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Dysmenorrhoea is associated with central changes in otherwise healthy women

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ABSTRACT

Patients with chronic pain conditions demonstrate altered central processing of experimental noxious stimuli, dysfunction of the hypothalamic–pituitary–adrenal axis, and reduced quality of life. Dysmenorrhoea is not considered a chronic pain condition, but is associated with enhanced behavioural responses to experimental noxious stimuli. We used behavioural measures, functional magnetic resonance imaging, and serum steroid hormone levels to investigate the response to experimental thermal stimuli in otherwise healthy women, with and without dysmenorrhoea. Women with dysmenorrhoea reported increased pain to noxious stimulation of the arm and abdomen throughout the menstrual cycle; no menstrual cycle effect was observed in either group. During menstruation, deactivation of brain regions in response to noxious stimulation was observed in control women but not in women with dysmenorrhoea. Without background pain (ie, in nonmenstrual phases), activity in the entorhinal cortex appeared to mediate the increased responses in women with dysmenorrhoea. Mean cortisol was significantly lower in women with dysmenorrhoea and was negatively correlated with the duration of the symptom. Additionally, women with dysmenorrhoea reported significantly lower physical but not mental quality of life. Thus, many features of chronic pain conditions are also seen in women with dysmenorrhoea: specifically a reduction in quality of life, suppression of the hypothalamic–pituitary–adrenal axis, and alterations in the central processing of experimental noxious stimuli. These alterations persist when there is no background pain and occur in response to stimuli at a site distant from that of the clinical pain. These findings indicate the potential importance of early and adequate treatment of dysmenorrhoea.

1. Introduction

Dysmenorrhoea (pain with menstruation) is common, affecting up to 90% of adolescent and young women at some time. Despite the availability of a variety of effective pharmacological treatments, it is frequently left untreated, particularly in adolescents [15]. In common with functional pain conditions such as irritable bowel syndrome (IBS) and fibromyalgia; end-organ pathology is frequently not identified (primary dysmenorrhoea). Dysmenorrhoea is not routinely considered as a chronic pain condition and is excluded from both the British and American definitions of chronic pelvic pain (CPP) [1,36]. It is, however, a frequent comorbid symptom in women with CPP [66].

Enhanced responses to experimental noxious stimuli and alterations in the central processing of such stimuli have been demonstrated in many chronic pain conditions, including IBS, fibromyalgia, vulvodynia, neuropathic pain, and rheumatoid arthritis (for meta-analysis see Apkarian et al. [3]). In addition, more recently the function of the hypothalamic–pituitary–adrenal (HPA) axis in patients with chronic somatic symptoms has become a focus for research. In humans, low cortisol levels or a reduced cortisol response have been reported in a number of chronic pain conditions, including CPP [41], IBS [12], fibromyalgia [40], whiplash [23], low back pain [28] and chronic facial pain [24]. Animal models suggest that repeated exposure to a stressor alters both basal levels of cortisol and the cortisol response to an additional acute stressor [58]. However, it remains unknown whether repeated episodes of pain are a sufficient stressor to affect HPA axis function or whether hypocortisolism and/or a blunted cortisol response predispose an individual to the development of chronic pain.

Psychophysical studies have demonstrated enhanced responses to experimental somatic [2,5,25,27]and visceral [14] stimuli in women with dysmenorrhoea compared with pain-free control subjects, supporting the notion that changes have occurred within the pain neuraxis. The present study had 2 aims: (1) to confirm previous observations of increased pain report in women with dysmenorrhoea, and (2) to explore whether this symptom is associated with other features observed in chronic pain conditions, such as altered psychology, diminished quality of life (QoL),

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reduced function of the HPA axis, and central changes in pain processing. If dysmenorrhoea is similar to other chronic pain conditions, then the experience of repeated monthly painful episodes by these women should be reflected in alterations in central processing of noxious stimuli, as well as a reduction in QoL and HPA axis function. Here, we used both behavioural measures and functional magnetic resonance imaging (FMRI) to investigate the response to experimental noxious stimuli in otherwise healthy women, with and without dysmenorrhoea, across the menstrual cycle. The design allowed us to control for the effects of hormonal variation and, interestingly, compare the groups at a time when there was a difference in background pain and when no such difference was present.

2. Methods

2.1. Subjects

The Central Oxfordshire Research Ethics Committee provided ethical approval for this study, and written informed consent was obtained from all subjects. Our aim was for 12 women with self-reported dysmenorrhoea ($\geqslant$4 of 10 on a numerical rating scale anchored with 0 = no pain and 10 = worst pain imaginable) and 12 control women (pain with menstruation $\leqslant$3 of 10) to complete the study. Women with pain persisting throughout the month (ie, with CPP rather than pure dysmenorrhoea) were excluded.

Subjects were recruited by advertisement and word of mouth to participate in a study to investigate women with and without dysmenorrhoea. No subject was recruited from a clinic. All subjects were required to have regular menstrual cycles, not to have used exogenous hormones or centrally acting medication for the preceding 6 months, and not to suffer from chronic pain conditions. Subjects completed a detailed medical questionnaire to ensure that they were eligible to participate in the study. This questionnaire included numerical rating scales for pain with menstruation and at other times throughout the month, the Rome III criteria for IBS [17], as well as detailed questions relating to bladder function, including symptoms associated with bladder filling and emptying, to allow identification of possible interstitial cystitis/painful bladder syndrome (IC/PBS). All subjects underwent verbal screening to ensure that they did not meet any of the exclusion criteria for magnetic resonance (MR) experimentation, such as the presence of implanted devices (including pacemakers, aneurysm clips, etc.), recent surgery, previous injury involving metal, nonremovable body piercings, and pregnancy.

Subjects were asked which group they considered themselves to be in when they volunteered; all subjects subsequently rated their pain with menstruation appropriately for the group they reported themselves to be in. A total of 13 control subjects and 17 women with dysmenorrhoea were recruited; 12 subjects in each group completed all parts of the study. One control subject only completed 1 scan successfully due to technical problems and commenced hormonal contraception before the other scans could be scheduled. Two subjects with dysmenorrhoea were recruited but withdrew before scanning commenced because of pressures of work; a third subject had the first scan but then moved to a different town, whereas a fourth underwent 2 scan sessions but was repeatedly unavailable for the menstrual-phase scan and then decided to withdraw from the study. One woman with dysmenorrhoea admitted to use of antipsychotic medication after her first scan and was therefore excluded from the study.

