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Brain morphological changes associated with cyclic menstrual pain

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ABSTRACT

Primary dysmenorrhea (PDM) is the most prevalent gynecological disorder for women in the reproductive age. PDM patients suffer from lower abdominal pain that starts with the onset of the menstrual flow. Prolonged nociceptive input to the central nervous system can induce functional and structural alterations throughout the nervous system. In PDM, a chronic viscero-nociceptive drive of cyclic nature, indications of central sensitization and altered brain metabolism suggest a substantial central reorganization. Previously, we hypothesized that disinhibition of orbitofrontal networks could be responsible for increased pain and negative affect in PDM. Here, we further tested this hypothesis. We used an optimized voxel-based morphometry (VBM) approach to compare total and regional gray matter (GM) increases and decreases in 32 PDM patients with 32 healthy age and menstrual cycle matched (peri-ovulatory phase) controls. Abnormal decreases were found in regions involved in pain transmission, higher level sensory processing, and affect regulation while increases were found in regions involved in pain modulation and in regulation of endocrine function. Moreover, GM changes in regions involved in top-down pain modulation and in generation of negative affect were related to the severity of the experienced PDM pain. Our results demonstrate that abnormal GM volume changes are present in PDM patients even in the absence of pain. These changes may underpin a combination of impaired pain inhibition, increased pain facilitation and increased affect. Our findings highlight that longer lasting central changes may occur not only in sustained chronic pain conditions but also in cyclic occurring pain conditions.

1. Introduction

Primary dysmenorrhea (PDM, menstrual pain without pelvic abnormality) is the most common gynecological disorder in the reproductive age. PDM patients suffer from cramping pain in the lower abdomen that starts with the menstruation and lasts for 24–72 h [6]. Between 20% and 90% of female adolescents have experienced PDM, and 15% have had severe pain [11]. The abnormal uterine activity in PDM is thought to be caused by excessive production of prostaglandins and leukotrienes which mediate hyperalgesia and inflammatory pain and cause vasoconstriction, ischemia and myometrial contraction [16]. Evidence point to the presence of central sensitization in PDM as indicated by hyperalgesia, especially in deep tissue, throughout the menstrual cycle [12]. Moreover, during the menstrual period hyperalgesia extends to non-referred pain areas [2].

Prolonged nociceptive input to the central nervous system can induce functional and structural alterations throughout the nervous system and is known to result in central sensitization [23]. Convergent studies have demonstrated that chronic sustained pain of various etiologies is accompanied by structural alterations in brain regions responsible for pain perception, behavior, and modulation [27]. Most studies found areas with significant decreases but not increases [27]. This has led to the notion of maladaptive brain atrophy that may be responsible for development and maintenance of the pain state. On the contrary, acute nociceptive infliction in healthy individuals has been associated with "adaptive plasticity", manifested as regional hypertrophy in pain-related areas [38].

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We recently reported abnormal brain metabolism during PDM pain [39]. Increased regional metabolism was found in orbitofrontal/medial prefrontal regions and left ventral posterior thalamus while decreased regional metabolism mainly was observed in the left dorsolateral prefrontal and sensorimotor regions. These results suggest that disinhibition of the thalamo-orbitofrontal–prefrontal network may underpin enhanced negative affect and altered pain perception in PDM. In addition, a compensatory inhibitory mechanism may account for the hypo-metabolism in sensorimotor areas in face of excessive viscero-nociceptive input.

Taken together, a chronic viscero-nociceptive drive of cyclic nature, indications of central sensitization and enhanced functional brain processing suggest a substantial central reorganization in PDM. Such reorganization may also occur in emotion-related brain regions since PDM, at least in the menstrual phase, can be associated with "state" anxiety, stress, and negative affect [8,14,30]. It is therefore highly possible that PDM is also associated with structural abnormalities in the brain. However, due to the unique cyclic nature of PDM it is unclear if such changes would exhibit a similar pattern of atrophic maladaptive changes as in most sustained chronic pain conditions. In addition, structural changes present in the pain-free state could provide a mechanism by which enhanced pain sensitivity is maintained throughout the menstrual cycle. Based on the above description, we hypothesized that the pain-free state in PDM sufferers would be associated with brain morphological alterations not only in regions responsible for pain transmission but also in regions subserving pain control/emotion regulation. We further hypothesized that regions involved in emotion regulation and regions responsible for disinhibition of pain and emotion regulation would exhibit a positive and a negative relationship with clinical symptoms, respectively.

