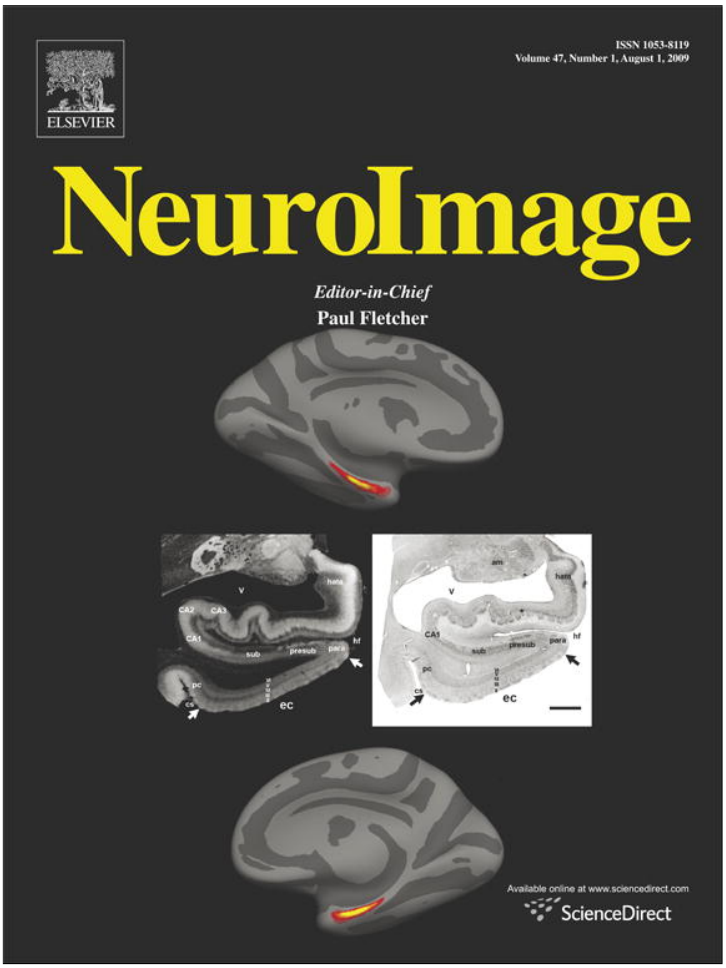

NeuroImage 47 (2009) 28–35

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Abnormal cerebral metabolism during menstrual pain in primary dysmenorrhea

Cheng-Hao Tu [a,b,1], David M. Niddam [b,c,1], Hsiang-Tai Chao [d], Ren-Shyan Liu [e], Ren-Jen Hwang [a,b,f], Tzu-Chen Yeh [b,g], Jen-Chuen Hsieh [a,b,c,g,*]

[a] Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan
[b] Laboratory of Integrated Brain Research, Department of Medical Research and Education, Taipei Veterans General Hospital, No.201, Sect.2, Shih-Pai Rd. Taipei 112, Taiwan
[c] Brain Research Center, National Yang-Ming University, Taipei, Taiwan
[d] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[e] Department of Nuclear Medicine, National Yang-Ming University, Taipei, Taiwan
[f] Chang Gung Institute of Technology, Tao-Yuan, Taiwan
[g] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 23 December 2008
Revised 10 March 2009
Accepted 31 March 2009
Available online 9 April 2009

ABSTRACT

Primary dysmenorrhea (PDM, menstrual pain without pelvic abnormality) is the most common gynecological disorder for women in the reproductive age. It is characterized by cramping pain and enhanced pain sensitivity during the menstruation period. PDM has been associated with peripheral and central sensitization. Abnormal brain mechanisms may further contribute to development and maintenance of the state. Using fluoro-deoxyglucose positron emission tomography, increased activity was observed in prefrontal/orbitofrontal regions and left ventral posterior thalamus while decreased activity mainly was observed in sensorimotor regions of the left hemisphere at onset compared to offset of PDM. These results were specific to menstrual pain and were not found in menstrual matched controls. Orbitofrontal activities were positively related to while somatosensory activities where negatively related to subjective pain ratings. These results show that ongoing menstrual pain in PDM is accompanied by abnormal brain metabolism. Disinhibition of thalamo-orbitofrontal-prefrontal networks may contribute to the generation of pain and hyperalgesia in PDM possibly by maintaining spinal and thalamic sensitization while increasing negative affect. Excessive excitatory input during menstrual pain may induce compensatory inhibitory mechanism in several somatic sensorimotor regions.

Introduction

Primary dysmenorrhea (PDM, menstrual pain without pelvic abnormality) is the most common gynecological disorder for women in the reproductive age. PDM patients suffer from disabling cramping pain emanating from the lower abdomen. The cramping pain typically starts with onset of the menstrual flow and last for 24 to 72 h (French, 2005; Harel, 2002). Epidemiological studies have shown that 20 to 90% of female adolescents have experienced PDM, and 15% have had severe PDM (French, 2005). PDM has been suggested to be a sex-hormone related disorder accompanied by a decrease of progesterone before menstruation. This is followed by a cascade response of prostaglandins and leukotrienes which mediate hyperalgesia and inflammatory pain and cause vasoconstriction, ischemia and myometrial contraction (Harel, 2002). Furthermore, the hyperalgesia observed in PDM is general and spans different spinal segments and other tissue systems such as skin and muscle (Giamberardino et al., 1997; Granot et al., 2001). Hyperalgesia also extends to referred pain areas (Bajaj et al., 2002). The aforementioned studies indicate an enhanced pain perception in patients with PDM, possibly as a result of both peripheral and central sensitization. However, it remains unknown whether PDM is associated with altered brain mechanisms.

In the study of brain mechanisms of pain, it is important to differentiate between acute and chronic pain states. Not only do the different time horizons and the perceived lack of pain control engage different emotional coping strategies, but chronic pain becomes maladaptive and is highly comorbid with mood and anxiety disorders (Gureje et al., 2008). Furthermore, chronic pain induces brain atrophy (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006), induces changes in brain chemistry (Grachev et al., 2000) and alters brain processing (Apkarian et al., 2005; Derbyshire, 2003; Kupers and Kehlet, 2006). It is, however, also of importance to differentiate between spontaneous ongoing pain and perturbations of these states by external stimuli leading to allodynia or hyperalgesia. The former may encourage passive emotional coping while

* Corresponding author. Institute of Brain Science and Brain Research Center, National Yang-Ming University, No 155, Sect., 2, Linong St., Taipei 112, Taiwan. Fax: +886 2 28745182.
E-mail addresses: jchsieh@ym.edu.tw, jchsieh@vghtpe.gov.tw (J.-C. Hsieh).
[1] Equally contributed to this work.

