The effect of the menstrual cycle on affective modulation of pain and nociception in healthy women

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Abstract

Research indicates pain may be influenced by the menstrual cycle. While the mechanisms underlying these effects are unclear, it is possible that menstrual phase-related changes in endogenous pain modulation contribute. The present study used well-validated methods to study affective modulation of pain and the nociceptive flexion reflex (NFR) in healthy women during two menstrual phases (mid-follicular vs. late-luteal). Women (N = 41) tracked their menstrual phases for three complete cycles and were asked to attend two laboratory testing sessions in the second and third cycles to assess affective modulation of pain and nociception (testing order counterbalanced). Menstrual phase was assessed from daily diaries, luteinizing hormone tests, and basal body temperature. At each session, emotionally charged pictures were presented and suprathreshold electrocutaneous stimulations were delivered during and in between pictures. Subjective and physiological emotional reactions were recorded in response to each picture and pain ratings and NFRs were recorded in response to each suprathreshold stimulus. Results suggested pictures effectively manipulated emotion in both menstrual phases. Moreover, arousing unpleasant pictures enhanced pain and NFR, whereas arousing pleasant pictures inhibited pain and NFR. These modulatory effects were similar in both menstrual phases. Together, these findings suggest that affective engagement of corticospinal mechanisms does not differ across these phases of the menstrual cycle. However, future research is needed to directly assess the relationship between affective modulation of pain/nociception and inter- and intra-individual differences in ovarian hormones and to extend these findings to women who suffer from menstrual cycle-related pain (e.g., premenstrual dysphoric disorder, fibromyalgia).

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1. Introduction

Research indicates pain perception may be influenced by the menstrual cycle [2,14,24,26,53,59]. While the mechanisms for menstrual cycle effects on pain are unclear, it is possible that menstrual phase-related changes in sex hormones alter endogenous pain modulation [15]. Indeed, animal studies have noted that estrogen can switch on/off an NMDA-ergic form of stress-induced hypoalgesia, and that sex hormones can influence endogenous opioidergic processes through multiple pathways (e.g., influencing synthesis, absorption, distribution, and metabolism of opioids) [see Ref. [9], for a review]. These findings are consistent with human evidence noting that sex differences in pain sensitivity are attenuated in women on oral contraceptives [20], and that estrogen replacement therapy elevates pain sensitivity [13] and increases risk for some chronic pain conditions [7,32,36]. Furthermore, endogenous sex hormone levels are correlated with experimental [14] and clinical pain [28]. To our knowledge however, no human study has examined the effect of the menstrual cycle (or sex hormones) on affective modulation of pain.

Indeed, affective processes modulate pain. Specifically, arousing positive emotions induce pain inhibition and arousing negative emotions induce pain facilitation [40,49,50]. These effects are believed mediated by a central circuit involving forebrain regions (e.g., anterior cingulate, amygdala, insula, hypothalamus), the periaqueductal gray (PAG), and the rostral ventromedial medulla [12,49,61,63]. Supporting this, imaging studies have demonstrated that viewing affectively charged pictures can activate supraspinal regions in this circuit [18,19,64] and modulate pain and nociception [27,50–52]. Interestingly, circulating estrogen can influence μ-opioid binding in this modulatory circuit (amygdala, hypothalamus) [56]. Thus, when taken together, menstrual cycle influences on pain sensitivity could be explained by menstrual phase-related changes in displeasure-induced pain facilitation and pleasure-induced pain inhibition.

The present study was designed to address this issue. Healthy, normally cycling women (N = 41) were asked to monitor their menstrual cycle for three complete cycles. Ovulation was verified by luteinizing hormone surge tests and basal body temperature.
Women were asked to attend pain testing sessions during their mid-follicular (Days 5–8) and late-luteal (1–6 days before menses) phases of their second and third cycles, with testing order counterbalanced. At each session, affectively charged pictures were presented during which suprathreshold electrocutaneous stimuli were delivered to evoke nociceptive responses (subjective ratings, nociceptive flexion reflexes [NFR]). Using these procedures four prior studies found arousing pleasant pictures inhibited pain and NFR (a physiological measure of spinal nociception, [54]), whereas arousing unpleasant pictures facilitated pain and NFR [38, 44, 50, 51]. These procedures allow us to determine whether affective modulation of pain and spinal nociception is influenced by menstrual phase. Based on a study of menstrual cycle influences on affective reactions to pictures [45], we predicted picture-evoked emotional responses would not vary by menstrual phase. Nonetheless, given that the late-luteal phase is associated with increased negative affect [41], decreased positive affect [1], and hyperalgesia in some experimental pain studies [14, 39, 57], we predicted that the late-luteal phase would be associated with greater displeasure-induced pain facilitation and/or less pleasure-induced inhibition.

