Affective disturbance associated with premenstrual dysphoric disorder does not disrupt emotional modulation of pain and spinal nociception

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Abstract

In healthy individuals, emotions modulate pain and spinal nociception according to a valence linear trend (ie, pain/nociception is highest during negative emotions and lowest during positive emotions). However, emerging evidence suggests that emotional modulation of pain (but not spinal nociception) is disrupted in fibromyalgia and disorders associated with chronic pain risk (eg, major depression, insomnia). The present study attempted to extend this work and to examine whether women with premenstrual dysphoric disorder (PMDD), a cyclical syndrome associated with debilitating affective symptoms during the late-luteal (premenstrual) phase of the menstrual cycle, is also associated with disrupted emotional modulation of pain. To do so, an affective picture-viewing procedure was used to study emotional modulation of pain and spinal nociception in 14 women with PMDD and 14 control women during mid-follicular, ovulatory, and late-luteal phases of the menstrual cycle (verified by salivary hormone levels and luteinizing hormone tests). At each phase, mutilation, neutral, and erotic pictures were presented to manipulate emotion. During picture viewing, suprathreshold electrocutaneous stimuli were presented to evoke pain and the nociceptive flexion reflex (NFR; a physiological measure of spinal nociception). Statistically powerful linear mixed model analyses confirmed that pictures evoked the intended emotional states in both groups across all menstrual phases. Furthermore, emotion modulated pain and NFR according to a valence linear trend in both groups and across all menstrual phases. Thus, PMDD-related affective disturbance is not associated with a failure to emotionally modulate pain, suggesting that PMDD does not share this pain phenotype with major depression, insomnia, and fibromyalgia.
developing chronic pain [62]. Thus, it is unknown whether women with PMDD show the disrupted emotional modulation of pain phenotype. Nonetheless, several lines of evidence are suggestive: 1) PMDD is associated with affective dysregulation (eg, depressed mood) [1]; 2) serotonin is associated with emotional processing and pain modulation, and is believed to play a role in PMDD [8,17,22,38,39,63]; 3) endogenous opioids are involved with pain modulation, and opioid system disruption is thought to contribute to PMDD-related symptoms [27,28,57]; and 4) sex hormones (eg, estrogen) are implicated in PMDD [3,54] and influence pain modulation [42,55].

To examine whether emotional modulation of pain is disrupted in PMDD, the present study administered a well-validated affective picture-viewing paradigm [41,49] during 3 phases of the menstrual cycle (mid-follicular, ovulatory, late-luteal) in 14 women with PMDD (without MDD) and 14 matched, psychopathology-free controls. Suprathreshold electric stimuli were delivered during mutilation, neutral, and erotic pictures to assess whether viewing the pictures modulated pain and NFR. In studies of healthy controls [43,46], pain and NFR are lowest during erotica viewing and highest during mutilation—an effect that is stable across menstrual phases [41,42]. Thus, this paradigm provides a method to examine 1) whether PMDD is associated with disrupted emotional modulation of pain and NFR, and 2) whether any disruption varies across menstrual phases. It was hypothesized that PMDD would be associated with a failure to emotionally modulate pain. Given evidence that pain-processing abnormalities in PMDD may be trait-like and not phase specific [32,57], no phase differences in emotional modulation were expected.

2. Methods

2.1. General overview of procedures

Women provided consent and were screened and trained to monitor their menstrual cycle during an initial laboratory visit. Thereafter, eligible participants attended 3 laboratory testing sessions during the mid-follicular (5–8 days after menses), ovulatory (1–2 days after luteinizing hormone [LH] surge), and late-luteal (1–6 days before menses) phases of their menstrual cycle (order of testing was counterbalanced across participants). Participants used LH surge urine tests to identify when ovulation occurred and to guide the scheduling of ovulation and late-luteal phase testing. Fig. 1 depicts the tasks in each testing session. Suprathreshold electric stimuli delivered during emotional modulation of pain/NFR procedures were set at the greater of 120% NFR threshold (maximum stimulation intensity was hypothesized to be 50 mA). Physiological signals were collected using a Grass Technologies (West Warwick, RI) amplifier. All physiological signals were sampled at 1000 Hz. Resting blood pressure was recorded using a Critikon Dinamap PRO 100 Monitor (Tampa, FL). Testing was completed in a sound-attenuated and electrically shielded testing chamber adjacent to the experimenter’s room. All electric stimuli (train of five 1-millisecond square wave pulses delivered at 250 Hz) were delivered by a Digitimer stimulator (D57A; Hertfordshire, England) and Nicolet stimulating electrode (Madison, WI) attached to the left leg over the retromalleolar pathway of the sural nerve. Maximum stimulation intensity was set at 50 mA. Physiological signals were collected using a Grass Technologies (West Warwick, RI) amplifier. All physiological signals were sampled at 1000 Hz. Resting blood pressure was recorded using a Critikon Dinamap PRO 100 Monitor (Tampa, FL) 3 times at 3-min intervals before experimental testing began.