1053-8119/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.03.080

the later may engage active emotional coping. As a visceral pain condition, PDM provides a unique opportunity to study ongoing visceral pain due to its cyclical nature of pain and pain-free states. Although a number of studies exist on central processing of chronic visceral pain (Derbyshire, 2003), these studies mainly applied external stimuli and thus investigated either allodynia or hyperalgesia.

The aim of the present study was to investigate if the cyclic cramping pain observed in PDM is associated with altered brain mechanisms. More specifically, we hypothesized that metabolic abnormalities might be found in regions involved in maintaining central sensitization, top-down pain modulation and emotion regulation. We also reasoned that metabolic changes in regions involved in generation of negative effect may be related to the individual severity of menstrual pain. To test these hypotheses, we used positron emission tomography (PET) as the imaging modality with ^{18}F-labaled fluoro-deoxyglucose (FDG). PET images from 17 patients in the dysmenorrheic phase (onset, 1st–3rd day) were compared to (1) the same patients in the offset phase (12th–16th day) of menstruation (internal control condition), and (2) 16 age and menstrual cycle matched healthy controls (external control condition). The control group was included in order to account for non-pain specific variations due to the menstrual cycle.

Materials and methods

Subjects

Seventeen right-handed PDM patients (19–29 y/o, mean ± SD: 23.1 ± 3.03 y/o) and 16 healthy right-handed female control subjects (mean ± SD: 21.7 ± 2.6 y/o), matched for age ($p = 0.172$), participated in the study. Another control subject did not complete all brain scans and was not included in the final analysis. Patients were recruited from the out-patient Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, and were diagnosed by the same gynecologist. The inclusion criteria for patients were (1) a regular menstrual cycle around 27–32 days; (2) PDM lasting longer than 6-months (4–16 years; mean ± SD: 9.17 ± 3.06 years) (3) the cramping pain during menstruation in the last 6-months should be rated higher than 4 (0 = not at all, 10 = the worst pain). The inclusion criteria for healthy control subjects were (1) a regular menstrual cycle around 27–32 days; (2) neither cramping pain nor other symptoms during menstruation in the last 6-months. Exclusion criteria for all subjects were pathological pituitary gland disorder, organic pelvic disease, psychological disorder, childbirth, positive pregnancy test or plan for pregnancy, and metal or pacemaker implant. Oral-contraceptive drugs were not allowed to be taken within 6-months of the scan, and no analgesic or antidepressant drugs were allowed 24 h prior to the scan. Before the study, participants gave their informed consent to the protocol, which had been approved by the Institutional Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki.

Experimental paradigm

All subjects received two PET scans. The first scan (onset condition) was performed on the 1st–3rd day of the menstrual cycle while the second scan (offset condition) was performed on the 12th–16th day of the menstrual cycle. For patients, a lower abdominal cramping pain was present in the onset condition but not in the offset condition. Blood samples were collected from all subjects before FDG administration to measure the level of estradiol (E2) and progesterone by radial immune assay (RIA) analysis. Due to a minimum of a 12-day interval between successive scans, according to the Institutional Safety Guidelines and the availability of scanner time, the offset scans could not be arranged at the surge of progesterone which usually occurs 1 to 10 days post-ovulation. For this reason, only E2 was used in the subsequent image analysis.

Psychological assessment

The pain experience of each patient was assessed by the McGill pain questionnaire (MPQ). It was administered during the inception interview and on the day of the first scan. Since the pain perception

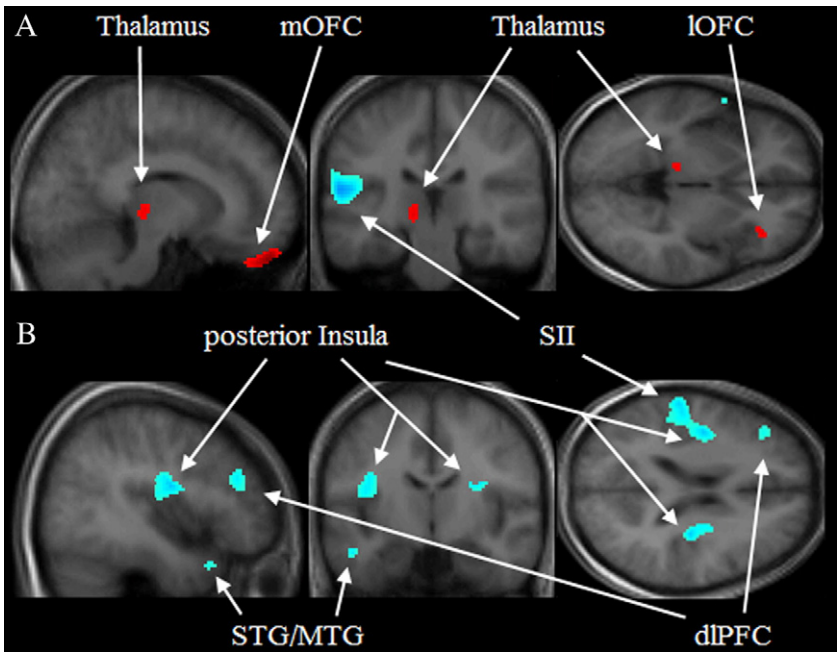

Fig. 1. Increased and decreased regional cerebral glucose metabolism at onset vs. offset of primary dysmenorrhea. Onset of PDM was associated with (A) increased activity in the left medial orbitofrontal cortex (mOFC), right lateral orbitofrontal cortex (lOFC, BA 47), and left thalamus and (B) decreased activity in bilateral posterior insula, left secondary somatosensory area (SII), left dorsolateral prefrontal cortex (dlPFC, BA 8/9), and left superior and middle temporal gyrus (STG/MTG, BA 21/22/38). Results are superimposed on the averaged anatomical T1 MRI from patients. Red/blue color represented activation/deactivation.

can be exacerbated by anxiety (Rhudy and Meagher, 2000) and depression (Bair et al., 2003; Gureje et al., 2008), both have been linked to PDM, the Spielberger state-trait anxiety inventory (STAI) and Center for Epidemiologic Studies — Depression scale (CES-D) (Roberts, 1980) were administered prior to each PET scan.

Image acquisition

Whole-brain 3D PET (ECAT7HR+, Siemens, Germany) scans were obtained at the National PET/Cyclotron Center, Taipei Veterans General Hospital. Subjects needed to fast for 8 h prior to PET scanning. Ten mCi FDG was administered intravenously via the intermedian cubital vein 30 min before subjects were placed into the scanner. Prior to the emission scan, a ^{68}Ga pin-source transmission scan was performed to adjust for tissue-induced noise. During scans, subjects were asked to relax with eyes closed and not to move. FDG data were acquired over 30 min with a matrix size of $128\times128\times63$ and field of view of $220\times220\times153$ mm^3.

