Do sex hormones influence emotional modulation of pain and nociception in healthy women?

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A B S T R A C T

Sex hormones may contribute to inter- and intraindividual differences in pain by influencing emotional modulation of pain and nociception. To study this, a well-validated picture-viewing paradigm was used to assess emotional modulation of pain and the nociceptive flexion reflex (NFR; physiologic measure of nociception) during mid-follicular, ovulatory, and late-luteal phases of the menstrual cycle in healthy normally cycling women (n = 40). Salivary estradiol, progesterone, and testosterone were assessed at each testing session. Emotional modulation of pain/NFR did not differ across menstrual phases, but low estradiol was associated with weaker emotional modulation of NFR (during all phases) and emotional modulation of pain (ovulatory and late-luteal phases). Given evidence that a failure to emotionally modulate pain might be a risk factor for chronic pain, low estradiol may promote chronic pain via this mechanism. However, future research is needed to extend these findings to women with disturbances of pain, emotion, and/or sex hormones.

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1. Introduction

Compared to men, women have a higher prevalence of many chronic pain conditions (e.g., fibromyalgia, migraine) and a greater sensitivity to noxious stimuli (e.g., Fillingim, 2000; Riley, Robinson, Wise, Myers, & Fillingim, 1998; Unruh, 1996). Moreover, some clinical pain varies across the menstrual cycle (Craft, 2007; LeResche, Manel, Sherman, Gandara, & Dworkin, 2003; Straneva et al., 2002). Thus when taken together, inter- and intraindividual differences in sex hormones may contribute to pain and pain modulation in humans (Craft, 2007).

Much of the research examining the relationship between hormones and human pain have used menstrual phase as a proxy for hormone levels without directly measuring them (e.g., Riley, Robinson, Wise, & Price, 1999; Sherman & LeResche, 2006). For example, estradiol and progesterone are relatively low during the early-follicular phase (days 1–5 of a 28 day menstrual cycle) and higher during the mid-luteal phase (days 17–24). Estradiol peaks prior to ovulation (day 14) triggering a rapid surge (and immediate return to baseline) in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Despite this general pattern, there can be tremendous inter- and intraindividual variability, as well as interindividual variability in sex hormones (Vitzthum, 2009). Surprisingly, few studies have actually measured hormone levels and responses to well-controlled pain stimuli to directly assess the relationships between hormones and nociceptive processing. Moreover, conclusions are difficult to draw from these studies because the direction of the relationships is not always consistent, and there have been several null findings (e.g., Fillingim et al., 1997; Klatzkin, Mechin, & Girdler, 2010; Okifuji & Turk, 2006; Ring, van Zanten, & Kavussanu, 2009; Soderberg, Poromaa, Nyberg, Backstrom, & Nordh, 2006; Stening et al., 2007; Teeper, Peters, Vedder, Schepelmann, & Lautenbacher, 2010). Variability across studies may reflect the complex effects of hormones (e.g., sometimes pronociceptive, sometimes antinociceptive), but may also stem from low statistical power because many had small sample sizes and used low-powered analytic procedures (e.g., zero-order correlations).

Additionally, most studies have focused on static measures of pain processing (e.g., pain threshold/tolerance), rather than dynamic measures of pain modulation. Indeed, pain is determined not only by the amount of nociceptive input, but also by central modulatory processes. Some of these processes inhibit pain, whereas others facilitate (disinhibit) it (Fields, Basbaum, &
Heinricher, 2006; Milian, 2002). As a result, experienced pain is the net effect of nociceptive input, inhibitory processes, and facilitatory processes. Recent thinking is that risk for some chronic pain may be determined by individual differences in central pain modulation (Edwards, 2005). As evidence for this, several chronic pain conditions are associated with reduced descending inhibition (Lautenbacher & Rollman, 1997; Pietschacker, Haag, Zaudig, & Lautenbacher, 2005; Yarnitsky, 2010). Even more convincing is a prospective study showing that disrupted preoperative pain inhibition predicts the development of chronic post-thoracotomy pain (Yarnitsky et al., 2008). Thus, given the importance of pain modulation in the risk for chronic pain, it is important to examine whether hormones are related to pain modulation.

To the best of our knowledge only three studies have examined the relationship between sex hormones and pain modulation. Two used a method of assessing pain inhibition known as conditioned pain modulation (CPM) that involves applying a tonic noxious stimulus to one part of the body to inhibit pain evoked at a distal body location. Both found that pain inhibition was the strongest during ovulation (Rezai, Hirschberg, Carlström, & Ernberg, 2012; Tousignant-Laflamme & Marchand, 2009), suggesting that weaker pain inhibition during other phases (e.g., follicular, luteal) may promote pain. Both studies measured several sex hormones (e.g., estradiol, progesterone, testosterone, LH, FSH), but only Tousignant-Laflamme and Marchand (2009) found a relationship: higher progesterone was associated with greater CPM-related inhibition during the ovulatory phase only.

The third study, conducted by our laboratory, examined emotional modulation of pain across the mid-follicular (days 5–8) and late-luteal (1–6 days prior to menses) phases in 41 healthy women (Rhody & Bartley, 2010). An emotional picture-viewing paradigm (Emotional Controls of Nociception; ECON) was used to manipulate emotion and suprathreshold electrocutaneous stimuli were delivered over the sural nerve to evoke pain and the nociceptive flexion reflex (NFR; a physiological correlate of spinal nociception). We reasoned that emotional modulation of pain might be even more sensitive to hormone influences than CPM-inhibition because supraspinal regions involved with emotional modulation circuits show sex differences in structure and function (e.g., Cahill, 2006; Tershner, Mitchell, & Fields, 2000; Zubieta et al., 2002) and are affected by sex hormones (e.g., Smith, Zubieta, & delCarmen, 1998; Vincent & Tracey, 2010). Consistent with prior studies (e.g., Rhudy, Williams, McCabe, Nguyen, & Vembo, 2005; Rhudy, Williams, McCabe, Russell, & Maynard, 2008), pain and NFR were modulated according to an emotional valence linear trend (pain and NFR were highest during unpleasant pictures and lowest during pleasant pictures), but this modulation did not vary across the menstrual phases (Rhudy & Bartley, 2010). Unfortunately, we did not assess ECON during the ovulatory phase, nor did we directly assess sex hormones. Given these limitations, it is yet unclear whether sex hormones influence emotional modulation of pain/NFR.