2.4. Prospective diagnosis of PMDD

To provide a preliminary diagnosis of PMDD at the initial session, a semi-structured interview was conducted [15]. Diagnosis was then confirmed at the end of the study after reviewing participants’ daily symptoms reported on a modified version of the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) calendar [40]. The PRISM calendar was used to record daily affective (eg, depressed), behavioral (eg, insomnia), and physical (eg, breast tenderness) symptoms; lifestyle impact; life events; and LH test results. Symptoms were rated daily for severity (0 = absent, 1 = mild, 2 = moderate, 3 = severe), increase or decrease (as indicated by up- and down-arrows), or presence (entered as an “X”) or absence (item left blank). Participants completed calendars daily for at least 3 consecutive menstrual cycles for verification of cycle regularity and to prospectively diagnose PMDD. To discourage retrospective reporting, participants were asked to mail calendars to our laboratory on a weekly basis.
According to DSM-IV-TR [1], the diagnostic criteria for PMDD includes having ≥5 of the following 11 symptoms present: 1) depressed mood, hopelessness, or self-deprecating thoughts; 2) anxiety, tension; 3) affective lability; 4) persistent and marked anger or irritability or increased interpersonal conflicts; 5) decreased interest in usual activities; 6) difficulty concentrating; 7) lethargy, easy fatigability, or marked lack of energy; 8) change in appetite, overeating, or specific food cravings; 9) hypersomnia or insomnia; 10) overwhelmed or feeling out of control; or 11) physical symptoms. At least 1 symptom must be depressed mood, anxiety, affective lability, or anger/irritability. Symptoms must interfere with work, school, or usual social activities and relationships with others. Symptoms must be prospectively confirmed from 2 consecutive symptomatic cycles. Based on these diagnostic criteria, women in the PMDD group were required to have a 30% increase in ≥5 PMDD symptoms from the follicular phase (days 5–10) PRISM ratings to the late-luteal phase (1–6 days before menses) PRISM ratings [19]. At least 1 of the symptoms had to be depressed mood, anxiety/tension, mood lability, anger, or irritability, and there had to be a symptom-free period during the follicular phase. Functional impairment was confirmed by the PRISM calendar by demonstrating lifestyle impact that was not evident during symptom-free days. Given the nature of the study requirements (ie, completion of only 3 cycle calendars), participants were said to have PMDD as long as they met criteria for at least 2 of the 3 monitored cycles (even if they were nonconsecutive). Women were considered healthy controls if they did not meet criteria for PMDD and experienced only mild affective symptoms during the mid follicular phase. Functional impairment was confirmed by the PRISM calendar by demonstrating lifestyle impact that was not evident during symptom-free days.

2.5. Severity of affective disturbance

In addition to the diagnosis of PMDD, severity of affective disturbance was assessed from the Center for Epidemiological Studies–Depression Scale (CES-D) at each testing session. The CES-D [37] is a 20-item self-report measure of depressive symptomatology, with higher scores indicating greater depression severity. The CES-D has good internal consistency and test–retest reliability, adequate discriminative and convergent validity, with scores ≥16 indicating clinically significant depression [37].

2.6. Hormone assessment

Urinary LH surge tests (Clearblue Easy; Swiss Precision Diagnostic, Bedford, UK) were conducted at home by participants to verify and identify the timing of ovulation. Participants were asked to take a digital photograph of each positive test and to e-mail it to experimenters to verify compliance.

Saliva for assaying estradiol and progesterone was collected on each testing day at the beginning of the session. Samples were refrigerated within 30 minutes after collection at −20 °C or less. On the day that they were assayed, they were thawed to room temperature, vortexed, and centrifuged for 15 minutes at approximately 3000 RPM (1500 × g). Samples were tested for salivary estradiol using a high-sensitivity enzyme immunoassay (catalog number 1-3702; Salimetrics LLC, State College, PA). The test had a lower limit of sensitivity of 0.1 pg/mL, a standard curve range from 1.0 pg/mL to 32.0 pg/mL, an average intra-assay coefficient of variation of 7.1%, and an average interassay coefficient of variation of 7.5%. The test assessing salivary progesterone (catalog number 1-1502) had a lower limit of sensitivity of 5.0 pg/mL, standard curve range from 10 pg/mL to 320 pg/mL, an average intra-assay coefficient of variation of 5.0 pg/mL, standard curve range from 10 pg/mL to 2430 pg/mL, an average intra-assay coefficient of variation of 6.2%, and an interassay coefficient of variation of 7.6%. Each assay was conducted twice and the results averaged [51].

