3177

Central Processing of Thermal Pain in Young Women With Primary Dysmenorrhea

Ya-Yun Chen[a,b], Cheng-Hao Tu[a,b], Wei-Chi Li[a], Hsiang-Tai Chao[c,d], Li-Fen Chen[a,b], Jen-Chuen Hsieh[a,b]

[a]Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan,
[b] Integrated Brain Research Unit, Division of Clinical Research, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan,
[c] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan,
[d] Department of Obstetrics and Gynecology, Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan.

Introduction

- Primary dysmenorrhea (PDM, menstrual pain without organic causes) is very common among women of reproductive age. We previously reported that PDM is associated with metabolic and morphological alterations in the brain[1,2].
- The central sensitization phenomena has been observed in Caucasian patients[4,5]. However, with sample size many times greater than previous reports, we detected no group or phase effect in thermal pain thresholds of the Taiwanese participants[3].
- The present functional MRI (fMRI) study combined with thermal pain stimuli aimed to:
  (1) compare the brain responses of the experimental noxious stimuli between women with and without PDM,
  (2) explore possible pain modulatory mechanism in Taiwanese PDM subjects, it could underpin the absence of thermal central sensitization in our previous report[3].

Materials and Methods

- **Participants**
  - 33 otherwise healthy subjects with PDM history lasting longer than 6 months and pain rating higher than 4 on a numerical rating scale (NRS, 0-10).
  - 36 healthy female controls (CON) (age matched) without menstrual pain.
- **Psychophysical and psychological assessments**
  - Long-Form McGill Pain Questionnaire for menstrual pain experience
  - Sort-Form Healthy Survey-36 for quality of life
  - Thermal quantitative sensory test (QST) for sensitization
  - Thermal individualized nociceptive test (NRS = 6) for applying to fMRI
- **Image processing**
  - Functional MRI data were collected by 3T-MRI and analyzed by SPM8.
  - Heat (38˚C, H) and painful (subject-specific, P) stimuli were applied on the left inner forearm to evoke pain-related brain responses.
- **Statistical analyses**
  - One- and two-sample *t*-tests for examination of stimulus-evoked activity and between-group differences, respectively (p_{FWE} < .05 at cluster level).
  - Correlation analyses between individualized nociceptive test and brain activation for possible pain modulatory mechanism.

Results

Table 1. Demographic data and baseline information

	PDM (n=33)	CON (n=36)	*p*-value
Age, y	22.88 ± 2.60	23.50 ± 1.99	.081
Age at menarche	12.23 ± 1.25	12.38 ± 1.27	.563
Years of menstruating	10.65 ± 2.92	11.13 ± 2.46	.287
Days of a menstrual cycle	29.36 ± 1.30	29.46 ± 0.99	.911
BMI[a]	20.69 ± 2.78	21.23 ± 3.18	.585
Edinburgh Handedness	81.18 ± 18.71	86.37 ± 16.14	.249
Menstrual pain experience			
Pain history, y	8.62 ± 2.97	N/A	N/A
Pain duration, d	2.15 ± 0.89	N/A	N/A
Absenteeism, %	66.7	N/A	N/A
Analgesic taken, %	57.6	N/A	N/A
Recalled pain scores[b]	6.34 ± 1.32	N/A	N/A
SF-36[a]			
PCS	48.40 ± 5.34	53.51 ± 9.26	< .001***
MCS	47.24 ± 7.20	53.92 ± 12.23	.002**

Mann-Whitney U test was used for these demographic data and baseline information. Data are presented as mean ± SD. BMI, body mass index; CON, controls; NA, not applicable; PDM, primary dysmenorrhea; SF-36, Short-Form Healthy Survey. [a] Two control subjects without the BMI and one PDM subject without SF-36 were excluded from the statistics. [b] Recalled pain scores were from numerical rating scale (0-10).
*p < .05; **p < .01; ***p < .001.