To address these limitations, the present study assessed ECON in 40 healthy, normally cycling women during the mid-follicular (days 5–8), ovulatory (within 48 h following LH surge), and late-luteal (1–6 days prior to menses) phases of the menstrual cycle. Salivary estradiol, progesterone, and testosterone were collected at each testing session. Statistically powerful linear mixed models were used to analyze the data. Based on studies of CPM-inhibition (Rezaii et al., 2012; Tousignant-Laflamme & Marchand, 2009), we predicted that emotional modulation of pain and NFR would be strongest during the ovulatory phase. But, given the lack of research on hormones and emotional modulation of pain/NFR, we did not make directional hypotheses for these relationships. However, estradiol might play a particularly important role because it affects mu opioid binding in regions important for emotion and pain modulation (e.g., amygdala, hypothalamus, nucleus accumbens) (Smith et al., 2006). Because we assessed subjective and physiological measures of emotional valence (i.e., valence/pleasure ratings, corrugator EMG) and emotional arousal (i.e., arousal ratings, skin conductance response [SCR]) in response to pictures, an ancillary goal was to examine the relationships between sex hormones and these emotional reactions.

2. Methods

2.1. Participants

Forty healthy, regularly cycling women were recruited from the surrounding community by radio/newspaper advertisement, flyers, online advertisements, and referrals from OB/GYN doctors. Participants were excluded for being less than 18 years of age, factors that could influence naturally occurring hormone levels (i.e., being menopausal or post-menopausal, use of hormone preparations in the last 6 months, failure to regularly cycle, hysterectomy, polycystic ovarian syndrome, endometriosis, pregnant or trying to become pregnant, pregnant in the last six months or currently breastfeeding), chronic health conditions (i.e., history of cardiovascular, neuroendocrine, or neurological disorders, Raynaud’s disease, hypotension), history of chronic pain, use of medications that could influence testing (i.e., current analgesics, antidepressant, or anxiolytic medication use), apparent cognitive impairment, current diagnosis of premenstrual dysphoric disorder (PMDD), or body mass index > 35 (due to difficulty getting a nociceptive reflex in persons with high adiposity). Participants were also excluded if they met criteria for any current Axis I pathology as assessed by the Structured Clinical Interview for DSM IV Axis I Disorders, Non-Patient Version (SCID-I-NP) (First, Spitzer, Gibbons, & Williams, 2002). Participants were provided an honorarium (up to $375) at the end of the experiment or upon withdrawal from the study. In general, participants were white (80%, n = 32), single (47.5%, n = 19), and employed at least part-time (65%, n = 26), with an average age of 29 years (SD = ±8.57). Most were well educated (mean years of education = 15 years, SD = ±2.48). Average body mass index (BMI) was 24.56 (SD = 3.96) and average blood pressure was 108/68 (SDbp = 11.02, SDdp = 8.78).

2.2. Apparatus, electrode application, and signal acquisition

A computer running LabVIEW software (National Instruments, Austin, TX) equipped with dual monitors was used. The computer controlled all stimuli, questionnaire presentation, and data acquisition. Physiological signals were amplified and filtered online using Grass Technologies (West Warwick, RI) Model 15LT amplifiers (with AC Modules 15A54 and DC Modules 15A12). Signals and experimental timing were monitored by an experimenter in an adjacent room by use of a 17 in. flat panel monitor. Picture stimuli and most questionnaires were presented by a projector onto a large screen positioned approximately 2 m in front of the participant, and sound attenuating headphones and a video camera allowed the experimenter to communicate with and monitor the participant from an adjoining room. Electrocutaneous trains of five 1 ms rectangular wave pulses at 250 Hz (experienced as a single stimulus) were delivered to the left ankle over the retromalleolar pathway of the sural nerve by use of a Digitimer stimulator (model D55A; Hertfordshire, England) and bipolar stimulating electrode (Nicolet, Madison, WI; 30 mm inter-electrode distance). A computer controlled the timing of the electric stimulations. The maximum stimulation intensity was set at 50 mA to ensure participant safety. Resting blood pressure was recorded prior to testing using a Critikon Dinamap PRO 100 Monitor (Tampa, FL) three times at 3-min intervals. A mechanical scale with attached height rod (Detecto, Webb City, MO) was used to assess weight and height for BMI.

Electromyographic (EMG) signals for biceps femoris muscle (i.e., hamstrings muscle to assess NFR) and corrugator muscle (i.e., eyebrow muscle to assess facial affect) activity were recorded using Ag-AgCl electrodes. Biceps femoris EMG was recorded from two 11 mm disc electrodes (F-E9-40-5; Grass Technologies) placed 10 cm superior to the popliteal fossa, amplified 20,000×, bandpass filtered (10–3000 Hz), and rectified online. Corrugator EMG was recorded from two 5 mm miniature electrodes (F-ESM-40-5; Grass Technologies) affixed over the corrugator muscle of the eyebrow, amplified 20,000×, bandpass filtered (30–1000 Hz), and rectified online. An 11 mm ground electrode was placed over the lateral epicondyle of the femur. To apply EMG and stimulating electrodes, the skin was initially cleaned with alcohol, slightly abraded using NuPrep gel (Weaver and Company, Aurora, CO) to attain impedences below 5 kΩ, and conductive gel (ECG, Grass Technologies) was applied. Skin conductance response was measured from two 11 mm silver electrodes filled with isotonic paste (EC3, Grass Technologies) affixed to the volar surface of the index and middle fingers of the non-dominant hand after the participant’s skin had been washed with soap and water and dried. All physiological signals were sampled at 1000 Hz.
2.3. Hormone assessment

Urinary LH surge tests (Clearblue Easy; Swiss Precision Diagnostic, Bedford, United Kingdom) were conducted at home by participants to verify and identify the timing of ovulation. The test is >99% accurate and easy for participants to interpret. Participants were asked to take a digital photo of the positive LH surge results and email it on the same day to experimenters for verification of compliance.