2.7. Emotional modulation of pain and spinal nociception

2.7.1. Determination of suprathreshold stimulus intensity

The intensity of the suprathreshold stimulations delivered during picture viewing was set at the higher of 120% NFR threshold or 120% pain threshold (Fig. 1). These thresholds were assessed using procedures identical to those used in another study [42]. In brief, both thresholds were determined using 3 up–down staircases of electrical stimulations. NFR threshold was defined as the average stimulation intensity (in mA) of the last 2 peaks and troughs of the up–down staircase, whereas pain threshold was defined as...
the average stimulus intensity (in mA) of the 4 stimuli immediately above and immediately below a rating of 50 on the last 2 staircases.

2.7.2. Affective picture stimuli

Seventy-two digital pictures from the International Affective Picture System (IAPS) [33] were chosen based on contents that elicited the strongest modulation of pain and NFR (ie, mutilation, neutral, erotic) [35,41,43]. Pictures were split into 3 equivalent sets to present at each testing session. Each set consisted of 24 pictures (8 mutilation, 8 neutral, 8 erotic). Picture set order was counterbalanced across participants and phases. Furthermore, the order of the 24 pictures within each testing session was randomized with the limitation that not more than 2 pictures of similar content were shown successively.

2.7.3. Affective reactions to pictures

Subjective reactions to pictures were assessed using a computerized version of the Self-Assessment Manikin (SAM) [6,41], a 2-item questionnaire that assesses valence/pleasure (unpleasant–pleasant) and arousal (calm–excited). This yielded ratings between 1 and 9 for each dimension, with higher scores indicating greater pleasure or arousal, respectively.

Picture-evoked corrugator EMG and SCR were also assessed. To avoid stimulus artifact from electrical stimulations, corrugator EMG and SCR were calculated only in response to pictures during which an electric stimulation was not delivered. The corrugator supercilii muscle draws the eyebrow down into a frown and correlates with affective valence/pleasure ratings [34]. Corrugator EMG was measured by 2 electrodes over the corrugator supercilii muscle, amplified (×20,000, and bandpass filtered (30–1000 Hz) online. Corrugator responding was calculated by subtracting the mean rectified EMG (in μV) in the 1 second before picture onset from the mean rectified EMG during the 6 seconds of picture presentation.

Skin conductance response (SCR) was used as a physiological measure of picture-evoked sympathetic arousal [5,34], and was recorded from 2 electrodes filled with isotonic paste affixed to the volar surface of the index and middle fingers. SCR was calculated by subtracting the mean skin conductance (in μS) in the 1 second before picture presentation onset from the peak skin conductance that occurred in the 2- to 6-second interval after picture presentation onset.

2.7.4. Nociceptive outcomes assessed during picture viewing

Within-subject changes in pain ratings were assessed from a computer-presented NRS that ranged from 0 to 100 with the following labels: 0 (no pain), 50 (painful), and 100 (maximum tolerable pain). Pain ratings were made after each electric stimulation. NFR magnitude was used to assess within-subject changes in spinal nociception and was calculated in standardized d units [45]. NRS was assessed from biceps femoris EMG recorded from 2 electrodes placed 10 cm superior to the popliteal fossa, and a ground electrode was placed over the lateral epicondyle of the femur. Biceps femoris EMG was amplified ×20,000 and bandpass filtered (10–300 Hz) online.

2.8. Procedure

All procedures were approved by the University of Tulsa ethics review board. In brief, participants were screened and given a complete overview of the study, and they provided informed consent. Participants then completed background questionnaires and the SCID-I. Eligible participants were next trained to monitor their menstrual cycle and randomly assigned to a phase testing order (eg, ovulatory–mid-follicular–late-luteal). Each of the 3 experimental testing sessions (Fig. 1) was scheduled at approximately the same time of the day for each participant to control for potential diurnal fluctuations in pain processing. Upon arrival at each testing session, participants were provided instructions for filling out rating scales (eg, NRS for pain, SAM for emotion), were instrumented for physiological recording, and then sat quietly during a 5-minute acclimation period. The rest of the session involved pain testing in the order noted in Fig. 1. Breaks were provided between procedures to allow participants time to recover from each task. Data from pain sensitivity outcomes and CPM are reported elsewhere [3,10]; therefore, only emotional modulation of pain/NFR data are reported here.