2.2. Noxious stimuli

A thermal resistor (developed in-house) was used to deliver the noxious thermal stimulation, as has been described previously [7,19,42]. Stimuli (see Section 2.3) were delivered to the midline lower abdomen (T10-12) and left inner forearm. The midline lower abdomen was chosen as the site for stimulation as it is an area to which dysmenorrhoea and other gynaecological pains are referred [37]. The inner arm was chosen as the control site.

2.3. Study design

All subjects underwent 3 experimental sessions. These sessions were scheduled for day 1 to 2, 10 to 12 and 20 to 22 of their menstrual cycle (where day 1 is the first day of menstruation). The order of these sessions was randomised across each group.

Immediately prior to each scan, subjects completed a state anxiety [54] and current pain questionnaire. Thermodes were placed as described earlier, and the subject was positioned in the scanner. A modified random staircase method was used to identify the temperature at each site that corresponded to a pain intensity rating of 5 of 10 (0 = no pain, 1 = just painful, 10 = extremely painful). During the functional scans, 10 stimuli of this temperature, each lasting 3 seconds, were delivered with an interstimulus interval of 55 to 65 seconds. Twelve seconds after the termination of each heat stimulus, a visual analogue scale (VAS) was displayed on the screen for 9 seconds, with the anchors "no pain" and "extremely painful." After 1second, a further VAS with the anchors "not unpleasant" and "extremely unpleasant" was displayed for 9 seconds. Subjects rated the pain intensity and unpleasantness of each stimulus with a slider using their right hand. The order of stimulation of the 2 sites was randomised across each group.

Blood for a hormone profile was drawn from an antecubital vein after completion of each scanning session. Prior to the day 20 to 22 scan, subjects used ovulation kits (InstAlert, Acon Laboratories, San Diego, CA, USA) for further confirmation of cycle phase.

In their own time, subjects also completed a detailed medical, gynaecological, and obstetric questionnaire. This included a set of validated psychological tools: trait anxiety [54], Beck Depression Inventory [9], Pain Catastrophising Scale (PCS) [56], and Pain Vigilance and Awareness Questionnaire [38], and a quality of life measure: the SF-36 [61].

2.4. MRI data acquisition

Subjects were scanned in a 3T Siemens/Varian MRI system with a bird-cage radiofrequency coil and a 4-channel phased-array receiver coil. A standard whole-brain gradient echo-planar imaging sequence was used for the 3 functional scans (repetition time = 3 seconds; echo time = 30 ms; 3.5-mm-thick axial slices; 200 volumes (the first 4 are dummy scans), field of view = 224 $\times$ 224 mm, matrix = 64 $\times$ 64 $\times$ 41, voxel size = 3.5 $\times$ 3.5 $\times$ 3.5 mm). A field map was also acquired with the same parameters to aid accurate registration. In addition, at one visit a T1-weighted high-resolution structural scan (64 slices $\times$ 3 mm) was taken for anatomical overlay of activation.

2.5. Analysis of serum hormone levels

Blood samples were centrifuged for 10 minutes at 1300 rpm, serum was extracted and stored at -80°C for batch analysis of samples by Pfizer Laboratory, New Haven, CT, USA, with commercially available assays (Axsym, Abbott Laboratories, Chicago, IL, USA). Total serum concentrations were assayed using a microparticle enzyme immunoassay technology for the sex steroid

hormones estradiol, progesterone, and testosterone, and a fluorescence polarisation immunoassay for cortisol.

2.6. Analysis of stimulus-evoked FMRI signal changes

All analyses were performed using FEAT (FMRIB Expert Analysis Tool) version 5.98, part of FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl) [52].

The following preprocessing steps were applied to each set of FMRI data: removal of the first 4 dummy volumes, removal of non-brain signal using a brain extraction tool [51], motion correction [35], B0 field unwarping [53], spatial smoothing using a Gaussian kernel of full-width-half-maximum of 5 mm, demeaning of each voxel time course, and nonlinear high-pass temporal filtering (cut-off: 90 seconds).

A general linear modelling approach was used to model the response to thermal stimuli. The stimulus input function was convolved with a gamma haemodynamic response function (standard deviation 3 seconds, mean lag 6 seconds) to generate the regressor of interest. The estimated motion parameters for each subject were included as covariates of no interest to reduce spurious activations due to head motion. Registration was performed to the subject's T1 high-resolution structural image and then to standard space (Montreal Neurological Institute 152 brain) using FLIRT (FMRIB's Linear Image Registration Tool) [34].

All higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 with automatic outlier detection [63,64]. Results were considered significant if $z > 2.3$, with a cluster threshold of $P < .05$ to correct for multiple comparisons.

Imaging data from the menstrual phase scan (day 1 to 2) was considered separately because of the potential confound of background pain/discomfort, whereas data from the 2 nonmenstrual phase scan sessions (day 10 to 12 and 20 to 22) were combined, as there was no significant difference in the temperature required to elicit a 5 of 10 rating for these 2 sessions in either group.

Given the results discussed in Section 3.4, activity within the entorhinal cortex (ERC) was extracted as has been described previously [43]. In brief, the median percentage increase in BOLD (Blood Oxygenation Level Dependent) signal was extracted using the area defined by the Harvard–Oxford cortical atlas as left entorhinal cortex, with a threshold at 80% as a mask.

3. Results

3.1. Psychological profiles and quality of life

No significant differences were seen between the groups in age, parity, or number of years of menstruation. Beck Depression Inventory score was significantly higher in women with dysmenorrhoea than in control women (5 ± 4 [mean ± standard deviation] versus 2 ± 3, unpaired 2-tailed *t*-test, $P = .040$); however, the values were not clinically significant (score <10 = no or minimal depression [10]). No significant differences were seen between the groups in any of the other psychological measures (Table 1).

