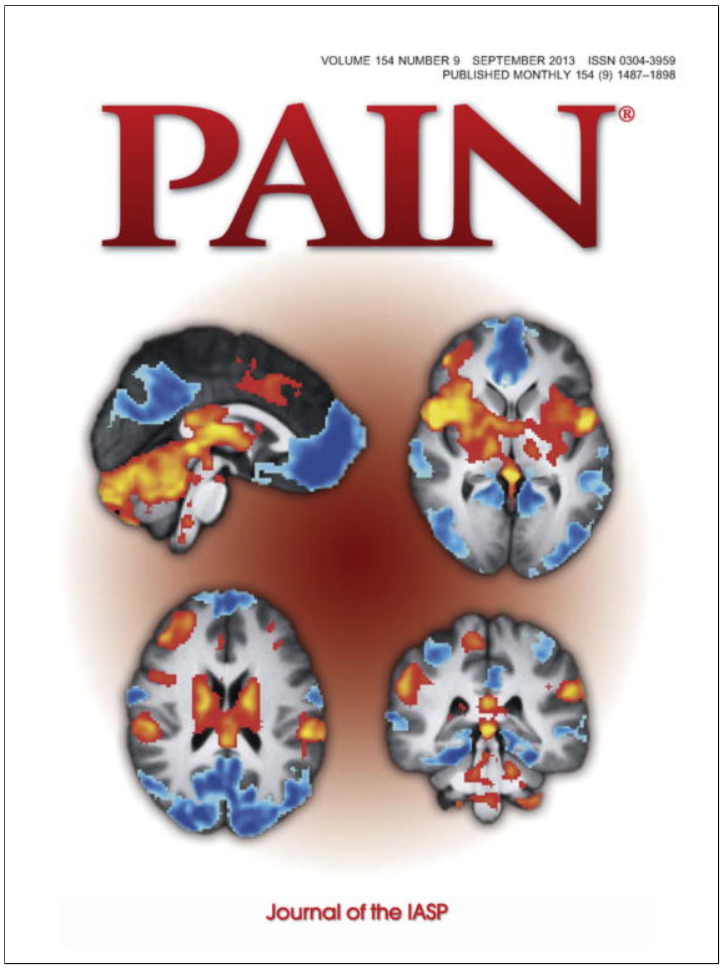

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Menstrual pain is associated with rapid structural alterations in the brain

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ABSTRACT

Dysmenorrhea is the most prevalent gynecological disorder in women of child-bearing age. Dysmenorrhea is associated with central sensitization and functional and structural changes in the brain. Our recent brain morphometry study disclosed that dysmenorrhea is associated with trait-related abnormal gray matter (GM) changes, even in the absence of menstrual pain, indicating that the adolescent brain is vulnerable to menstrual pain. Here we report rapid state-related brain morphological changes, ie, between pain and pain-free states, in dysmenorrhea. We used T1-weighted anatomic magnetic resonance imaging to investigate regional GM volume changes between menstruation and periovulatory phases in 32 dysmenorrhea subjects and 32 age- and menstrual cycle-matched asymptomatic controls. An optimized voxel-based morphometry analysis was conducted to disclose the possible state-related regional GM volume changes across different menstrual phases. A correlation analysis was also conducted between GM differences and the current menstrual pain experience in the dysmenorrhea group. Compared with the periovulatory phase, the dysmenorrhea subjects revealed greater hypertrophic GM changes than controls during the menstruation phase in regions involved in pain modulation, generation of the affective experience, and regulation of endocrine function, whereas atrophic GM changes were found in regions associated with pain transmission. Volume changes in regions involved in the regulation of endocrine function and pain transmission correlated with the menstrual pain experience scores. Our results demonstrated that short-lasting cyclic menstrual pain is associated not only with trait-related but also rapid state-related structural alterations in the brain. Considering the high prevalence rate of menstrual pain, these findings mandate a great demand to revisit dysmenorrhea with regard to its impact on the brain and other clinical pain conditions.

1. Introduction

Dysmenorrhea (menstrual pain with or without pelvic abnormality) is a widely presented gynecological disorder for women in the child-bearing age. Epidemiological studies reported that 40% to 90% of female adolescents have experienced dysmenorrhea, and ~15% have had severe pain [12]. Absenteeism from work due to severe dysmenorrhea caused tremendous socioeconomic loss in the United States alone [10]. Females with dysmenorrhea suffer from disabling, cramping pain emanating from the lower abdomen with the onset of menstrual flow that persists for 24 to 72 hours [30]. Recent studies further disclosed that central sensitization exists in dysmenorrhea because hyperalgesia spans different spinal segments and multiple tissue systems (eg, skin and muscle) and extends to nonreferred pain areas during the menstrual phase [3,13]. Moreover, dysmenorrhea is often comorbid with irritable bowel syndrome (IBS) and fibromyalgia [30], which are 2 clinical

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pain conditions with central sensitization [7,32] and a greater prevalence in females [8,22]. Clinical symptoms have also been found to be increased in IBS patients with dysmenorrhea, and the treatment of dysmenorrhea can improve the symptoms of IBS [1,14]. Thus, dysmenorrhea may not only affect the subject's quality of life but may also affect other clinical pain conditions.