2. Methods

2.1. Participants

Participants were recruited from the University of Tulsa psychology subject pool, as well as the surrounding community by radio/newspaper advertisement, flyers, and email distribution. Participants were excluded for: <18 years of age; menopausal or post-menopausal; use of hormone preparations in the last 6 months; failure to regularly cycle in the 2 months prior to study inclusion; history of hysterectomy; pregnant or trying to get pregnant; pregnant in the last 6 months or currently breastfeeding; body mass index >35 (due to difficulty getting a nociceptive flexion reflex); history of cardiovascular, neuroendocrine, or neurological disorders; Raynaud’s disease; hypertension; history of chronic pain; current opioid, antidepressant, or anxiolytic medication use; or recent psychological trauma as defined by DSM-IV-TR [3]. Based on preliminary health screening, 68 women were found to be potentially eligible and invited to participate, but 15 declined participation (e.g., scheduling problems, unable to commit to study length, never showed up for testing session) leaving 53 participants. Ten of those women were later found to not meet inclusion criteria (7 anovulatory, 1 irregular cycle, 1 using pain meds, 1 using hormone birth control). Two women withdrew because they reported the electric stimulations were too painful. Forty-one women are included in the final analyses; most were white non-Hispanic (71%), married (73%), and employed full-time (56%). Average age was 31 years (SD = 8.86) and average education was 15 years (SD = 1.79). All subjects included in analyses had regular menstrual cycles ranging from 21.67 to 37.67 days (M = 28.98, SD = 3.28). Average length of the entire luteal phase was 14.74 days (SD = 3.48). Thirty-four women completed both testing sessions and completed all 71 sessions each only session. Reasons given for completing only one session were: scheduling (n = 3), health problems unrelated to menstrual cycle (n = 1), and procedures too painful (n = 3). Participants were provided course credit or an honorarium up to $185 for their participation.

2.2. Menstrual cycle monitoring and phase determination

Menstrual cycles were monitored using the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) [42]. The PRISM calendar contains affective (e.g., depressed), behavioral (e.g., insomnia), and physical (e.g., breast tenderness) symptoms that are rated daily for severity (absent, mild, moderate, and severe). Participants were asked to complete the calendars daily for three menstrual cycles. To discourage retrospective reporting, subjects were asked to mail in calendars on a weekly basis. Pain testing sessions were scheduled within the mid-follicular and late-luteal phases of the participant’s menstrual cycle during cycles 2 and 3, with testing order counterbalanced between subjects. The mid-follicular phase was defined as Days 5–8 following menses onset and the late-luteal phase was defined as Days 1–6 preceding menses. Twenty-one females attended their first testing session during their mid-follicular phase and 20 attended their first testing session during their late-luteal phase. Of the 37 women who completed the mid-follicular testing session 33 (89%) were tested during Days 5–8 (M = 7.54, SD = 1.17). Of the 38 women who completed the late-luteal testing session 30 (79%) were tested 1–6 days preceding menses (M = 4.84, SD = 3.24). Verification of ovulation was assessed from luteinizing hormone (LH) surge determined from self-administered home urine tests (e.g., QTests) and basal body temperature (BBT). Participants were asked to call the laboratory to schedule the late-luteal phase session after a positive LH test, which was retained and dated for confirmation of results by an experimenter.