The women with dysmenorrhoea had significantly lower values on their assessment of the physical component (PCS) of their quality of life (SF-36) (49 ± 9 versus 56 ± 2, $P = .017$), but there was no difference in the mental component (51 ± 5 versus 52 ± 6, $P = .800$) (Fig. 1).

3.2. Behavioural data

The women with dysmenorrhoea rated their pain with menstruation significantly higher than control women (6.1 ± 1.6 versus 1.3 ± 1.3, $P < .001$), but there were no differences in their ratings of pain with ovulation or intercourse, or of pelvic pain during the remainder of the cycle. As expected, background pain ratings were significantly different between the groups during the menstrual phase (2.8 ± 2.0 versus 0.6 ± 1.2, $P = .004$) but not at the other visits (Table 1).

The women with dysmenorrhoea required a significantly lower temperature than the control women to obtain a pain intensity rating of 5 of 10 at both sites (arm: $F = 6.7$, $P = .02$; abdomen: $F = 6.0$, $P = .02$) (Table 2). There was no significant effect of day of cycle on the temperature required in either group (Fig. 2). Considering all the women (controls and dysmenorrhoea), the mean temperature required over all 3 visits was significantly negatively correlated with their rating of the severity of pain with menstruation (arm: $r = -0.415$, $P = .04$; abdomen: $r = -0.427$, $P = .04$) (Fig. 3).

On-line ratings (ratings obtained during the FMRI scan) of both pain intensity and unpleasantness were not significantly different between the groups and did not vary with the menstrual cycle (data not shown).

3.3. Hormonal data

As expected, there was a significant main effect of the menstrual cycle on serum levels of estradiol, progesterone, and testosterone, but no effect of group (Table 3). However, there was a significant main effect of group on serum cortisol levels with no effect of the menstrual cycle. When cortisol levels across all 3 visits were combined, women with dysmenorrhoea had significantly lower mean cortisol levels than controls (5.6 ± 1.9 versus 8.7 ± 3.0 μg/dL, $P = .005$).

In the women with dysmenorrhoea, a significant negative correlation was observed between the number of years that dysmenorrhoea had been present and the mean serum cortisol level, such that the longer subjects had experienced dysmenorrhoea, the lower their cortisol levels ($r = -0.77$, $P = .004$). To confirm that this observation was not an effect of age or menstruation per se (as opposed to painful menstruation), these 2 relationships were examined in the control group. There was no correlation between mean serum cortisol levels and either age ($r = -0.218$, $P = .5$) or number of years of menstruation ($r = -0.25$, $P = .44$) in this group (Fig. 4).

3.4. Imaging data

As expected, group mean activations in response to noxious thermal stimuli of both sites, in both groups, at each visit, included brain areas known to be associated with the perception of pain. Fig. 5 illustrates the response to noxious stimulation during the menstrual phase for the 2 groups, and Tables 4A and B give a comprehensive list of the clusters activated.

During the menstrual phase, there was no significant difference between the groups in brain activity increases in response to noxious stimulation of either site. However, unlike controls, no deactivation was seen in response to noxious stimulation of the arm in the women with dysmenorrhoea, and only the occipital cortex deactivated in response to stimulation of the abdomen in this group, compared with the widespread deactivations seen in controls (Fig. 5, Tables 4A and B).

During nonmenstrual phases, no brain areas were more active in response to noxious stimulation of the abdomen in controls compared with women with dysmenorrhoea. However, the left ERC and inferior/middle temporal gyrus were significantly more active in response to stimulation of the abdomen (Fig. 6, Table 5) in women with dysmenorrhoea compared with controls. No areas of significant difference were seen between the 2 groups in response to noxious stimulation of the arm, although the left ERC

Table 1
Subject characteristics.

	Controls (n = 12)	Women with dysmenorrhoea (n = 12)	*P* value (unpaired, 2-tailed *t*-test)
Age	32 ± 10	30 ± 7	NS
No. years menstruation	19 ± 10	17 ± 6	NS
No. parous	3	3	NS
Trait anxiety	33 ± 4	37 ± 9	NS
Hypervigilance	27 ±15	31 ± 15	NS
Catastrophising	6 ± 4	7 ± 10	NS
Depression	2 ± 3	5 ± 4	.04*
State anxiety day 1	32 ± 7	33 ± 9	NS
State anxiety day 10	33 ± 7	36 ± 12	NS
State anxiety day 20	30 ± 5	35 ± 15	NS
PCS	56 ± 2	49 ± 9	.017*
MCS	52 ± 6	51 ± 5	NS
Pain with menstruation	1.3 ± 1.3	6.1 ± 1.6	.000**
Dyspareunia	0 ± 0	1 ± 2	NS
Background pain day 1	0.6 ± 1.2	2.8 ± 2.0	.004**
Background pain day 10	0.3 ± 0.6	0.8 ± 1.2	NS
Background pain day 20	0.3 ± 0.9	0.7 ± 2.0	NS

Summary of the characteristics of subjects participating in this study. Data are expressed as mean ± SD.
MCS, mental component score of SF36; NS, nonsignificant; PCS, physical component score of SF36.
* Significant at $P < .05$
** Significant at $P < .01$

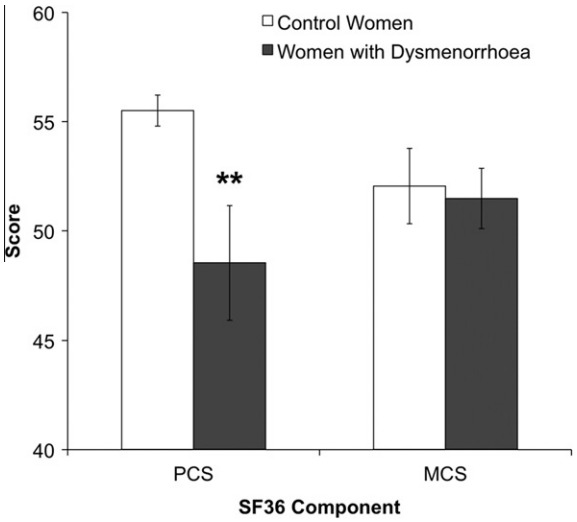

Fig. 1. Quality of life measures in women with and without dysmenorrhoea. Data are expressed as mean ± standard error of the mean. Unpaired *t*-tests were used to compare the groups. Women with dysmenorrhoea reported significantly lower on the physical component of the SF-36 when compared with control women ($P = .01$). There was no difference in scores on the mental component between the groups ($P = .8$). **$P = .01$. MCS, mental component summary; PCS, physical component summary.