Saliva for assaying estradiol, progesterone, and testosterone was collected on days of pain testing. To avoid potential contamination of saliva that could impact immunooassay, participants were asked to abstain from alcohol use 12 h prior to sample collection, eating a meal 60 min before testing, and brushing their teeth 45 min before saliva was collected. Further, 10 min prior to sample collection, participants rinsed their mouths with water to eliminate any contaminants. Each participant was asked to allow saliva to pool in her mouth, then passively salivate into a test tube (Salimeters, 2005). Samples were refrigerated within 30 min and stored at ≤-20°C until they were shipped on dry ice to Salimeters LLC (State College, PA) to be analyzed for estradiol, progesterone, and unbound testosterone levels. On the day the samples were assayed, they were thawed to room temperature, vortexed, and then centrifuged for 15 min. Salivary estradiol was assessed from a high-sensitivity enzyme immunooassay (Cat. No. 1-3702) that 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 inter-assay coefficient of variation 7.5%. Salivary progesterone (Cat. No. 1-1502) had a lower limit of sensitivity 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 inter-assay coefficient of variation of 7.6%. Salivary testosterone (Cat. No. 1-2402, *I*=2121) had a lower limit of sensitivity of 1.0 nmol/L, standard curve range from 6.1 pg/mL to 600 pg/mL, an average intra-assay coefficient of variation of 4.6%, and an average inter-assay coefficient of variation of 9.8%. Each assay was conducted twice and averaged to obtain more reliable data.

2.4. Questionnaires

2.4.1. Demographics/health status questionnaire

A custom-made questionnaire was used to obtain demographic as well as health-related exclusion criteria.

2.4.2. Daily diary for menstrual cycle tracking

A modified version of the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) (Red, 1985) calendar was used to record menstrual symptoms, menses onset/offset, and LH test results. Participants completed calen-
dars daily for at least three consecutive cycles to verify cycle regularity. Participants were asked to mail in calendars on a weekly basis to discourage retrospective reporting. These symptoms were used to verify participants did not meet PMDD criteria.

2.4.3. Pain ratings

Following each electric stimulus, participants rated their sensation using a computer-presented numerical rating scale (NRS) used in several prior studies (France, France, al’Abi, Ring, & McIntyre, 2002; France & Suchowicki, 2001; Rhudy et al., 2005; Terry et al., 2011). Arranged from bottom-to-top, the scale was labeled: 0 (no sensation), 1 (just noticeable), 2 (uncomfortable), 3 (painful), 4 (very painful), 5 (pain threshold), and 6 (pain intolerable). Participants were asked to rate their sensation based on the numbers they see on their computer mouse. The advantage of using such a scale is that it is possible to determine whether manipulations (e.g., emotional modulation) can cause a previously painful sensation to become non-painful (or vice versa).

2.4.4. Picture ratings

Subjective reactions to pictures were assessed using the Self-Asessment Manikin (SAM: Bradley & Lang, 1994). The SAM is a two-item questionnaire that assesses emotional valence/placidity (unpleasant/pleasant) and arousal (calm/excited). A computerized version of the SAM was presented following each emotional picture (Rhudy et al., 2005). Participants used a computer mouse to make ratings between 1 and 9 on each scale (higher scores = greater pleasure or arousal).

2.5. Emotional Controls of Nociception (ECON): modulation of pain and NFR

To assess emotional modulation of pain/NFR at each testing session, 24 pictures were presented that depicted mutilation, neutral, and erotic contexts. Each picture was shown for 4 s, with inter-picture intervals varied randomly from 12 to 22 s. Suprathreshold electric stimuli were delivered during half of pictures (4 stimula-
tions per content) and 6 inter-picture intervals (to reduce predictability). Therefore, a total of 18 stimulations were delivered during the picture-viewing phase. Electric stimulations were delivered 3-5 s after picture onset and 1-21 s after inter-picture stimulus onset to reduce predictability. After the offset of each picture, participants rated their emotional responses using the SAM. The NRS was administered following the presentation of each painful stimulus. If the painful stimulus occurred during a picture, the NRS was presented after picture-offset. Variable the participant was rating the SAM and/or NRS, the experiment was paused by the computer until the partic-

### Footnotes

1. Multitrait (Set 1: picture numbers = 3051, 3053, 3060, 3068, 3080, 3130, 3170, 9525; *M* = 1.42, *SD* = 1.71; Set 2: picture numbers = 3010, 3063, 3064, 3071, 3110, 3266, 3400, 9434; *M* = 1.43, *SD* = 1.16; Set 3: picture numbers = 3000, 3030, 3069, 3100, 3102, 3120, 3150, 3156; *M* = 1.40, *SD* = 1.74). Neutral (Set 1: picture numbers = 5520, 7006, 7008, 7040, 7060, 7080, 7170, 7235; *M* = 4.97, *SD* = 2.87; Set 2: picture numbers = 5500, 7004, 7025, 7043, 7050, 7053, 7110, 7161; *M* = 5.00, *SD* = 2.80; Set 3: picture numbers = 4400, 4647, 4650, 4658, 4677, 4687, 4695; *M* = 4.98, *SD* = 2.85). Erotic (Set 1: picture numbers = 4400, 4415, 4459, 4465, 4466, 4672, 4690, 4694, 4800; *M* = 6.29, *SD* = 1.60).
2.6. Procedure

Procedures were fully approved by the University of Tulsa ethics review board. A phone screen was conducted with interested participants to evaluate inclusion/exclusion criteria. Those who appeared to be eligible were invited to an initial laboratory session in which informed consent was obtained and a comprehensive assessment of eligibility was conducted (health status questionnaire, BMI, SCID-I). Eligible participants were trained to monitor their menstrual cycles and randomly assigned to a phase testing order (e.g., ovulatory–mid-follicular–late-luteal). Participants tracked their cycles using the PRISM calendar for 3 total cycles to verify phases for testing sessions were accurately targeted and confirmation of cycle regularity (e.g., rate symptoms, noted days of menses onset/offset, documented LH surge). Testing sessions were scheduled at approximately the same time of day to control for potential diurnal variations in pain.