Data processing and statistics

Images were processed and analyzed with statistical parametric mapping (SPM2, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, UK), running under Matlab 6.5 (Mathworks Inc., Sherborn, MA, USA). First, an FDG template was created from all controls according to the procedures by Gispert et al. (2003). Then, within each subject images were realigned, averaged, and normalized to the FDG template. The normalization parameters from the mean image were used to normalize each of the realigned images. These were further smoothed with a 3D Gaussian kernel (FWHM = 12 mm).

The overall grand mean from PET scans was centered and normalized to 100, and global variance across scans was removed by analysis of covariance (ANCOVA). Comparison of onset versus offset was performed within groups and between groups. Additionally, within the patient group, regions covarying with (1) MPQ scores, (2) pain duration (in years), and (3) maxima found in the onset versus offset comparison were mapped, separately. To account only for pain-related factors, significant psychological and hormonal parameters were included in the statistical models as covariates of no interests. The *t*-maps were transformed into *z*-maps. Since a priori knowledge existed on the brain network engaged in response to visceral pain, e.g., prefrontal, orbitofrontal, somatosensory, motor, insula, and anterior cingulate cortices (ACC), as well thalamus and midbrain regions (Derbyshire, 2003), an uncorrected voxel threshold of $p<0.005$ and an extend threshold of 35 voxels was exploited. Significance was considered when regions passed a spherical small volume correction centered at peak location (radius = 6 mm, $p<0.05$). To further elucidate patient specific effects in the between-group analysis, activity passing an uncorrected voxel threshold of $p<0.01$ was reported. Anatomical structures were labeled in Talairach space, coordinates of maxima were transformed using XjView4 (http://people.hnl.bcm.tmc.edu/cuixu/xjView/).

Differences in psychological and hormonal parameters within and between groups were examined by a paired *t*-test and two-sample *t*-test (SPSS 13.0, SPSS Inc., USA), respectively. The relationship between MPQ sub-scales was examined with a 2-tailed Kendall's *Tau b* correlation analysis. Results were considered significant when passing $p<0.05$.

Results

Psychological and hormonal data

The MPQ scores verified that patients experienced dysmenorrhea at onset of menstruation (onset: total scores [range, 0–78], 32.88 ± 15.16; present pain intensity [PPI; range, 0–5], 2.59 ± 1.28; sensory scores [range, 0–42], 18.12 ± 7.71; affective scores [range, 0–14], 4.76 ± 3.05; evaluative [range, 0–5], 2.82 ± 2.00; offset: no pain). Correlation analysis revealed that total scores were significantly correlated with sensory scores ($r=0.827$, $p<0.001$), affective scores ($r=0.833$, $p<0.001$), evaluative scores ($r=0.448$, $p=0.02$), and PPI ($r=0.453$, $p=0.019$). The sensory scores were also significantly correlated with affective scores ($r=0.693$,

Table 1
Significant brain responses for within and between-group comparisons.

Area	BA	Zmax	Size	Coordinate			Area	BA	Zmax	Size	Coordinate		
				x	*y*	*z*					*x*	*y*	*z*
Pon>Poff							**Pon<Poff**						
L Orbital Frontal G	11*	3.61	164	−8	50	−30	L Post Insula	13#	3.30	797	−40	−8	20
R Sup Frontal G	9	3.30	37	14	54	42	R Post Insula	13#	3.29	174	32	−18	20
R Inf Frontal G	47*	3.30	36	36	32	−8	L SII	40#	3.94	797	−54	−24	14
L Thalamus		2.84	47	−12	−28	−2	L Precentral G	6	3.63	98	−62	2	8
							L Mid Frontal G	9	3.10	93	−42	34	26
							L Sup Frontal G	8	2.77	91	−34	40	38
							L Mid Frontal G	47	3.00	91	−48	48	−10
							L Mid Temporal G	21#	3.41	136	−50	−16	−18
							L Sup Temporal G	38#	2.89	136	−38	18	−30
							L Sup Temporal G	22	3.27	81	44	−58	12
Con>Coff							**Con<Coff**						
L Cerebellum	Culmen	3.12	123	−6	−46	−26	L PCC	23	3.52	244	−2	−34	22
							R PCC	23	3.01	244	10	−42	22
							R Inf Parietal L	40	3.43	71	50	−44	26
							L Parahippo G	19	3.19	166	−36	−50	−6
(Pon − Poff)>(Con − Coff)							**(Pon − Poff)<(Con − Coff)**						
R PCC	23	3.21	479	4	−44	24	L SII	40	4.29	1110	−56	−26	16
L PCC	23	2.89	479	−4	−34	26	L Post Insula	13	2.81	1110	−42	−10	18
R Sup Frontal G	8/9	2.85	19	16	56	42	L Mid Frontal G	9/46	3.52	664	−38	42	36
L Sup Frontal G	11	2.46	4	−8	58	−28	L Precentral G	6	2.75	28	−60	4	6
L Parahipppo G	37	2.37	4	−34	−48	−8	R Sup Frontal G	9	2.45	11	44	46	34
L Thalamus		2.54	44	−12	−30	−4							

BA: Brodmann area; Zmax: peak *Z* value; Size: cluster size; Pon: onset condition of patients; Poff: offset condition of patients; Con: onset condition of controls; Coff: offset condition of controls; L: left; R: right; Post: posterior; Sup: superior; Mid: middle; Inf: inferior; G: gyrus; L: lobule; SII: secondary somatosensory area; PCC: posterior cingulate cortex; Parahippo: parahippocampal. '*' and '#' denotes positive and negative covariation with MPQ total pain rating, respectively.

$p<0.001$), and affective scores were correlated with evaluative scores ($r=0.396$, $p=0.046$) and PPI ($r=0.53$, $p=0.008$).

Onset of PDM was associated with significant elevation of "state" anxiety compared to offset (score ranges: 20–80; onset: 48 ± 10.65, offset: 38.18 ± 8.92, $p=0.002$) and compared to the onset in controls (onset: 40.12 ± 5.7, $p=0.013$). No difference was observed between offset conditions in patients and controls. Both "trait" anxiety (score ranges: 20–80) and depression scores (score ranges: 0–60) did not differ significantly between conditions and groups.

The RIA measurement of blood E2 was significantly lower in onset condition than offset condition in both patients (onset = 45.29 ± 25.47 pg/ml, offset = 93.67 ± 55.03 pg/ml, $p=0.005$) and controls (onset = 38.27 ± 13.16 pg/ml, offset = 90.85 ± 71.53 pg/ml, $p=0.01$).