Table 2
Temperature required (°C) to obtain a pain intensity rating of 5 of 10.

		Controls (n = 12)	Women with dysmenorrhoea (n = 12)	*P* value (unpaired, 1-tailed, *t*-test)
Arm	Day 1	51.5 ± 3.9	47.6 ± 5.1	.021*
	Day 10	52.4 ± 2.7	48.1 ± 4.6	.006**
	Day 20	52.1 ± 3.7	47.8 ± 4.5	.009**
Abdomen	Day 1	52.7 ± 3.6	49.0 ± 3.6	.010*
	Day 10	53.0 ± 3.4	49.7 ± 4.5	.027*
	Day 20	53.2 ± 4.2	49.7 ± 3.7	.021*

Data are expressed as mean ± SD. Repeated-measures analysis of variance was used to assess for a main effect of group, and unpaired 1-tailed *t*-tests to perform post-hoc comparisons of the 2 groups at each timepoint (as women with dysmenorrhoea were hypothesised to require less temperature a priori). There was a significant main effect of group for both sites (arm: $F = 6.7$, $P = .02$; abdomen: $F = 6.0$, $P = .02$).
* Significant at $P < .05$.
** Significant at $P < .01$.

and inferior/middle temporal gyrus showed greater activity in the women with dysmenorrhoea compared with the controls if the subthreshold data were examined.

To study this observation in more detail, the median activity in the left ERC was extracted for each subject at each timepoint in response to stimuli at each site. A significant correlation between mean activity in this area over the 3 scan sessions in response to noxious stimulation and subjects' ratings of their pain with menstruation was observed (arm: $r = 0.44$, $P = .03$; abdomen: $r = 0.58$, $P = .003$) (Fig. 7).

4. Discussion

The data presented here demonstrate that many of the features associated with chronic pain conditions are also seen in women with dysmenorrhoea, specifically a reduction in quality of life, suppression of the HPA axis, and altered central processing of experimental stimuli such that a significantly lower temperature compared with controls produces the same pain intensity rating (ie, central amplification of nociceptive inputs occurs). At a neuronal level, this increased sensitivity to noxious stimuli appears to be mediated by activity in the entorhinal cortex, a region previously implicated in the augmentation of pain perception by anxiety [42] and anticipation [19]. Additionally, minimal deactivation in response to noxious stimuli during menstruation in women with dysmenorrhoea may represent alterations in resting state networks in this group [60]. It is of particular interest that the altered central response persists when there is no background pain and occurs in response to stimuli at a site distant to that of the clinical pain. Furthermore, it appears that there is a spectrum of central changes influenced both by the severity of pain experienced and by the length of time the symptom has been present.

4.1. Lack of menstrual cycle effect

The available evidence in the literature regarding the influence of the menstrual cycle on pain perception is, at best, inconclusive.

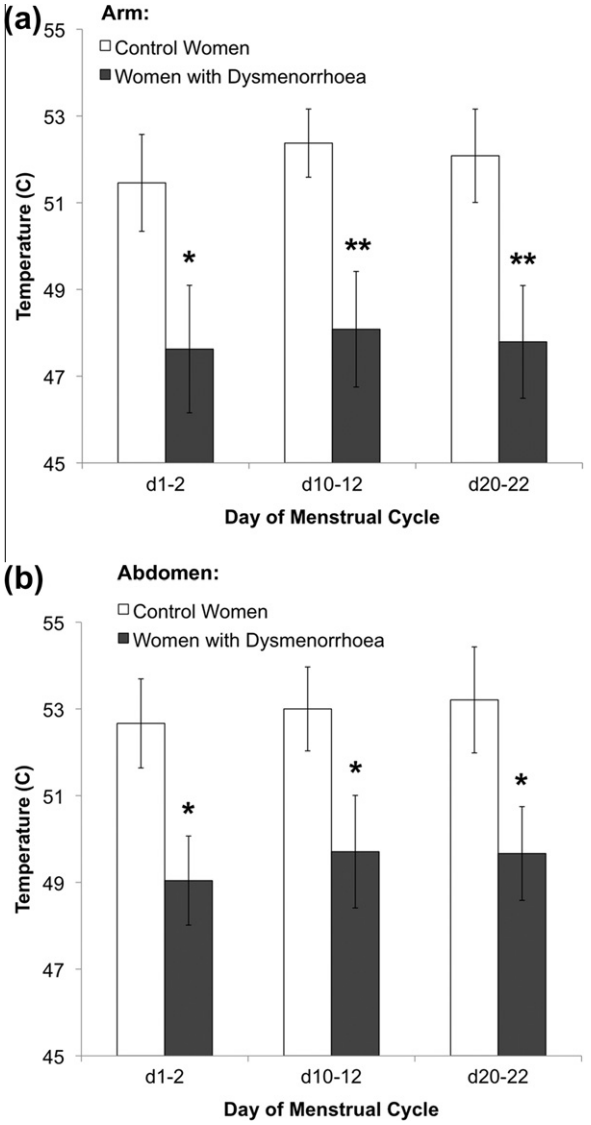

Fig. 2. The temperature required to obtain a pain intensity rating of 5/10 on (A) the left inner arm and (B) the midline lower abdomen at 3 timepoints across the menstrual cycle (day 1 to 2, day 10 to 12, and day 20 to 22) in women with and without dysmenorrhoea. Data are expressed as mean ± standard error of the mean. Repeated-measures analysis of variance was used to assess for a main effect of group, and unpaired *t*-tests to perform post-hoc comparisons of the 2 groups at each timepoint: $^{*}P < .05$; $^{**}P < .01$. (A) Arm. There was a significant main effect of group; women with dysmenorrhoea required a significantly lower temperature to obtain the same pain intensity rating as control women ($F = 6.7$; $P = .02$). There was no significant effect of timepoint or a group * timepoint interaction. (B) Abdomen. There was a significant main effect of group; women with dysmenorrhoea required a significantly lower temperature to obtain the same pain intensity rating as control women ($F = 6.0$; $P = .02$). There was no significant effect of timepoint or a group * timepoint interaction.