Pain testing sessions were scheduled within the mid-follicular, ovulatory, and late-luteal phases of the participant’s menstrual cycle. At each testing session (Fig. 1), a complete overview of the procedures was provided again, informed consent and health status were re-reviewed, participants were instrumented, and saliva was collected. Participants were then provided instructions for filling out the NRS for pain and SAM for emotion and then sat quietly during a 5-min acclimation period. The rest of the session included testing in the following fixed order: NFR threshold, pain threshold, emotional modulation of pain/NFR (ECON), conditioned pain modulation, electrocutaneous pain tolerance, McGill Pain Questionnaire-Short Form rating of electrocutaneous tolerance, ischemic pain tolerance assessment, and McGill Pain Questionnaire-Short Form rating of ischemia tolerance. Breaks were provided in between procedures to allow participants time to recover from each task and to allow restroom breaks if needed. Only data from the emotional modulation of pain/NFR is presented here, other data are reported elsewhere (Bartley et al., under review). At the end of the session, each participant was asked to continue menstrual cycle monitoring until three cycles were completed.

2.7. Data analysis

The MIXED procedure in SPSS 17.0 was used for all analyses (Hox, 2010). These multilevel analyses included subject ID as the grouping variable to define Level 2 units (participants). 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. The error structure of repeated measures (i.e., correlation of the errors for the within-subjects dependent variables) was modeled as a first-order autocorrelation matrix (AR1) due to autocorrelation between trials/responses proximal in time (SPSS Inc., 2005). Mean contrasts were used to decompose significant F-tests. Significance was set at p < .05 (two-tailed).

For analyses of mean hormone levels, menstrual phase (mid-follicular, ovulatory, late-luteal) was entered as a categorical predictor in multilevel ANOVAs. Each participant contributed up to 3 rows of data (one for each menstrual phase). To examine whether emotional reactions (SAM, corrugator EMG, SCR) or pain outcomes (pain ratings, NFR) varied across menstrual phases, menstrual phase and picture content (mutilation, neutral, erotic) were entered as categorical predictors in multilevel 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 x 3 phases = 72); 36 rows of data for analyses of physiological emotional reactions (12 unstimulated pictures x 3 phases = 36), and 36 rows of data for analyses of pain outcomes (12 stimulations during pictures x 3 phases = 36). 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 a testing session (Rhudy, Bartley, & Williams, 2010), therefore a significant positive regression slope for this variable reflects sensitization and a significant negative slope reflects habituation.

To determine whether hormone levels were associated with emotional reactions or emotional modulation of pain/NFR, 6 mixed effect regression models were conducted (one for each outcome). To create dependent variables for these analyses, first the outcomes were averaged by picture content and menstrual phase. Then, change scores were created for every variable (for every phase) that were based on whether the variable followed a valence linear trend (e.g., mutilation + neutral + erotic) or an arousal quadratic trend (e.g., [mutilation + erotic] x neutral). For variables whose means correspond to a valence linear trend (i.e., valence ratings, corrugator EMG, pain ratings, NFR) the following formula was used for the change score: mean response during mutilation minus mean response during erotic. The approach is consistent with a recent study that examined supraspinal correlates of emotional modulation of NFR/pain using fMRI (Roy, Piche, Chen, Peretz, & Rainville, 2009). For variables corresponding to an arousal quadratic trend (arousal ratings, SCR), the following formula was used for the change score: (responses averaged across mutilation and erotic) minus mean response during neutral. This resulted in a change score for every variable and menstrual phase that captures the degree of change in the variable associated with emotional reactivity and emotional modulation of pain/NFR. Thus, each participant contributed up to 3 rows of data (one for each menstrual phase) for these analyses. Predictors in these regression models were menstrual phase, estradiol level, progesterone level, testosterone level, and interactions between each hormone and phase. The interactions tested whether the relationships between hormones and pain outcomes were moderated by menstrual phase.

![Fig. 1](https://example.com/fig1.png)
Table 1  
Means and SEMs for hormone levels and menstrual symptoms by menstrual phase.

<table>
<thead>
<tr>
<th>Hormone levels</th>
<th>Mid-follicular</th>
<th>Ovulatory</th>
<th>Late-luteal</th>
<th>Inferential statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/mL)</td>
<td>4.01*</td>
<td>4.66*</td>
<td>4.95*</td>
<td>F(2, 62) = 3.25, p = .046</td>
</tr>
<tr>
<td>Progesterone (pg/mL)</td>
<td>90.38*</td>
<td>132.28*</td>
<td>226.82*</td>
<td>F(2, 68) = 38.50, p &lt; .001</td>
</tr>
<tr>
<td>Testosterone (pg/mL)</td>
<td>63.70*</td>
<td>62.04*</td>
<td>62.04*</td>
<td>F(2, 65) = 0.70, p = .50</td>
</tr>
</tbody>
</table>

Note: Means in the same row that share a superscript are not significantly different at p < .05. MDQ = Menstrual Distress Questionnaire.

3. Results

3.1. Preliminary analyses

Of the 40 participants, 31 completed testing during all three menstrual phases, 3 completed two phases (all were mid-follicular and late-luteal), and 6 completed only one phase (1 late-luteal, 3 ovulation, 2 mid-follicular). Thus, 36 participants completed testing at mid-follicular, 34 at ovulation, and 35 at late-luteal. All 40 participants were included in analyses because SPSS MIXED uses maximum likelihood estimation that does not exclude cases with missing data.

Of the 36 women who completed the mid-follicular testing session 31 (86.1%) were tested during days 5–8 (M = 7.36, SD = .99) of the menstrual cycle and all were tested before ovulation. Of the 35 women who completed the late-luteal testing session, the exact timing of the late-luteal testing session could only be verified for 33 women due to a failure of some to return menstrual calendars after they dropped out. Of the 33 women, 27 (81.8%) were tested 1–6 days preceding menses (M = 4.30, SD = 2.17) and all were tested after a positive ovulation test. Of the 35 women tested during ovulation, all were tested in the 48 h immediately following a positive ovulation test.

3.2. Mean hormone levels

Table 1 reports means, SEMs, and inferential statistics for hormone levels by menstrual phase. Results from 4 hormone assays were excluded from analyses (blood contaminant in saliva led to loss of 1 mid-follicular estradiol, 1 mid-follicular progesterone, and 1 mid-follicular testosterone assay; 1 progesterone value at ovulation was >3 SD larger than all others). Results indicated estradiol and progesterone, but not testosterone, varied by menstrual phase. Estradiol was higher during the late-luteal phase compared to the mid-follicular phase. Progesterone was lowest during the mid-follicular phase, intermediate during the ovulatory phase, and highest during the late-luteal phase.