2.3. Apparatus

During pain testing, experimenters monitored physiological signals, experimental timing, and participant behavior from an adjacent room. A video camera with a microphone allowed the experimenter to monitor and hear the participant, whereas a microphone connected to a 40-W audio amplifier (Radio Shack, Fort Worth, TX; Part #32-2054) allowed the experimenter to communicate with the participant, who was wearing sound attenuating headphones. All data acquisition, as well as stimuli and questionnaire presentation, was controlled by a PC equipped with dual monitors, A/D board (PCI-6036E or PCI-6031E; National Instruments, Austin, TX), and LabView software. One video output from the computer was used to present questionnaires and pictures via an LCD projector onto a large screen 2–3 m in front of the participant. A second video output was displayed to a 17” flat panel monitor so that an experimenter could monitor physiological signals and experimental timing.

A Grass instruments stimulator (Model S88, West Warwick, RI), stimulus isolation unit (Model SIU8T), constant current unit (Model C1CU1), and bipolar stimulating electrode (Nicolet, 019-401400, Madison, WI) were used to deliver noxious electrocutaneous stimuli to the left ankle over the retromalleolar pathway of the sural nerve. The onset/offset of the stimulator was controlled by computer and a custom-built computer-controlled voltage regulator varied the current to the participant (max current = 40 mA).

2.4. Electrode application and psychophysiological signal acquisition

Sampling rate of psychophysiological signals was set at 1000 Hz and signals were collected/filtered using a Grass Instruments Model 15LT Bipolar Amplifier with one Dual DC (15A12) and two Quad AC (15A54) modules. All recording electrodes were Ag–AgCl. To apply all electromyography (EMG) and stimulating electrodes, the skin was first degreased with alcohol, slightly abraded using Nuprep gel to achieve impedances below 5 KΩ, and then electrodes were filled with conductive gel (EC60, Grass Instruments) before they were secured to the skin using adhesive collars. Left corrugator EMG activity was assessed using miniature electrodes placed over the left eyebrow as recommended by Fridlund and Cacioppo [16]. Corrugator EMG was amplified, bandpass
filtered (30 Hz–1 kHz), and rectified. NFR recording was assessed by attaching two electrodes over the biceps femoris muscle of the left leg 10 cm superior to the popliteal fossa and a common ground electrode was placed over the lateral epicondyle of the left femur. The raw biceps femoris EMG was amplified, bandpass filtered (10–300 Hz), and rectified. Skin conductance electrodes were filled with isotonic paste (EC33, Grass Instruments) and secured to the volar medial surface of the right index and middle fingers.

2.5. NFR threshold assessment

Suprathreshold stimuli delivered during picture viewing was set at 120% NFR threshold; therefore, NFR threshold was assessed prior to picture viewing. Procedures for assessing NFR threshold were similar to our previous studies [50,51]. Trains of five 1 ms rectangular wave pulses at 250 Hz (i.e., 3 ms ISI) were delivered to the sural nerve with a varying inter-train interval of 8–12 s to reduce stimulus predictability. The first train started at 0 mA (current) and was increased in steps of 1.5 mA until an NFR was detected. The NFR was defined as a mean biceps femoris EMG response in the 90–150 ms post-stimulus interval that exceeded mean EMG activity during the 60 ms pre-stimulus baseline interval by 1.4 SD, as suggested by empirical evidence [46]. Using the 90–150 ms timeframe reduces potential contamination by the non-nociceptive RII reflex, startle responses, and/or voluntary movements [11]. The stimulus intensity was then decreased in 0.75 mA steps until an NFR was no longer observed. This up–down staircase process was repeated two more times, but with the use of 0.5 mA steps. A computer-presented numerical rating scale (NRS) was administered immediately following the presentation of each stimulus. The scale ranged from 0 to 100 with the following labels: 0 (no sensation), 1 (just noticeable), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable). Participants responded by moving an indicator to a position along the line that corresponded to their rating and submitted their answer by computer mouse. NFR threshold was defined as the average stimulation intensity (in mA) of the last two peaks and troughs of the up–down staircase process from three women before the 40 mA maximum stimulation was reached.[45]

2.6. Affective modulation of pain and nociception

Within-subject changes in pain ratings were assessed from the same computer-presented numerical rating scale (NRS) used during NFR threshold assessment [50]. NFR magnitude has been shown to correlate with subjective pain intensity [8,22,50]; therefore, NFR magnitude was used to assess within–subject changes in spinal nociception. NFR magnitude was calculated from Cohen’s d (d = [mean EMG in the 90 to 150 ms post-shock interval – mean EMG response in the 60 to 0 ms pre-shock baseline]/pooled standard deviation of the two intervals) [47]. This response definition was selected because, relative to other scoring methods (e.g., peak response, area under the curve), it correlates better with subjective pain ratings and has better distributional properties [43,47].