Factorial analysis of regional cerebral glucose metabolism

In order to account for effects solely due to menstrual pain, variations in "state" anxiety scores and blood E2 levels were incorporated as covariates of no interest in the factorial analysis. Since scores from MPQ sub-scales correlated, we only used total MPQ pain rating as covariate in the additional analysis.

Within group contrasts revealed that the cramping menstrual pain in patients was associated with increased regional metabolism in the left medial orbitofrontal cortex (mOFC, Brodmann area [BA] 11), right lateral orbitofrontal cortex (lOFC, BA47), right medial prefrontal cortex (mPFC, BA 9), and left ventral posterior thalamus (Fig 1A, Table 1). Among these, mOFC and lOFC positively covaried with pain ratings. Significant metabolic decrease at the onset were observed in bilateral posterior insula, left secondary somatosensory cortex (SII), left premotor cortex, left dorsolateral prefrontal cortex (dlPFC, BA 8/9), and left superior and middle temporal gyri (STG/MTG, BA 21/38). Several of these areas covaried negatively with pain ratings (Fig. 1B, Table 1). None of the regions mentioned above significantly covaried with pain duration. Pain duration was significantly positively correlated with the regional activity in right claustrum (cluster peak [*x*, *y*, *z*]: 30, 6, 18; *Z* score = 4.54), left

Table 2
Brain regions covarying with regional maxima for dysmenorrheic patients.

Activation area							Deactivation area						
Area	BA	Zmax	Size	Coordinate			Area	BA	Zmax	Size	Coordinate		
				x	*y*	*z*					*x*	*y*	*z*
Left Orbital Frontal G (−8, 52, −30)							**Left SII (−56, −24, 14)**						
L Sup Temporal G	39/40	3.16	147	−50	−58	26	***R Sup Frontal G***	***9***	***−3.59***	***57***	***18***	***56***	***42***
R Orbital G	47	3.05	59	12	24	−30	R SII	40	4.52	1457	64	−20	16
L Postcentral G	2	2.90	52	−46	−22	46	R Mid Temporal G	39	3.78	1457	60	−66	10
L Parahippo G	Amygdala	2.81	37	−20	−2	18	R Sup Temporal G	22	3.40	1457	64	−36	12
L Lentiform N	Putamen	4.02	506	16	14	−6	***R Post Insula***	***13***	***3.18***	***1457***	***40***	***−30***	***18***
R Lentiform N	Putamen	3.19	221	−22	10	6	R Mid Occipital G	19	2.91	60	40	−68	10
R Cerebellum	Pyramis	3.01	145	18	−78	−30	L Inf Frontal G	47	3.44	398	−46	30	−10
R Cerebellum	Tuber	2.79	145	32	−82	−30	L Mid Temporal G	37	2.90	51	−44	−60	6
Right Inf Frontal G (36, 32−8)							**Left Post Insula (−40, −8, 20)**						
R Precentral G	4	3.55	226	28	−20	66	***R Post Insula***	***13***	***4.05***	***508***	***30***	***−20***	***16***
R Inf Frontal G	11	3.16	42	30	26	−24	R Sup Frontal G	10	3.22	47	18	72	2
R Sup Frontal G	6	3.06	114	−6	6	64	R Cuneus	18	3.21	108	2	−92	14
L Sup Frontal G	6	2.95	106	10	−2	64	L Fusiform G	37	3.30	84	−46	−36	−14
L Postcentral G	5	2.70	42	−26	−40	70	R Caudate N	Body	3.30	508	18	−18	20
							L Cerebellum	Pyramis	2.86	39	−40	−80	−34
Right Sup Frontal G (14, 54, 42)							**Right Post Insula (32, −18, 20)**						
R Medial Frontal G	8	3.94	2323	4	36	40	***L Post Insula***	***13***	***3.60***	***265***	***−40***	***−10***	***20***
L Medial Frontal G	10	2.87	2323	−4	66	10	L Mid Temporal G	19	3.47	70	−34	−60	16
L Sup Frontal G	9/10	3.13	2323	−6	56	40	L Cuneus	18	3.15	344	−6	−72	14
L Sup Frontal G	6	2.97	2323	−8	34	60	R PCC	30	3.03	164	0	−64	10
L ACC	32	2.90	2323	−10	24	38	R Caudate N	Body	2.99	503	16	−14	20
R Mid Frontal G	8	2.75	465	46	20	44							
L Mid Frontal G	4/6	2.95	121	−38	4	42							
L SII	***40***	***−2.97***	***64***	***−58***	***−24***	***14***							
L Thalamus		***3.58***	***391***	***−12***	***−30***	***−2***							
R Lentiform N	Putamen	3.15	97	18	6	2							
Left Thalamus (peak: −12, −28, −2)							**Left Mid Frontal G (peak: −42, 34, 26)**						
L Parahippo G	34	5.11	7496	−16	6	−16	L Sup Frontal G	10	4.20	3368	−34	58	12
R Parahippo G	34	4.16	7496	12	−10	−18	R Sup Frontal G	10	2.98	97	32	56	26
L Caudate N	Body	4.51	7496	−16	−20	24	L Inf Frontal G	47	3.77	3368	−30	32	−18
R Caudate N	Body	2.75	7496	12	2	20	L Mid Frontal G	46	3.44	3368	−38	44	6
L Parahippo G	Amygdala	3.81	7496	−32	−6	−12	R Mid Frontal G	46	3.00	40	46	20	18
R Lentiform N	Putamen	3.65	7496	28	6	−6	L Mid Frontal G	9	3.20	3368	−44	4	20
L ACC	24	3.39	7496	−6	30	14	R Inf Frontal G	9	3.00	94	60	8	24
R ACC	24	2.99	7496	10	16	28	L Inf Frontal G	44	2.97	3368	−56	8	14
R ACC	32	3.20	7496	0	26	36	L Precentral G	6	2.65	3368	−64	−10	32
R Inf Frontal G	***47***	***3.01***	***54***	***36***	***32***	***−2***							
R Sup Frontal G	***9***	***3.96***	***152***	***16***	***56***	***40***							
L Precentral G	4/6	3.11	152	−46	−12	42							
L Sup Frontal G	8	2.99	63	−40	18	56							

N: nucleus; ACC: anterior cingulate cortex; positive and negative *Z*-values denote positive and negative covariation, respectively. See Table 1 for details. Loci in bold and italics denote covarying maxima from Table 1.