3.3. Emotional responses to pictures

Table 2 reports means, SEMs, and inferential statistics for emotional responses. There was a significant main effect of picture content for valence ratings, arousal ratings, corrugator EMG, and SCR. Relative to neutral pictures, mutilation pictures led to greater unpleasantness (lower valence), corrugator EMG activity, subjective arousal, and SCRs (all p < .05); whereas erotic pictures led to greater pleasure (valence), subjective arousal, and SCRs (all p < .05). Mutilation also led to higher corrugator EMG activity, subjective arousal, and SCRs than erotica (all p < .05). There was also a significant main effect of menstrual phase for subjective arousal and SCR. Interestingly, the late-luteal phase was associated with lower subjective arousal, but higher physiological arousal (SCR), relative to the other two phases (ps < .01). There were no significant Content × Phase interactions.

3.4. Emotional modulation of pain and NFR

Before analysis of pain outcomes, a mixed effects ANOVA with suprathreshold stimulus intensity as the dependent variable and menstrual phase as a categorical predictor found that stimulation intensity did not significantly differ across menstrual phases and thus was not a confound in subsequent analyses.

Table 2  
Means and SEMs for subjective and physiological emotional reactions to pictures by picture content and menstrual phase.

<table>
<thead>
<tr>
<th>Valence ratings (1–9)</th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
<th>Inferential statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutilation</td>
<td>1.49</td>
<td>0.11</td>
<td>1.50</td>
<td>0.11</td>
<td>1.49</td>
<td>0.11</td>
<td>Phase: F(2, 1000) = .59, p = .55</td>
</tr>
<tr>
<td>Neutral</td>
<td>4.98</td>
<td>0.11</td>
<td>4.93</td>
<td>0.11</td>
<td>4.93</td>
<td>0.11</td>
<td>Content: F(2, 1899) = 2874.39, p &lt; .001</td>
</tr>
<tr>
<td>Erotica</td>
<td>6.10</td>
<td>0.11</td>
<td>5.97</td>
<td>0.11</td>
<td>6.00</td>
<td>0.11</td>
<td>P X C: F(4, 1913) = .24, p = .92</td>
</tr>
<tr>
<td>Arousal ratings (1–9)</td>
<td>M</td>
<td>SEM</td>
<td>M</td>
<td>SEM</td>
<td>M</td>
<td>SEM</td>
<td>Inferential statistics</td>
</tr>
<tr>
<td>Mutilation</td>
<td>5.49</td>
<td>0.22</td>
<td>5.50</td>
<td>0.22</td>
<td>5.43</td>
<td>0.22</td>
<td>Phase: F(2, 993) = 7.17, p &lt; .001</td>
</tr>
<tr>
<td>Neutral</td>
<td>2.21</td>
<td>0.22</td>
<td>2.35</td>
<td>0.22</td>
<td>2.35</td>
<td>0.22</td>
<td>Content: F(2, 1905) = 860.02, p &lt; .001</td>
</tr>
<tr>
<td>Erotica</td>
<td>4.86</td>
<td>0.22</td>
<td>4.90</td>
<td>0.22</td>
<td>5.23</td>
<td>0.22</td>
<td>P X C: F(4, 1919) = .52, p = .31</td>
</tr>
<tr>
<td>Corrugator EMG (ΔµV)</td>
<td>M</td>
<td>SEM</td>
<td>M</td>
<td>SEM</td>
<td>M</td>
<td>SEM</td>
<td>Inferential statistics</td>
</tr>
<tr>
<td>Mutilation</td>
<td>1.98</td>
<td>0.26</td>
<td>1.81</td>
<td>0.27</td>
<td>1.74</td>
<td>0.26</td>
<td>Phase: F(2, 699) = .13, p = .88</td>
</tr>
<tr>
<td>Neutral</td>
<td>0.10</td>
<td>0.26</td>
<td>0.05</td>
<td>0.27</td>
<td>0.24</td>
<td>0.26</td>
<td>Content: F(2, 1065) = 55.77, p &lt; .001</td>
</tr>
<tr>
<td>Erotica</td>
<td>0.27</td>
<td>0.26</td>
<td>0.26</td>
<td>0.27</td>
<td>0.38</td>
<td>0.26</td>
<td>P X C: F(4, 1073) = .83, p = .79</td>
</tr>
<tr>
<td>SCR (ΔµS)</td>
<td>M</td>
<td>SEM</td>
<td>M</td>
<td>SEM</td>
<td>M</td>
<td>SEM</td>
<td>Inferential statistics</td>
</tr>
<tr>
<td>Mutilation</td>
<td>0.08</td>
<td>0.03</td>
<td>0.08</td>
<td>0.03</td>
<td>0.15</td>
<td>0.025</td>
<td>Phase: F(2, 449) = 3.54, p = .03</td>
</tr>
<tr>
<td>Neutral</td>
<td>0.03</td>
<td>0.03</td>
<td>0.04</td>
<td>0.03</td>
<td>0.05</td>
<td>0.025</td>
<td>Content: F(2, 855) = 11.51, p &lt; .001</td>
</tr>
<tr>
<td>Erotica</td>
<td>0.06</td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
<td>0.09</td>
<td>0.025</td>
<td>P X C: F(4, 858) = .97, p = .42</td>
</tr>
</tbody>
</table>

P = picture, C = content.

* Comparison with neutral was significant at p < .05 (according to the main effect of picture content).
of emotional modulation across menstrual phases, \(F(2, 66) < 1, p = .47\) (\(M_{\text{Mid}} = 21.10\) mA, \(SEM = 1.81\); \(M_{\text{Ov}} = 23.17\) mA, \(SEM = 1.82\), \(M_{\text{Late}} = 21.73\) mA, \(SEM = 1.82\)).