2.6.3. Nociceptive reactions assessed during picture viewing

Suprathreshold electrocutaneous stimulations set at 120% NFR threshold were delivered during and in between affective pictures. Within-subject changes in pain ratings were assessed from the same computer-presented numerical rating scale (NRS) used during NFR threshold assessment [50]. NFR magnitude has been shown to correlate with subjective pain intensity [8,22,50]; therefore, NFR magnitude was used to assess within–subject changes in spinal nociception. NFR magnitude was calculated from Cohen’s d (d = [mean EMG in the 90 to 150 ms post-shock interval – mean EMG response in the 60 to 0 ms pre-shock baseline]/pooled standard deviation of the two intervals) [47]. This response definition was selected because, relative to other scoring methods (e.g., peak response, area under the curve), it correlates better with subjective pain ratings and has better distributional properties [43,47].

2.7. Menstrual cycle-related symptoms

2.7.1. Menstrual Distress Questionnaire (MDQ)

This 47-item questionnaire is used to assess symptoms related to the menstrual cycle. The eight scales composing the MDQ include pain, impaired concentration, behavior change, autonomic reactions, water retention, negative affect, arousal, and control [35]. Instructions were, “For each item circle the number for the category that best describes your experience over the past three days.” Responses were based on a 5-point Likert scale ranging from 0 (none) to 4 (present severe). The MDQ has good internal consistency [60] and test–retest reliabilities [23].
2.7.2. Positive and Negative Affect Schedule (PANAS)

The PANAS [62] is a 20-item measure used to assess positive (10 items) and negative (10 items) affect. This questionnaire was used as a baseline measure of mood before the beginning of each experimental testing. Responses were based on a 5-point Likert scale ranging from 0 (very slightly or not at all) to 4 (extremely). For each item, participants were asked “to what extent you feel this way right now, that is, at the present moment.” The PANAS has good test–retest reliability and internal consistency and demonstrates excellent convergent and discriminant validity [62].

2.8. Procedure

All procedures were fully approved by the University of Tulsa Ethics Review Board. Interested participants were administered a brief phone screen to evaluate inclusion/exclusion criteria. Potentially eligible participants were invited to attend an initial laboratory visit during which a thorough overview of the study was provided, informed consent was obtained, and then a comprehensive assessment of inclusion/exclusion criteria was conducted. If deemed eligible, participants were trained to monitor their menstrual cycle for three cycles. Cycle 1 was used to establish cycle length and ovulation timing and pain testing occurred in cycles 2 and 3.

Based on menstrual cycle tracking, participants were scheduled for two pain testing sessions, one in the mid-follicular phase (Days 5–8) and one during the late-luteal phase (Days 1–6 prior to menses onset), with the testing order counterbalanced between subjects. Each testing session was scheduled at approximately the same time of day to control for possible diurnal variations in pain processing. At each session, a complete overview of the procedures was provided following by review of informed consent and health status. Afterwards, subjects were provided instruction on the NRS for rating pain and the SAM for rating emotional pictures. Next, pressure pain thresholds were assessed from six body sites (data not presented), followed by psychophysiological sensor application and PANAS administration. NFR threshold was then assessed to determine the level of stimulation to use during picture viewing. To assess affective modulation of pain and NFR, 24 affectively charged pictures were presented. Each picture was shown for 6 s and inter-picture intervals varied randomly from 12 to 22 s. Suprathreshold stimuli set at 120% NFR threshold were delivered to the retromalleolar pathway of the left sural nerve in trains of five 1 ms rectangular wave pulses at 250 Hz. Suprathreshold stimuli were delivered during 50% of pictures (4 stimulations per content) and 6 inter-picture intervals. Therefore, a total of 18 stimulations were delivered during the picture-viewing phase. We have previously shown that 3–4 shocks per picture content provides a reliable estimate of nociceptive responding [38,50]. Electric stimulations were randomly delivered 3–5 s after picture onset and 11–21 s after inter-picture interval onset in order to reduce predictability. After the presentation of each picture, participants rated their emotional response on the SAM. The NRS was administered following the presentation of each suprathreshold stimulus. If the suprathreshold stimulus occurred during a picture, the NRS was presented after picture offset. To ensure that a picture or suprathreshold stimulus was not delivered during a rating period, the experimental timing was paused until the participant submitted their ratings. After picture viewing, participants filled out the MDQ. The session also included additional pain testing that was assessed after picture viewing (diffuse noxious inhibitory controls, electrocutaneous pain threshold and tolerance, ischemia pain threshold and tolerance), but these data will be reported elsewhere. At the end of the session, the participant was reminded to continue monitoring their menstrual phases for three complete cycles. After all procedures were completed, the participant was provided their honorarium.