To assess emotional modulation of pain/NFR, affectively charged pictures were presented for 6 seconds each (random interpicture intervals = 12–22 s). Suprathreshold electric stimuli were delivered during 50% of pictures (4 stimulations per content) and 6 interpicture intervals (to reduce predictability). Electric stimulations were randomly delivered 3 to 5 seconds after picture onset and 11 to 21 seconds after interpicture interval onset. After the presentation of each picture, participants rated the pictures using the SAM. The NRS was administered after the presentation of each suprathreshold stimulus. At the end of the session, each participant was reminded to continue filling out PRISM calendars until 3 cycles were completed. Participants were provided an honorarium after all testing sessions were completed, or upon withdrawal from the study.

2.9. Data analysis

Group differences on participant characteristics and background variables were conducted using independent-samples t tests or χ² analyses. The MIXED procedure in SPSS 17.0 was used for analysis of emotional reactions and pain outcomes [29]. These analyses included subject ID as the grouping variable to define level 2 units (participants). Menstrual phase (mid-follicular, ovulatory, late-luteal), group (HC, PMDD), and picture content (mutilation, neutral, erotic) were entered as categorical predictors in linear mixed-model analyses of variance (ANOVAs). These ANOVAs were conducted on data at the trial-by-trial level (rather than averaging by picture content and phase), such that each participant contributed up to 72 rows of data for analysis of subjective emotional reactions (24 pictures × 3 phases = 72), 36 rows of data for analyses of physiological emotional reactions (12 unstimulated pictures × 3 phases = 36), or 36 rows of data for analyses of pain outcomes (12 stimulations during pictures × 3 phases = 36). The error structure of the repeated measures was modeled as AR1 because of autocorrelation between trials/responses proximal in time. Follow-up comparisons to significant F tests were conducted using Fisher’s least significant difference (LSD) tests. To control for any sensitization or habituation effects unrelated to emotional modulation, a continuous predictor was entered in all models that coded for the order of pictures or electrical stimulations within each menstrual phase (this removes this systematic variability in the outcomes from the denominator of F tests and improves...
statistical power). The SPSS MIXED procedure uses Satterthwaite estimation for the denominator degrees of freedom (df), which produces noninteger values that vary from analysis to analysis. For ease of reporting, these degrees of freedom wererounded to the nearest integer. Significance was set at $P < .05$ (2-tailed).

3. Results

3.1. Participant characteristics

Table 1 reports means, standard deviations, and inferential statistics for participant characteristics. Results indicate that matching was successful; groups did not differ on any background variable ($P > .05$). However, consistent with what would be expected from the PMDD diagnosis, women in the PMDD group reported more CES-D depressive symptoms, which were significantly higher during the late-luteal phase (PMDD = 20.07 [SD = 13.32], HC = 10.07 [SD = 5.92], $P = .016$), but not during the mid-follicular (PMDD = 17.69 [SD = 11.75], HC = 11.71 [SD = 9.60], $P = .159$) or ovulatory (PMDD = 16.36 [SD = 12.88], HC = 10.77 [SD = 7.22], $P = .181$) phases.

One HC did not complete the ovulation testing session, and 1 woman with PMDD did not complete the mid-follicular testing session. However, the maximum likelihood estimation used in the SPSS MIXED procedure does not exclude cases with missing data; therefore, all women were included in all analyses.

3.2. Ovarian hormone levels

A significant main effect of menstrual phase was found for estradiol and progesterone (Table 2), indicating that they varied across menstrual phases, but levels were unaffected by group (ie, nonsignificant main effect of group and Group $\times$ Menstrual Phase interaction). Estradiol was higher during ovulation, relative to mid-follicular and late-luteal phases ($P < .05$), which were not different from one another ($P = .95$). Progesterone was lower during mid-follicular, relative to ovulation and late-luteal phases ($P < .001$), which were not different from each other ($P = .20$).