Due to its cyclical nature of pain and pain-free states, dysmenorrhea provides a unique opportunity to study both trait- and state-related brain alterations in response to spontaneous recurrent pain. Where state-related changes are associated with the presence of menstrual pain, trait-related changes exist even in the absence of symptoms. We recently reported abnormal state-related functional and trait-related structural brain alterations in dysmenorrhea [28,29]. Our positron emission tomography study findings suggested that disinhibition of a thalamo-orbitofrontal prefrontal network may promote central sensitization in dysmenorrhea during menstruation. In addition, 1 recent functional magnetic resonance imaging (MRI) study of dysmenorrheic women corroboratively disclosed trait-related functional alterations in the central processing of experimentally induced heat pain [31]. Results from our optimized voxel-based morphometry (VBM) analysis disclosed that trait-related gray matter (GM) volume changes in regions involved in top-down pain modulation and in the generation of negative affect were related to the severity and the duration of the experienced menstrual pain. It remains unknown whether the state-related functional changes are paralleled by rapid state-related structural alterations of the brain.

Experimental acute nociceptive input may result in rapid changes in both regional brain responses and regional GM volumes within weeks [5,26]. Such alterations may mirror changes in pain perception. Other clinical studies further reported that the functional and structural alterations may partially revert after the nociceptive input has been terminated [21,24]. It is conceivable that state-related structural alterations exist in dysmenorrhea and that these, at least partially, overlap with the regions exhibiting trait-related alterations. Hence, in the present study, we investigated regional GM alterations between menstrual phases, ie, the symptomatic and asymptomatic states, in dysmenorrhea subjects and in asymptomatic controls. The possible relationship between regional GM volume differences and severity of menstrual pain was also probed. Based on our previous studies, we reasoned that state-related changes may exist in brain areas involved in pain modulation, pain transmission, affective experience generation, and regulation of endocrine function.

2. Methods

2.1. Subjects

Thirty-two right-handed dysmenorrhea subjects and 32 right-handed asymptomatic female controls, matched for both calendar age and gynecological age, participated in the present study (Table 1). All participants were college or graduate school students or college graduates. The dysmenorrhea subjects were screened and the diagnosis was confirmed at the outpatient clinics of Department of Obstetrics and Gynecology, Taipei Veterans General Hospital. The inclusion criteria for the dysmenorrhea group were a regular menstrual cycle ~27 to 32 days, the first occurrence of menstrual pain within the first 2 years of menarche, and average cramping pain level in the past 6 months rated >4 on a verbal numerical scale (0 = not at all, 10 = the worst imaginable pain). For asymptomatic controls, the inclusion criteria were similar to the dysmenorrhea subjects but without menstrual pain. Exclusion criteria for all subjects were chronic pain disorders, pathological pituitary gland disease, organic pelvic disease, psychiatric disorder, childbirth, positive pregnancy test results, immediate planning for pregnancy, and having metal/pacemaker implant. No oral contraceptives and analgesics/antidepressant should have been taken within 6 months and 24 hours before the MRI scanning, respectively. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, and written informed consent was obtained from all subjects.

Table 1
Demographic and behavioral data.

	Dysmenorrhea (n = 32)	Control (n = 32)	P Value (2 tailed)
Age, y			
Calendar	24.40 ± 3.23	23.75 ± 2.68	.380
Gynecological	12.16 ± 2.87	11.44 ± 2.64	.302
STAI-state (range, 20–80)			
MC phase	47.31 ± 11.23[a]	34.41 ± 7.92	.000[b]
OV phase	28.56 ± 7.87[a]	36.63 ± 7.94	.331
STAI-trait (range, 20–80)			
MC phase	45.59 ± 8.36	38.28 ± 7.67	.001[b]
OV phase	44.25 ± 8.44	39.69 ± 7.38	.025[c]
CES-D (range, 0–60)			
MC phase	17.81 ± 9.30[a]	9.75 ± 7.24	.000[b]
OV phase	12.88 ± 6.93[a]	10.34 ± 0.85	.182
Menstrual pain experience			
Pain history, y	10.31 ± 3.30	–	–
Absenteeism, %	59.3	–	–
Drug taken, %	56.5	–	–
MPQ total scores			
Recalled	36.06 ± 11.29	–	–
Current	35.06 ± 13.22	–	–

CES-D, Center for Epidemiologic Studies–Depression Scale; MC, menstruation; MPQ, McGill Pain Questionnaire; OV, periovulatory; STAI, Spielberger State-Trait Anxiety Inventory.
[a] Significant differences between 2 phases within 1 group at $P < .001$.
[b] Significant differences between 2 groups at $P < 0.001$.
[c] Significant differences between 2 groups at $P < 0.05$.