2.9. Data analysis and hypotheses

The MIXED procedure in SPSS 14.02 was used for all analyses due to the increased power with these models and also because cases with the missing data are not excluded [25]. It is worth noting that analyses that included only the 34 participants that completed both testing sessions resulted in the exact same conclusions. Analyses included subject ID as the grouping variable. Linear mixed model ANOVAs were conducted to determine whether there were menstrual phase differences in menstrual cycle symptoms (MDQ, PANAS) or NFR threshold. These analyses entered Menstrual Phase (mid-follicular vs. late-luteal) as a nominal predictor. For emotional responses to pictures (SAM ratings, corragor EMG, SCR) and nociceptive reactions to suprathreshold stimuli (pain ratings, NFR magnitude) during pictures, linear mixed model ANOVAs were conducted on data at the trial-by-trial level (rather than averaging by picture content and phase). In these analyses, the error structure was modeled as AR1 due to autocorrelation between trials/responses proximal in time. Menstrual Phase and Picture Content (mutilation, neutral, and erotic) were entered as nominal variables. Follow-up mean comparisons to significant F-tests were conducted using Fisher’s LSD tests. Testing order (mid-follicular/late-luteal vs. late-luteal/mid-follicular) was also entered as an IV in all analyses to control for differences in counterbalancing order, but was non-significant in all models (ps > 0.14). The SPSS MIXED procedure uses Satterthwaite estimation for the denominator degrees of freedom (df) which produces non-integer values that vary from analysis to analysis. For ease of reporting, these dfs were rounded to the nearest integer. Cohen’s d was reported as the effect size for mean comparisons. Significance was set at p < 0.05 (two tailed).

We predicted that emotional responses to pictures would not vary by menstrual phase. However, affective modulation of pain and nociception was expected to vary by phase. Specifically, the late-luteal phase was expected to be associated with greater facilitation by mutilation pictures and less inhibition by erotic pictures. As such, significant Menstrual Phase × Picture Content interactions were expected in the analyses of pain ratings and NFR magnitude.

3. Results

3.1. Preliminary analyses

Table 1 reports means, standard deviations, and inferential statistics for the Menstrual Distress Questionnaire (MDQ), Positive and Negative Affect Schedule (PANAS), and NFR threshold. These variables did not vary by menstrual phase. It is important that NFR threshold did not vary by phase, because the suprathreshold stimulus intensity during picture viewing was set at 120% NFR threshold. So, affective modulation of pain and nociception was not confounded by phase differences in suprathreshold stimulus intensity.