3.3. Emotional reactions to pictures

Table 3 presents the inferential statistics and Table 4 presents the means and SEM for emotional reactions to pictures. There was a significant main effect of picture content for all reactions (valence, corrugator EMG, arousal, SCR). Mean contrasts indicated that, compared to neutral, mutilation pictures were associated with lower valence ratings, higher corrugator EMG, higher arousal ratings, and higher SCR ($P < .05$). In addition, compared to neutral, erotica was associated with higher valence ratings and higher arousal ratings ($P < .05$). Furthermore, mutilation was higher than erotica on arousal ratings and corrugator EMG ($P < .05$). All other comparisons were nonsignificant ($P > .47$). However, these main effects were qualified by significant Group $\times$ Picture Content interactions for valence and arousal ratings. These interactions were decomposed by examining the simple effect of group. The only significant contrast indicated that PMDD had lower valence ratings of neutral, compared to HC ($P = .02$). All other contrasts were nonsignificant ($P > .25$). A significant main effect of menstrual phase was noted for arousal ratings, indicating that subjective arousal was highest during the mid-follicular phase, intermediate during the late-luteal phase, and lowest during ovulation (mean$_{fol}$ = 4.55 vs mean$_{ov}$ = 4.15 vs mean$_{lat}$ = 4.32; all $P < .03$). Significant order effects for valence (B = 0.007, $P = .032$) and arousal (B = 0.017, $P < .001$) indicated that these ratings increased (ie, higher pleasure, higher arousal) across the series of 24 pictures within each testing day.

3.4. Emotional modulation of pain and nociception

One PMDD participant did not achieve an NFR threshold before the 50 mA maximum stimulus intensity was reached during the ovulation phase. Her suprathreshold stimulus intensity was set at 50 mA for that phase. Given the failure to achieve reliable NFRs, her ovulation NFR magnitude data could not be included in the emotional modulation analyses.

Suprathreshold stimulation intensity did not significantly vary by menstrual phase ($F_{2,54} = 1.93, P = .16$), group ($F_{1,28} = 1.17$), or the interaction ($F_{2,54} < 1$). Therefore, any differences observed in the emotional modulation data should not be confounded by differences in stimulus intensity.

Table 3 presents the inferential statistics, and Table 4 presents the means and SEM for pain and NFR. A significant main effect of picture content was found for both pain and NFR (Fig. 2). Mean contrasts indicated that viewing erotica led to lower pain and smaller NFRs, compared to neutral and mutilation ($P < .05$). In addition, mutilation was associated with larger NFRs relative to neutral ($P < .01$). No other comparison was significant ($P > .40$). The Group $\times$ Picture Content, Menstrual Phase $\times$ Picture Content, and Group $\times$ Picture Content $\times$ Menstrual Phase interactions were nonsignificant for pain and NFR; therefore, emotional modulation of pain and spinal nociception was similar for both groups of women across all 3 menstrual phases (Table 4).

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HC</th>
<th>PMDD</th>
<th>t test</th>
<th>Cohen's $d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29.29</td>
<td>31.07</td>
<td>0.59</td>
<td>0.22</td>
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<tr>
<td>Education level (y)</td>
<td>15.50</td>
<td>15.68</td>
<td>0.20</td>
<td>0.08</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.72</td>
<td>24.56</td>
<td>0.62</td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>106.48</td>
<td>105.79</td>
<td>0.14</td>
<td>0.06</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68.21</td>
<td>70.28</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Menstrual cycle length (days)</td>
<td>28.45</td>
<td>29.55</td>
<td>0.70</td>
<td>0.27</td>
</tr>
<tr>
<td>Luteal phase length (days)</td>
<td>14.80</td>
<td>14.18</td>
<td>0.45</td>
<td>0.17</td>
</tr>
</tbody>
</table>

### Abbreviations:

HC, healthy control women; PMDD, women with premenstrual dysphoric disorder; SD, standard deviation.

### Note:

All group comparisons were nonsignificant at $P < .05$.
Means and standard errors of the mean for emotional reactions and pain outcomes by group, picture content, and menstrual phase.

Table 2

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Mid-follicular</th>
<th>Ovulation</th>
<th>Late-luteal</th>
<th>F tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>3.78</td>
<td>0.45</td>
<td>5.24*</td>
<td>4.37</td>
</tr>
<tr>
<td>PMDD</td>
<td>3.34</td>
<td>0.44</td>
<td>4.28*</td>
<td>3.57</td>
</tr>
<tr>
<td>Progesterone (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>78.31*</td>
<td>18.83</td>
<td>20.57</td>
<td>165.55</td>
</tr>
<tr>
<td>PMDD</td>
<td>63.88*</td>
<td>20.17</td>
<td>159.40</td>
<td>156.74</td>
</tr>
</tbody>
</table>

Abbreviations: HC, healthy control women; PMDD, women with premenstrual dysphoric disorder; SEM, standard error of the mean. Bold typeface added to highlight statistical significance.