2. Methods

2.1. Subjects

Thirty-two right-handed PDM patients (23.84 ± 2.99 y/o; pain duration [mean ± SD], 10.19 ± 3.25 years; menstrual duration [mean ± SD], 11.66 ± 2.84 years) and 32 age-matched right-handed healthy female subjects (23.81 ± 2.80 y/o; menstrual duration [mean ± SD], 11.78 ± 2.57 years) participated in the study. All participants were university students, university graduates or students of graduate school. Patients were recruited from the outpatient clinics of Department of Obstetrics and Gynecology of Taipei Veterans General Hospital. One gynecologist (HTC) screened all the patients and confirmed the PDM diagnosis. The patient inclusion criteria were (1) a regular menstrual cycle around 27–32 days; (2) a duration of PDM longer than 6 months; and (3) cramping pain during menstruation in the last 6 months rated higher than 4 on a visual analogue scale (0 = not at all, 10 = the worst pain). The inclusion criteria for healthy control subjects were similar to the patients but without menstrual pain symptoms. Exclusion criteria for all subjects were pathological pituitary gland disease, organic pelvic disease, psychiatric disorder, childbirth, positive pregnancy test, immediate planning for pregnancy, and having metal/pacemaker implant. The participants were devoid of oral-contraceptive drugs within 6-months prior to magnetic resonance imaging (MRI). Neither analgesics nor antidepressant was taken 24 h before the MRI scanning. Twenty-one PDM patients had previously had sickness absenteeism from school/work. Twenty patients took non-steroidal anti-inflammatory drugs only during menstrual period for pain management. Five patients adopted non-medicinal approaches, e.g., hot compression and shower, for pain relief. The rest did not receive any active intervention. All participants gave their written informed consent to the protocol, which had been approved by the Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Psychological assessment

The recalled overall experience of lower abdominal menstrual pain of each PDM patient was assessed by the McGill pain questionnaire (MPQ), administered during the inception interview. Note that assessment of pain threshold and hyperalgesia was not performed in PDM patients or in healthy controls. The Spielberger state-trait anxiety inventory (STAI) and Center for Epidemiologic Studies-Depression scale (CES-D) were administered prior to MRI scanning to evaluate the subject's anxiety and depression level.

2.3. Image acquisition

We obtained T1-weighted, 3D gradient-echo anatomical MRI using a 3D-FSPGR sequence (TR = 8.548 ms, TI = 400 ms, flip angle = 15°, matrix = 256 × 256 × 124, in-plane field of view [FOV] = 260 × 260 × 1.5 mm^3) on a 1.5 T MRI scanner (Excite, GE Inc., USA). The scan was performed during the subject's pain-free peri-ovulatory period (i.e., the 12th–16th day of their menstrual cycles [MC]) to address *trait-related* morphological information without overt acute pain confrontation (*state-related*). Urine kits for luteinizing hormone were used to verify that the subjects were scanned during their peri-ovulatory period [19,20]. Fifty percent of the patients were scanned in the pre-ovulatory period, 12.5% on the ovulation day, and 37.5% in the post-ovulatory period. 62.5% of the controls were scanned in the pre-ovulatory period, 6.25% on the ovulation day, and 31.25% in the post-ovulatory period. Shimming of the magnetic field was performed prior to MRI scanning and tri-pilot images were used for the adjustment of the location of FOV. Subjects laid with their eyes closed inside the scanner and were instructed to not move during the scan.

2.4. Data processing and statistics

The T1-MRI images were processed using a modified optimized voxel-based morphometry (VBM) protocol [13] in Statistical Parametric Mapping 8 (SPM8, Wellcome Trust Center for Neuroimaging, Institute of Neurology, University College London, London, UK), running under Matlab 2008a (Mathworks Inc., Sherborn, MA, USA). The gray matter (GM) compartment was first segmented out using the New Segment toolbox, an optimized GM template was then created using the DARTEL toolbox with default settings. The individual GM images were then normalized to the optimized template and transformed to standard space according to the registration parameters and deformation maps. Tissue volume was preserved by modulating voxel value in the GM images (by multiplying the Jacobian determinants). These volume-corrected GM images were further smoothed with a 3D Gaussian kernel (FWHM = 8 mm) prior to statistic analysis.