2.2. Image acquisition

All subjects received underwent 2 T1-weighted, 3-dimensional gradient-echo anatomic MRI scans using a 3-dimensional fast spoiled gradient recall sequence (TR = 8.548 ms, TI = 400 ms, flip angle = 15°, matrix = 256 × 256 × 124, in-plane field of view = 260 × 260 × 1.5 mm^3) on a 1.5-T MRI scanner (Excite; GE Healthcare Inc., Milwaukee, WI). One scan was performed in the menstruation phase (MC phase, days 1–3 of the menstrual cycle), whereas the other scan was performed in the periovulatory phase (OV phase, days 12–16 of the menstrual cycle). The scan order in each group was counterbalanced among the subjects. Lower abdominal cramping pain should be present during the MC but not the OV phase in dysmenorrhea subjects. Urine kits for luteinizing hormone were used to verify ovulation during the OV phase for each subject. Shimming of the magnetic field was performed before MRI scanning, and tripilot images were used for the adjustment of the location of the field of view. Subjects laid with their eyes closed inside the scanner and were instructed to not move during the scan.

2.3. Psychological assessment

Using the McGill Pain Questionnaire, we assessed the recalled overall and current experience of lower abdominal menstrual pain for each dysmenorrhea subject during the inception interview and before MRI scanning in the MC phase, respectively. The Spielberger State-Trait Anxiety Inventory and Center for Epidemiologic Studies-Depression scale were administered before MRI scanning in

both the MC and OV phases to evaluate subjects' anxiety and depression status.

2.4. Imaging preprocessing

The magnetic resonance images were preprocessed using the same procedure as that used in our previous study [28]. In brief, the GM images were segmented from the individual anatomic images, normalized with the optimized template into standard Montreal Neurological Institute space, modulated with Jacobian determinants, and smoothed with a 3-dimensional Gaussian kernel (full width at half maximum = 8 mm) for statistical analysis using Statistic Parametric Mapping 8 (Wellcome Trust Center for Neuroimaging, University College London, London, UK). Any voxel with a GM value <0.2 was excluded to keep homogeneity and avoid a possible edge effect around the border demarcating the GM and white matter.

2.5. Statistical analysis

Differences in anxiety scores, depression scores, and total GM volume within and between groups were examined by a 2-tailed paired *t* test and 2-sample *t* test using SPSS 17.0 (SPSS Inc., Chicago, IL), respectively. Results were considered significant when $P < .05$.

For the VBM analysis, we applied a general linear model using Statistic Parametric Mapping 8 to test the possible state-related morphological changes. We constructed a statistical model using repeated-measures analysis of variance and included the interaction effect between group and phase. State-related changes were then specifically assessed with 1-tailed *t* tests between the 2 phases within each group. The age, total GM volume, state anxiety scores, and depression scores were input as covariates of no interest. To minimize the possible interference from gonadal hormone changes, we also performed 1-tailed *t* tests between groups for menstrual phase differences (ie, dysmenorrhea [MC vs OV] vs control [MC vs OV]) with all 4 covariates of no interest. A correlation analysis was also performed between GM differences (voxelwise subtracted between 2 phases) and current menstrual pain experience scores in dysmenorrhea subjects, with the differences of state anxiety and depression scores between phases as covariates of no interest.

Because a priori knowledge existed for the brain regions engaged by menstrual pain, we selected several spherical regions of interest (ROIs) (radius = 12 mm) centered at previously reported peak locations [28,29] (Supplementary Table 1). The GM changes in these ROIs were deemed significant when passing an uncorrected voxel threshold of $P < .005$ followed by a family-wise error correction *P* value of <.05 with a small volume correction. The coordinates of cluster maxima were transferred from standard Montreal Neurological Institute space into Talairach space using mni2tal.m (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/), and the anatomic structures were labeled using the Talairach Client (http://www.talairach.org/).

3. Results

3.1. Behavioral assessments

All 32 dysmenorrhea subjects had a long history of menstrual pain (mean ± SD = 10.31 ± 3.30 years). The menstrual pain lasted between 1 and 3 days within a single cycle (mean ± SD = 1.61 ± 0.60 days). The McGill Pain Questionnaire scores confirmed that dysmenorrhea subjects had experienced severe menstrual pain (recalled overall experience: 36.06 ± 11.29; current experience: 35.06 ± 13.22). Nineteen dysmenorrhea subjects (59.3%) reported absence from school or work due to menstrual pain, and 18 dysmenorrhea subjects (56.5%) reported occasional self-medication with over-the-counter analgesics (Table 1). In control subjects, no menstrual-related pain was reported. Twelve control subjects (37.5%) reported mild to moderate discomfort in the lower back and 5 control subjects (15.6%) reported mild to moderate swelling of the inner thigh. Only 3 controls reported occasional mild menstruation-related diarrhea. No menstruation-related vomiting and nausea were reported in controls.

During the MC phase, the state anxiety (dysmenorrhea: 47.31 ± 11.23, control: 34.41 ± 7.92, $P < .001$), trait anxiety (dysmenorrhea: 45.59 ± 8.36, control: 38.28 ± 7.67, $P = .001$), and depression scores (dysmenorrhea: 17.81 ± 9.30, control: 9.75 ± 7.24, $P < .001$) were significantly increased in dysmenorrhea subjects compared with controls. However, during the OV phase, only trait anxiety was significantly higher in dysmenorrhea subjects (dysmenorrhea: 44.25 ± 8.44, control: 39.69 ± 7.38, $P = .025$). The state anxiety and depression scores did not significantly differ between dysmenorrhea subjects and controls during the OV phase. Moreover, in dysmenorrhea subjects, the state anxiety and depression scores were significantly elevated in the MC phase compared with the OV phase (state anxiety: 28.56 ± 7.87, $P < .001$;

Table 2
Gray matter volume changes between menstrual phases.