A main effect of menstrual phase for NFR indicated that reflexes were smaller during the late-luteal phase, compared to ovulation and mid-follicular phases (meanLut = 1.40 vs meanOv = 1.42 vs meanmid = 1.27; P < .05). The significant order effect for pain ratings was associated with a positive regression slope (B = 0.79, P < .001), which indicated that pain ratings sensitized by an average of 9.5

Table 3

<table>
<thead>
<tr>
<th>Valence ratings</th>
<th>Corrugator EMG</th>
<th>Arousal ratings</th>
<th>SCR</th>
<th>Pain ratings</th>
<th>NFR magnitude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>F</td>
<td>df</td>
<td>F</td>
<td>df</td>
</tr>
<tr>
<td>Menstrual phase</td>
<td>2, 765</td>
<td>0.17</td>
<td>2, 394</td>
<td>0.14</td>
<td>2, 830</td>
</tr>
<tr>
<td>Content</td>
<td>2, 1480</td>
<td>2, 827</td>
<td>20.57</td>
<td>2, 1593</td>
<td>606.28</td>
</tr>
<tr>
<td>Group</td>
<td>1, 28</td>
<td>1.28</td>
<td>1, 28</td>
<td>0.32</td>
<td>1, 28</td>
</tr>
<tr>
<td>Phase x content</td>
<td>4, 1485</td>
<td>0.91</td>
<td>4, 824</td>
<td>1.19</td>
<td>4, 1598</td>
</tr>
<tr>
<td>Group x phase</td>
<td>2, 765</td>
<td>1.49</td>
<td>2, 395</td>
<td>1.79</td>
<td>2, 830</td>
</tr>
<tr>
<td>Group x content</td>
<td>2, 1478</td>
<td>14.31*</td>
<td>2, 827</td>
<td>2.21</td>
<td>2, 1592</td>
</tr>
<tr>
<td>Order</td>
<td>1, 877</td>
<td>4.60</td>
<td>1, 504</td>
<td>0.05</td>
<td>1, 926</td>
</tr>
</tbody>
</table>

Abbreviations: Content, picture content; df, numerator and denominator degrees of freedom; EMG, electromyography; HC, healthy control women; NFR, nociceptive flexion reflex; PMDD, women with premenstrual dysphoric disorder; SCR, skin conductance response. Bold typeface added to highlight statistical significance.

Table 4

<table>
<thead>
<tr>
<th>Mid-follicular</th>
<th>Ovulation</th>
<th>Late-luteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valence ratings (1-9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mut</td>
<td>1.48</td>
<td>0.21</td>
</tr>
<tr>
<td>Neu</td>
<td>5.38</td>
<td>0.21</td>
</tr>
<tr>
<td>Ero</td>
<td>6.12*</td>
<td>0.21</td>
</tr>
<tr>
<td>Corrugator EMG (ApV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mut</td>
<td>1.22</td>
<td>0.21</td>
</tr>
<tr>
<td>Neu</td>
<td>4.68*</td>
<td>0.21</td>
</tr>
<tr>
<td>Ero</td>
<td>6.00*</td>
<td>0.21</td>
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<tr>
<td>Arousal ratings (1-9)</td>
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<td></td>
</tr>
<tr>
<td>Mut</td>
<td>5.77</td>
<td>0.55</td>
</tr>
<tr>
<td>Neu</td>
<td>2.43</td>
<td>0.55</td>
</tr>
<tr>
<td>Ero</td>
<td>5.05*</td>
<td>0.55</td>
</tr>
<tr>
<td>SCR (ApS)</td>
<td>0.39</td>
<td>0.09</td>
</tr>
<tr>
<td>Mut</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Neu</td>
<td>0.15</td>
<td>0.09</td>
</tr>
<tr>
<td>Ero</td>
<td>0.13*</td>
<td>0.09</td>
</tr>
<tr>
<td>Pain ratings (0-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mut</td>
<td>63.65</td>
<td>4.37*</td>
</tr>
<tr>
<td>Neu</td>
<td>63.71</td>
<td>4.38*</td>
</tr>
<tr>
<td>Ero</td>
<td>57.37</td>
<td>4.42</td>
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<tr>
<td>NFR (d score)</td>
<td>1.63</td>
<td>4.40*</td>
</tr>
<tr>
<td>Mut</td>
<td>1.53</td>
<td>4.41</td>
</tr>
<tr>
<td>Neu</td>
<td>1.32*</td>
<td>4.43</td>
</tr>
<tr>
<td>Ero</td>
<td>1.34*</td>
<td>4.43</td>
</tr>
</tbody>
</table>

Abbreviations: EMG, electromyography; Ero, erotic; HC, healthy control women; Mut, mutilation; NFR, nociceptive flexion reflex; Neu, neutral; PMDD, women with premenstrual dysphoric disorder; SCR, skin conductance response. Note: Data in parentheses in the table body are standard error of the mean.

