Increased Posterior Cingulate, Medial Frontal and Decreased Temporal Regional Homogeneity in Depressed Mothers.

A Resting-State Functional Magnetic Resonance Study.

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Abstract

Objective: To explore the neural pathophysiology of postpartum depression through analyzing fMRI regional homogeneity in postpartum depressed mothers during resting state. Methods: 10 depressed mothers and 11 healthy mothers were recruited and underwent functional MRI scanning during resting state. Results: Compared with healthy mothers, the depressed mothers showed significantly increased posterior cingulate, medial frontal and decreased temporal gyrus regional homogeneity. Conclusions: The results suggest that abnormal neural activities existed in depressed mothers and which may play an important role in psychopathology of postpartum depression.

1. Background

Postpartum depression (PPD) is a significant public health problem that affects 15% of new mothers and confers adverse consequences for mothers, children, and their families. Hypothalamic-pituitary-adrenal axis dysregulation [1] and hypoestrogenemia [2] appear to be important pathophysiological
processes in postpartum depression. However, the neural mechanisms involved in postpartum depression remain unclear.

In recent years, neuroimaging technology such as functional magnetic resonance imaging (fMRI) and PET have greatly advanced our understanding of neural activity of brain. In these technologies, fMRI scan during resting-state is favored by many researchers. In resting-state scans, subjects do not need to perform any task, the information collected is defined as baseline information of brain function, that can reflect the state of the central nervous system based on the spontaneous functional activity and helps us to understand nature activity of the brain.

Some progresses have been made on nonpostpartum depression and found there existed abnormal brain function activities. Anand et al. [3] reported cortico-limbic low-frequency blood fluctuations correlations were decreased in depression in resting state. Greicius et al. [4] reported resting-state subgenual cingulate and thalamic functional connectivity with the default-mode network were higher in depression. However there is little fMRI study on postpartum depression. Only Moses-Kolko EL et al. [5] using emotional faces to PPD patients and reported abnormally reduced dorsomedial prefrontal cortical activity and effective connectivity with amygdala in response to negative emotional faces. These studies show brain dysfunction existed in depression and postpartum depression, but the results are inconsistent and the etiology still unclear.

So far, no study had been made for detecting the mechanism of PPD through resting-state fMRI scans. How about the postpartum depression central mechanism? What is the neural activity difference between the PPD mothers and normal mothers? In this paper we propose that abnormal brain existed in depressed mothers during resting state and we attempted to detect the neural activity in postpartum depression by using functional magnetic resonance imaging (fMRI) scan in resting-state to offer more information for understanding the pathogenesis of PPD.

2. Methods

2.1. Subjects

Twelve patients with PPD mothers within 16 weeks of giving birth were recruited from out-patients at obstetric clinic for postpartum review at the First People's Hospital of Xiao Shan district, Hangzhou, China.

These patients met CCMD-3 diagnostic criteria (China Classification and diagnostic criteria for mental disorders in Version 3) for (single phase) depressive episodes, also met DSM-IV criteria (U.S. Diagnostic and Statistical Manual of mental disorders 4th edition for postpartum major depression disorder criteria. All patients were in their first episodes of depression, and had never been on medication. Confirmation of the diagnosis was made by a clinical psychiatrist. All patients had no history of neurological or head injury or any other relevant medical or additional psychiatric disease and physical diseases.

Twelve healthy mothers within 16 weeks of giving birth were recruited from out-patients to obstetric clinic for postpartum review at the First People's Hospital of Xiao Shan district, Hangzhou, China. None of them had a current or past history of depression or had other mental disorders. All of them had no substance abuse or any other relevant physical disease.

All subjects were right-handed, normal hearing and signed the informed consent. This study was approved by the Medical Ethics Committee of First People's Hospital of Xiao Shan district, Hangzhou, China.

2.2. MR imaging
Imaging data were acquired using a Siemens (Germany) 1.5 T magnetic resonance imaging scanner. All subjects were placed a head coil to reduce head motion and underwent a 6-min resting-state scan. They were informed to hold still, keep their eyes closed and do not think of anything.