Factorial comparison was performed between PDM and control groups using SPM8. Age and total GM volume variance across subjects were treated as covariates of no-interest ("nuisance" covariates) and were removed by analysis of covariance. Any voxel with a GM value <0.2 was excluded to keep homogeneity and evade the possible edge effect around the border demarcating the GM and white matter (WM). The *t*-maps were transformed into *z*-maps. Since a priori knowledge existed for the pain matrix engaged in visceral pain and menstrual pain (i.e., medial and dorsolateral prefrontal, orbitofrontal, somatosensory, insular, and cingulate cortices; thalamus, hypothalamus, and basal ganglia [7,39]), an uncorrected voxel threshold of $p < 0.005$ and an extend

threshold of 100 voxels (uncorrected cluster-based $p < 0.322$) were used for thresholding.

To disclose the possible relationship between the morphological alterations and PDM duration (in years) as well as recalled pain experience, we conducted a 2-step correlation analysis for patients: (1) statistical maps from the group comparisons were used as an inclusive mask to test for a correlational relationship within these regions (uncorrected $p < 0.005$). To further test for trends in the data, a lowered threshold was also applied ($p < 0.01$). (2) Whole-brain correlation analysis to disclose the brain regions relevant to these factors (uncorrected $p < 0.005$ with extend threshold of 100 voxels). Anatomical structures of cluster maxima were labeled in Talairach space using the Talairach Client (http://www.talairach.org/client.html). The coordinates were transferred from MNI space into Talairach space using min2tal.m, an extension program for coordinate transformation (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

Difference in total GM volume between groups was examined by a two-sample *t*-test using SPSS 13.0 (SPSS Inc., USA). The relationship between total GM volume and patient's PDM duration (in years) was examined with a 2-tailed Pearson correlation analysis. Results were considered significant when passing $p < 0.05$.

3. Results

3.1. Psychological data

The MPQ scores ascertained that PDM patients had experienced severe menstrual pain (total score [range, 0–78]: 37.09 ± 11.39; recalled menstrual pain intensity [range, 0–5], 3.47 ± 1.02). As expected and in agreement with our previous study [39], "state" anxiety (score ranges: 20–80; patients: 37.69 ± 6.98, controls: 37.84 ± 7.85, $p = 0.933$), "trait" anxiety (score ranges: 20–80; patients: 43.41 ± 8.31, controls: 41.38 ± 7.64, $p = 0.312$), and depression scores (score ranges: 0–60; patients: 13.50 ± 6.70, controls: 12.19 ± 8.15, $p = 0.484$) did not differ significantly between groups.

3.2. Global difference in brain morphometry

The anatomical MRIs of both patient and control groups were visually inspected by an experienced neuroradiologist (TCY), and all anatomical images included in the analysis were found to be normal (without any macroscopic abnormality). No significant difference was found in total GM volume between patient and control groups (patient: 658.49 ± 50.07 ml; control: 674.23 ± 42.64 ml; $p = 0.181$). No significant correlation was found between total GM volume and patient's PDM duration ($p = 0.549$).

3.3. Regional difference between groups

PDM patients disclosed increased regional GM volume in the right posterior hippocampus/parahippocampus (Fig. 1A), anterior/dorsal posterior cingulate cortex (ACC/dPCC, Brodmann area [BA] 23/24) along the cingulate gyrus, dorsal midbrain (periaqueductal gray [PAG]), hypothalamus (Fig. 1C), left ventral portion of precuneus (BA 31; Fig. 1D), left superior/middle temporal gyrus (STG/MTG, BA 22; Fig. 1E), and right cerebellar tonsil (Table 1). PDM patients demonstrated regional GM volume reduction in the