MC > OV							MC < OV						
Anatomic area	BA	Size	*t* Score	Coordinate			Anatomic area	BA	Size	*t* Score	Coordinate		
				x	y	z					x	y	z
Dysmenorrhea													
Left orbital gyrus	11	124	3.16	−9	48	−20	Left SII	41	344	3.33	−53	−30	13
Left precentral gyrus	6	96	3.58	−63	3	12	Left ACC/dPCC	23	585	4.33	−5	−18	33
Left inferior temporal gyrus	20	66	3.39	−56	−24	−21							
Right hypothalamus	–	140	4.05	6	−6	−9							
Control													
No significant changes													
Dysmenorrhea > Control													
Left orbital gyrus	11	142	3.27	−14	45	−27	Left SII	41	355	3.61	−51	−31	12
Left precentral gyrus	6	96	3.41	−62	5	12	Left ACC/dPCC	23	274	3.65	−5	−19	33
Right postcentral gyrus	3	52	3.73	20	−40	70							
Right precuneus	7	38	3.31	15	−61	60							
Right hypothalamus	–	204	4.35	5	−4	−11							

ACC/dPCC, anterior/dorsoposterior cingulate cortex; BA, Brodmann area; MC, menstrual phase; OV, periovulatory phase; SII, secondary somatosensory cortex.
Note: Size is the number of voxels in the cluster; peak coordinates refer to Montreal Neurological Institute space.

depression: 12.88 ± 6.93, $P < .001$). Such significant changes were not observed in controls (Table 1).

3.2. Brain morphological changes

Fifty-two of 64 subjects (81.25%) underwent 2 scans within a single cycle. Due to scheduling difficulties, 11 subjects (6 dysmenorrhea subjects and 5 controls) underwent scanning over 2 cycles and 1 control subject was scanned over 3 cycles. Sixteen of the scans in the OV phase in the dysmenorrhea group (12.5% of total scans) had been used in our previous study [28]. The anatomic MRIs were visually inspected by an experienced neuroradiologist (T.-C.Y.), and all anatomic images included in the analysis were found without any macroscopic abnormalities. No significant difference was found in total GM volume between dysmenorrhea and control subjects in both phases (dysmenorrheal subjects in the MC phase: 653.08 ± 44.72 mL, control subjects in the MC phase: 670.67 ± 43.57 mL, $P = .116$; dysmenorrhea subjects in the OV phase: 654.60 ± 44.64 mL, control subjects in the OV phase: 671.41 ± 43.38 mL, $P = .132$) (Table 1).

Within the ROIs, dysmenorrhea subjects revealed significant hypertrophic GM changes during the MC phase compared with the OV phase in the left orbital gyrus within the medial orbitofrontal cortex ([mOFC], Brodmann area [BA] 11), left precentral gyrus within the premotor cortex (BA 6), left inferior temporal gyrus (BA 20), and right hypothalamus, whereas atrophic GM changes were found in left secondary somatosensory cortex ([SII], BA 41) and left cingulate gyrus within the border of anterior and dorsoposterior part of the cingulate cortex ([ACC/dPCC], BA 23) (Table 2). No significant change between the 2 phases was found in control subjects (Table 2). The between-group comparison for menstrual phase differences analysis further revealed significant greater hypertrophic changes in the left mOFC, left premotor cortex, right postcentral gyrus within primary somatosensory cortex (BA 3), right precuneus (BA 7), and right hypothalamus, whereas greater atrophic changes were found in the SII and ACC/dPCC in dysmenorrhea subjects than in controls (Fig. 1, Table 2). The GM volume differences within the right caudate nucleus and hypothalamus were significant positively correlated, whereas the thalamus was negatively correlated with the current menstrual pain experience scores (Fig. 2, Table 3). To ensure that the findings of the present study are consistent and replicable across groups of independent samples, we performed 2 subgroup comparisons between phases (MC vs OV) in the dysmenorrhea group. The 2 subgroups consisted