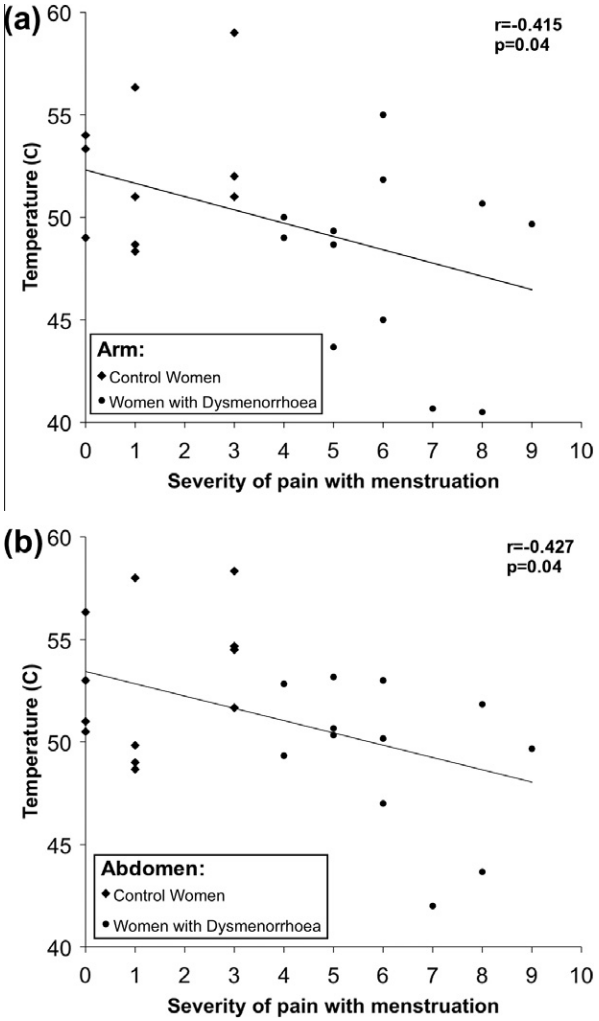

Fig. 3. The relationship between severity of pain with menstruation and mean temperature required to obtain a pain intensity rating of 5 of 10 across the 3 timepoints on the left inner arm and the midline lower abdomen. Pearson's correlation was used to investigate the relationship: $^{*}P < .05$. (A) Arm. Mean temperature was significantly negatively correlated with severity of pain with menstruation ($r = -0.415$, $P = .04$). (B) Abdomen. Mean temperature was significantly negatively correlated with severity of pain with menstruation ($r = -0.427$, $P = .04$).

Discrepancies between these results are partly due to the many different noxious stimuli used and the wide variation in the definition of menstrual cycle phase [49]. We found no menstrual cycle effect on the perception of moderately painful somatic stimuli in both healthy women and those with dysmenorrhoea. This is in agreement with other work in both pain-free women [2,4,16,21,25,27,29,33,44,50,55,57] and those with dysmenorrhoea [27] and interstitial cystitis [44]. However, in contrast, a few studies do suggest that an influence is exerted on the perception of noxious muscular and visceral stimuli in those with painful conditions [25,31,44].

The women in this study were screened to ensure they only had pain during menstruation, yet the differences observed between the groups persisted beyond the time of menstruation and therefore cannot be explained by the presence of background pain. Furthermore, although the pain of dysmenorrhoea is localised to the lower abdomen, pelvis, and lower back, the increased sensitivity was demonstrable in response to stimuli of the arm as well as the abdomen. This evidence suggests that repeated episodes of dysmenorrhoea lead to long-lasting central changes, rather than a local response to the presence of background pain.

4.2. QoL and psychological measures

The mean SF-36 PCS for healthy women of this age is 53.1 [62]. Therefore, despite the pain of dysmenorrhoea only being present for between 1day and a few days per month, it can be seen to have an impact on the perception of physical QoL, with 8 of the 12 women with dysmenorrhoea in this study having a PCS below that expected of a healthy population. Behavioural interventions have not been convincingly demonstrated to be effective in the treatment of

Table 3
Hormonal data.

		Controls	Women with dysmenorrhoea	Main effect of menstrual cycle	Main effect of group
Estradiol (pg/mL)	Day 1 to 2	43 ± 24	42 ± 11	F = 7.7	NS
	Day 10 to 12	119 ± 98	109 ± 63	$P = .002^{**}$	
	Day 20 to 22	99 ± 56	126 ± 60		
Progesterone (ng/mL)	Day 1 to 2	1.54 ± 2.64	0.63 ± 0.48	F = 9.5	NS
	Day 10 to 12	0.29 ± 0.25	0.20 ± 0.11	$P = .001^{**}$	
	Day 20 to 22	6.88 ± 7.50	9.26 ± 9.77		
Testosterone (ng/mL)	Day 1 to 2	0.22 ± 0.09	0.19 ± 0.09	F = 4.0	NS
	Day 10 to 12	0.30 ± 0.09	0.23 ± 0.07	$P = .029^{*}$	
	Day 20 to 22	0.28 ± 0.11	0.23 ± 0.12		
Cortisol (μg/dL)	Day 1 to 2	9.3 ± 6.0	6.2 ± 2.7	NS	F = 6.2
	Day 10 to 12	9.5 ± 4.5	5.9 ± 2.9		$P = .024^{*}$
	Day 20 to 22	7.7 ± 3.1	5.1 ± 1.8		

Summary of serum steroid hormone levels after each scan session. Data are expressed as mean ± SD. Repeated-measures general linear models were used to investigate the effects of group and menstrual cycle.
NS, not significant.
* Significant at $P < .05$.
** Significant at $P < .01$.