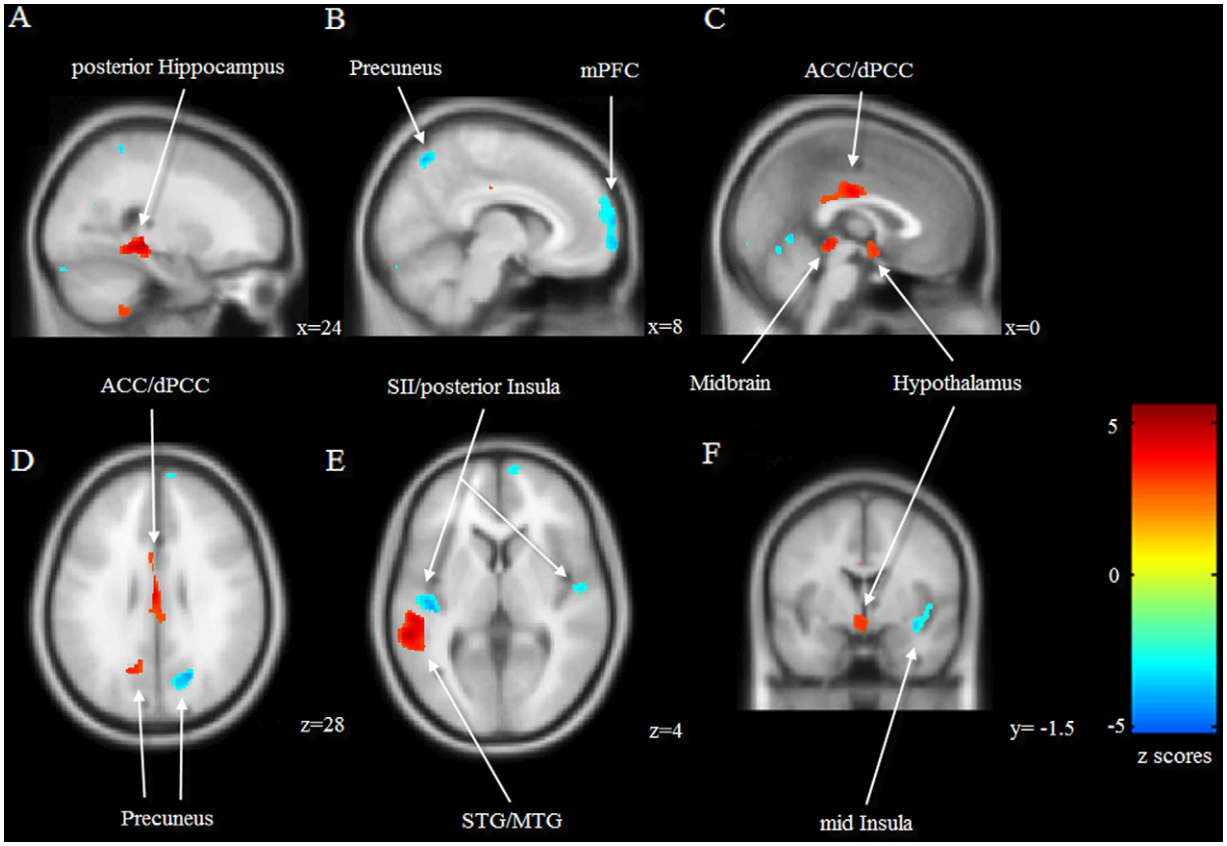

Fig. 1. Significant regional gray matter volume changes in PDM patients. Morphological changes in PDM patient were associated with increased GM volume in the (A) right posterior hippocampus; (C) anterior/dorsal posterior cingulate cortex (ACC/dPCC, BA 23/24), midbrain, and hypothalamus; (D) left ventral portion of precuneus (BA 31), (E) left superior/middle temporal gyrus (STG/MTG, BA 22). Decreased GM volumes were observed in the (B) right central portion of precuneus (BA 7) and medial prefrontal cortex (mPFC, BA 10); (D) right ventral portion of precuneus (BA 7/31); (E) bilateral secondary somatosensory cortex (SII)/posterior insula; (F) mid insula (13). The results are superimposed on the SPM T1 template, and red/blue colors represent increased/decreased volume.

Table 1
Significant gray matter volume change between groups.