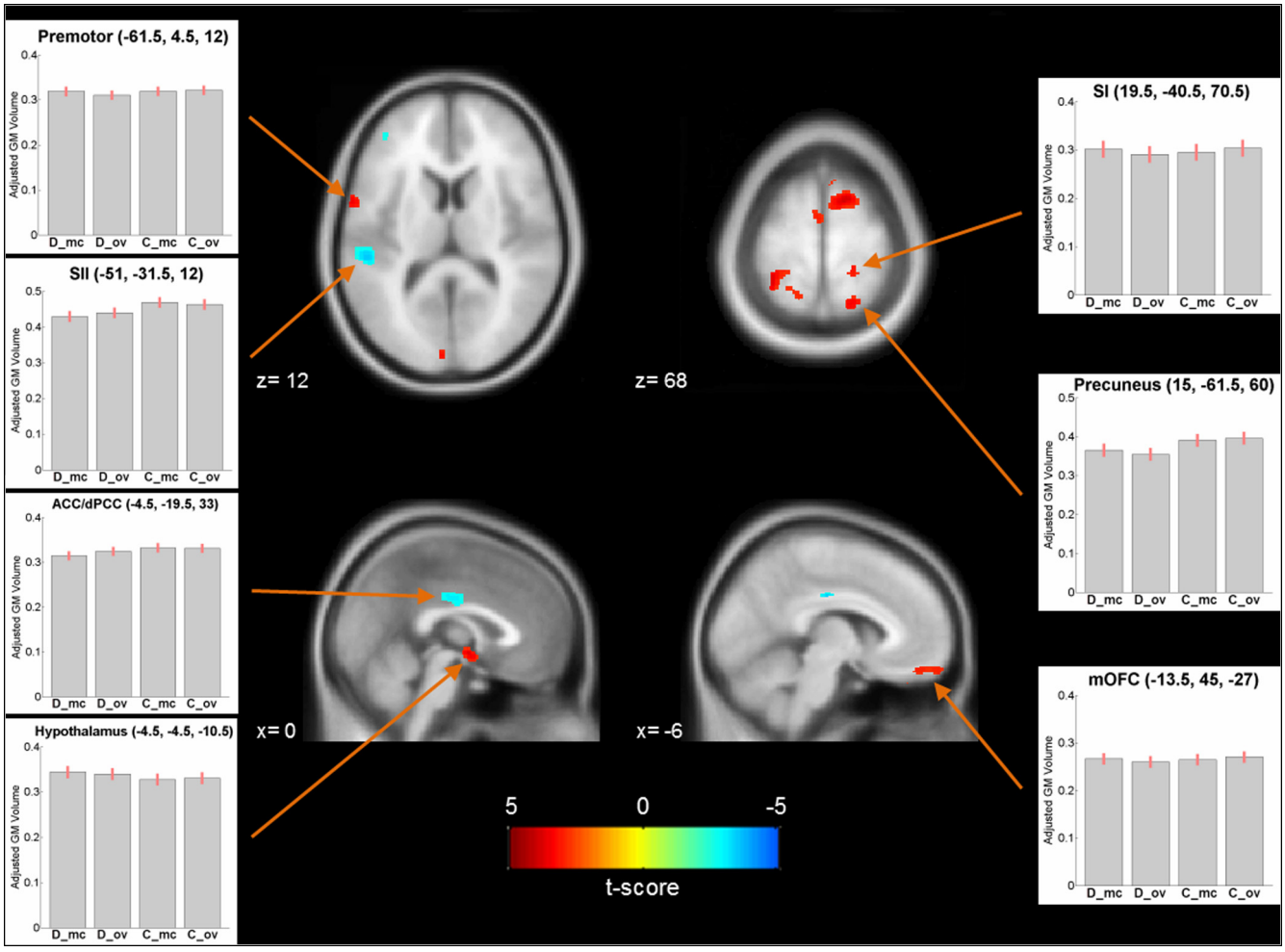

Fig. 1. Significant gray matter volume changes in a priori regions of interest. The between-group comparison of menstrual phase differences (menstrual phase [mc] vs periovulatory phase [ov]) showed significant greater hypertrophic changes in the left medial orbitofrontal cortex (mOFC), left premotor cortex, right primary somatosensory cortex (SI), right precuneus, and right hypothalamus, whereas greater atrophic changes were found in the left secondary somatosensory cortex (SII) and left anterior/dorsoposterior cingulate cortex (ACC/dPCC) in dysmenorrhea subjects than in controls. Significance was considered when passing a familywise error correction $P < .05$ using a small volume correction. Regions with anatomic labeling denote significant changes. The results are superimposed on the SPM T1 template, and warm/cold colors represent increase/decrease gray matter volume, respectively. The color bar represents t scores. The bar charts show the adjusted gray matter volume at the peak voxel of each region (coordinates in Montreal Neurological Institute space) for each phase in 2 groups (D, dysmenorrhea; C, control). The error bar corresponds to a 90% confidence interval.