Fig. 2 depicts the means and SEMs for emotional modulation of pain and NFR. Analysis of pain ratings identified a significant main effect of picture content, \(F(2, 871) = 54.51, p < .001\); but the main effect of menstrual phase \(F(2, 350) = 1.35, p = .26\) and the Phase \(\times\) Content interaction \(F(4, 877) = 1.04, p = .39\) were non-significant. Pain ratings were lower during erotic than during neutral or mutilation pictures \((p < .001)\), but the neutral vs. mutilation comparison was non-significant \((p = .22)\). The stimulus order main effect indicated pain sensitized within a testing session \((B = .0512, p < .001)\). Analysis of NFR magnitude identified a significant main effect of picture content \((F(2, 905) = 20.83, p < .001)\), but the Phase \(\times\) Content interaction was non-significant, \(F(4, 918) < 1, p = .96\). Compared to neutral pictures, NFRs were smaller during erotic pictures and larger during mutilation pictures \((p < .01)\). Also, NFRs were smaller during erotic pictures than mutilation pictures \((p < .001)\). Further, a significant main effect of menstrual phase \((F(2, 385) = 9.67, p < .001)\) indicated NFRs were smaller on average during ovulation than the mid-follicular or late-luteal phases \((p < .001)\). The stimulus order main effect indicated NFRs habituated within a testing session \((B = .0009, p = .01)\).

For exploratory purposes, analyses were conducted to determine whether emotional modulation of pain and NFR varied from the first to the third testing session (independently of menstrual phase). To do so, the analyses above were repeated except that testing session (session 1, session 2, session 3) was substituted for the menstrual phase variable in both analyses. For pain, the main effect of testing session was non-significant \((F(2, 304) = 1.31, p = .27)\), but there was a significant main effect of picture content \((F(2, 870) = 53.06, p < .001)\) and a marginally significant Testing Session \(\times\) Picture Content interaction \((F(4, 876) = 2.36, p = .052)\). Examination of the simple effects of picture content indicated that the neutral vs. erotic comparison was significant across all testing sessions \((p < .001)\), but the mutilation vs. neutral comparison was only significant at the first testing session \((p = .005)\) not testing sessions 2 and 3 \((p > .17)\). Thus, the effect of mutilation was stronger in the first session. For NFR, the main effect of picture content was significant \((F(2, 897) = 19.81, p < .001)\), but not the main effect of testing session \((F(2, 379) = 1.04, p = .64)\) or the Testing Session \(\times\) Picture Content interaction \((F(4, 910) < 1, p = .79)\). Thus, testing session did not affect modulation of NFR.

3.5. Relations between hormones and emotional reactions

Table 3 presents the results of linear mixed model regressions and Fig. 3 depicts scatterplots of significant relationships. There were no significant predictors of valence ratings or SCR. However, progesterone was a significant predictor of arousal ratings \((B = -.0044, p = .038)\) and corrugator EMG \((B = -.0043, p = .036)\). Progesterone was associated with reduced subjective arousal in response to emotional pictures (i.e., mutilation and erotica) compared to neutral, and greater corrugator activity during mutilation compared to erotica. Neither relationship was moderated by menstrual phase.

3.6. Relations between hormones and modulation of pain/NFR

Table 3 presents the results of linear mixed model regressions and Fig. 4 depicts scatterplots of significant relationships. There was a significant interaction between estradiol and menstrual phase in the prediction of pain modulation. As can be seen in Fig. 4, estradiol was positively associated with pain modulation during ovulatory \((B = 1.30)\) and late-luteal \((B = 1.31)\) phases (difference in slopes non-significant; \(p = .99)\), but there was a negative association

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Valence ratings</th>
<th>Arousal ratings</th>
<th>Corrugator EMG</th>
<th>SCR</th>
<th>Pain ratings</th>
<th>NFR magnitude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\rho)</td>
<td>(p)</td>
<td>(\rho)</td>
<td>(p)</td>
<td>(\rho)</td>
<td>(p)</td>
</tr>
<tr>
<td>Menstrual phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>1.37</td>
<td>.258</td>
<td>2.11</td>
<td>.126</td>
<td>0.24</td>
<td>.789</td>
</tr>
<tr>
<td>Progesterone (Prog)</td>
<td>0.16</td>
<td>.694</td>
<td>4.44</td>
<td>.038</td>
<td>4.53</td>
<td>.036</td>
</tr>
<tr>
<td>Testosterone (test)</td>
<td>1.19</td>
<td>.278</td>
<td>0.01</td>
<td>.935</td>
<td>0.09</td>
<td>.768</td>
</tr>
<tr>
<td>E2 (\times) Phase</td>
<td>1.62</td>
<td>.203</td>
<td>0.29</td>
<td>.747</td>
<td>0.79</td>
<td>.456</td>
</tr>
<tr>
<td>Prog (\times) Phase</td>
<td>0.50</td>
<td>.608</td>
<td>1.78</td>
<td>.173</td>
<td>0.56</td>
<td>.576</td>
</tr>
<tr>
<td>Test (\times) Phase</td>
<td>0.25</td>
<td>0.776</td>
<td>0.57</td>
<td>.560</td>
<td>1.29</td>
<td>.279</td>
</tr>
</tbody>
</table>

Note: For variables that follow a valence linear trend (i.e., valence ratings, corrugator, pain, and NFR), change score DVS = mutilation minus erotica. For variables that follow an arousal quadratic trend (i.e., arousal ratings, SCR), change score DVS’ = (average of mutilation and erotica) minus neutral. Degrees of freedom were 1, 103 for all hormone predictor main effects and 2, 103 for menstrual phase main effect and all interactions. For ease of identification, bolded statistics were statistically significant.
between estradiol and pain modulation during the mid-follicular phase \((B = -1.61; \text{comparisons to other slopes were significant, } p < .05)\). This indicates that higher estradiol was associated with greater emotional modulation of pain during ovulation and late-luteal phases \((i.e., \text{pain greater during mutilation than erotica})\), but with abnormal pain modulation during the mid-follicular phase \((i.e., \text{pain higher during erotica than mutilation})\). Interestingly, there was also a significant main effect of menstrual phase. The amount of pain modulation \((i.e., \text{the difference between mutilation and erotica})\) was greatest during the mid-follicular phase \((M = 7.44, \text{SEM} = 2.07)\), intermediate during the late-luteal phase \((M = 6.02, \text{SEM} = 1.73)\), and smallest during ovulation \((M = 5.88, \text{SEM} = 1.65)\); but, none of these mean comparisons were statistically significant \((p > .55)\). Therefore, the follow-up contrasts are consistent with the results from the multilevel ANOVA reported in the previous section indicating emotional modulation of pain does not differ across menstrual phases.