3.2. Emotional responses to pictures

Results suggested that emotion was effectively induced by pictures during both menstrual phases (Fig. 1). A significant main effect of Picture Content for valence/pleasure ratings (F[2, 1753] = 2135.32, p < 0.001) indicated that, compared to neutral pictures, valence was higher during erotic pictures (p < 0.001, d = 3.00) and lower during mutilation pictures (p < 0.001, d = 3.54). The comparison between erotica and mutilation was also significant (p < 0.001, d = 3.00). A significant main effect of Picture Content for corragor EMG (F[2, 844] = 42.47, p < 0.001) indicated corragor EMG was greater during mutilation pictures than erotic (p < 0.001, d = 0.59) and neutral pictures (p < 0.001, d = 0.60).
A significant main effect of Picture Content for pain ratings \( (F[2, 776] = 9.65, p < 0.001) \) indicated that, compared to neutral pictures, pain was greater during mutilation pictures \( (p = 0.001, d = 0.24) \) and erotic \( (p = 0.097, d = 0.08) \) pictures elicited greater SCR, although significance for erotic did not meet the \( p < 0.05 \) criterion. Moreover, mutilation evoked slightly greater SCR than erotic \( (p = 0.007, d = 0.17) \). The main effect of Menstrual Phase was significant for SCR \( (F[1, 407] = 9.24, p = 0.005) \), indicating that SCR was higher during the mid-follicular phase \( (d = 0.23) \); but, this main effect was non-significant for all other emotional responses \( (p > 0.38) \). The Menstrual Phase \( \times \) Picture Content interaction was non-significant for valence/pleasure ratings \( (F[2, 1737] = 0.54, p = 0.58) \), arousal ratings \( (F[2, 1745] = 1.73, p = 0.18) \), corrugator EMG \( (F[2, 859] = 0.03, p = 0.97) \), and SCR \( (F[2, 826] = 0.17, p = 0.84) \).

3.3. Nociceptive reactions during picture viewing

Results from nociceptive reactions indicated that mutilation pictures facilitated pain and NFR whereas erotic pictures inhibited pain and NFR (Fig. 2). However, contrary to hypotheses, these modulatory effects were not influenced by menstrual phase. The significant main effect of Picture Content for pain ratings \( (F[3, 1026] = 27.97, p < 0.001) \) indicated that, compared to neutral pictures, pain was greater during mutilation pictures \( (p = 0.016, d = 0.08) \) and lower during erotic pictures \( (p < 0.001, d = 0.15) \). Plus, pain was higher during mutilation than erotic \( (p < 0.001, d = 0.23) \). Compared to pain ratings during inter-picture intervals, pain ratings were higher during mutilation pictures \( (p = 0.002, d = 0.26) \).

Fig. 1. Subjective and physiological emotional reactions to pictures. Measures of valence/pleasure are on the left (pleasure ratings, corrugator EMG) and measures of arousal are on the right (arousal ratings, skin conductance response). Pictures effectively manipulated emotion, such that unpleasant pictures (mutilation) decreased reports of pleasure, increased corrugator EMG (indicative of facial frowning), and increased subjective and sympathetic arousal (assessed from skin conductance). Pleasant pictures (erotic) increased reports of pleasure and arousal. Emotion-induction was similar during mid-follicular and late-luteal phases of the menstrual cycle.
The present study assessed the influence of viewing emotionally charged pictures on pain and spinal nociception (as assessed from the NFR) during two menstrual phases (mid-follicular vs. late-luteal) in 41 healthy, regularly cycling women. To overcome problems noted with previous studies of menstrual cycle and pain processing [21,55], a within-subject design was used and menstrual phases were determined using daily diaries, luteinizing hormone urine tests, and basal body temperature. These procedures allowed us to verify menstrual phase, exclude women who were anovulatory, and control for inter-individual variability that would be attributed to error in a between-subject design.

Pictures manipulated affective valence and arousal. Mutilation pictures elicited subjective reports of displeasure and arousal, and evoked corrugator muscle activity (a muscle associated with facial frowning) and sympathetic nervous system activation (assessed from skin conductance). By contrast, erotic pictures elicited subjective reports of pleasure and arousal, but also lower corrugator activity than mutilation. While skin conductance response was higher during erotica, this did not reach statistical significance. These affective reactions were similar in both mid-follicular and late-luteal phases indicating emotional processing was not influenced by the menstrual cycle. This is consistent with another study that found no differences in affective responses to IAPS pictures when they were presented during menstrual, ovulatory, mid-luteal, and premenstrual phases [45].

