Resting-State Functional Connectivity during Pregnancy

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INTRODUCTION: Pregnancy is associated with structural, physiological and functional changes which affects maternal behaviors and activities. It has been suggested that neural activity is enhanced by pregnancy in order to adapt to these changes [1]. Moreover, it has been reported that spatial working memory [2] and hippocampal neuronal dendritic spine density [3] varied during pregnancy. These functional and structural changes might affect the functional connectivity in the brain. Recently, resting-state functional connectivity MRI (fcMRI) has been intensively used to investigate neural connectivity in healthy and diseased humans and rodents [4-7]. However, little is known on the effects of pregnancy in neural connectivity. In this study, the effects of pregnancy on resting-state functional connectivity in the brain were explored using a pregnant rat model.

MATERIALS AND METHODS: Animal Preparation: Pregnant Sprague-Dawley rats (3.5 months, G17, N = 5) and non-pregnant female controls (3.5 months, N = 4) were MRI scanned under mechanical ventilation with isoflurane anesthesia (1.5%). **MRI Protocols:** All MRI measurements were acquired utilizing the 7T Bruker scanner with a quadrature surface coil. Resting-state functional connectivity MRI (fcMRI) acquisition were performed using a single-shot GE-EPI sequence with TR/TE = 1000/18 ms, flip angle = 30°, FOV = 32×32mm^2, MTX = 64×64, ten 1-mm-thick slices (0.2 mm apart), and a total of 280 data points. RARE T2W images were acquired using TR/TE = 4200/36 ms as an anatomical reference for EPI images. **Data Analysis:** All fcMRI data were compensated for slice timing, co-registered and detrended, as well as temporally low-pass filtered for obtaining low frequency fluctuations. Subsequently, inter-animal co-registration was performed in the two groups. GIFT v1.3h (Group ICA Toolbox) was utilized for decomposing different networks. Four 2×2-seed-voxels, as well as four respective regions of interest were selected based on atlas and networks observed in GIFT. Cross-correlation maps (cc-maps) were obtained with the application of the STIMULATE software as well as the 2×2-seed-voxels and regions of interest (ROI) in each individual. Statistical evaluation was conducted on the cc-maps using Welch's t-test and results were considered significant when $p < 0.05$. (*, ** and *** denote $p<0.05$, $p<0.01$ and $p<0.001$, respectively, and n.s. denotes insignificant or $p > 0.05$.)

RESULTS: With reference to Fig.1a, the cc-maps had similar coverage and correlation strength for both non-pregnant and pregnant subjects in the motor cortex (with a correlation threshold of 0.3). However, with reference to Fig.1b to Fig.1d, the cc-maps varied among non-pregnant and pregnant subjects in the caudate putamen, hippocampus and thalamus (with a correlation threshold of 0.3). The results displayed in Fig. 2 shows that there was significant increase in resting-state functional connectivity for the pregnant group in the caudate putamen ($p<0.01$), hippocampus ($p<0.01$) and thalamus ($p<0.001$). However, there were no significant difference in resting-state functional connectivity of the motor cortex between the pregnant group and non-pregnant group.

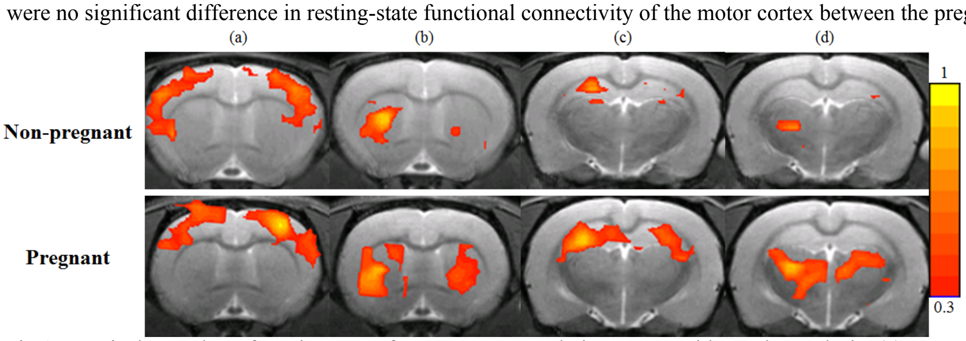

Fig.1 Typical samples of resting-state fcMRI cross-correlation maps with seed voxels in (a) motor cortex, (b) caudate putamen, (c) hippocampus and (d) thalamus overlaid on T2W image of the pregnant rat and the adult female rat.

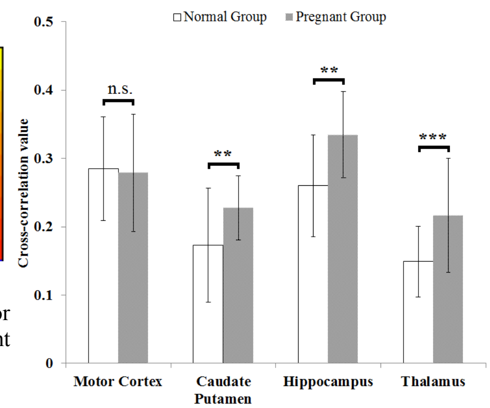

Fig.2 Mean and standard deviation of cross-correlation maps reflecting the resting-state functional connectivity of the respective networks.

DISCUSSION: The strength and spatial distribution of the spontaneous fluctuations in fcMRI signal is altered by pregnancy. Specifically, the effects of pregnancy at G17 increase the spontaneous fluctuations in fcMRI signal in the caudate putamen, hippocampus and thalamus; whereas the spontaneous fluctuations in fcMRI signal were similar in the motor cortex in the pregnant group compared to control group. It is believed that pregnancy stimulates spatial learning and memory in females [1] and it has been demonstrated that pregnancy affects spatial performance which relates to spatial working memory [2]. Hippocampus plays an important role in memory and spatial navigation. Hence, these might be the reasons for the increase in resting-state functional connectivity for the pregnant group in the hippocampus. Furthermore, it is accepted that the caudate putamen is related to emotions [8, 9] and emotional changes is common during pregnancy [10]. Thus, the increase of the functional connectivity in the caudate putamen might probably relate to the emotional changes during pregnancy. Lastly, it has been documented that the functional connectivity in the thalamus increased with subjects having major depression [11]. Pregnant subjects are more susceptible to depression [12], though it is uncertain that the pregnant animals in our study were under depression. Therefore, the reasons for the increase in functional connectivity of the thalamus in the pregnant group are to be elucidated.

CONCLUSION: The results of this study demonstrate the changes of resting-state functional connectivity induced by pregnancy. Interestingly, there was significant increase in resting-state functional connectivity in the caudate putamen, hippocampus and thalamus during late pregnancy (G17). The longitudinal effects of pregnancy, as well as, the effects on other functional networks are to be explored.

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