In the prediction of emotional modulation of NFR, estradiol was the only significant predictor \((B = .067, p = .002)\). As can be seen in Fig. 4, higher estradiol was associated with better emotional modulation of NFR, and this relationship was not moderated by menstrual phase.
4. Discussion

This study examined the relationships between hormones and (1) emotional reactivity, (2) emotional modulation of pain, and (3) emotional modulation of spinal nociception (NFR) in healthy women. As expected, estradiol was lower during the mid-follicular phase compared to the late-luteal phase, whereas progesterone was lowest during the mid-follicular phase, intermediate during the ovulatory phase, and highest during the late-luteal phase.

4.1. Emotional reactivity and hormone status

Results indicated pictures elicited emotional responses consistent with previous studies (Bradley et al., 2001; Rhudy & Bartley, 2010). Relative to neutral, mutilation pictures evoked displeasure (lower valence), corrugator EMG activity, subjective arousal, and sympathetic activation (SCR), whereas erotic pictures evoked greater pleasure (higher valence), subjective arousal, and sympathetic activation (SCR). Moreover, measures of emotional arousal, but not valence, varied by menstrual phase-effects that were independent of picture content. Consistent with early studies of menstrual cycle effects on autonomic arousal (Asso, 1978; Little & Zahn, 1974; Rosenberg, 1980), skin conductance reactivity was greatest during the late-luteal phase. By contrast, subjective arousal to picture stimuli was lowest during the late-luteal phase. The reason for this divergence is unknown, but suggests that subjective appraisal of sympathetic arousal may be less accurate during the late-luteal phase. Alternatively, participants could have been basing their arousal appraisals on another physiologic process not assessed in the current study. Little and Zahn (1974) found that resisting skin conductance was lower during the luteal phase, whereas SCRs in response to mental tasks were higher. Thus, women in our study may have based their arousal appraisals on basal sympathetic levels during the late-luteal phase. However, we did not record long enough periods of basal skin conductance in the current study to test this hypothesis.

Interestingly, arousal ratings were negatively associated with progesterone levels, but there was no association between any hormone and SCRs. Given that progesterone levels were highest during the late-luteal phase than other phases, and that progesterone was negatively correlated with arousal ratings, this suggests that lower subjective arousal during the late-luteal phase is probably due to elevated progesterone (Fig. 3). By contrast, the lack of relationships between SCR and hormones indicates that augmented SCRs during the late-luteal phase must stem from a mechanism other than progesterone, estradiol, or testosterone. Of note, the observed relationships between progesterone and emotional arousal may not be specific to women, because a study of men given 100 mg of progesterone found that it reduced stress-evoked subjective arousal while having equivocal effects on stress-evoked physiologic arousal (Childs, Van Dam, & Wit, 2010).

Although corrugator EMG reactivity did not vary by menstrual phase, higher progesterone was associated with greater corrugator response to mutilation pictures relative to erotica. Thus, progesterone may promote facial displays of emotion to mutilation stimuli. This finding would be consistent with research indicating that high progesterone is associated with greater sensitivity to cues depicting threat or disgust, but not other emotions (Conway et al., 2007). Indeed, mutilation pictures depict graphic injuries to humans (physical threat) and are often described as disgusting (Lang et al., 1993). Thus when taken together, progesterone appears to dampen stimulus–evoked subjective arousal (i.e., a sedative-like effect) and promote (facial) communication about potential environmental threats. These emotional effects might promote successful reproduction by helping to protect the mother and the developing fetus during pregnancy (when progesterone is high). However, it is important to keep in mind that these notions are speculative because causal relationships cannot be determined from the current correlational design.

4.2. Pain/nociception modulation and hormone status

Consistent with numerous prior studies (e.g., Rhudy & Bartley, 2010; Rhudy, Bartley, Williams, McCabe, et al., 2010; Rhudy et al., 2005), emotional picture-viewing modulated pain and NFR according to a valence linear trend. Specifically, pain and NFR were higher during mutilation and lower during erotica (Fig. 2). As we have noted before (Rhudy & Bartley, 2010), these modulatory effects did not differ across mid-follicular and late-luteal phases, but the current study extends this work to show that emotional modulation also does not differ during the ovulatory phase. Despite this, NFRs were generally smaller during the ovulatory phase, regardless of the picture content (Fig. 2), and this phase-related inhibition of NFR cannot be attributed to lower suprathreshold stimulus intensities used during ovulatory phase testing. Given that NFR is under tonic descending inhibition from supraspinal controls (Sandrini et al., 2005), this suggests that tonic inhibition of spinal nociception may be increased during ovulation. This is consistent with two studies that found descending inhibition was strongest during ovulation (Rezaei et al., 2012; Trougignant-Laflamme & Marchand, 2009). By contrast, menstrual phase did not influence overall pain response in the current study, as indicated by similar levels of average pain in each menstrual phase and our analysis of pain sensitivity outcomes reported elsewhere (Bartley et al., under review). Together, these data highlight that multiple processes modulate pain and nociception; tonic modulation of NFR can diverge from pain, and these tonic effects occur independently of emotional modulation of pain and NFR.

Importantly, even though menstrual phase did not influence emotional modulation of pain and NFR, estradiol was associated with modulation of both outcomes. Generally, higher estradiol was associated with stronger emotional modulation (i.e., a larger mutilation vs. erotica difference in pain/NFR), except that the relationship was reversed for pain modulation during the mid-follicular phase (Fig. 4). By contrast, estradiol was associated with stronger emotional modulation of NFR in all three phases. To test whether the phase-dependent effect of estradiol on pain modulation represents an interaction between estradiol and progesterone (i.e., the positive slope for estradiol may require the presence of progesterone), we conducted a post hoc analysis that included the interaction, but it failed to reach significance (p = .18). Therefore, at this time it is unclear why the effects of estradiol differ during the mid-follicular phase.

Although future research is needed to determine the mechanisms that contribute to the relationship between estradiol and emotional modulation of pain/NFR, it might be mediated by the endogenous opioid system. Indeed, Smith et al. (2006) found that women administered exogenous estradiol had increased mu opioid receptor binding potential in supraspinal regions involved with emotion, pain, and pain modulation (e.g., thalamus, hypothalamus, nucleus accumbens, amygdala), and the increased binding potential was associated with reduced pain.