Patient > control							Patient < control						
				Coordinate							Coordinate		
Anatomical area	BA	Size	Z_{max}	*x*	*y*	*z*	Anatomical area	BA	Size	Z_{max}	*x*	*y*	*z*
L STG/MTG	22	1861	5.01	−53	−39	−5	L SII/post insula	13	837	4.38	−45	−22	10
L ACC/dPCC	23/24	572	3.9	−3	−15	30	R SII/post insula	13	112	2.99	54	−10	6
L Precuneus	31[#]	316	3.41	−15	−55	24	R Precuneus	7/31	433	3.83	21	−67	28
R Parahippo G	27	1174	4.37	24	−30	−5	R Precuneus	7	301	3.75	6	−67	56
L Midbrain		146	3.56	−2	−36	−6	R med frontal G	10[*]	773	3.82	6	69	12
L Hypothalamus		218	3.15	−5	−4	−6	R STG/mid insula	38/13	260	3.47	36	0	−12
R Cerebellar tonsil		427	3.24	32	−40	−51	R sup parietal L	5	118	3.16	24	−46	65
							R Culmen		214	3.57	15	−90	−23
							R Cerebellar tonsil		231	3.77	−18	−40	−45

BA, Brodmann area; size, number of voxels in the cluster; Z_{max}, peak *Z* value; L, left; R, right; sup, superior; med, medial; post, posterior; G, gyrus; L, lobule; SII, secondary somatosensory cortex; ACC, anterior cingulate cortex; dPCC, dorsal posterior cingulate cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus; Parahippo, parahippocampal. Note that the depicted regions survived a spherical small-volume correction, radius = 8 mm, at $p < 0.05$.
[*] Denotes negative correlation with pain experience at $p < 0.005$.
[#] Denotes positive correlation with pain experience at $p < 0.01$.

right medial frontal gyrus within medial prefrontal cortex (mPFC, BA 10), right central portion of precuneus (BA 7; Fig. 1B), right ventral portion of precuneus (BA 7/31; Fig. 1D), bilateral secondary somatosensory cortices [SII]/posterior insula (BA 13; Fig. 1E), right STG/mid insula (BA 38/13; Fig. 1F), right culmen, and left cerebellar tonsil (Table 1).

3.4. Correlation analysis

Only the GM volume of a single region from the group comparison was found to correlate with clinical parameters at $p < 0.005$ (Table 1). The GM volume of right superior frontal gyrus within mPFC (BA 10) was negatively correlated with MPQ scores (cluster peak [*x*, *y*, *z*] = 11, 63, 30; $Z = 3.28$; spatial extend: 8 voxels). At a lowered threshold ($p < 0.01$), the GM volume of left precuneus (cluster peak = −12, −57, 21; $Z = 2.52$; spatial extend: 15 voxels) correlated positively with MPQ scores.

For the whole-brain analysis, the correlation between regional GM volume and PDM patient's MPQ scores revealed a positive correlation in the right ACC/dPCC and rectal gyrus within bilateral mOFC (BA 11). Negative correlation was found in the superior frontal gyrus within bilateral dorsolateral PFC (dlPFC, BA 8 and BA 9/10), right precentral gyrus within premotor cortex (BA 6) and right inferior frontal gyrus within lateral OFC [lOFC]/anterior insula (BA 47/13) (Table 2 and Fig. 2A). For patient's PDM duration, positive correlation with regional GM volume was observed in the right STG/MTG (BA 22), right inferior temporal gyrus (BA 20) and rectal gyrus within right medial orbitofrontal cortex (mOFC, BA 11). Negative correlation was noted in the left superior parietal lobule (BA 5), left postcentral gyrus (primary somatosensory cortex [SI], BA 2/3), right central precuneus (BA 7), and left putamen (Table 2 and Fig. 2B).

4. Discussion

In the present study, VBM was used to investigate total and regional GM volume increases and decreases in the brain of PDM patients relative to healthy matched controls. Our results demonstrate that abnormal GM changes are present in PDM patients in their pain-free state. The regions exhibiting morphological changes comprised a constellation of discrete, but interacting, systems involved in pain processing. Abnormal decreases were found in regions involved in pain transmission, higher level sensory processing, and affect regulation while increases were found in regions involved in pain modulation and in regulation of endocrine function. Moreover, GM changes in key regions involved in top-down pain modulation and in generation of negative affect were related to clinical symptoms.

4.1. Gray matter decreases in PDM patients

The regions exhibiting GM decreases subserve in part visceral sensation and emotion-laden pain regulation. Both SII/posterior insula and mid-anterior insula receive afferents from visceral organs and appear to be important for the integration of sensory information with pain affect [5,7]. The mPFC substantially contribute to inhibitory modulation of the affective state in addition to the visceromotor control [21]. The negative correlation between pain

Table 2
Regional gray matter volumes covarying with total MPQ score and pain duration in PDM patients.

