78	22	−30	58
Supplementary motor area	6	4.01	−6	−16	64
Postcentral gyrus	1	3.58	10	−36	66
PDM>CON					
Negative					
Premotor cortex, dorsal	6	6.67	−22	−8	70
Rumination					
PDM					
Negative					
Cerebellum	—	4.10	38	−84	−36
Total PCS					
PDM					
Negative					
Cerebellum	—	4.38	38	−86	−40
Trait-related FC (POV phase)					
Total PCS					
PDM>CON					
Negative					
Medial PFC, ventral/ACC	10	3.74	10	52	2
Helplessness					
PDM>CON					
Negative					
Medial PFC, ventral/ACC	10	3.83	10	52	2
Rumination					
PDM>CON					
Negative					
Medial PFC, ventral/ACC	10	3.76	10	52	2
Magnification					
PDM					
Positive					
Fusiform gyrus	20	5.62	56	−38	−26
Posterior parietal cortex	7	5.17	22	−68	46
Premotor cortex, dorsal	6	4.86	−20	−8	66

Peak coordinates refer to the Montreal Neurological Institute space. Significance was set at the uncorrected voxel level $P < 0.005$, followed by family-wise error rate (FWE)-corrected cluster level $P < 0.05$.
* Pain catastrophizing: pain rumination, pain helplessness, and pain magnification scores of the PCS.
ACC, anterior cingulate cortex; BA, Brodmann area; CON, control; FC, functional connectivity; MEN phase, menstruation phase; PCS, pain catastrophizing scale; PDM, primary dysmenorrhea; PFC, prefrontal cortex; POV phase, periovulatory phase.

4.2. Trait changes during the POV stage

4.2.1. Adaptive hypoconnectivity of PAG-PPC FC

The PPC is a critical substrate of the dorsal attention system[19] that participates in the reappraisal of emotion,[12] and its activity is correlated with attention-related pain modulation.[67] The less attentive the subject, the less intense the pain experienced, as effected through opioid mechanisms.[61] This is evidenced by the positive correlation between PAG-PPC FC and the pain magnification subscale of the PCS in PDM (**Fig. 3A**). We observed a hypoconnectivity of PAG-PPC FC (**Fig. 1**); damping