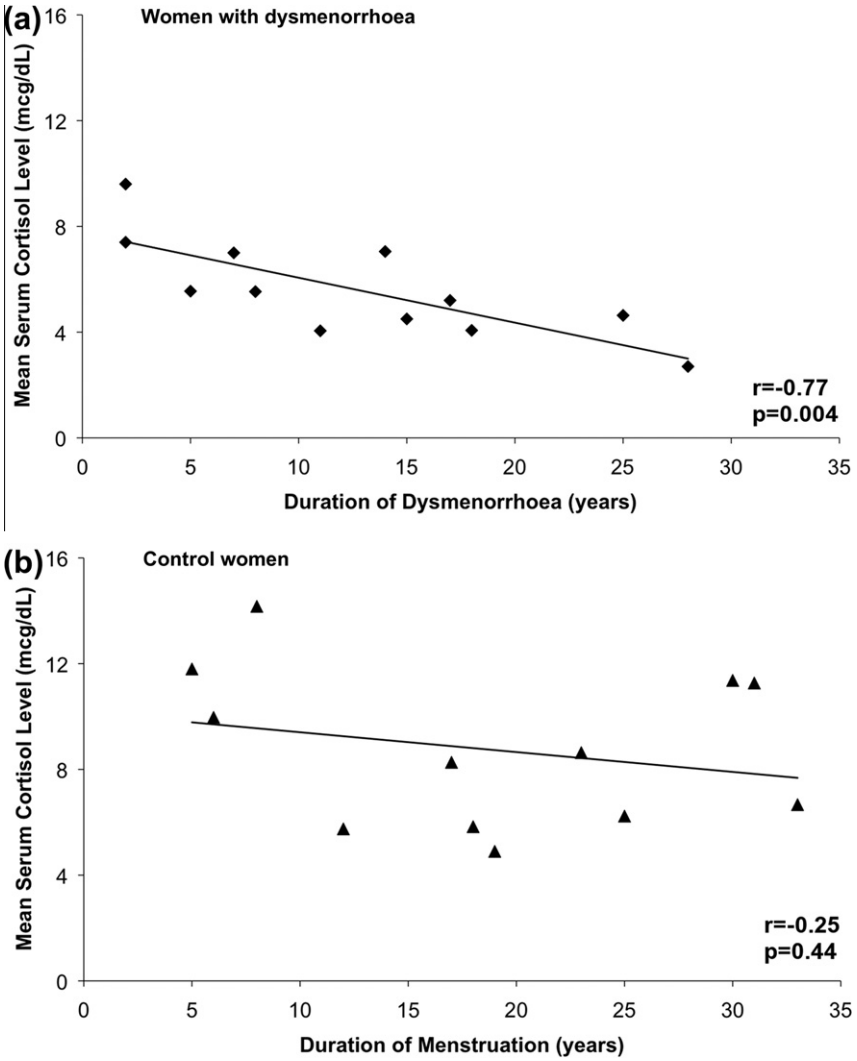

Fig. 4. The relationship between mean cortisol (across 3 timepoints) and duration of (A) dysmenorrhoea in women with dysmenorrhoea and (B) menstruation in control women. Pearson's correlation was used to investigate the relationships. (A) Women with dysmenorrhoea. Mean serum cortisol levels were significantly negatively correlated with the number of years of dysmenorrhoea (r = −0.77; $P = .004$). (B) Control women. There was no significant correlation between mean serum cortisol levels and the number of years of menstruation (r = −0.25; $P = .44$) or age (r = −0.218, $P = .5$) in the pain-free women.