The scanning sessions included the following (were as follows):

- T1-weighted axial image: repetition time/echo time (TR/TE)=3000/18 ms; thickness/ gap=4/0 mm; matrix: 256×144; field of view (FOV)=256×192 mm; Three-dimensional T1-weighted whole-brain images: 3D-FLASH sequence, TR/TE=14/4.92 ms, 120 slices FOV=230×230 mm, matrix=256×192, flip angle=15°; The resting-state fMRI image: echo planar imaging (EPI) pulse sequence, 28 slices; TR/TE=2000/20 ms; thickness/gap=4/0 mm; matrix=64×64; FOV=230×230 mm; flip angle=90°.

2.3. Imaging data analysis

Image preprocessing was conducted using statistical parametric mapping software (SPM8, Welcome Department of Imaging Neuroscience, London, UK).

The first 5 volumes of each functional time series were discarded because of instability of the initial MRI signal and adaptation of subjects to the circumstance, leaving 175 volumes for further analysis. The next processing were time slice, realignment, smooth. We calculated the maximum exclusion movement values for each of planes of translation (x, y, and z) and each of planes of rotation (roll, pitch, and yaw) for every participant. The subjects who had more than 2 mm maximum displacement in x, y, or z and 2°of angular motion during the whole fMRI scan was excluded.

The fMRI images were normalized to the standard SPM8 echo planar imaging template, re-sampled to 3-mm cubic voxels. The resulting fMRI data were temporally band-pass filtered (0.01–0.08 Hz) to reduce low frequency drift and physiological high frequency respiratory and cardiac noise for further ReHo analysis.

2.4. ReHo analysis

The ReHo analysis was done by ReHofMRI1.0 software (http://www.nlpr.ia.ac.cn/english/mic/YongHe/Research.htm) and the analysis has been used in previous study[6].

ReHo analysis assumed that the selected voxel is similar with adjacent voxels, voxels at the same time sequence showed similar changes, with the Kendall value (Kendall’S coefficient concordance, KCC) calculated as an indicator to measure the similarity of the time series of a given voxel to its nearest adjacent 26 voxels. The formula calculated for KCC value was as followed:

\[
W = \frac{1}{12} K^2 \left( \frac{1}{n} \sum_i R_i^3 - n \left( \frac{R}{n} \right)^3 \right)
\]

\(W\): the KCC of a given voxels, ranging from 0 to 1; \(R_i\): the sum rank of the \(i\)th time point;
\(\overline{R} = \frac{(n+1) \times K}{2}: \) the mean of the \(R_i\)s; \(K\): the number of time series within a measured cluster; \(K=27; n\): the number of ranks.)

Each person’s fMRI image data drew one KCC image(ReHo image). Then each voxel ReHo value of the whole brain is divided by the mean voxel ReHo value of the whole brain then get the average ReHo image. The resulting fMRI data were spatially smoothed with a Gaussian kernel of 6×6×6 mm^3 full-width at half-maximum.
The KCC program was coded in REST software (http://resting-fmri.msourceforge.net) by the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China.

2.5. Statistic analysis

To explore the ReHo differences between the depressed mothers and healthy mothers, a two-sample t-test was performed on the individual normalized ReHo image in a voxel-by-voxel manner. Voxels with a p value<0.01 (uncorrected) and cluster size> 10 voxels were used to determine significant difference.

Independent-samples T test analyses were performed with SPSS 11.0 software. Group statistical analysis was performed using SPM8.

3. Results

3.1. Subjects

Two depressed mothers and one healthy mother were excluded due to poor image quality. There are left 10 mothers with PPD and 11 healthy mothers.

Basic characteristics of subjects were analyzed by independent-samples T test and details in Table 1. The age and the education years difference between postpartum depression mothers and healthy mothers were not significant(P>0.05)

Table 1 t test for age and education level of depressed mothers and healthy mothers (x ± s)

<table>
<thead>
<tr>
<th></th>
<th>Depressed mother n=10</th>
<th>Healthy mother n=11</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>27.58 ± 4.56</td>
<td>27.16±3.68</td>
<td>0.80</td>
</tr>
<tr>
<td>Education year</td>
<td>12.03±3.77</td>
<td>12.08±3.53</td>
<td>0.65</td>
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</table>

3.2. ReHo: depressed mothers versus healthy mothers

As shown in Table2, the the depressed group showed a significant ReHo increase in posterior cingulated, cingulate gyrus, frontal lobe, parietal lobe, medial frontal gyrus, medial frontal gyrus(P<0.01) compared with healthy mothers.