The pattern of modulation observed for nociceptive reactions evoked during pictures was consistent with our prior studies [38,50–52]. Arousing unpleasant pictures increased pain and NFR, whereas arousing pleasant pictures decreased pain and NFR. Contrary to hypotheses, these modulatory effects were similar in both menstrual phases (Fig. 2). This failure to find menstrual phase-related changes in affective modulation of pain cannot be explained by phase-related differences in suprathreshold stimulus intensity, because NFR threshold was similar in both phases (suprathreshold intensity was set at 120% NFR threshold). Moreover, our failure to find phase-related changes in affective modulation of pain is not likely a result of Type II error, because powerful linear mixed model statistical procedures were used to optimize our sample size (i.e., cases with the missing data were not dropped). We further safeguarded against Type II error by examining the simple effects of picture content even when the Menstrual Phase × Picture Content interaction was non-significant. Those analyses confirmed that affective modulation was present in both phases. Thus, when taken together, our results suggest that affective reactions to emotionally laden pictures and affective modulation of pain and nociception are similar during mid-follicular and late-luteal phases of the menstrual cycle.

The only significant effect of menstrual phase was that pain ratings of suprathreshold stimuli were lower during the late-luteal phase, regardless of the picture content. Given that studies examining experimental pain comparing the mid-follicular with the late-luteal phase have typically found enhanced pain during the late-luteal phase [14,39,57] or no differences between phases [29,58], this finding seems counterintuitive. However, a meta-analysis [53] of two studies using electrocutaneous stimulation found that pain sensitivity was lower during the luteal phase than the follicular phase, an effect opposite that of other stimulus modalities (e.g., ischemia, pressure, and heat). While our results are consistent with these studies of electrocutaneous pain, it is unclear whether comparisons can be accurately drawn given that menstrual phases were not defined by the same days of the cycle in those prior studies. Regardless, our failure to find a main effect of menstrual phase on NFR magnitudes during picture viewing or menstrual phase differences in NFR thresholds suggests the reduced pain perception during the late-luteal phase is not due to spinal influences, but rather supraspinal processes or report bias.

4.1. Implications

The effect of corticospinal processes on pain and nociception (engaged via picture viewing) was similar in both menstrual

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**Fig. 2.** Subjective (top panel) and physiological (bottom panel) reactions to suprathreshold electrocutaneous stimulations evoked during and in between affective pictures. Mutilation pictures enhanced pain and the nociceptive flexion reflex (NFR, a measure of spinal nociception) and erotic pictures inhibited pain and NFR. These modulatory effects were similar during the mid-follicular and late-luteal phases of the menstrual cycle. “Interval” refers to nociceptive reactions evoked during inter-picture intervals.

$d = 0.08$, similar during neutral pictures ($p = 0.61$, $d = 0.005$), and lower during erotic pictures ($p < 0.001$, $d = 0.15$). The significant main effect of Picture Content for NFR magnitude ($F[3, 1050] = 21.65, p < 0.001$) indicated that, compared to neutral pictures, NFRs were larger during mutilation pictures ($p < 0.001$, $d = 0.28$) and smaller during erotic pictures ($p < 0.001$, $d = 0.21$). Moreover, NFRs were larger during mutilation compared to erotica ($p < 0.001$, $d = 0.48$). Compared to NFRs during inter-picture intervals, NFRs were larger during mutilation pictures ($p < 0.001$, $d = 0.30$), similar during neutral pictures ($p = 0.58$, $d = 0.01$), and smaller during erotic pictures ($p < 0.001$, $d = 0.20$). The main effect of Menstrual Phase was significant for pain ratings ($F[1, 336] = 26.52, p < 0.001$), but not NFR ($F[1, 347] = 1.19, p = 0.28$), indicating pain ratings were lower on average during the late-luteal phase ($d = 0.04$). The Menstrual Phase × Picture Content interaction was non-significant for pain ratings ($F[3, 1027] = 0.88, p = 0.45$) and NFR ($F[3, 1054] = 0.90, p = 0.97$). Nevertheless, to guard against possible Type II error that can occur when trying to detect an interaction, we conducted simple effects tests for Picture Content at each menstrual phase. This simple effect was significant for both phases for pain ratings ($p < 0.0001$) and NFR magnitudes ($ps < 0.0001$) suggesting pictures modulated nociceptive responses similarly in both phases.
phases in this sample of healthy women. Therefore, the results of the present study suggest that phase-related changes in affective modulation of pain and spinal nociception may not contribute to phase-related changes in pain sensitivity. Moreover, this means that emotion regulation strategies to increase positive emotions and decrease negative emotions should be effective for reducing afferent nociceptive activity and managing pain in this population, regardless of menstrual phase.