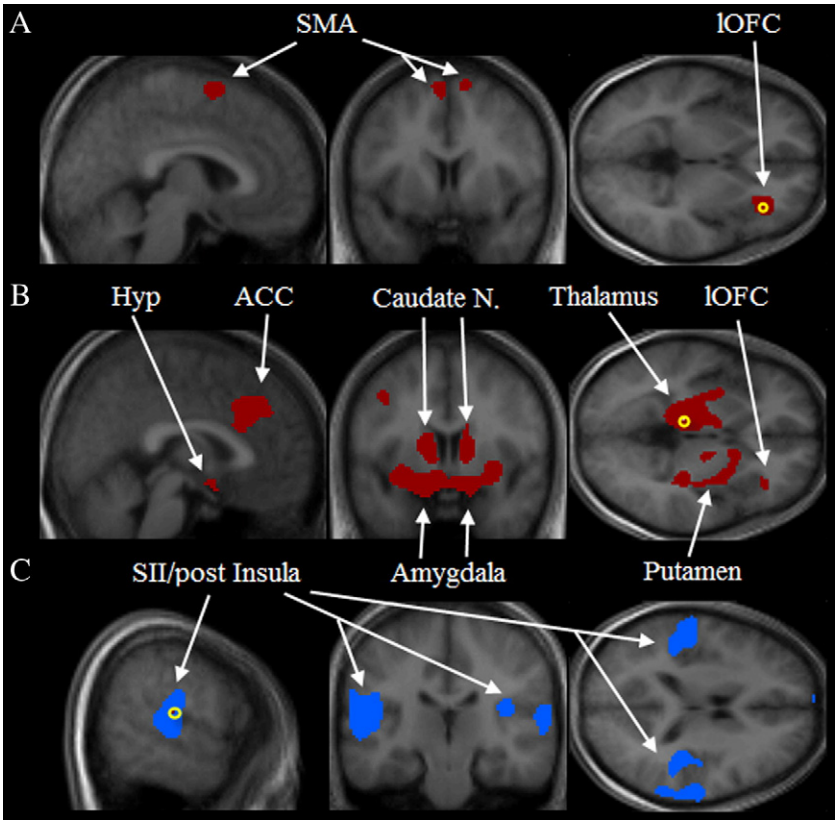

Fig. 2. Regions positively covarying with seed regions (yellow circle) for primary dysmenorrhea patients. (A) The right lateral orbitofrontal cortex (lOFC) positively covaried with bilateral supplementary motor area (SMA). (B) The left ventral posterior thalamus positively covaried with the hypothalamus (Hyp), anterior cingulate cortex (ACC), caudate nucleus, amygdala, ventral putamen and right lOFC. (C) The left secondary somatosensory area (SII) positively covaried with right SII and bilateral posterior insula. Results are superimposed on the averaged anatomical T1 MRI from patients. Red and blue colors represent regions with increased or decreased activity relative to onset in patients from Fig. 1.

inferior temporal gyrus (BA 20; cluster peak: −46, −2, −34; *Z* score = 3.48), and right superior temporal gyrus (BA 38; cluster peak: 34, 6, −34; *Z* score = 3.48). In controls, only left cerebellum showed significantly increased regional metabolism, while bilateral posterior cingulate cortex (PCC), right inferior parietal lobule, and left parahippocampal gyrus showed significant decreased regional metabolism (Table 1).

Comparing patients and controls, increase in regional metabolism was found in bilateral PCC and decreases in left SII and dlPFC (Table 1). To further elucidate pain specific/non-specific activity, findings at a lowered threshold (uncorrected $p<0.01$) were reported. This yielded similar results as in the factorial comparison (Table 1).

Functional covariation with pain-related areas in patients

Covariation analysis was performed for the four main loci showing increased metabolism at onset compared to offset of PDM as well as for main deactivated regions (cluster peaks; Table 2). Of the four activated regions, the left thalamus positively covaried with the right lOFC and mPFC while right mPFC covaried with left thalamus. Both thalamus and mPFC also positively covaried with anterior cingulate cortex and right putamen. The four main loci further covaried with distinct networks of regions (Table 2). The right lOFC positively covaried with motor related areas (Fig. 2A), while the right mPFC also covaried positively with frontal and prefrontal regions as well as negatively with left SII. The left thalamus further covaried with basal ganglia and limbic areas (Fig. 2B).

Decreased activity in the left SII covaried positively with an area in the right hemisphere covering SII and posterior insula and covaried negatively with right mPFC. Posterior insula in the two hemispheres covaried with each other (Table 2, Fig. 2C). The deactivation of left dlPFC positively covaried with frontal and prefrontal regions.

Discussion

Primary dysmenorrhea provides a unique opportunity to study spontaneous clinical pain due to its cyclical nature of pain and pain-free states. Numerous studies have investigated the central representation of acute visceral pain and visceral hyperalgesia (Derbyshire, 2003; Lu et al., 2004; Verne et al., 2003) but none have explored that of visceral menstrual pain in PDM. In the present study, PDM was associated with abnormal metabolic changes in several brain regions involved in various aspects of pain processing. The main finding was increased regional glucose metabolism in thalamic, orbitofrontal and prefrontal areas and decreased regional metabolism in lateral somatic sensorimotor areas when comparing the pain-free state with the pain state in the patient group. Analysis of the difference of differences between the two subject groups yielded similar findings albeit at a lowered threshold. Although the later type of analysis is associated with loss of sensitivity it has the advantage that it accounts for non-specific effects related to variations in menstrual cycle. While regions exhibiting abnormal cerebral glucose metabolism in the present study by no means are uniquely involved in processing of menstrual pain, the constellation of hyper- and hypo-metabolic regions observed in our study revealed a cerebral representation of menstrual pain which differed from that of acute visceral pain and other types of ongoing pain (Apkarian et al., 2005; Derbyshire, 2003; Fumal et al., 2006; Kulkarni et al., 2007; Kupers and Kehlet, 2006; Schreckenberger et al., 2005; Sprenger et al., 2007). Our results cannot be attributed to elevated "state" anxiety or decreased E2 at onset of menstruation in

patients since our statistical model discounts these effects. Elevation of "state" but not "trait" anxiety at onset is in agreement with a previous observation (Granot et al., 2001) and may result from the lack of perceived controllability of chronic pain.

