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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

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