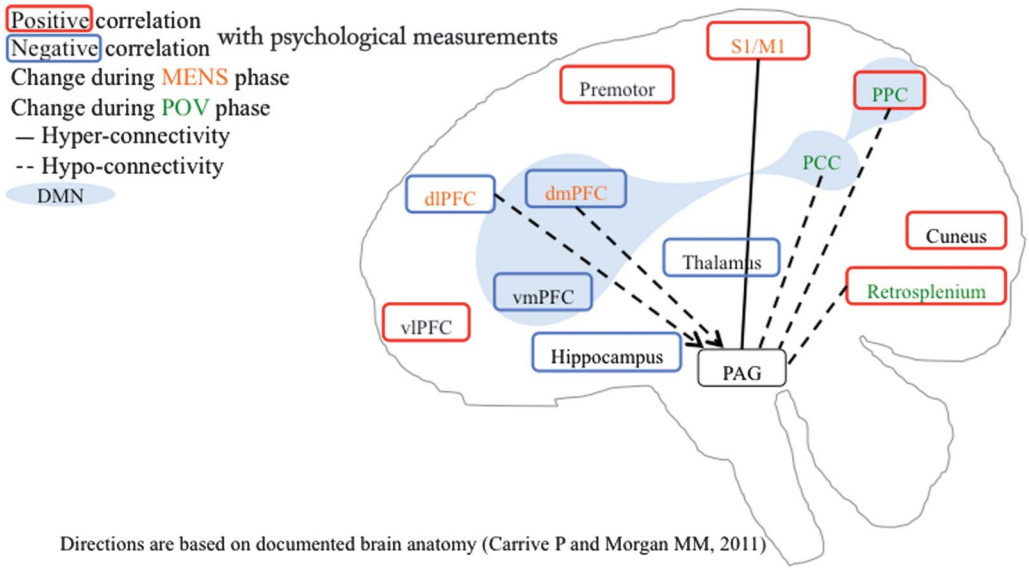

Figure 4. Diagram of altered periaqueductal gray matter networks in primary dysmenorrhea (PDM). The networking between the periaqueductal gray (PAG) and related brain regions was in accordance with the documented brain anatomy and information obtained from functional magnetic resonance imaging and diffusion tensor imaging studies (Supplementary Table 1, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154). Notably, all components of the default mode network (ie, the dorsomedial prefrontal cortex [dmPFC], the posterior cingulate cortex [PCC], and the posterior parietal cortex [PPC]) showed hypoconnectivity with the PAG throughout the menstrual cycle; therefore, these can be regarded as *trait* changes. Moreover, hypoconnectivity of the PAG with the dorsolateral prefrontal cortex (dlPFC), components of descending pain modulatory systems, was also found. In contrast, the only hyperconnectivity of the PAG with the primary somatosensory cortex/primary motor cortex (S1/M1) in PDM mirrored the acute features during the menstruation phase. The functional connectivity (FC) between the PAG and the ventrolateral prefrontal cortex, premotor cortex, S1/M1, PPC, cuneus, and retrosplenium was positively correlated with psychological measurements, whereas the FC between the PAG and the ventromedial prefrontal cortex, dmPFC, dlPFC, thalamus, and hippocampus was negatively correlated with psychological measurements. All these brain regions, except the PCC, are involved in various pain-related cognitive and appraisal components of central pain processing, which might be hallmarks of adaptive or maladaptive neuroplasticity of the endogenous pain control systems in PDM.

the PAG-PPC circuitry (a coping strategy) may be beneficial to subjects with chronic pain.

4.2.2. Maladaptive hypoconnectivity of the PAG-PCC/retrosplenium FCs

The PCC and retrosplenium are the posterior components of the DMN.[30] These structures represent anatomical hubs in the DMN and are connected to all other intrinsic DMN areas. The PCC and retrosplenium are often activated by episodic memory retrieval.[10] Dysfunction of the PCC/retrosplenium is noted in patients with cognitive impairment and/or chronic pain[24]; therefore, the hypoconnectivity of PAG-PCC/retrosplenium FC in PDM (**Fig. 1**) may be a manifestation of chronicity. Notably, all major components of the DMN (ie, the dmPFC, the PCC, and the PPC) showed hypoconnectivity with the PAG throughout the menstrual cycle; therefore, alterations in PAG-DMN FC can be regarded as *trait* changes, possibly a reflection of chronification.

4.2.3. PAG-hippocampus/thalamus FCs as a signature of pain memory

The hippocampus is critical for the central processing of anxiety and long-term memory.[63] The thalamus can be a substrate of the pro-nociceptive pathway[26,37] and can consolidate sensory experience for pain recollection.[20] Our data suggest that PAG modulation has important effects on pro-nociceptive hippocampal and thalamic processing. The strength of PAG-hippocampus FC and PAG-thalamus FC was a strong predictor of the pain rating of the overall recalled pain experience (McGill pain questionnaire at the time of inception): the stronger the FC, the less the evaluation subscale of the PRI (Supplementary Table 5, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154). Interestingly, patients with PDM rated their pain at the inception (by recollective estimation) higher than the actual pain experienced (based on the evaluation dimension but not the sensory or affective dimension; Supplementary Table 3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154), which is in agreement with reports in the literature that chronic patients are inclined to overestimate their mnemonic pain experience.[23]

5. Conclusions

To our knowledge, this is the first study to provide the important and novel insights into the hitherto unexplored dynamics of descending pain modulatory systems in PDM. We present in this neuroimaging study the theory of maladaptive neuroplasticity of the descending pain modulatory systems as a plausible causality linking antecedent long-term PDM to later functional chronic pain disorders. Our data show functional brain imaging signs of acute and chronic pain (**Fig. 4** and Supplementary Table 7, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A154), suggesting that long-term PDM should be considered a unique pain condition with dual features. The chronic features are manifested in the *trait* changes of PAG-DMN hypoconnectivity, which may serve as hallmark of maladaptive neuroplasticity of the descending pain modulatory systems in PDM. The maladaptive changes may contribute to the development of co-occurring functional disorders later in life because such hypoconnectivity has been deemed as a coterminal and

underpinning signature of many functional and chronic pain disorders (eg, migraine,[47] fibromyalgia,[18] and temporomandibular disorder[37]). This study also implicates that tackling moderate to severe PDM vigorously and treating PDM aggressively as early as possible may be of clinical significance to prevent the pain chronification in the brain.[8,31]

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A154.

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