Table 2 Increased ReHo in depressed mothers
<table>
<thead>
<tr>
<th>Area</th>
<th>side</th>
<th>BA</th>
<th>Voxels</th>
<th>Talairach Coordinates</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>L</td>
<td>31</td>
<td>19</td>
<td>-3</td>
<td>-57</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>R</td>
<td>31</td>
<td>16</td>
<td>6</td>
<td>-27</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>R</td>
<td>14</td>
<td>27</td>
<td>-33</td>
<td>27</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>R</td>
<td>12</td>
<td>45</td>
<td>-63</td>
<td>36</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>R</td>
<td>9</td>
<td>10</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>R</td>
<td>30</td>
<td>27</td>
<td>-24</td>
<td>33</td>
</tr>
</tbody>
</table>

### 3.3.3 ReHo: healthy mothers versus depressed mothers

As shown in Table 3, the depressed group showed a significant ReHo decrease in inferior temporal gyrus, middle temporal gyrus, superior temporal lobe, frontal lobe (P<0.01) compared with healthy mothers.

**Table 3** Decreased Reho in depressed mothers

<table>
<thead>
<tr>
<th>Area</th>
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<th>BA</th>
<th>Voxels</th>
<th>Talairach Coordinates</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>x</td>
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<tr>
<td>Inferior temporal gyrus</td>
<td>R</td>
<td>20</td>
<td>35</td>
<td>54</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>R</td>
<td>15</td>
<td>11</td>
<td>54</td>
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<td>Superior temporal lobe</td>
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<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>4</td>
<td>11</td>
<td>-42</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>6</td>
<td>14</td>
<td>-21</td>
</tr>
</tbody>
</table>

### 4. Discussion

This is the first fMRI study to our knowledge to detect neural mechanism of PPD with fMRI during resting state.

In this study we found a ReHo increase in posterior cingulate, cingulate gyrus. This is consistent the previous functional imaging studies in major depression. Structural imaging studies have shown decreased posterior cingulate volume in patients with depression [7].

PET (single photon emission computed tomography) and SPECT (Single photon emission computed tomography) studies reported that increased posterior cingulate metabolic in major depression [8]. Cingulate gyrus is an important part of the default network (DMN) [9]. The default network coordination disorder may affect brain function in transformation modulation from the resting state to cognitive tasks. Dysfunction of cingulate in PPD mothers may imply their DMN dysfunction and which may play a role in the pathogenesis for the patients to transformation from one state to the other. Posterior cingulated also played an important role in the extraction in episodic memory. Posterior cingulate abnormalities in patients with PPD may imply negative episodic memory strengthening in depressed mothers.

Medial frontal cortex involved in the integration of environmental information, emotional integration
and episodic memory functions. Positron emission tomography study [10] found that, increased metabolism in mPFC during resting state in major depression. We found increased ReHo in medial PFC may imply that after the stress such as pregnancy, childbirth and postpartum feeding baby, depressed mothers may be in a over-compensated state to integrate the environmental information, emotional integration and episodic memory.

Temporal lobe is a complex area of memory, emotion and other mental activities and has important implications for patients in the depression.

A preliminary study shows that temporal lobe white matter abnormalities existed in depression patients [11]. There are also studies which reported ReHo value decreased in depression on the left lateral temporal lobe and left medial temporal lobe, indicating that these two brain regions decreased neural spontaneous activity consistency and revealed that coordination dysfunction of the basic state of temporal lobe [12].

There are some other studies suggest depression, negative cognitive anxiety are related with spontaneous neural activity of temporal lobe in depression patients and consistency with the Beck's Depression “biased cognitive theory” in 1967. The hypothesis consider that there exists negative, distorted perception in the handling internal and external information in depression patients, and temporal lobe brain regions is the key brain regions for the basis and is closely related to negative emotion.

We found deceased temporal lobe REHO in depressed mothers imply that this region may relate the symptom of depression, anxiety, negative cognition in PPD mothers.

Although we found abnormal brain regions in postpartum depression in this study, what is the role of these abnormal brain regions in the pathogenesis of postpartum depression is still need more research.

There is some research we can do such as to find if the HPA axis, estrogen dysfunction and the pregnancy, childbirth and postpartum stress relate with these brain abnormalities so to give more information for understanding the pathogenesis of the postpartum.

References