A main effect of menstrual phase for NFR indicated that reflexes were smaller during the late-luteal phase, compared to ovulation and mid-follicular phases (meanLut = 1.40 vs meanOv = 1.42 vs meanmid = 1.27; P < .05). The significant order effect for pain ratings was associated with a positive regression slope (B = 0.79, P < .001), which indicated that pain ratings sensitized by an average of 9.5

* P < .05.

** P < .05 for hormone level compared to mid-follicular and late-luteal phases.

*** P < .05 for hormone level compared to ovulation and late-luteal phases.
units across the 12 suprathreshold stimulations delivered at each menstrual phase (ie, 0.79 × 12 = 9.5). No other main effect or interaction was significant.

4. Discussion

This study examined emotional modulation of pain and NFR in women with and without PMDD. Analyses indicated that groups were well-matched and there were no group differences in sex hormones, although hormones did vary across menstrual phases: estradiol was higher during the ovulatory phase compared to other phases, and progesterone was lower during the mid-luteal phase relative to other phases. Consistent with having cyclical affective disturbance, the PMDD group had higher depressive symptoms during the late-luteal phase.

4.1. Emotional responding in PMDD

Pictures evoked the intended emotional responses in both groups. Mutilation pictures increased displeasure (decreased valence ratings), corrugator EMG (frowning), and subjective and physiological arousal (SCR), whereas erotic pictures increased subjective pleasure (valence) and arousal. These reactions were similar across all menstrual phases, except that subjective arousal was lowest during ovulation, intermediate during late-luteal, and highest during mid-follicular.

Despite the affective disturbance in PMDD, there was only 1 minor difference in emotional reactions to pictures: women with PMDD rated the neutral pictures as less pleasant than controls. This lack of group difference in emotional reactivity is consistent with 2 prior studies that presented affective pictures to women with PMDD [2,16]. Both found no group or phase differences on valence ratings, arousal ratings, or modulation of the startle reflex (a physiological measure of valence). However, 1 study did find that startle modulation was enhanced in women with PMDD when elicited during cues that signaled an impending pleasant or unpleasant picture [2]. The authors argued that this represented differences in emotional anticipation, not processing of the affective picture. Therefore, it does not appear that PMDD is associated with disrupted emotional processing of visual stimuli, even during the late-luteal phase when PMDD-related symptomatology is augmented. Together, these findings are important because they mean that emotion-induction procedures to assess emotional modulation of pain and NFR were successful and similar in both groups.

4.2. Emotional modulation of pain and NFR in PMDD

Contrary to hypotheses, emotional modulation of pain and NFR was not disrupted in women with PMDD. Pain and NFRs were highest during mutilation pictures, intermediate during neutral pictures, and lowest during erotic pictures; although the mutilation versus neutral comparison was not statistically significant for pain ratings. Moreover, emotional modulation of pain and NFR was consistently observed across all 3 phases in both groups. These findings have at least 4 implications.

First, they suggest that the mechanisms that mediate emotional modulation of pain and NFR are intact in women with PMDD. Affective pictures engage 2 independent pain modulation circuits: 1) supraspinal circuitry involved in pain modulation, and 2) brain-to–spinal cord circuitry involved in NFR modulation. This was first suggested by a study that noted that emotional modulation of pain and NFR could diverge [48], and was confirmed by a functional magnetic resonance imaging study that found that emotional modulation of pain was associated with activity in the orbitofrontal cortex, subgenual cingulate cortex, cuneus, and insula, whereas emotional modulation of NFR was associated with activity in the dorsolateral prefrontal cortex, parahippocampal gyrus, thalamus, amygdala, and brainstem nuclei [50]. Therefore, women with PMDD can engage circuits to modulate nociception at the spinal level where the signal first enters the CNS, but also at the supraspinal level as the signal is further processed to produce pain experience.

Second, group differences in emotional modulation of pain/NFR do not contribute to PMDD-related hyperalgesia. Published studies have noted that women with PMDD have heightened reactivity to noxious stimuli. The first study (PMDD = 11, controls = 10) examined pressure pain during the luteal and follicular phases [32] and found no group differences in pain thresholds and tolerances, but pain ratings were higher in PMDD across both phases. The second study (PMDD = 7, controls = 11) assessed ischemia pain thresholds and tolerances during the luteal phase and found lower thresholds and tolerances in PMDD [19]. The third study (PMDD = 28, controls = 28) also measured ischemia thresholds and tolerances, but during follicular and luteal phases, and found lower pain thresholds and tolerances in PMDD across both phases [57]. However, in the most recent study [30], women without PMDD (and no history of depression; n = 18) were compared to women with PMDD who did (n = 10) or did not (n = 17) have a history of MDD. No hyperalgesia on ischemia or cold pressor pain was found for women with PMDD, regardless of MDD history. We also assessed measures of pain sensitivity and CPM in the current sample, and found that women with PMDD were hyperalgesic (as assessed by ratings of electric stimuli) across all menstrual phases [3]. Although there were trends for hyperalgesia on ischemia threshold, this did not reach statistical significance [3]. Furthermore, CPM was not disrupted in the PMDD group, nor did it vary across phases [10]. Collectively, these studies of PMDD suggest there is PMDD-related hyperalgesia that is independent of menstrual phase and CPM inhibition, and the current study indicates that hyperalgesia is not due to a disruption of emotional modulation of pain/NFR.