Abnormal hypermetabolism in thalamo-orbitofrontal-prefrontal regions

Hypermetabolism was observed during ongoing menstrual pain in the posterior portion of thalamus covering the ventral–posterior nucleus and the pulvinar. Visceral nociceptive afferents are known to project to the ventral–posterior portion of thalamus via the dorsal column (DC) (Al-Chaer et al., 1998; Ness, 2000; Willis et al., 1999). The DC pathway is considered part of a facilitatory loop that can intensify noxious visceral responses and may be necessary for the maintenance of sensitization associated with chronic visceral pain (Palecek and Willis, 2003; Saab et al., 2004). This is corroborated by the substantial pain relief resulting from DC transection in patients suffering from pelvic cancer (Gildenberg, 2001). The DC pathway has also been implicated in facilitatory modulation of visceromotor functions under inflammatory conditions (Palecek and Willis, 2003). The pulvinar has been implicated in relay of somatosensory information and in directed attention towards sensory stimuli (Romanski et al., 1997). Evidence also suggested a role for the pulvinar in pain processing. Pulvinotomy has previously been used for pain relief in patients with intractable pain albeit with limited long-term effects (Hariz and Bergenheim, 1995; Yoshii and Fukuda, 1979; Yoshii et al., 1980).

In animal models, visceral sensory/nociceptive afferents project from ventral posterior parts of thalamus to visceral sensory areas in lateral posterior OFC/anterior insula (Carmichael and Price, 1995; Jasmin et al., 2004). Pulvinar projections to lateral posterior OFC are also known to exist although these are not the primary source of input (Ongur and Price, 2000; Romanski et al., 1997). Evidence suggests that the lateral posterior OFC serves as an entry point for multimodal sensory information to be further processed in lateral orbitofrontal and in medial prefrontal networks (Kringelbach and Rolls, 2004). The lateral orbitofrontal network provides evaluation of affective stimuli based on, among others, encoding of reward/punishment magnitude (O'Doherty et al., 2001). Furthermore, the lOFC of the right hemisphere has preponderantly been associated with evaluation of aversive stimuli and regulation of negative emotion (O'Doherty et al., 2001). In agreement with this, we found a significant covariation of activity in right lOFC with subjective pain ratings (total MPQ scores consisting of correlated sensory, affective and evaluative scores). The evaluation further serves as substrate for generation of the subjective affective experience as well as for motivation of adaptive behavior through connections to mOFC and mPFC (Kringelbach, 2005).

The mOFC is considered important for monitoring and generation of the subjective affective experience (Kringelbach, 2005). Previous studies indicate that the affective valence is also encoded in this region (Kringelbach, 2005). This notion is further supported by our finding of covariation of mOFC with subjective pain ratings and covariation with activity in amygdala and ventral putamen. Both of these structures are known to be involved in emotion processing and to have direct connections with OFC (Ongur and Price, 2000). Interestingly, mOFC (BA11) has also been suggested to be a region where visceral information is transferred to visceromotor output areas in the medial prefrontal network such as mPFC (BA9). Output projections from this region include areas involved in autonomic function such as hypothalamus and periaqueductal grey (PAG) (Bandler et al., 2000).

Abnormal hypometabolism in lateral sensorimotor regions

In the present study, hypometabolism in mainly left lateral sensorimotor regions was observed during menstrual pain. These regions encompassed dlPFC, posterior insula, SII, and premotor area. Several of these brain regions also covaried negatively with subjective pain ratings. In general, dlPFC is considered an area for integration of somatosensation for generation of behavior through motor and premotor areas (Fuster, 1997). Previous findings suggest that dlPFC may play a key role in top-down inhibition during pain processing. Similar to our results, dlPFC activity was found to be inversely related to thalamic and lOFC activity as well as to subjective pain ratings (Lorenz et al., 2003). Furthermore, dlPFC was found to modulate the effective connectivity between the midbrain and thalamus in such a way that low dlPFC activity was associated with higher correlated activity between midbrain and thalamus. In another study, dlPFC activity during spontaneous chronic back pain was found to be inversely related to mPFC activity which was positively related to subjective pain intensity (Baliki et al., 2006). As previously suggested (Apkarian et al., 2004), dysfunctional dlPFC mechanisms may lead to disinhibition of orbitofrontal networks resulting in increased negative affect. Taken together, it is conceivable that reduced dlPFC metabolism and increased metabolism in thalamus and orbitofrontal regions, as observed in our study, may represent dlPFC disinhibition of thalamic and orbitofrontal circuits. Such a mechanism may be a key factor in generation of pain and hyperalgesia in PDM by maintaining spinal and thalamic sensitization while increasing negative affect.

Our finding of prominent hypometabolism in several sensorimotor regions was unexpected since these regions are known to encode stimulus intensity-related properties. Posterior insula and SII are known to be interconnected key areas for processing of sensory-discriminative information (Kupers and Kehlet, 2006; Tracey and Mantyh, 2007). In agreement with this, posterior insula and SII were found to covary. Although unknown, hypometabolism in these regions may reflect a compensatory inhibitory mechanism in response to excessive excitatory input and the generalized hyperalgesia observed in PDM (Giamberardino et al., 1997; Granot et al., 2001). Prolonged nociceptive input from the periphery may not only lead to central hyperexcitability but also to central reorganization. Alternatively, it can be speculated that hypometabolism in somatic sensorimotor regions may represent reduced behavioral responsiveness to the external environment. In this context, chronic pain of visceral origin is often associated with quiescent behavior possibly promoting healing and limiting further damage. The functional significance of left lateralized hypometabolism in somatic sensorimotor regions remains to be clarified.

The central expression of menstrual pain and other types of pain

The constellation of hyper- and hypo-metabolic regions observed in our study revealed a cerebral representation of menstrual pain which differed from that of acute visceral pain and other types of ongoing pain (Apkarian et al., 2005; Derbyshire, 2003; Fumal et al., 2006; Kulkarni et al., 2007; Kupers and Kehlet, 2006; Schreckenberger et al., 2005; Sprenger et al., 2007). In contrast to previous visceral pain studies, activation of anterior insula was not found while activity in somatosensory and motor areas decreased during menstrual pain. Also, previous studies on ongoing pain mainly revealed a prominent deactivation of (posterior) thalamus (Di Piero et al., 1991; Hsieh et al., 1995; Iadarola et al., 1995; Mountz et al., 1995) but not activation as in the present study. It is reasonable to ask whether these differences could be due to the FDG-PET methodology applied in this study. In two recent FDG-PET studies on recurrent pain, arthritic pain and cluster headache, hypermetabolism was observed in anterior insula and orbitofrontal cortices (Kulkarni et al., 2007; Sprenger et al., 2007). In arthritic pain hypermetabolism was also observed in thalamus, posterior insula, and primary and secondary somatosensory cortices. Another FDG-PET study on tonic muscle pain found activity in anterior and mid insula (Schreckenberger et al., 2005). Thus, the absence of anterior insular activity in the present study is most likely not due to the FDG-PET methodology. Rather, results from these and our studies suggest that an equivocal expression of pathological ongoing pain of different origin may not exist.