The current results also imply that progesterone (and possibly estradiol) may not influence the corticospinal circuitry responsible for affective modulation of pain and spinal nociception. When averaged across Days 5–8, estradiol and progesterone levels are at relatively low levels, but are higher when averaged across Days 1–6 preceding menses (although the difference is more dramatic for progesterone because estradiol levels on Days 1–3 preceding menses are similar to levels during Days 5–8 after menses onset) [15,34]. Therefore, if the modulatory circuitry were altered by these hormones (especially progesterone) then affective modulation of pain should have varied by menstrual phase. But before firm conclusions can be drawn, future studies need to measure ovarian hormones to directly assess whether hormone levels are associated with pain modulation. Indeed, the inter-individual and intra-individual variability in ovarian hormones that occur within and across menstrual phases can be significant and should be measured and taken into account.

This was the first study to use the picture-viewing paradigm to examine pain modulation on more than one occasion in the same group of participants. Given that affective modulation of pain and NFR were consistently observed on both occasions, the current study provides the first evidence that affective modulation is stable across time in healthy individuals. This implies the current paradigm, which we have referred to elsewhere as Emotional Controls of Nociception (ECON, [52]), is a reliable method for studying affective modulation of pain in longitudinal studies.

4.2. Limitations and future directions

The present study had a number of methodological strengths that bolster confidence in our findings, such as: LH surge tests to verify ovulation, assessment of subjective and physiological outcomes, powerful statistical procedures, a within-subject design, phase tracking for three cycles, well-validated methods for pain modulation, and a large sample relative to other studies of menstrual cycle and experimental pain. Nonetheless, a few limitations should be mentioned. For example, we did not measure hormone levels. As noted previously, it is important to take into account the variability in hormone levels within-phase, between-phase, and between-subjects. To address this problem, a current study is underway that employs a non-invasive method of assessing hormone levels (e.g., saliva [17]). Second, we chose emotionally charged picture stimuli to evoke affective modulation because they reliably modulate nociceptive reactions [10,27,50]. However, it is possible that other methods of emotion-induction (e.g., odors, conditioned fear, imaginal techniques) may activate pain modulatory mechanisms that are sensitive to menstrual cycle influences [33,48]. Third, we used electrocutaneous stimulation so that we could elicit the NFR to study descending modulation of spinal nociceptive processes. However, electrocutaneous stimulation has been criticized because it activates multiple fiber types (nociceptive and non-nociceptive) and evokes pain sensations that are less natural than other stimulus modalities (e.g., ischemia, pressure, and heat). As a result, other stimulus modalities may be more sensitive to menstrual cycle effects [53]. Fourth, we chose to study pain only during the mid-follicular and late-luteal phases to minimize the number of testing sessions participants had to attend, and because comparisons between these phases have been shown to produce some of the most robust effects on pain sensitivity [53]. Nevertheless, it is possible that fluctuations in sex hormones associated with other phases (e.g., ovulation) influence pain modulation. And finally, our results may not generalize to clinical populations, such as women with greater menstrual cycle-related symptomology (e.g., premenstrual syndrome [PMS], premenstrual dysphoric disorder [PMDD]; [58]) or women with chronic pain (e.g., fibromyalgia; [31,37]). Indeed, our sample did not report significant late-luteal phase-related elevations in menstrual symptoms or phase-related changes in positive and negative affect. Moreover, pressure pain threshold and ischemic pain threshold/tolerance were not influenced by menstrual phase in the present sample [4]. Therefore, the mechanisms that might generate hyperalgesia during the late-luteal phase may not have been engaged (or present) in our healthy sample of women. For these reasons, it is important that future studies examine menstrual cycle influences on affective modulation in clinical populations of women. A current study is underway to address this issue.

4.3. Summary

In sum, the present study suggests that affective modulation of pain and spinal nociception does not vary between the mid-follicular and late-luteal phases in healthy women. However, future studies are needed to directly assess the relationships between hormone levels and affective modulation of pain, and to replicate these findings in clinical populations (e.g., women with chronic pain or PMDD).

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