4.3. Implications

As previously noted, pain is determined by nociceptive input as well as inhibitory and facilitatory processes, and some chronic pain may stem from a failure of descending inhibition (e.g., Yarnitsky, 2010). Following this reasoning, we originally hypothesized that
“healthy” emotional modulation of pain and NFR would be characterized by augmented pleasure-inhibited induction of pain/NFR and reduced displeasure-induced facilitation of pain/NFR (Rhudy & Williams, 2005). However, we have since revised this hypothesis after studying several at-risk populations. We found that persons with fibromyalgia (FM; Rhudy et al., 2013), major depressive disorder (MDD; Terry, DelVentura, Bartley, Vincent, & Rhudy, 2013), and primary insomnia (DelVentura, Terry, Bartley, & Rhudy, 2013; DelVentura, Terry, Bartley, Kerr, & Rhudy, 2011) all have intact emotional modulation of NFR (mutilation > erotica), but fail to emotionally modulate pain (i.e., mutilation = neutral = erotica). Given that these groups either have chronic pain or have disorders with a high risk for developing chronic pain (e.g., Gupta et al., 2007; Kroenke et al., 2011), we believe that a failure to emotionally modulate pain may represent a risk factor for chronic pain development (Rhudy et al., 2013).

Being able to inhibit and facilitate pain means an organism can respond flexibly to environmental demands, thus promoting its survival (Walters, 1994). For example, in some circumstances it is important to emotionally inhibit pain (e.g., during consummatory behaviors, procreation, or the presence of imminent threat) and in other circumstances it is important to emotionally facilitate pain (e.g., to promote recuperation or improve detection of somatic threat) (Bolles & Fanselow, 1980; Foo & Mason, 2009; Komisaruk & Whipple, 2000; Walters, 1994). Thus, it appears important to be able to up- and down-regulate pain signaling at spinal and supraspinal levels.

If our revised hypothesis is correct, then one implication of the present study is that estradiol helps to promote healthy emotional modulation of pain and nociception (at least during ovulation and late-luteal phases). Thus, women with low estradiol levels may be at increased risk of chronic pain because it impairs emotional modulation of pain and NFR. Consistent with this, FM is associated with lower basal estrogen (Riedel, Layka, & Neeck, 1998) and a failure to emotionally modulate pain (Rhudy et al., 2013). Moreover, some chronic pain is initiated or worsened by menopause when estradiol levels naturally decline (Meriggioli, Nanni, Bachiocco, Vodo, & Aloisi, 2012).

Our observation that estradiol is associated with enhanced emotional modulation of pain is consistent with evidence indicating estradiol can be both antinociceptive and pronociceptive (Craft, 2007). The present study suggests the direction of its influence might be partially determined by a woman’s emotional state. In the presence of negative affect, estradiol is pronociceptive, but in the presence of positive affect, it is antinociceptive. Given this, it is tempting to speculate that another implication of our findings is that varying emotional states might have contributed to the mixed findings of studies examining the relationship between estradiol and experimental pain (different paradigms might evoke different amounts of negative, and perhaps positive, emotions) (e.g., Fillingim et al., 1997; Klatzkin et al., 2010; Okifuji & Turk, 2006).

A final implication is that our study underscores the importance of directly measuring sex hormones to determine their relationships with pain processing. Many prior studies, including some from our laboratory, have used menstrual cycle as a proxy for hormone levels (e.g., Bartley & Rhudy, 2013; Rhudy & Bartley, 2010; Riley et al., 1999). The biggest problem with this approach is that it ignores the tremendous inter- and intra-individual differences in hormone levels across women and within phases. As can be seen in Fig. 4, minimum and maximum levels of estradiol were similar across all 3 phases even though mean levels differed. Using menstrual phase as a proxy, we would not have identified the relationships between estradiol and pain/NFR modulation or progesterone and corrugator EMG, and we might have assumed that the phase-related changes in SCR were related to progesterone.

4.4. Study limitations

This study had a number of strengths including verification of phase and regularity (via hormone levels and LH tests), direct measurement of hormones, recruitment of a relatively large sample size for this type of study, monitoring of 3 consecutive menstrual cycles, use of a well-validated emotional modulation paradigm, assessment of subjective and physiological outcomes, and use of powerful statistical analyses. Further, this is the first study to directly examine the relationships between hormones and emotional modulation of pain/NFR and to assess emotional modulation during ovulation. Nonetheless, a few limitations are worth noting.

First, our sample comprised healthy pain-free women in order to rule out the confounding effects of chronic pain and disease. As a result, our findings may not generalize to women with disruptions of pain, emotion, or hormones. Second, we assessed hormones from saliva rather than serum. Although saliva is non-invasive and appears to be a valid method to assess sex hormones (Gandara, LeResche, & Mancl, 2007; Gann, Giovanazzi, Van Horn, Branning, & Chatterton, 2001), assaying from serum is a more established method and may be more reliable (c.f., Gandara et al., 2007; Lu, Bentley, Gann, Hodges, & Chatterton, 1999). And finally, multiple pain tasks were assessed at each phase and the order was not counterbalanced. Thus we cannot rule out that there were order effects. However, NFR threshold and pain threshold had to be assessed first to determine the suprathreshold stimulation intensity, and we purposefully scheduled emotional modulation of pain/NFR testing earlier than more intense tasks (e.g., pain tolerance). Further, we scheduled breaks in between tasks to allow participants time to recover.

4.5. Conclusion

In sum, this study found that emotional modulation of pain and spinal nociception (NFR) did not vary across the mid-follicular, ovulatory, or late-luteal phases of the menstrual cycle in healthy women. Nonetheless, progesterone was associated with reduced subjective arousal to emotional pictures and greater corrugator EMG activity in response to unpleasant mutilation pictures. Additionally, estradiol was associated with enhanced emotional modulation of pain and NFR, except during the mid-follicular phase in which it was associated with abnormal emotional modulation of pain. Given prior evidence that disrupted emotional modulation of pain might be a risk factor for chronic pain, low estradiol may promote chronic pain by disrupting emotional modulation of pain and NFR. However, future research is needed to determine whether these findings generalize to women with disturbances of pain, emotion, and/or sex hormones.

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