The decreased thalamic blood flow as observed in cancer pain (Di Piero et al., 1991), fibromyalgia (Mountz et al., 1995) and neuropathic pain (Hsieh et al., 1995; Iadarola et al., 1995) had been suggested as an expression of overall inhibitory and compensatory mechanism (Iadarola et al., 1995) but can be difficult to reconcile with our current study and other clinical and primate electrophysiological studies (Hirayama et al., 1989; Lenz et al., 1989; Rinaldi et al., 1991; Weng et al., 2000). As discussed previously, enhanced thalamic activity during menstrual pain may indicate increased relay of ascending nociceptive transmission or descending modulation. This is substantiated by the positive covariation between thalamic and lOFC metabolic changes in our study. It is therefore conceivable that the thalamus-lOFC covariation represents a causal functional relationship. Varied patterns of insula engagement were also noted in studies on arthritic pain and headache (Kulkarni et al., 2007; Sprenger et al., 2007). Although anterior insula is considered a visceral sensory area intersecting thalamus and lOFC, a recent study showed that this region is not indispensable for conscious perception of pain (Starr et al., 2009). Thus, the different patterns of brain activity should be ascribed to different natures of different types of clinical pain.

Comment on the FDG-PET methodology

In this study, we used FDG as the indicator of cerebral glucose metabolism which correlates with neural activity (Sokoloff, 1977). The FDG-method is less influenced by global cerebral blood flow which has been shown to be reduced by pain stimulation itself (Coghill et al., 1998; Phelps et al., 1979). Furthermore, due to the longer half-life of FDG this method reflects longer lasting metabolic changes which may be more suitable for imaging of long-lasting ongoing pain (in hours) in contrast to the kinetics of blood flow (in seconds). However, this comes at the cost of temporal resolution, e.g. the number of consecutive scans possible, and the robustness of regional responses to brief painful stimuli. The limited possibility for repeated measurements produces statistically less powerful data-sets.

Conclusion

This study shows that ongoing menstrual pain in dysmenorrhea is accompanied by abnormal brain metabolism in several brain regions involved in various aspects of pain processing. Our findings suggest that disinhibition of thalamo-orbitofrontal-prefrontal networks may contribute to the generation of pain and hyperalgesia in PDM possibly by maintaining spinal and thalamic sensitization while increasing negative affect. Furthermore, excessive excitatory input during menstrual pain may induce compensatory inhibitory mechanism in somatic sensorimotor regions. It remains to be elucidated whether these functional changes are purely peripherally driven or if central changes have occurred that outlasts the cyclic pain sensation and may exacerbate the pain.

Acknowledgments

This work was supported by grants from the Taipei Veterans General Hospital-University System of Taiwan Joint Research Program [VGHUST95-P1-04]; Taipei Veterans General Hospital [V95D-010, V95ER1-001]; National Science Council [NSC 96-2752-B-010-008-PAE]; and Aim for the Top University Plan from Ministry of Education.

References

Al-Chaer, E.D., Feng, Y., Willis, W.D., 1998. A role for the dorsal column in nociceptive visceral input into the thalamus of primates. J. Neurophysiol. 79, 3143–3150.

Apkarian, A.V., Sosa, Y., Sonty, S., Levy, R.M., Harden, R.N., Parrish, T.B., Gitelman, D.R., 2004. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J. Neurosci. 24, 10410–10415.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., Zubieta, J.K., 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain. 9, 463–484.

Bair, M.J., Robinson, R.L., Katon, W., Kroenke, K., 2003. Depression and pain comorbidity: a literature review. Arch. Intern. Med. 163, 2433–2445.

Bajaj, P., Madsen, H., Arendt-Nielsen, L., 2002. A comparison of modality-specific somatosensory changes during menstruation in dysmenorrheic and nondysmenorrheic women. Clin. J. Pain. 18, 180–190.

Baliki, M.N., Chialvo, D.R., Geha, P.Y., Levy, R.M., Harden, R.N., Parrish, T.B., Apkarian, A.V., 2006. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J. Neurosci. 26, 12165–12173.

Bandler, R., Keay, K.A., Floyd, N., Price, J., 2000. Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain. Res. Bull. 53, 95–104.

Carmichael, S.T., Price, J.L., 1995. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J. Comp. Neurol. 363, 642–664.

Coghill, R.C., Sang, C.N., Berman, K.F., Bennett, G.J., Iadarola, M.J., 1998. Global cerebral blood flow decreases during pain. J. Cereb. Blood. Flow. Metab. 18, 141–147.

Derbyshire, S.W., 2003. A systematic review of neuroimaging data during visceral stimulation. Am. J. Gastroenterol. 98, 12–20.

Di Piero, V., Jones, A.K., Iannotti, F., Powell, M., Perani, D., Lenzi, G.L., Frackowiak, R.S., 1991. Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy. Pain 46, 9–12.

French, L., 2005. Dysmenorrhea. Am. Fam. Physician 71, 285–291.

Fumal, A., Laureys, S., Di Clemente, L., Boly, M., Bohotin, V., Vandenheede, M., Coppola, G., Salmon, E., Kupers, R., Schoenen, J., 2006. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain 129, 543–550.

Fuster, J.M., 1997. The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe3rd ed. Lippincott Williams and Wilkins- Raven, New York and Philadelphia.

Giamberardino, M.A., Berkley, K.J., Iezzi, S., de Bigontina, P., Vecchiet, L., 1997. 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 71, 187–197.

Gildenberg, P.L., 2001. Myelotomy through the years. Stereotact. Funct. Neurosurg. 77, 169–171.

Gispert, J.D., Pascau, J., Reig, S., Martinez-Lazaro, R., Molina, V., Garcia-Barreno, P., Desco, M., 2003. Influence of the normalization template on the outcome of statistical parametric mapping of PET scans. NeuroImage 19, 601–612.

Grachev, I.D., Fredrickson, B.E., Apkarian, A.V., 2000. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 89, 7–18.

Granot, M., Yarnitsky, D., Itskovitz-Eldor, J., Granovsky, Y., Peer, E., Zimmer, E.Z., 2001. Pain perception in women with dysmenorrhea. Obstet. Gynecol. 98, 407–411.

Gureje, O., Von Korff, M., Kola, L., Demyttenaere, K., He, Y., Posada-Villa, J., Lepine, J.P., Angermeyer, M.C., Levinson, D., de Girolamo, G., Iwata, N., Karam, A., Guimaraes Borges, G.L., de Graaf, R., Browne, M.O., Stein, D.J., Haro, J.M., Bromet, E.J., Kessler, R.C., Alonso, J., 2008. The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. Pain 135, 82–91.