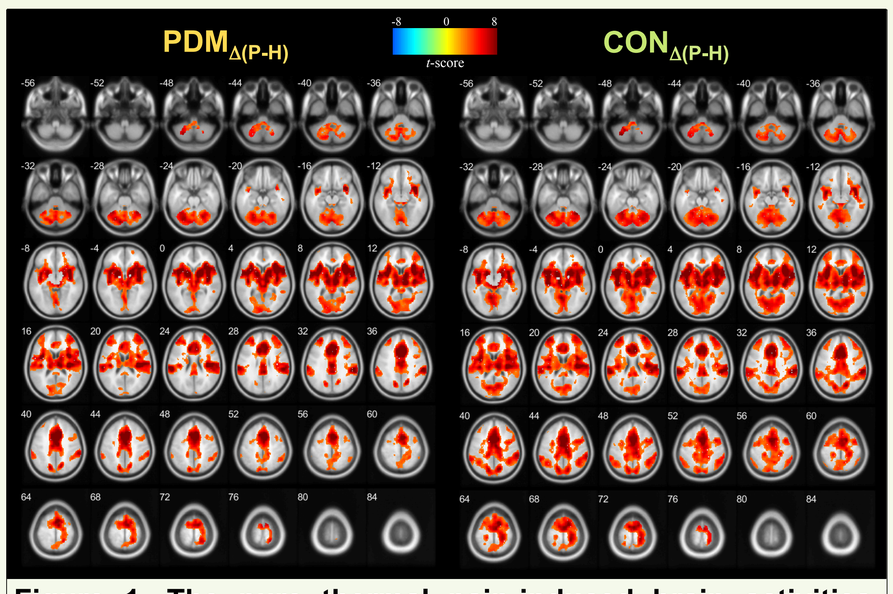
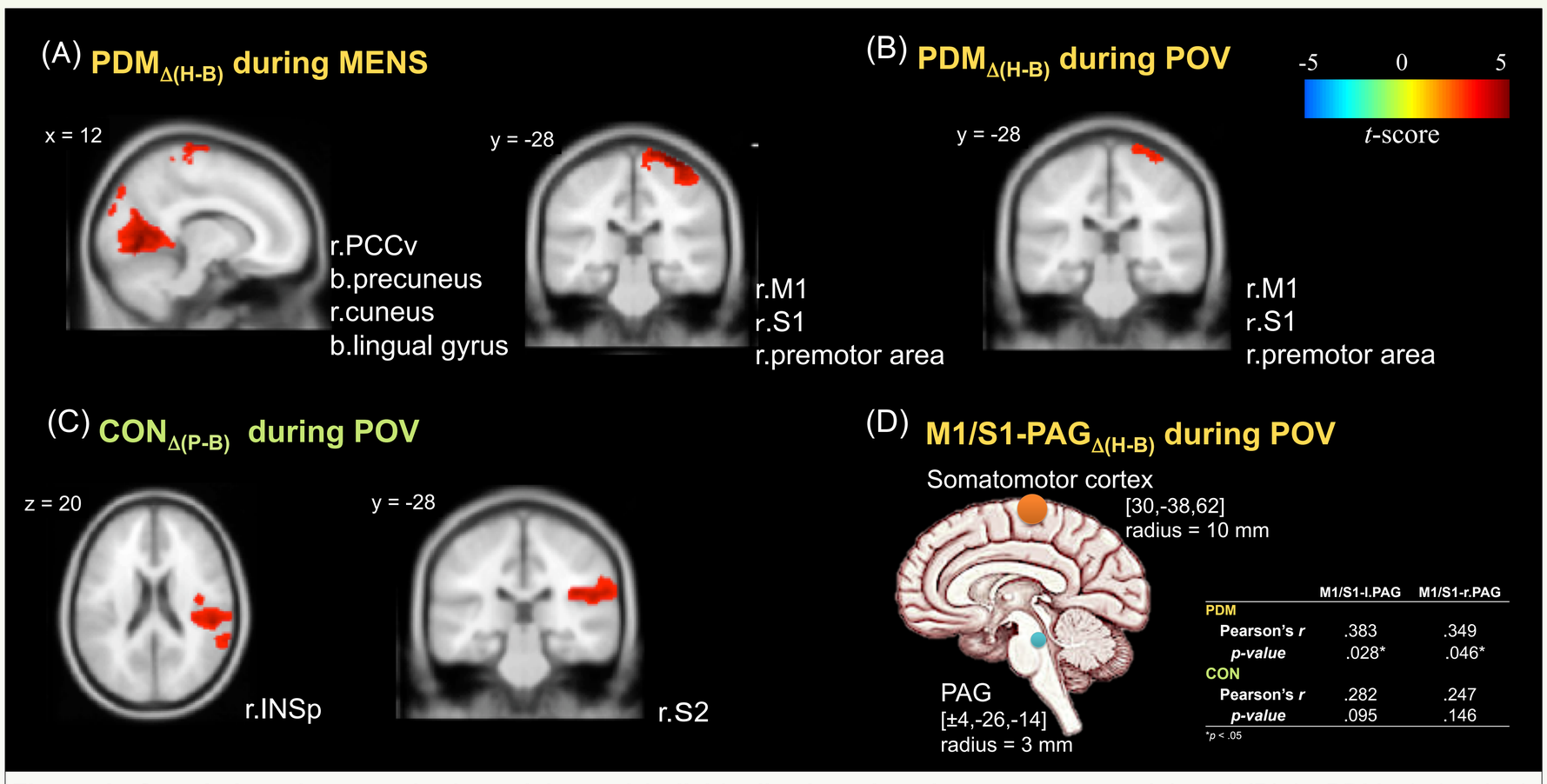