Third, our findings provide additional evidence that PMDD and MDD have distinct phenotypes, even though there is symptom overlap. Indeed, during the late-luteal phase, PMDD symptomatology can look very similar to a major depressive episode. Moreover, MDD is associated with increased risk of future PMDD [14] and PMDD is associated with increased risk of future MDD [24]. However, the present study suggests that the presence of intact emotional modulation of pain differs between these disorders. In a prior study we found that MDD was associated with a failure to emotionally modulate pain, although NFR modulation was intact [60]. We hypothesized this phenotype might reflect risk for chronic pain given that fibromyalgia and insomnia (a pain risk factor) were both associated with a similar emotional modulation phenotype [11,44]. Interestingly, another study also found that PMDD and...
MDD have different pain phenotypes [30]: women with prior MDD, but not PMDD, had dampened pain sensitivity, whereas women with current PMDD without prior MDD had pain sensitivity similar to control women. Together, these studies provide additional evidence that PMDD and MDD are distinct entities [13] and also suggest unique pathways for pain risk in these 2 disorders. However, this is speculative until longitudinal studies can confirm this.

Fourth, emotional modulation of pain and NFR do not covary with menstrual phase–related changes in estradiol or progesterone. Emotional modulation was noted in all 3 menstrual phases in both groups, even though estradiol and progesterone levels varied across phases. This is somewhat surprising, given that sex hormones influence emotional processing [25,52,59] and pain modulation [9,18,20]. However, it is possible that individual differences in hormone levels might covary with individual differences in emotional modulation (as we have noted in healthy women [42]); however, our small sample precludes this analysis. Nonetheless, the current observations are consistent with 2 studies that found that emotional modulation of pain/NFR did not vary across menstrual phases in healthy women [41,42].

The present study also found that NFR magnitudes were lower during the late-luteal phase relative to other phases—an effect that was independent of picture content and group. This suggests that spinal nociception was tonically dampened during the late-luteal phase. To our knowledge, this is the first study to observe this. One study found the opposite: NFR thresholds were lower (enhanced nociception) during the mid-luteal phase relative to the late-follicular phase in healthy women [58]. However, 2 studies from our laboratory found that NFR thresholds did not vary across menstrual phases [3,4]. Future research is needed to clarify these discrepancies.

4.3. Study strengths and limitations

This study addressed several limitations noted in other investigations of experimental pain and the menstrual cycle [53]: namely, assessed hormone levels, verified ovulation, verified menstrual phases, verified menstrual cycle regularity, counterbalanced testing order, and use of a within-subject design. Moreover, PMDD was diagnosed prospectively, and a well-validated method to assess emotional modulation of pain and spinal nociception was used [41,47,49]. Nonetheless, a few limitations of the current study must be noted. First, our sample sizes were small. However, we used powerful statistical modeling and sample sizes that have previously allowed us to detect group differences in emotional modulation [11,44,60]. In addition, our sample sizes are on par with many studies of PMDD [2,16,23,32], and reflect how difficult it is to recruit this population. Participants must be willing to 1) track symptoms for several cycles to diagnosis PMDD, 2) attend several testing sessions, and 3) be tested during a period of severe symptomatology. Given this, it is not surprising that sample sizes are often small. A second limitation is related. The PMDD sample may not be representative of other women with PMDD. Even though the group met the prospectively assessed PMDD criteria, they may be more resilient, better at coping, and/or less symptomatic than other women with PMDD. Third, the PMDD diagnosis is based on self-report; therefore, groups may differ primarily on their perceptions of symptoms rather than on physiological processes that modulate pain. Therefore, additional research is needed to determine what contributes to enhanced symptomatology in this population of women.

4.4. Conclusion

In sum, based on our study results, women with PMDD do not differ from control women in their emotional reactions to affective pictures or in emotional modulation of pain and spinal nociception. Therefore, PMDD-related symptoms are not likely related to a disruption of the circuits that mediate these modulatory processes.

Conflict of interest statement

The authors have no conflicts of interest to report.

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References