Positive correlation							Negative correlation						
				Coordinate							Coordinate		
Anatomical area	BA	Size	Z_{max}	*x*	*y*	*z*	Anatomical area	BA	Size	Z_{max}	*x*	*y*	*z*
Total MPQ score													
R ACC	24	117	4.08	9	2	36	L sup frontal G	9/10	623	3.98	−21	50	27
R Rectal G	11	944	3.78	6	33	−17	R sup frontal G	8	303	3.29	24	38	51
L Rectal G	11	515	3.3	−11	14	−21	R Precentral G	6	745	3.75	62	5	13
							R inf frontal G	47/13	112	3.66	47	27	9
Pain duration													
R STG/MTG	22	550	4.4	68	−39	15	L sup parietal L	5	293	4.28	−23	−42	64
R inf temporal G	20	629	4.24	66	−30	−26	L Postcentral G	2/3	491	3.66	−54	−27	42
R Rectal G	11	454	4.23	12	26	−24	R Precuneus	7	159	3.56	27	−72	39
							L Putamen		214	2.84	−26	11	3

Inf, inferior. See Table 1 for other abbreviation details. Note that the depicted regions survived a spherical small-volume correction, radius = 8 mm, at $p < 0.05$.

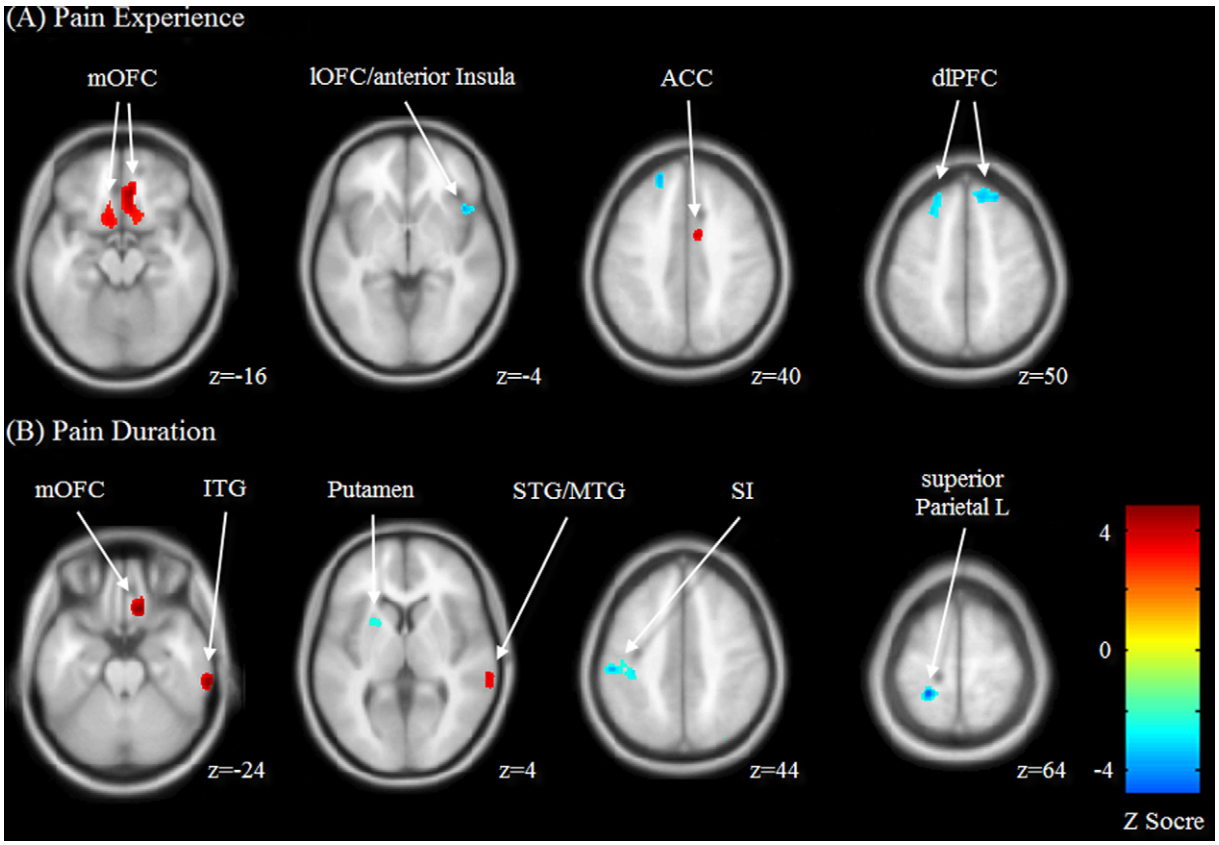

Fig. 2. Regional gray matter volumes covarying with the menstrual pain experience (total MPQ scores) and duration (in years) in PDM patients. (A) Bilateral medial orbitofrontal cortices (mOFC, BA 11) and right anterior cingulate cortex (ACC) covaried positively with the menstrual pain experience while bilateral dorsolateal prefrontal cortices (dlPFC) and right lateral OFC (lOFC)/anterior insula covaried negatively with the menstrual pain experience. (B) The right mOFC, inferior temporal gyrus (ITG, BA 20), and superior/middle temporal gyrus (STG/MTG, BA 22) covaried positively with the menstrual pain duration while left putamen, primary somatosensory cortex (SI), and superior parietal lobule covaried negatively with the menstrual pain duration. Results are superimposed on SPM T1 template. Red and blue colors represent significant positive and negative correlation, respectively.

scores and mPFC volume suggests abnormal disinhibition of regions contributing to the generation of the pain experience. Regions in the posterior medial wall corresponding to the anterior–ventral and central precuneus also exhibited GM decreases. Functionally, precuneus can be segregated into anterior sensorimotor functions, central cognitive functions, and posterior visuo-spatial functions [3,26]. The anterior portion is known to be structurally and functionally connected to regions also exhibiting decreased GM volume in the present study, including SII/posterior insula, the superior parietal lobe, and the superior temporal gyrus [26]. The central precuneus exhibits, among others, connectivity with dorsomedial and dorsolateral prefrontal cortices [26]. These findings are in part in accordance with the present study and our study on brain metabolic changes during menstrual pain in which hypometabolism was observed in bilateral SII/posterior insula and hyper-metabolism in mPFC [39].

