

HIPPOCAMPAL CONNECTIVITY MODULATED BY MENSTRUAL CYCLE: A RESTING STATE STUDY

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Introduction

The hippocampus and parahippocampal cortex are involved in spatial navigation abilities (1). It is also known that women's spatial abilities vary during the menstrual cycle, associated with varying hormonal levels (2), suggesting that the observed variations in spatial abilities may be mediated by hormone effects on hippocampal structures. In this preliminary study, we examined changes in resting state inter-regional correlations during different menstrual cycle phases (3). We hypothesized that the functional connectivity of the hippocampus and parahippocampus with other brain regions would be different during the early follicular phase compared to the mid-luteal phase.

Methods

Using a Siemens 3T Trio system, six healthy, right-handed women (age 24.4±5.5 yrs) were studied after providing written informed consent. All participants were naturally cycling (cycle 29-32 days) and did not use hormonal contraception. They were asked to record their date of menstrual onset the month before the experiment, and confirm that their cycles were regular. Participants were scanned twice, once during their early follicular phase (low estrogen and progesterone) and once during their mid-luteal phase (high estrogen and progesterone). The early follicular phase examined spanned the time from the onset of menstruation to the third day of the menstrual cycle. The mid-luteal phase ranged from the 20th day to the 24th day of the menstrual cycle. Participants were counterbalanced to control for effects of novelty or unfamiliarity with the scanning environment. Half were scanned first during the early follicular phase, and half were scanned first during the mid-luteal phase.

During the scan, all participants were instructed to lie still with closed eyes, while remaining awake. EPI acquisition parameters included: TR/TE= 2900/30 ms, in-plane matrix=64×64, FOV=192 mm×192 mm, bandwidth=2232 Hz/Px, 48 axial slices, thickness/ gap=2.5/0.5 mm, and 248 volumes in a total acquisition time of 8 min. To correct for geometric distortion, a gradient echo field mapping scan was performed after the two resting-state sessions. The last acquisition was a 3D T1-weighted sequence (voxel size=1mm³), used for spatial normalization of the EPI data.

Data preprocessing was done using SPM8 and Matlab 7.8. The first 8 volumes were discarded for MR signal equilibration. Preprocessing included slice time correction, geometric distortion correction using the field maps, and realignment. One of the participants showed peak-to-peak head motion greater than 1.5mm or 2deg and was excluded. Next the structural images were coregistered to the mean EPI data, and the coregistered structural images were segmented, with the segmentation providing MNI normalization parameters that were used to transform the EPI data to MNI space. Functional images were then smoothed using an 8mm FWHM Gaussian smoothing kernel.

We selected seed ROIs in two 5mm-radius spheres centered at (±20,-8,-22) mm in the left and right hippocampus and parahippocampus (3), and then examined voxel-wise bivariate correlations of the two seeds with the rest of the brain separately, using the CONN Toolbox (<http://web.mit.edu/swg/software.htm>). Two conditions were examined for each subject, the early follicular phase and the mid-luteal phase. Each condition had two resting state sessions. The time series were temporally band-pass filtered (0.01-0.08 Hz). White matter signal, cerebrospinal fluid signal, and 6 head motion estimates were entered as nuisance variables in the statistical model. After determining the mean connectivity maps of the two cycle phases, we compared differences between the early follicular phase and mid-luteal phase, using a paired *t*-test in SPM. A critical threshold corrected for multiple comparisons ($p < 0.01$, cluster size=1998 mm³) was determined using of AlphaSim in REST toolbox (<http://restfmri.net/forum>). The regions of interest were selected using the AAL Atlas.

Results and Discussion

The left hippocampus and parahippocampus showed inter-regional connectivity with the bilateral superior occipital gyrus and cuneus, and the right middle frontal gyrus were significantly higher in the mid-luteal phase than in the early follicular phase. In contrast, we observed no significant difference in relation to the right hippocampus and parahippocampus connectivity in the two menstrual phases. The results are displayed in radiology convention, with *t*-value color bar on the right. Fig.1 illustrates that the left hippocampus and parahippocampus show resting state correlations with frontal, parietal, occipital and temporal lobes, as well as other limbic regions, and these results are similar to a previous study (4). The seed region is marked by an arrow. Fig.2 shows the paired *t*-test result contrasting inter-regional correlations in the two cycle phases, and cluster peaks at (21,-85,-34), (-18,-97,25), and (27,53,22), $t=4.6$, $p(\text{AlphaSim}_{\text{corrected}}) = 0.05$.

Our results show that the connectivity between the left hippocampus and the superior occipital and middle frontal gyri may be modulated by the menstrual cycle phase. The laterality of the effect may be due to partial volume effects resulting from variation in hippocampal gray matter volumes during menstrual cycle (3). The regions showing variable connectivity with the hippocampal structures, includes the superior occipital gyrus and the cuneus involved in visual processing, and the right middle frontal region which was reported to be more activated in the luteal phase than in the early follicular phase during a mental rotation task (2), which is consistent with the results of our resting state study. The patterns of functional connectivity shown in this study may provide new clues for understanding the mechanism of how spatial abilities are modulated by hormone during menstrual cycle.

The left hippocampus and parahippocampus showed inter-regional connectivity with the bilateral superior occipital gyrus and cuneus, and the right middle frontal gyrus were significantly higher in the mid-luteal phase than in the early follicular phase. In contrast, we observed no significant difference in relation to the right hippocampus and parahippocampus connectivity in the two menstrual phases. The results are displayed in radiology convention, with *t*-value color bar on the right. Fig.1 illustrates that the left hippocampus and parahippocampus show resting state correlations with frontal, parietal, occipital and temporal lobes, as well as other limbic regions, and these results are similar to a previous study (4). The seed region is marked by an arrow. Fig.2 shows the paired *t*-test result contrasting inter-regional correlations in the two cycle phases, and cluster peaks at (21,-85,-34), (-18,-97,25), and (27,53,22), $t=4.6$, $p(\text{AlphaSim}_{\text{corrected}}) = 0.05$.

References

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Acknowledgements: This work was supported by the Ministry of Science and Technology of China (Grants 2005CB522800, 2010IM030800), National Nature Science Foundation of China (Grants 90820307)

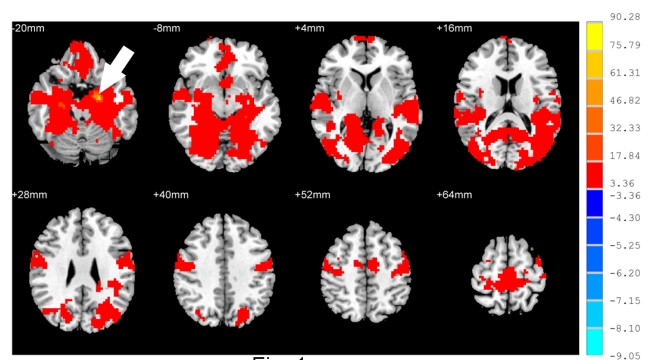


Fig. 1

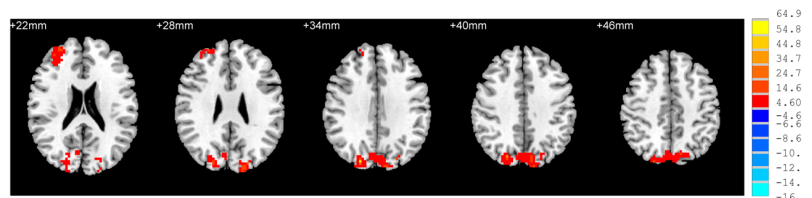


Fig. 2