

# The Effect of Menstrual Cycle on Women's Visceral Pain Perception

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**Introduction:** The documented effect of gender on pain perception raises questions on the role of gonadal hormones in somatic and visceral pain [1, 2]. The purpose of this study was to examine the effect of menstrual cycle on the brain response to multi level visceral pain stimulations in healthy women using fMRI.

**Methods:** This study was HIPAA compliant and approved by the IRB of the Pennsylvania State University College of Medicine. Eleven healthy female volunteers aged 20-40 years participated after giving written consent. The visceral stimulation was realized by periodically inflating and deflating a silicon balloon in the rectum to multi levels of barostat-controlled pressure. In each study, the participant was subjected to 3-6 increasing levels of pressure (from 10 to 60 mmHg, sequentially), depending on the individual's pain threshold. The timing and duration of the visceral stimulation were automatically synchronized by TTL signals incorporated in the MRI pulse-timing program. Ten participants finished the study during the follicular phase, 9 during the luteal phase, and 8 finished during both phases. Blood progesterone level was monitored on the same day of fMRI to confirm the two menstrual phases (Table 1). Anxiety levels were assessed before and after each study using a State and Trait Anxiety Index (STAI); no significant difference was found (two-sample two-tailed t-test,  $p = 0.83$ ). fMRI was performed on a Bruker 3 T system with EPI (TR / TE = 4000 ms / 35 ms, 20 4-mm-thick axial slices to cover the top 2/3 of the brain, FOV =  $25 \times 25 \text{ cm}^2$ , matrix =  $128 \times 96$ , 77 repetitions). Immediately after each fMRI scanning, participants provided ratings of their pain sensation to the visceral stimulation on a 0–10 Likert-type scale. fMRI data were normalized to the Montreal Neurological Institute brain template [3] and smoothed with a gaussian kernel of  $6 \times 6 \times 6 \text{ mm}^3$  (FWHM). Activation maps in response to each pressure level from each individual were generated by comparing the brain signal during stimulation and baseline. Correlation between pressure and brain activation was studied as well as the comparison of the two phases of menstrual cycle. The effect of order of the two fMRI examinations on the brain response to visceral stimulation was studied and found to be negligible.

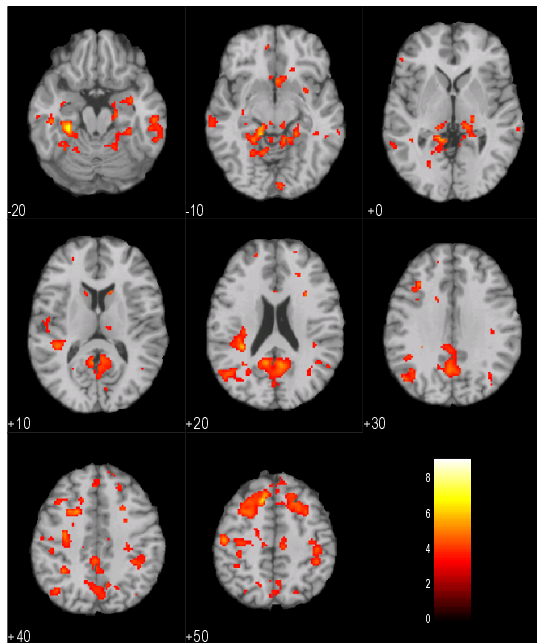
**Results:** Activation maps showed that the brain response was mainly located in the somatosensory cortex, pain matrix, and limbic system. Strong linear correlations between the levels the stimulation and brain response in the sensory cortex, cingulate, prefrontal cortex, thalamus, insula, and hippocampus was observed during the luteal phase (Fig. 1). Although there was no significant perception difference of the same level of visceral stimulation between the two menstrual phases (two-sample two-tailed t-test,  $p > 0.1$ ), stronger activation to maximum pressure stimulation was observed at bilateral prefrontal cortices and left anterior cingulate during the luteal phase (ANOVA,  $p < 0.001$ , Fig. 2). A paired t-test showed an increased activation during the luteal phase at bilateral prefrontal cortices ( $n = 8$ ,  $p < 0.001$ , extent threshold = 6), indicating an augmented sensitivity to visceral pain. Further analysis showed that when using visceral stimulation pressure as a covariate, stronger activation was present at the bilateral prefrontal cortex, thalamus, and left insula cortex during the luteal phase than during the follicular phase (ANCOVA,  $p < 0.01$ ). These brain areas are known to be associated with visceral pain perception and processing.

**Conclusion:** Healthy women demonstrated an increase in brain activation to visceral pain stimulation during the luteal phase than during the follicular phase of the menstrual cycle. This finding supports the notion that the visceral pain perception may be augmented during the luteal phase at the central nervous system level.

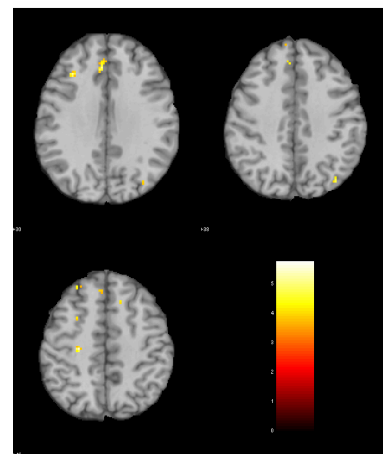
### References:

1. Arendt-Nielsen L, Bajaj P, Drewes AM. Eur J Pain. 2004;8:465-72.
2. Mayer EA, Berman S, Chang L, Naliboff BD. Eur J Pain. 2004;8:451-63.
3. Collins DL, et al. IEEE Trans Med Imaging 1998;17:463-468.

	Follicular	Luteal
	n = 10	n = 9
Progesterone	$0.77 \pm 0.63$	$8.70 \pm 5.17$



**Figure 1.** Brain structures showing positive correlation between activation and visceral stimulation during the luteal phase ( $n = 9$ ) ( $p < 0.001$ , extent threshold = 6).



**Table 1.** Blood progesterone level (ng/ml) at the time receiving fMRI confirmed the two menstrual phases (two-sample two-tailed t-test,  $p = 0.0017$ ).

**Figure 2.** Stronger brain response to maximum pressure stimulation during the luteal phase ( $n = 9$ ) than the follicular phase ( $n = 10$ ) (ANOVA,  $p < 0.001$ , extent threshold = 6).