Harel, Z., 2002. A contemporary approach to dysmenorrhea in adolescents. Paediatr. Drugs. 4, 797–805.

Hariz, M.I., Bergenheim, A.T., 1995. Thalamic stereotaxis for chronic pain: ablative lesion or stimulation? Stereotact. Funct. Neurosurg. 64, 47–55.

Hirayama, T., Dostrovsky, J.O., Gorecki, J., Tasker, R.R., Lenz, F.A., 1989. Recordings of abnormal activity in patients with deafferentation and central pain. Stereotact. Funct. Neurosurg. 52, 120–126.

Hsieh, J.C., Belfrage, M., Stone-Elander, S., Hansson, P., Ingvar, M., 1995. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63, 225–236.

Iadarola, M.J., Max, M.B., Berman, K.F., Byas-Smith, M.G., Coghill, R.C., Gracely, R.H., Bennett, G.J., 1995. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. Pain 63, 55–64.

Jasmin, L., Burkey, A.R., Granato, A., Ohara, P.T., 2004. Rostral agranular insular cortex and pain areas of the central nervous system: a tract-tracing study in the rat. J. Comp. Neurol. 468, 425–440.

Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat. Rev. Neurosci. 6, 691–702.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72, 341–372.

Kulkarni, B., Bentley, D.E., Elliott, R., Julyan, P.J., Boger, E., Watson, A., Boyle, Y., El-Deredy, W., Jones, A.K., 2007. Arthritic pain is processed in brain areas concerned with emotions and fear. Arthritis Rheum. 56, 1345–1354.

Kupers, R., Kehlet, H., 2006. Brain imaging of clinical pain states: a critical review and strategies for future studies. Lancet. Neurol. 5, 1033–1044.

Lenz, F.A., Kwan, H.C., Dostrovsky, J.O., Tasker, R.R., 1989. Characteristics of the bursting pattern of action potentials that occurs in the thalamus of patients with central pain. Brain Res. 496, 357–360.

Lorenz, J., Minoshima, S., Casey, K.L., 2003. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 126, 1079–1091.

Lu, C.L., Wu, Y.T., Yeh, T.C., Chen, L.F., Chang, F.Y., Lee, S.D., Ho, L.T., Hsieh, J.C., 2004. Neuronal correlates of gastric pain induced by fundus distension: a 3 T-fMRI study. Neurogastroenterol. Motil. 16, 575–587.

Mountz, J.M., Bradley, L.A., Modell, J.G., Alexander, R.W., Triana-Alexander, M., Aaron, L.A., Stewart, K.E., Alarcon, G.S., Mountz, J.D., 1995. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthritis Rheum. 38, 926–938.

Ness, T.J., 2000. Evidence for ascending visceral nociceptive information in the dorsal midline and lateral spinal cord. Pain 87, 83–88.

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. 4, 95–102.

Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219.

Palecek, J., Willis, W.D., 2003. The dorsal column pathway facilitates visceromotor responses to colorectal distention after colon inflammation in rats. Pain 104, 501–507.

Phelps, M.E., Huang, S.C., Hoffman, E.J., Selin, C., Sokoloff, L., Kuhl, D.E., 1979. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. Ann. Neurol. 6, 371–388.

Rhudy, J.L., Meagher, M.W., 2000. Fear and anxiety: divergent effects on human pain thresholds. Pain 84, 65–75.

Rinaldi, P.C., Young, R.F., Albe-Fessard, D., Chodakiewitz, J., 1991. Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. J. Neurosurg. 74, 415–421.

Roberts, R.E., 1980. Reliability of the CES-D Scale in different ethnic contexts. Psychiatry. Res. 2, 125–134.

Romanski, L.M., Giguere, M., Bates, J.F., Goldman-Rakic, P.S., 1997. Topographic organization of medial pulvinar connections with the prefrontal cortex in the rhesus monkey. J. Comp. Neurol. 379, 313–332.

Saab, C.Y., Park, Y.C., Al-Chaer, E.D., 2004. Thalamic modulation of visceral nociceptive processing in adult rats with neonatal colon irritation. Brain Res. 1008, 186–192.

Schmidt-Wilcke, T., Leinisch, E., Ganssbauer, S., Draganski, B., Bogdahn, U., Altmeppen, J., May, A., 2006. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. Pain 125, 89–97.

Schreckenberger, M., Siessmeier, T., Viertmann, A., Landvogt, C., Buchholz, H.G., Rolke, R., Treede, R.D., Bartenstein, P., Birklein, F., 2005. The unpleasantness of tonic pain is encoded by the insular cortex. Neurology 64, 1175–1183.

Sokoloff, L., 1977. Relation between physiological function and energy metabolism in the central nervous system. J. Neurochem. 29, 13–26.

Sprenger, T., Ruether, K.V., Boecker, H., Valet, M., Berthele, A., Pfaffenrath, V., Woller, A., Tolle, T.R., 2007. Altered metabolism in frontal brain circuits in cluster headache. Cephalalgia 27, 1033–1042.

Starr, C.J., Sawaki, L., Wittenberg, G.F., Burdette, J.H., Oshiro, Y., Quevedo, A.S., Coghill, R.C., 2009. Roles of the insular cortex in the modulation of pain: insights from brain lesions. J. Neurosci. 29, 2684–2694.

Tracey, I., Mantyh, P.W., 2007. The cerebral signature for pain perception and its modulation. Neuron 55, 377–391.

Verne, G.N., Himes, N.C., Robinson, M.E., Gopinath, K.S., Briggs, R.W., Crosson, B., Price, D.D., 2003. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. Pain 103, 99–110.

Weng, H.R., Lee, J.I., Lenz, F.A., Schwartz, A., Vierck, C., Rowland, L., Dougherty, P.M., 2000. Functional plasticity in primate somatosensory thalamus following chronic lesion of the ventral lateral spinal cord. Neuroscience 101, 393–401.

Willis, W.D., Al-Chaer, E.D., Quast, M.J., Westlund, K.N., 1999. A visceral pain pathway in the dorsal column of the spinal cord. Proc. Natl. Acad. Sci. U. S. A. 96, 7675–7679.

Yoshii, N., Fukuda, S., 1979. Effects of unilateral and bilateral invasion of thalamic pulvinar for pain relief. Tohoku. J. Exp. Med. 127, 81–84.

Yoshii, N., Mizokami, T., Ushikubo, T., Kuramitsu, T., Fukuda, S., 1980. Long-term follow-up study after pulvinotomy for intractable pain. Appl. Neurophysiol. 43, 128–132.