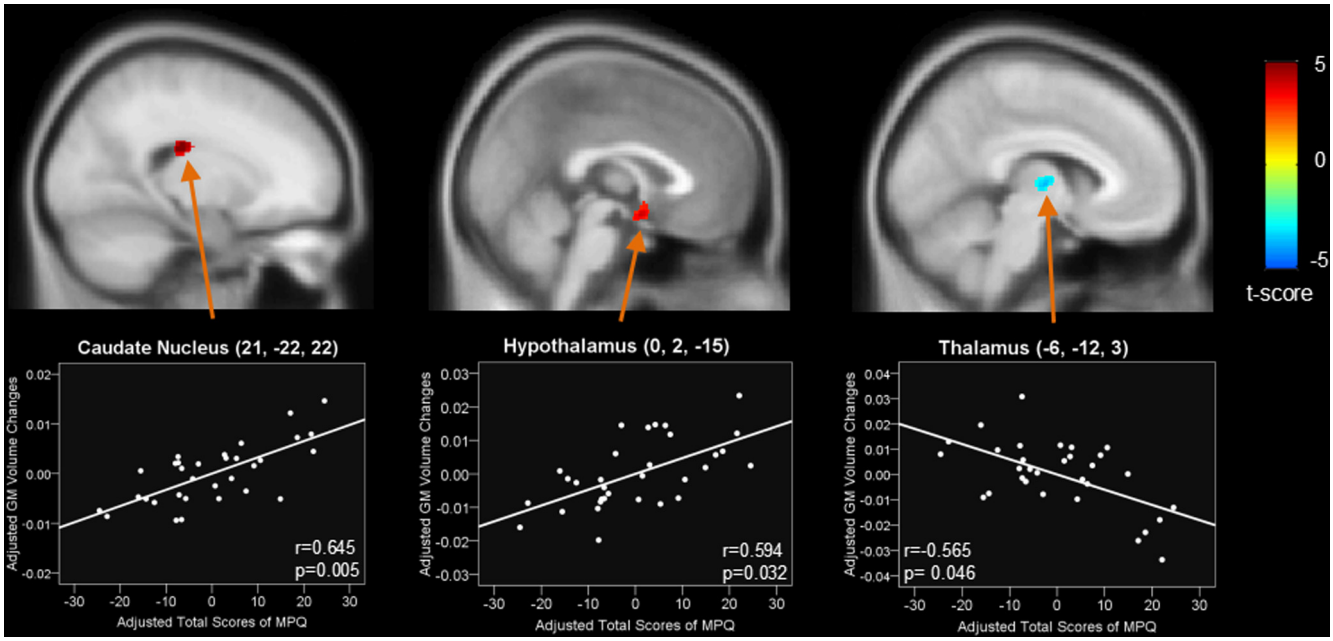

Fig. 2. Gray matter (GM) volume changes correlated with current menstrual pain experience in dysmenorrhea. Positive correlation between the current menstrual pain experience and GM volume changes between phases (menstrual phase vs periovulatory phase) was found in the right caudate nucleus and the hypothalamus while negative correlation was found the in left thalamus in dysmenorrhea. (Top) The results are superimposed on the SPM T1 template, and warm/cold colors represent positive/negative correlation, respectively. The color bar represents *t* scores. (Bottom) The scatterplots disclose the relationship between the adjusted GM volume changes at peak voxel (coordinates in Montreal Neurological Institute space) and the adjusted total pain rating index scores of the McGill Pain Questionnaire (MPQ). The corresponding correlation coefficients (r) and corrected *P* values (familywise correction using a small volume correction) are provided.

Table 3
Gray matter volume changes covarying with current menstrual pain experience (total pain rating index scores of McGill Pain Questionnaire) in dysmenorrheic patients.

Anatomic area	BA	Size	*t* Score	Coordinate		
				x	y	z
Positive						
Right caudate nucleus	Body	55	4.80	21	−22	22
Hypothalamus		71	3.89	0	2	−15
Negative						
Left thalamus		32	3.71	−6	−12	3

BA, Brodmann area.
Note: Size is the number of voxels in the cluster; peak coordinates refer to Montreal Neurological Institute space.

of 16 nonoverlapped (independent group) and 16 overlapped dysmenorrhea subjects (overlapped with our previous study [28]). Similar patterns of GM volume changes were observed in the a priori selected ROIs in the whole-group (32 dysmenorrhea subjects) and subgroup (16 dysmenorrhea subjects each) analyses, albeit a higher level of significance in the whole-group analysis due to larger sample size.

4. Discussion

In the present study, we used an optimized VBM method to investigate state-related brain morphological alterations in dysmenorrhea in response to 1 to 3 days of menstrual pain. In dysmenorrhea subjects, several regions exhibited significant GM volume changes between menstrual phases. Changes were found in regions involved in pain modulation, pain transmission, affective experience generation, and regulation of endocrine function. These regions also exhibited trait-related changes in our previous VBM study [28]. The changes in the caudate nucleus, hypothalamus, and thalamus were further significantly correlated with the current menstrual pain experience. These findings suggest that spontaneous recurrent pain results in rapid state-related changes in macroscopic brain structures and that adaptive and maladaptive changes may be engaged simultaneously and dynamically.

Several microscopic mechanisms may account for the rapid GM alterations found in this study. It has been suggested that the macroscopic GM changes may be related to change in spine/synapse density, neuronal genesis/apoptosis, cell size changes, and changes of interstitial fluid or blood flow [18]. Considering the menstrual pain only present in 1 to 3 days, the GM alterations in dysmenorrhea subjects may be more related to the spine/synapse turnover rather than neuronal genesis/apoptosis. Where exercise-induced neurogenesis may need days to weeks [19], the changes in dendritic spines may take place within a few days [27]. Also, change of the sensory experience has been associated with an altered turnover rate of spines [27]. Thus, the rapid GM changes in the present study likely reflect the reorganization of spines/synapses, ie, elimination or creation of spines/synapses according to the change of the sensory experience.

