Brain Networks Modulated by Menstrual Cycle: a Resting State Study

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Introduction

A number of studies have investigated alternations in spatial abilities, short-term memory and emotions during the female menstrual cycle. It has been reported that the hippocampus (*1*) and amygdala (*2*) are two areas exhibiting the sorts of functional or structural changes that may be responsible for related cyclic modulations in cognition and emotion. In this study, we examined changes in resting state functional connectivity during different phases of the menstrual cycle, and tested the hypothesis that the inter-regional connection of the major functional networks (*3*) and with hippocampus and amygdala may be different activity patterns during the early follicular compared to the midluteal phase of the menstrual cycle.

Methods

Eighteen healthy, right-handed women (age 24.1±3.3 yrs) were recruited with written informed consent. All participants had natural menstrual cycles (29-32 days) without using hormonal contraceptives. The participants were asked to record the date of menstrual onset the month prior to the experiment, and reported regular menstrual cycles. On a Siemens 3T Trio Tim MRI system, the participants were scanned twice: during the early follicular phase (low level of estrogen and progesterone in the 0 ~ 3rd day of the menstrual cycle) and during the mid-luteal phase (high level of estrogen and progesterone in the 20th ~ 24th day of the menstrual cycle). Participants were counterbalanced with controls to remove effects caused by unfamiliarity with the scanning environment.

Two resting state fMRI scans were performed (with eyes closed), while remaining awake during a total acquisition time of 12 min. A gradient-echo EPI sequence was used with the following parameters: TR/TE/FA = 2900 ms/30 ms/90°, matrix= 64×64, FOV=192 mm × 192 mm, bandwidth = 2232 Hz/Px, 48 axial slices, thickness/gap = 2.5/0.5 mm. To correct for geometric distortion, a field map was obtained using a gradient echo sequence run after the resting-state fMRI scans. Finally, a 3D MP-RAGE sequence was used to acquire T1-weighted images used as an anatomic reference (voxel size = 1 mm^3 isotropic).

The images were processed using SPM8. The first 8 volumes were discarded to ensure the remaining volumes were acquired at equilibrium, followed by slice timing correction, geometric distortion correction using field maps, image realignment, normalization to the MNI space, and smoothing with an 8mm FWHM Gaussian kernel.

To examine the major brain networks, we used Dosenbach's *(3)* region of interest (ROI) definitions, including 160 ROIs of 10 mm radius each, covering of the majority of the cerebral cortices and cerebellum. Based on a previous meta-analysis (ref?), the 160 ROIs were partitioned into six functional networks: cingulo-opercular, frontoparietal, default mode, sensorimotor, occipital, and cerebellar networks. After examining ROI-based voxel-wise bivariate correlations using the CONN Toolbox (http://web.mit.edu/swg/software.htm), we compared the differences between the early follicular and mid-luteal phases, using a paired t-test for each network. A threshold corrected for multiple comparisons ($p<0.001$, cluster size=594 mm^3) was determined using an AlphaSim correction. Since these six major networks did not include the hippocampus and amygdala, regions that have been reported to modulate their activity during the menstrual cycle (ref?), we added 10mm spheres centered in the bilateral hippocampus and parahippocampus (±20, -8, -22), and the bilateral amygdala (±20, 0 ,-20) as seeds.

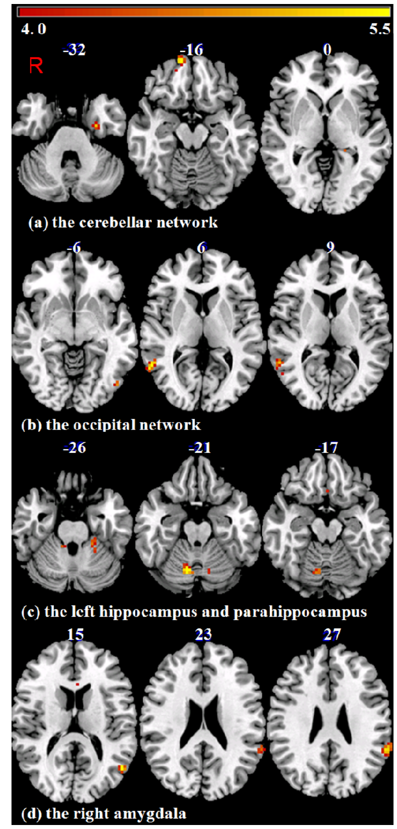

Fig. 1. *t*-Maps showed significantly higher ($p<0.001$, uncorrected) functional connectivity of ROIs in the mid-luteal phase than in the early follicular phase.

Results and Discussion

It was observed that the mid-luteal phase showed significantly higher ($p<0.001$, uncorrected) inter-regional correlations than the early follicular phase in the cerebellar (Fig. 1a) and occipital (Fig. 1b) networks, as well as in the left hippocampus and parahippocampus (Fig. 1c), and right amygdala networks (Fig. 1d) (Note that a *t*-value color bar is displayed on the top of Fig. 1). Regions showing different correlations in the two phases are summarized in Table 1 (t=3.97, $p_{AlphaSim\_corrected}$ = 0.05). The paired *t*-test showed that none of the seed regions selected in this study had inter-regional connectivity that was significantly higher in the early follicular phase.

Table 1. Cluster peak coordinates and anatomical regions

Seeds	Cluster peak (*x, y, z mm*)	Label (AAL Atlas)
Cerebellar network	12, 63, -15	Frontal_Sup_Orb_R
	-27, -9, -33	Parahippocampus_L
	-21, -36, 0	Hippocampus_L
Occipital network	57, -54, 6	Temporal_Mid_R
	64, -63, 9	Temporal_Mid_R
	-48, -75, -6	Occipital_Inf_L
left hippocampus, parahippocampus	11, -66, -23	Cerebellum
right amygdala	-51, -66, 15	Temporal_Mid_L
	-60, -45, 27	Supramarginal_L

Figure 1 and Table 1 illustrate that the correlation of the cerebellum network with the frontal cortex, parahippocampus and hippocampus, and the correlation of the occipital network with the middle temporal cortex and inferior occipital cortex were both significantly higher in the mid-luteal phase. The results in the cerebellar and occipital networks were consistent with a previous PET study (*4*), which showed that the mid-luteal phase was associated with significantly higher glucose metabolism in the temporal cortex, occipital cortex and cerebellum. The cerebellar network has been thought to be involved in task level control, and to provide rapid feedback to frontal-parietal and cingulo-opercular task control networks *(3)*. Our findings in the cerebellar and hippocampal networks suggest that the inter-regional influences between the cerebellum and hippocampus could be modulated during the menstrual cycle, which may affect moment-to-moment task error-processing. This result may relate to behavioral results showing that fine motor skills in the mid-luteal phase were better than in the early follicular phase *(5)*. The right amygdala showed stronger correlations with middle temporal cortex, a finding consistent with a previous study which used a facial emotion recognition task to demonstrate that amygdala and middle temporal cortical activity can be modulated by the menstrual cycle (*2*). The pattern of functional connectivity shown in this study may provide new insights into understanding how the major brain networks, as well as hippocampus and amygdala, are modulated by the menstrual cycle.

References: 1.X. Protopopescu et al., Hippocampus 18, 985 (2008). 2. B. Derntl et al., Psychoneuroendocrinology 33, 1031 (2008). 3. N. U. F. Dosenbach et al., Science 329, 1358 (2010). 4. E. Reiman et al., Human Reproduction 11, 2799 (1996). 5. P. M. Maki et al., Neuropsychologia 40, 518 (2002).

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