Menstrual cycle phases differentially influence pain and spinal nociception, but not emotional modulation of these outcomes

Ellen L. Terry, MA, Emily J. Bartley, PhD, Shreela Palit, BS, Satin L. Martin, MA, Kara L. Kerr, BA, Bethany L. Kuhn, BS, Jennifer L. DeVentura, MA, Yvette M. Gúereca, BS, & Jamie L. Rhudy, PhD
Department of Psychology, The University of Tulsa, 800 South Tucker Drive, Tulsa, OK 74104

Introduction
Few human studies have examined whether pain modulation varies across the menstrual cycle. One method to study descending modulation of pain and spinal nociception is the emotional control of nociception (ECON) paradigm. In this paradigm, standardized emotionally-charged pictures are presented to evoke emotional reactions, while nociceous electrocutaneous stimuli are delivered to the sural nerve to evoke pain and a physiological correlate of spinal nociception (i.e., nociceptive flexion reflex, NFR). Using this methodology, unpleasant pictures reliably enhance pain and NFR, whereas pleasant pictures reliably inhibit pain and NFR. Using ECON, our laboratory has shown that emotional modulation of pain and NFR does not differ between the mid-follicular and late-luteal phases of the menstrual cycle. Nevertheless, a recent study by another lab found that endogenous pain inhibition (assessed by conditioned pain modulation) was greatest during ovulation, relative to the follicular and luteal phases (which did not differ from one another), therefore, emotional modulation may be influenced by ovulation.

Objective
To determine if menstrual cycle phases (e.g., mid-follicular, ovulatory, and late-luteal) influence emotional modulation of pain and physiological pain responses (i.e., NFR), as well as emotional reactions to affective picture stimuli.

Methods
Participants
Healthy Female Participants: N = 55
- Participants Demographics: While non-Hispanic (70.9%), married (40.4%), employed full-time (34.8%), years of education = 15.5 (SD = 2.2), average age = 29.5 yrs (SD = 8.42)

Exclusion Criteria:
- < 18 yrs of age
- Failure to regulate cycle within 2 months of study inclusion
- Loss of hormone preparations within past 6 months
- Pregnant within past 6 months
- Menopausal or post-menopausal
- Current acne illness
- Cardiovascular, musculoskeletal, circulatory, or hearing problems
- Chronic pain condition (e.g. migraine, back pain)
- Recent use of psychiatric medication
- Current use of aspirin or antithrombotic medication

Procedure
Informed Consent
Participants were asked to attend 3 laboratory testing sessions during the mid-follicular, ovulatory, and late-luteal phases of their menstrual cycle (order counterbalanced) and Emotional Controls of Nociception procedures were administered.

Menstrual phases and ovulation were verified using daily diaries, luteinizing hormone surge tests, and salivary levels of estradiol and progesterone.

In each session, participants viewed pictures varying in emotional valence (mutileation, neutral, erotic) while nociceous electrocutaneous stimuli were delivered (50% of participants balanced across menstrual phases).

Electrocutaneous stimulus intensity was set at the 120% NFR threshold or 120% of pain threshold (whichever was higher).

Pain ratings and NFR magnitudes were recorded following every electrocutaneous stimulation.

Pain thresholds (whichever was higher) were determined for each participant. Electrocutaneous stimulus intensity was set at the 120% NFR threshold or 120% of pain threshold (whichever was higher).

The International Affective Picture System (APS; Center for the Study of Emotion and Attention, 2000)

In total, there were 84 pictures presented in the following categories:
- Mutilation
- Neutral
- Erotic

- Self-Assessment Manikin (Bradley & Lang, 1994)

Valence (Pleasure) Ratings: 1 (unhappy) to 9 (happy)
Arousal Ratings: 1 (calm) to 9 (excited)
Subjective emotional reactions assessed following presentation of each picture

Experimental Procedure

Pain Ratings made following each stimulation

Results: Nociceptive Flexion Reflex

- Overall, results indicated NFR demonstrated significant emotional modulation (ηp2 = .08, p < .05), but this modulation did not differ by menstrual phase. A main effect of menstrual phase indicated NFRs were enhanced during the late-luteal phase, relative to other phases (regardless of picture valence) (p < .05).

Subjective Emotional Evaluation

Nociceptive Flexion Reflex (NFR)

- NFR is a spinally-mediated protective withdrawal reflex elicited by Aδ fiber activation, and its magnitude correlates with pain rating
- NFR magnitude = mean of biceps femoris EMG in 90-150 ms post-stimulus interval minus mean of 60 ms pre-stimulus interval, divided by the pooled standard deviation (Cohen’s d value)

Conclusions
Together, these findings suggest menstrual phases differentially influence pain and spinal nociception, an effect that is independent of emotional modulation.

Data Analysis

Variables were analyzed using 3 (Picture Content: mutilation, neutral, erotic) X 3 (Phase: Mid-Follicular, Ovulatory, and Late-Luteal) mixed linear model ANOVAs using SPSS 17.0.

Planned simple effects tests conducted if interaction significant

- Overall, results indicated pain demonstrated significant emotional modulation (ηp2 = .08, p < .05), but this modulation did not differ by menstrual phase. In contrast to NFR, pain did not vary by menstrual phase.

Results: Picture Ratings

Valence Ratings
- Overall, results indicate mutilation pictures were rated as more unpleasant and arousing and erotic pictures were rated as more pleasant and arousing (although, in general, viewing than mutilation pictures) regardless of menstrual cycle phase (p < .05).

Arousal Ratings
- Overall, results indicate mutilation pictures were rated as more unpleasant and arousing and erotic pictures were rated as more pleasant and arousing (although, in general, viewing than mutilation pictures) regardless of menstrual cycle phase (p < .05).

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