Of particular interest is the finding of significant hypothalamic GM hypertrophy between menstrual phases and the positive correlation with the current menstrual pain experience in dysmenorrhea subjects. In our previous study, we found trait-related changes in the hypothalamus but no significant relationship with pain duration or overall recalled menstrual pain experience [28], leaving the possibility open that this finding could be an epiphenomenon. However, the present results suggest that the GM alterations in hypothalamus may instead represent a primary change (ie, a change directly related to the presence of menstrual pain). The hypothalamus plays an important role in the spinobulbospinal loop, a modulatory pathway that may exacerbate negative affect and pain [25]. The GM changes between phases in the caudate nucleus further positively correlated with the menstrual pain experience. Hypertrophic alterations between phases were also found in the mOFC in the present study. Anatomically, the hypothalamus

and the caudate nucleus receive afferent projections from the mOFC [17]. The mOFC is not only considered important for modulation of visceromotor functions but also for monitoring and generating the subjective affective experience [16,17]. The caudate nucleus is functionally related to the physical and emotional components of the individual pain experience [23]. Thus, the hypertrophic changes in these regions during the MC phase in dysmenorrhea may echo the negative affect associated with menstrual pain. Taken together, the hypertrophic changes in these medial structures could reflect maladaptive plasticity, underpinning the hyperalgesia known to exist in dysmenorrhea [3,13].

The hypothalamus is also involved in regulation of the menstrual cycle through the hypothalamic-pituitary-gonadal axis. Because serum levels of gonadal hormones were not assessed in the present study, a hormonal effect on GM alterations in dysmenorrhea cannot be entirely excluded. However, the between-group comparison for menstrual phase differences probably minimizes the hormonal influence because the hormonal variations across menstrual phases are accounted for by the between-phase effect in the controls. Notably, no demonstrable between-phase difference of GM volume was found in the control group. Previous studies in healthy subjects reported that regional GM volume may vary across the menstrual phases or according to the levels of gonadal hormones [20,33]. However, all of these regions were not found in our study and may have been excluded by our analysis. Also, serum estrogen and progesterone levels do not differ between dysmenorrhea subjects and controls in both MC and OV phases [34]. Our preliminary data on serum estrogen and progesterone levels in an ongoing study further support this (unpublished data).

Another major finding in this study is the GM hypotrophy in the SII and the negative correlation in the thalamus with the current menstrual pain experience. Reduced metabolism and trait-related GM hypotrophy in dysmenorrhea were previously found in the SII [28,29]. Thalamus is known to relay nociceptive input from the periphery to regions involved in sensory discrimination, including the SII [9]. It is conceivable that cyclic nociceptive input from the periphery may lead to adaptive state-related thalamic reorganization to reduce the impact of menstrual pain. The consistent changes observed in the SII may further reflect longer lasting down-stream compensatory plasticity. It remains unclear whether the primary state-related changes in the thalamus maintain the trait-related changes observed in the sensory discriminative pathway [28] or whether these changes represent chronification.

Clinically, dysmenorrhea is often comorbid with other idiopathic pain disorders [30]. For example, IBS patients have more severe clinical symptoms with concomitant dysmenorrhea than with IBS alone, and the treatment of dysmenorrhea can improve the symptoms of IBS [14]. Interestingly, IBS is also associated with a higher prevalence rate in females [8]. Furthermore, the hypothalamus has also been found to be enlarged in IBS patients [6]. It was previously proposed that dysmenorrhea may act as a precursor stage in women who progress to chronic pelvic pain since dysmenorrhea often is reported before the development of chronic pelvic pain [2]. Therefore, the repetitive rapid plasticity in the brain in conjunction with the early onset of dysmenorrhea may result in a cumulative maladaptive effect that predisposes to other clinical pain conditions. More studies are needed to probe the possible relationship between dysmenorrhea and other clinical pain conditions.

Although pelvic imaging (eg, ultrasonography) was not performed in the present study on a routine base, the dysmenorrhea may be attributed more to being primary (menstrual pain without pelvic abnormality) than secondary (menstrual pain with pelvic abnormality) in nature for the following reasons. First, primary dysmenorrhea in general occurs within the first 2 years after the menarche, whereas secondary dysmenorrhea usually occurs years after menarche [11]. Second, the onset of menstrual pain in primary dysmenorrhea usually begins with the menses and lasts for 1 to 3 days, whereas in secondary dysmenorrhea, the menstrual pain may start days before the menses and persist beyond the end of the menses [30]. Third, primary dysmenorrhea is associated with a normal ovulatory cycle [15], whereas secondary dysmenorrhea is often associated with an irregular ovulatory cycle. A normal ovulatory cycle was confirmed in all participants in the present study by the use of urine kits. Finally, in subjects in whom menstrual pain of secondary origin was suspected, pelvic sonography was conducted to rule out organic factors. Nevertheless, it is suggested that pelvic ultrasonography or other advanced pelvic imaging procedures should be routinely performed to affirm the nature of dysmenorrhea in future studies.

4.1. Conclusions

In summary, our results suggest that adaptive and maladaptive structural changes in the brain may be engaged simultaneously and dynamically. On the one hand, the hypertrophic changes found in the medial structures could reflect maladaptive plasticity underpinning hyperalgesia. On the other hand, the cyclic nociceptive input from the periphery may also lead to adaptive reorganization to reduce the impact of menstrual pain. Considering the high prevalence and early onset of menstrual pain, these findings mandate a great demand to revisit dysmenorrhea regarding its impact on the brain and other clinical pain conditions. Like migraine, dysmenorrhea might be considered a chronic disease with episodic features but largely confined to the menstrual phase [4].