Figure 1. The pure thermal pain-induced brain activities. Both groups showed highly activity in the bilateral insula, anterior cingulate cortex (ACC), thalamus, somatosensory cortex (S1) and secondary somatosensory cortex (S2), etc. There is no significant survival difference between two groups. Uncorrected p < .005 at peak level followed by p_{FWE} < .05 at cluster level.



	M1/S1-l.PAG	M1/S1-r.PAG
PDM		
Pearson's *r*	.383	.349
p-value	.028*	.046*
CON		
Pearson's *r*	.282	.247
p-value	.095	.146

*p < .05

Figure 2. Correlations between brain activity and individualized nociceptive temperature. (A) and **(B)** In PDM, during both menstruation (MENS) and periovulatory (POV) phases, the temperature was positively correlated with brain activity in the somatomotor cortex (M1/S1) under "Heat-Baseline (H-B)" condition. However, a positive correlation in a large cluster including the right ventral posterior cingulate cortex (r.PCCv), cuneus, bilateral precuneus, and linual gryrus was only shown during MENS under "H-B" condition. This cluster survived the between-phase comparison. **(C)** In CON, a positive correlation in a cluster covering the right posterior insula (r.INSp) and right secondary somatosensory cortex (r.S2) was displayed under "Pain-Baseline (P-B)" condition during POV phase. **(D)** A positive correlation between M1/S1 and periaqueductal gray (PAG) was exhibited during POV phase in PDM.

Discussion

●Both groups demonstrated typical central representation of thermal pain as previous reported[6]; however, no significant group difference was found in these pain-related regions. This result was consistent with the QST data.

●The correlation between the M1/S1 and the temperatures of the moderate pain under "H-B" condition through both phases in PDM connoted that the PDM have a *trait-related* top-down modulation toward thermal stimulation. Our reasoning is supported by the correlation between M1/S1 and periaqueductal gray (PAG) during POV phase in PDM. Increased M1/S1 activation could be appreciated as a descending pain modulation via PAG for pain alleviation[8]. As a result, it may explain why Taiwanese PDM subjects showed no sensitization phenomena on the noxious stimuli[7,8].

●The correlation results suggested that PDM subjects with altered pain coding mechanism. However, in the CON group, we found positive correlations in the INSp and S2 engaged in this mechanism under painful stimuli. It revealed that the CON group with normal pain coding mechanism but that of the PDM group has changed.

Conclusion

●Our findings indicate that the PDM subjects develop the unique pattern for central processing of thermal stimulations. When given painful stimuli, the pain matrix of the PDM subjects functions normally; nevertheless, the pain coding mechanism is absent. The pain modulation for thermal stimulation is demonstrated in PDM subjects.

References

1. Tu et al. (2009), Neuroimage, 47(1), 28-35.
2. Tu et al. (2010), Pain, 150(3), 462-468.
3. Lee et al. (2014), PLoS ONE, 9, 11.
4. Arendt-Nielsen et al. (2014), Acta obstetricia et gynecologica Scandinavica, 93(8), 741-748.
5. Vincent et al. (2011), Pain, 152(9), 1966-1975.
6. Tseng et al. (2010), Hum Brain Mapping, 31,743-757.
7. Garcia-Larrea et al. (2013), PAIN, 154, S29-S43.
8. Bushnell et al. (2013), Nature Reviews Neuroscience, 14(7), 502-511.