Recurrent and inevitable PDM distress may partially account for the reduced GM observed [42]. We have previously shown that state anxiety is substantially elevated during menstrual pain [39]. In animal models, atrophic changes in mPFC under repeated stress have been reported [33]. Patients with bipolar disorder and post-traumatic stress disorder also revealed reduced volumes in mPFC and insula [4,25,31]. Functionally, the posterior insula response to visceral pain has also been shown to be sensitive to stress [34]. It is thus conceivable that the GM decreases constitute a response to the excessive cyclic viscero-sensory input that occurs in PDM and that this represents a compensatory response.

4.2. Gray matter increases in PDM patients

The regions exhibiting GM increases constitute in part the neural circuitries subserving modulation of aversive responses and endocrine function. The hypothalamus is particularly interesting since it has the potential to influence menstrual pain through interacting pathways. First, the hypothalamus plays a decisive role in a feedback loop that regulates the menstrual cycle. Through the hypothalamic–pituitary–gonadal axis the hypothalamus responds to elevated estrogen levels. Interestingly, in the late phase of the menstrual cycle an abnormal elevated estrogen level has been found in PDM but without any known effect on hypothalamus [43]. Estrogen plays a central role in regulating uterine prostaglandin synthesis [15]. Thus, concomitant with increased prostaglandin release resulting in pain, a periodic increased estrogen assault on hypothalamus may also take place. It can be hypothesized that such an assault could result in longer lasting reactive structural changes.

The second possible role of hypothalamus in menstrual pain is through regulation of the stress system. PDM is thought to be aggravated, but not generated, by emotional stress [42]. Abnormal hippocampal feedback to hypothalamus has been hypothesized as a generating mechanism [40]. As a target for stress hormones hippocampus is in itself a region that is sensitive to stress [29]. Congruent with this hippocampal hypertrophy was found in this study. Also, cortisol released via the hypothalamic–pituitary–adrenal axis has been found to vary across the menstrual cycle in

women with PDM with the highest level during the menstrual phase [18]. However, no relationship was found between cortisol levels and menstrual pain [18].