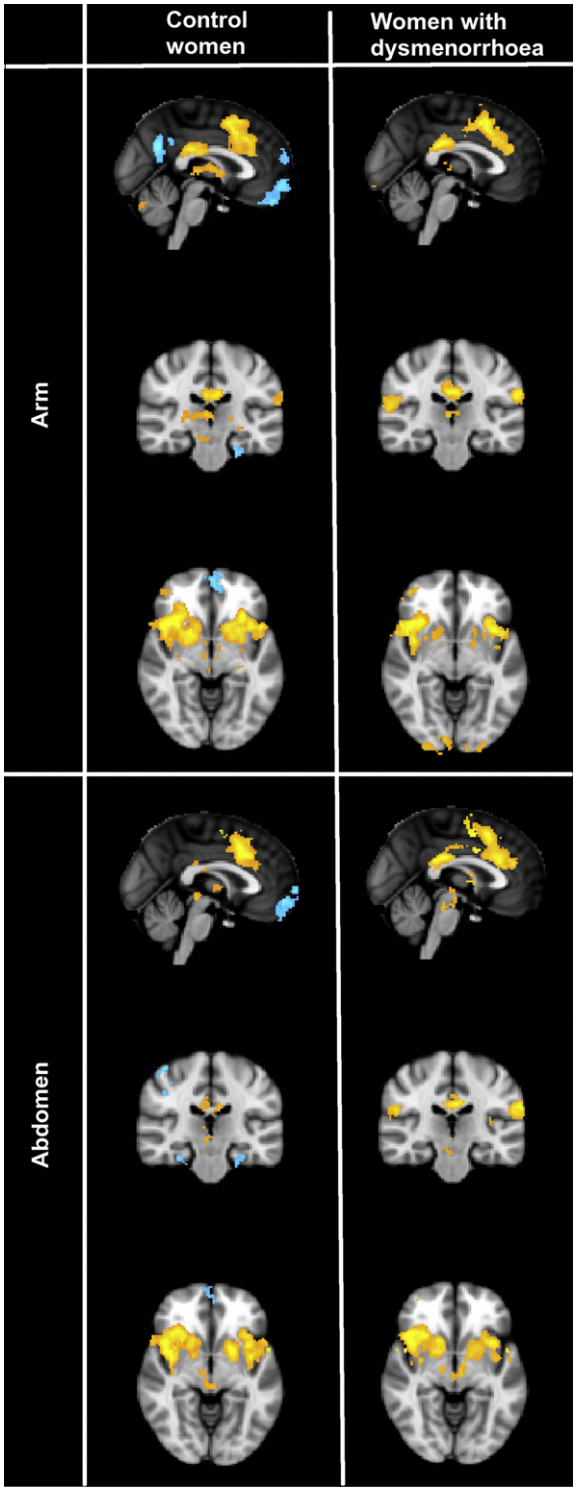

Fig. 5. Results of a mixed-effects analysis of the average group response to noxious thermal stimulation of the left arm and midline lower abdomen for the 2 groups (control women and women with dysmenorrhoea) during menstruation (day 1 to 2). Data shown are the results of mixed-effects analyses with outlier deweighting and are corrected for multiple comparisons, $z > 3$, $P < .05$. Images shown are x = 45, y = 51, z = 33, and are representative. All areas of activation above threshold are listed in Table 4A and B. Images are presented radiologically, with yellow representing activation and blue deactivation.

dysmenorrhoea [46], thus it is not surprising that we were unable to demonstrate significant differences in the psychological profiles and MCS between the groups.

4.3. Augmentation of pain perception by the ERC

The ERC, a component of the hippocampal formation, is particularly known for its role in memory formation [32]. However, the hippocampus and the ERC itself have also been shown to have a role in pain processing [39,45]. Although activation of the hippocampus in response to a noxious stimulus is not consistently seen in either healthy controls or chronic pain patients [3], evidence suggests that both structural [65] and functional [18] changes occur in the hippocampus with chronic pain. Functional alterations in the ERC in chronic pain patients may represent increased anxiety or anticipation of or attention to the stimulus, as acute manipulation of these factors in healthy subjects is associated with activity in this region [19,59].

4.4. Imaging during the menstrual phase

During menstruation there was a significant difference between the groups in their background pain rating but not in any of the other behavioural measures obtained. Scheduling experimental sessions on the first day of menstruation (day 1) was difficult, therefore many of the women were tested on day 2. That the pain of dysmenorrhoea is usually worst at the start of menstruation [22] probably explains the difference between background pain rating on the day of the menstrual scan (2.8 ± 2.0) and the rating of their usual pain with menstruation (6.1 ± 1.6).

Comparing the response to the noxious stimuli during menstruation, it is striking that although the activation patterns are remarkably similar, the women with dysmenorrhoea demonstrated no significant deactivations in response to stimulation of the arm and only of the occipital cortex in response to the abdomen (Tables 4A and B, Fig. 5). One explanation for this finding is that brain areas where deactivation would usually occur during the experience of pain [3] are already maximally deactivated by the pain of dysmenorrhoea, so further deactivation in response to a noxious stimulus is not observed. Alternatively, alterations in resting state (default mode network) activity may be present in the women with dysmenorrhoea. Default mode network activity is increasingly being investigated [60], and is known to vary depending on the cognitive load of a task [47]. Alterations in the activity of this network have been demonstrated in patients with chronic back pain [6], and thus may also occur in women with dysmenorrhoea. Further investigation of this observation requires studies designed specifically to assess activity in these networks. That deactivation of the ERC is seen in the control women during menstruation but not in the women with dysmenorrhoea further supports a central role for the ERC in the augmentation of pain perception in this group of women with dysmenorrhoea.

4.5. Cortisol

Acute stress causes a rapid rise in serum cortisol levels, facilitating a response to the stressful situation [48]. Animal studies have demonstrated an opioid-independent system of stress-induced analgesia that is blocked by suppression of the HPA axis [20]. Recent evidence suggests that this system may be mediated by endocannabinoids [30]. The endocannabinoid receptor CB_1 is found in particularly high levels in the hippocampus and entorhinal cortex [13]. Thus, the augmentation of pain perception by the entorhinal cortex, seen in the women with dysmenorrhoea, could potentially be secondary to a failure of endocannabinoid-mediated stress-induced analgesia in this region.

The data presented here are in support of an effect of repeated painful episodes on the activity of the HPA axis. Although cortisol levels are known to decrease with age, these data clearly demonstrate a relationship between the number of years over which

Table 4A
Summary of regions activated or deactivated by noxious thermal stimulation of the left arm and midline lower abdomen in women with and without dysmenorrhoea during the menstrual phase: activations.

Region of activation	Arm		Abdomen	
	Control women (*z* score)	Women with dysmenorrhoea (*z* score)	Control women (*z* score)	Women with dysmenorrhoea (*z* score)
Right insula	5.57	5.30	5.57	5.22
Left insula	5.24	4.84	5.40	5.07
Right SII	4.75	4.94	–	5.04
Left SII	4.0	4.6	4.82	4.84
Cerebellum	4.65	3.9	–	4.43
ACC	4.78	5.04	5.13	4.79
PCC	4.68	4.46	3.89	4.89
Right caudate	4.94	3.8	3.66	3.58
Left caudate	–	–	3.76	3.02
Right putamen	4.91	3.55	3.71	3.85
Left putamen	3.95	3.23	4.85	3.76
Right thalamus	4.6	3.99	3.61	3.24
Left thalamus	3.67	3.14	–	3.25
Right premotor cortex	4.4	4.8	4.70	4.10
Left premotor cortex	4.2	4.0	5.05	4.0
Right amygdala	4.73	–	–	–
Left amygdala	3.6	–	–	–
Right orbitofrontal cortex	3.75	3.18	5.11	3.68
Left orbitofrontal cortex	–	3.87	4.71	3.91
PAG	3.0	–	3.48	–
Occipital pole	–	3.8	4.03	–
Right hippocampus	–	3.19	–	–
Brainstem (not PAG)	3.6	–	3.17	3.69

Results are expressed as peak *z* scores derived from a mixed-effects analysis with outlier deweighting and a threshold at $z > 3.0$, $P < .05$.
–, no significant activations in this region; ACC, Anterior cingulate cortex; PAG, Periaqueductal gray; PCC, Posterior Cingulate cortex.

Table 4B
Summary of regions activated or deactivated by noxious thermal stimulation of the left arm and midline lower abdomen in women with and without dysmenorrhoea during the menstrual phase: deactivations.