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.05.022.

References

[1] Altman G, Cain KC, Motzer S, Jarrett M, Burr R, Heitkemper M. Increased symptoms in female IBS patients with dysmenorrhea and PMS. Gastroenterol Nurs 2006;29:4–11.
[2] As-Sanie S, Harris RE, Napadow V, Kim J, Neshewat G, Kairys A, Williams D, Clauw DJ, Schmidt-Wilcke T. Changes in regional gray matter volume in women with chronic pelvic pain: a voxel-based morphometry study. PAIN® 2012;153:1006–14.
[3] Bajaj P, Madsen H, Arendt-Nielsen L. A comparison of modality-specific somatosensory changes during menstruation in dysmenorrheic and nondysmenorrheic women. Clin J Pain 2002;18:180–90.
[4] Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. Neurology 2008;71:848–55.
[5] Bingel U, Schoell E, Herken W, Buchel C, May A. Habituation to painful stimulation involves the antinociceptive system. PAIN® 2007;131:21–30.
[6] Blankstein U, Chen J, Diamant NE, Davis KD. Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. Gastroenterology 2010;138:1783–9.
[7] Blumenstiel K, Gerhardt A, Rolke R, Bieber C, Tesarz J, Friederich HC, Eich W, Treede RD. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. Clin J Pain 2011;27:682–90.

[8] Chang FY, Lu CL, Chen TS. The current prevalence of irritable bowel syndrome in Asia. J Neurogastroenterol Motil 2010;16:389–400.
[9] Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3:655–66.
[10] Dawood MY. Nonsteroidal anti-inflammatory drugs and changing attitudes toward dysmenorrhea. Am J Med 1988;84:23–9.
[11] Dawood MY. Dysmenorrhea. In: Sciarra JJ, editor. Gynecology and obstetrics, vol. 1. Philadelphia: Lippincott Williams and Wilkins; 2004.
[12] French L. Dysmenorrhea. Am Fam Physician 2005;71:285–91.
[13] Giamberardino MA, Berkley KJ, Iezzi S, de Bigontina P, Vecchiet L. Pain threshold variations in somatic wall tissues as a function of menstrual cycle, segmental site and tissue depth in non-dysmenorrheic women, dysmenorrheic women and men. PAIN® 1997;71:187–97.
[14] Giamberardino MA, Costantini R, Affaitati G, Fabrizio A, Lapenna D, Tafuri E, Mezzetti A. Viscero-visceral hyperalgesia: characterization in different clinical models. PAIN® 2010;151:307–22.
[15] Harel Z. A contemporary approach to dysmenorrhea in adolescents. Paediatr Drugs 2002;4:797–805.
[16] Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 2005;6:691–702.
[17] Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol 2004;72:341–72.
[18] May A. Experience-dependent structural plasticity in the adult human brain. Trends Cogn Sci 2011;15:475–82.
[19] Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 2007;104:5638–43.
[20] Protopopescu X, Butler T, Pan H, Root J, Altemus M, Polanecsky M, McEwen B, Silbersweig D, Stern E. Hippocampal structural changes across the menstrual cycle. Hippocampus 2008;18:985–8.
[21] Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. J Neurosci 2009;29:13746–50.
[22] Sauer K, Kemper C, Glaeske G. Fibromyalgia syndrome: prevalence, pharmacological and non-pharmacological interventions in outpatient health care. An analysis of statutory health insurance data. Joint Bone Spine 2011;78:80–4.
[23] Scott DJ, Heitzeg MM, Koeppe RA, Stohler CS, Zubieta JK. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J Neurosci 2006;26:10789–95.
[24] Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011;31:7540–50.
[25] Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends Pharmacol Sci 2004;25:613–7.
[26] Teutsch S, Herken W, Bingel U, Schoell E, May A. Changes in brain gray matter due to repetitive painful stimulation. Neuroimage 2008;42:845–9.
[27] Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 2002;420:788–94.
[28] Tu CH, Niddam DM, Chao HT, Chen LF, Chen YS, Wu YT, Yeh TC, Lirng JF, Hsieh JC. Brain morphological changes associated with cyclic menstrual pain. PAIN® 2010;150:462–8.
[29] Tu CH, Niddam DM, Chao HT, Liu RS, Hwang RJ, Yeh TC, Hsieh JC. Abnormal cerebral metabolism during menstrual pain in primary dysmenorrhea. Neuroimage 2009;47:28–35.
[30] Tu F. Dysmenorrhea: contemporary perspectives. PAIN® 2007;15.
[31] Vincent K, Warnaby C, Stagg CJ, Moore J, Kennedy S, Tracey I. Dysmenorrhoea is associated with central changes in otherwise healthy women. PAIN® 2011;152:1966–75.
[32] Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. World J Gastroenterol 2007;13:3699–704.
[33] Witte AV, Savli M, Holik A, Kasper S, Lanzenberger R. Regional sex differences in grey matter volume are associated with sex hormones in the young adult human brain. Neuroimage 2010;49:1205–12.
[34] Ylikorkala O, Puolakka J, Kauppila A. Serum gonadotrophins, prolactin and ovarian steroids in primary dysmenorrhoea. Br J Obstet Gynaecol 1979;86:648–53.