A third plausible pathway involves the spino-bulbo-spinal loop which is a pain modulatory pathway that may lead to enhanced negative affect and pain amplification [37]. Key components of this circuit include hypothalamus and PAG. Other regions providing cortical feedback to this loop include amygdala, hippocampus and ACC. The ACC/dPCC, a hypertrophic region in this study, is a region consistently associated with pain responses in chronic pain patients [41]. Another region more loosely connected to this circuit is the ventral precuneus/PCC which also exhibited hypertrophy and a positive correlation with the pain experience. The ventral precuneus/PCC has anatomical connections to ACC, medial temporal regions, as well as to dorsal medial frontal cortex [3,26]. It is thought to subserve self-referential cognitive and emotional processing [3,41]. Unlike the regions mentioned above, we had no strong a priori hypothesis for the hypertrophy observed in STG/MTG and cerebellum. It is however important to mention that although their role in pain processing remains to be elucidated they are frequently found in studies on central processing of pain.

4.3. Gray matter changes and clinical symptoms

A particular noteworthy finding in the present study is on the one hand the negative correlation between the GM volumes of bilateral dlPFC and pain scores and on the other hand the positive correlations between bilateral mOFC and ACC with pain scores. A dysfunctional dlPFC, a region important for top-down pain control, has been implicated in disinhibition of orbitofrontal networks including ACC which may lead to enhanced negative affect [1,24]. The particular relationship with pain scores suggests that such a mechanism may contribute to the cause of pain rather than being the consequence of pain [35]. In chronic back pain an inverse relationship was found between bilateral dlPFC and pain duration suggesting top-down disinhibition via dlPFC to be a key mechanism [1]. The right lateral posterior portion of OFC/anterior insula also showed an inverse relationship with pain scores. This region is known to subserve polymodal integration including integration of viscero-sensory information which is further processed in medial orbitofrontal areas [21]. Our finding suggests a compensatory mechanism in face of excessive input.

Considering correlations with PDM duration, somatosensory regions primarily exhibited a negative relationship. A positive relationship was found with mOFC as mentioned above and with a region located in the vicinity of the temporo-parietal junction. The latter region has been implicated in attentional reorientation [17] and more importantly in identifying and attending to salient features of the sensory environment [9]. The region responds tonically to sustained pain or stimuli of tonic salience [9]. It can be hypothesized that structural alterations in this region occur as a consequence of extended periods of highly salient PDM pain.

4.4. Methodological considerations

Macroscopic changes detected with VBM may arise from different types of alterations on the microscopic level. Conventionally, hypotrophy and hypertrophy have been ascribed to neuronal apoptosis and genesis, respectively. However, several other factors are also likely to contribute such as changes in e.g., cell size, spine/synapse density, microglia, blood flow, and interstitial fluid [28,32,36]. With the current MRI techniques the specific contribution of these factors cannot be determined and results have to be interpreted with caution.

The limited number of studies on morphological changes in chronic pain has yielded different findings [36], although some overlap has been described [28]. The majority of the studies only reported regionally decreased GM volumes [36] compared to decreases and increases in this study. In one study on fibromyalgia, GM changes were found in several similar regions as in this study including medial prefrontal cortex, parahippocampus and ACC/dPCC albeit with volume decreases for the latter two [22]. A substantial portion of the variability may be attributed to factors such as the etiology of the pain, frequency of pain episodes, pain duration, age and gender of the study population, and medication. For example, it has previously been suggested that a young study population, as in this study, could result in predominantly increased GM volumes [36].

Neuroplasticity can be considered either adaptive or maladaptive. Previous neuroimaging studies reported that regional GM volume can increase rapidly within a short time period (days to months) as reactive plasticity to regular nociceptive input and intensive exercise/learning [10,38]. Such changes may be considered to the benefit of the individual. However, when changes maintain or exacerbate a state that is not to the benefit of the individual they have become maladaptive. In context of chronic pain, protracted nociceptive input may result in decreased inhibition or increased facilitation.

5. Conclusions

Our results demonstrated that abnormal GM changes were present in PDM patients even in the absence of pain. This shows that not only sustained pain but also cyclic occurring menstrual pain can result in longer lasting central changes. Although the functional consequences remain to be established these results indicate that the adolescent brain is vulnerable to menstrual pain. Longitudinal studies are needed to probe hormonal interaction, fast-changing adaptation (intra-menstrual cycle) and whether such changes are reversible or not.

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