Region of deactivation	Arm		Abdomen	
	Control women (*z* score)	Women with dysmenorrhoea (*z* score)	Control women (*z* score)	Women with dysmenorrhoea (*z* score)
Precuneous	4.31	–	–	–
Frontal medial cortex	4.28	–	3.98	–
Left temporal fusiform cortex	4.32	–	4.22	–
Right temporal fusiform cortex	3.57	–	4.26	–
Left occipital cortex	4.33	–	4.01	4.23
Right occipital cortex	3.89	–	–	3.80
Left entorhinal cortex	3.62	–	3.58	–
Right entorhinal cortex	–	–	3.32	–
Right primary somatosensory cortex	–	–	3.74	–

Results are expressed as peak *z* scores derived from a mixed-effects analysis with outlier deweighting and a threshold at $z > 3.0$, $P < .05$.
–, No significant activations in this region.

dysmenorrhoea has been experienced and serum cortisol levels that is not present when considering age or years of menstruation in the controls. This interpretation does not, however, negate the possibility that an abnormal cortisol response may predispose a person to develop a chronic pain condition. Altered activity of the HPA axis may explain the frequent comorbidity of dysmenorrhoea with other chronic pain conditions and provide a potential mechanism by which a specific pain condition may develop into a widespread regional or systemic condition such as fibromyalgia [8].

4.6. Implications for clinical practice

The presence of central changes in association with dysmenorrhoea suggest that the symptom should be treated promptly and adequately in all women. The adolescent nervous system is considerably more plastic than that of an adult [11], and thus potentially more susceptible to the influence of repeated painful episodes. Therefore, treatment of dysmenorrhoea may be particularly important in this population. Furthermore, recent work has demonstrated improvement in the symptoms of other pain conditions subsequent to adequate treatment of coexisting dysmenorrhoea [26]. Thus, we suggest that any woman presenting with chronic pain be assessed for dysmenorrhoea, and if this symptom is present, adequate treatment should be initiated.

4.7. Conclusion

The combination of behavioural, imaging, quality of life, and endocrine evidence presented here suggest that dysmenorrhoea is associated with central changes that persist beyond the time of menstruation. Without a longitudinal study it is not possible to know whether these alterations are a cause or an effect of repeated episodes of pain. However, these data support the idea that central changes occur secondary to the pain. Such changes could possibly predispose this group of women to developing a chronic

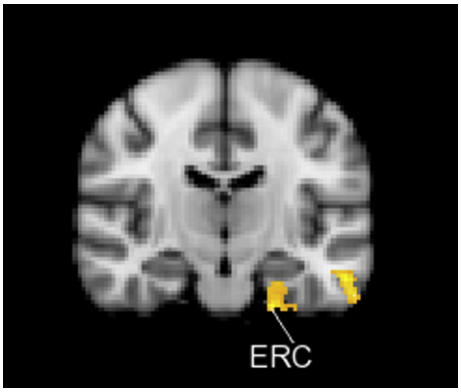

Fig. 6. Results of a mixed-effects analysis comparing brain activation in response to noxious stimulation of the abdomen in control women and women with dysmenorrhoea. Data from the day 10 to 12 and day 20 to 22 scan sessions were combined. Data shown are the results of mixed-effects analyses with outlier deweighting and are corrected for multiple comparisons, $z > 2.3$, $P < .05$. No brain areas were more active in the contrast Control–Dysmenorrhoea (not shown). The left entorhinal cortex and inferior/middle temporal gyrus were significantly more active in the contrast Dysmenorrhoea–Control. These areas of activation are shown in Table 5.

Table 5
Summary of regions where greater activation is seen in women with dysmenorrhoea than in control women in response to noxious stimulation of the abdomen during nonmenstrual phases.

Region of activation		z score	Coordinates		
			x	y	z
Middle temporal gyrus	L	3.51	−50	2	−26
Inferior temporal gyrus	L	3.46	−50	−6	−30
Entorhinal cortex	L	3.27	−22	−16	−36

Results are expressed as peak z scores derived from a mixed-effects analysis with outlier deweighting with a threshold at $z > 2.3$, $P < .05$.

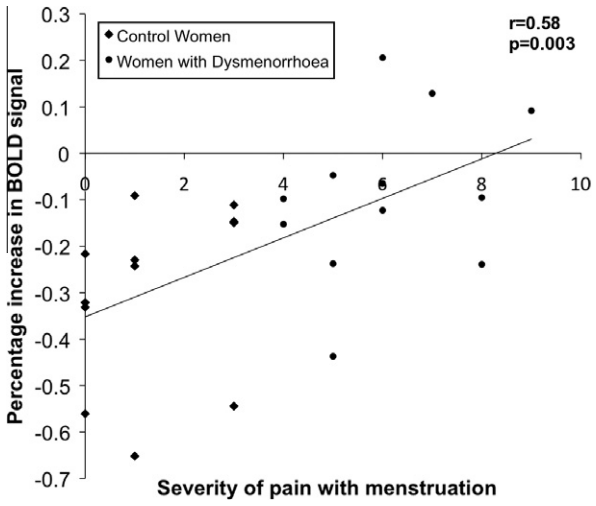

Fig. 7. The relationship between severity of pain with menstruation and activity in the left entorhinal cortex in response to noxious stimulation of the abdomen. Data represent mean activity across the 3 scan sessions. Pearson's correlation was used to investigate the relationship. Activity in the left entorhinal cortex was significantly positively correlated with self-reported severity of pain with menstruation across all subjects ($r = 0.58$, $P = .003$).

pain condition after a relatively minor insult (eg, IBS after a bout of gastroenteritis), and plausibly, partly contribute to the gender differences observed in the prevalence of chronic pain conditions.

In the light of the normal psychological profiles of these women and the negative connotations associated with the label of a chronic pain syndrome, it is difficult to know whether these data should be considered supportive evidence for a reclassification of dysmenorrhoea as a chronic pain condition, or inclusion within the definition of chronic pelvic pain. At the very least, however, dysmenorrhoea should be considered a condition worthy of treatment whatever the age of the woman.

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