Disruption within brain default mode network in postpartum women without depression

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Abstract

Previous studies have demonstrated that cognitive dysfunction is associated with neurophysiological changes in postpartum period. This study aimed to investigate the intrinsic functional connectivity (FC) pattern within the default mode network (DMN) and its associations with cognitive dysfunction in postpartum women without depression revealed by resting-state functional magnetic resonance imaging (fMRI).

Resting-state fMRI scans were acquired from 21 postpartum women and 21 age- and education-matched nulliparous women. The posterior cingulate cortex (PCC) was selected as the seed region to detect the FC patterns and then determine whether these changes were related to specific cognitive performance.

Compared with the nulliparous women, postpartum women had a significantly decreased FC between the PCC and the left medial prefrontal cortex (mPFC). After correcting for age and education, the reduced FC between the PCC and the left mPFC was positively correlated with the poorer Clock-Drawing Test (CDT) scores in postpartum women (r = 0.742, P < .001).

The present study mainly demonstrated decreased resting-state FC pattern within the DMN regions that was linked with impaired cognitive function in postpartum women. These findings illustrated the potential role of the DMN in postpartum women that will provide novel insight into the underlying neuropathological mechanisms in postpartum period.

Abbreviations: AVLT = Auditory Verbal Learning Test, BOLD = blood oxygenation level-dependent, CDT = Clock-Drawing Test, CFT = Complex Figure Test, DMN = default mode network, DST = Digit Span Test, DSST = Digit Symbol Substitution Test, EPDS = Edinburgh Postnatal Depression Scale, FA = flip angle, FC = functional connectivity, FD = framewise displacement, FDR = false discovery rate, fMRI = functional magnetic resonance imaging, FOV = field of view, MMSE = Mini Mental State Exam, MoCA = Montreal Cognitive Assessment, mPFC = medial prefrontal gyrus, PCC = posterior cingulate cortex, ROI = regions of interest, TE = echo time, TMT = trail-making test, TR = repetition time, VFT = verbal fluency test.

Keywords: cognitive dysfunction, default mode network, postpartum women, resting-state fMRI

1. Introduction

Postpartum women have been associated with an increasing risk of cognitive dysfunction, primarily presenting as recent memory loss, forgetfulness, difficulty concentrating, and distractibility.[1–5] Women during the postpartum period will experience a multitude of physical and environmental changes.[2,6] Cognitive dysfunction in postpartum period may play a pivotal role in various postpartum disorders.[7–9] However, the exact neural mechanism of postpartum-related cognitive impairment still remains unclear.

Previous neuroimaging techniques have been used to investigate the brain alterations in postpartum women. Several studies have used task-based functional magnetic resonance imaging (fMRI) to investigate the brain activity during the postpartum period.[10,11] Resting-state fMRI based on spontaneous blood oxygenation level-dependent (BOLD) responses has proved to be useful noninvasive
neuroimaging to reveal the disease induced neural dysfunction associated with neuropathology,[12,13] which has been used to detect the abnormal brain functional connectivity (FC) in postpartum depressed women.[14–18] Nevertheless, few studies have investigated the FC in postpartum women without depression.

As an important resting-state FC network, the default mode network (DMN), consisting of nodes in the posterior cingulate cortex (PCC), precuneus, angular gyrus and medial prefrontal gyrus (mPFC), is most active at rest and shows reduced activity when a subject enters a task-based state involving attention or goal-directed behavior.[12] As the key region of DMN, the PCC plays a pivotal role in emotion and distressing information processing.[19] During cognitive processing, the PCC is functionally linked to the DMN regions, such as the mPFC.[19] The anteroinferior PCC has more outward and preventative aspects of self-relevant thought, including duties and responsibilities to others.[20] Postpartum women would be expected to have a stronger focus on infant-related responsibilities and be more involved in considering the intentions of others, especially the newborn.[15] Moreover, changes in endogenous sex steroid hormone during the postpartum period may cause widespread neural alterations, such as the PCC.[17] In addition, aberrant brain activity of the PCC in postpartum women has been confirmed in prior studies.[15,21,22] Therefore, cognitive impairment in postpartum women may be linked with the FC alterations of PCC. However, the abnormal FC activity of the PCC in postpartum women and its effect on cognitive function remains largely unknown.

The aim of this study was to investigate whether resting-state DMN was disrupted in postpartum women compared with nulliparous women. We hypothesized that abnormal FC patterns of the PCC within the DMN could be detected in postpartum women and would correlate with cognitive deficits.

2. Materials and methods

2.1. Subjects

In this study, a total of 42 subjects (aged between 20 and 40 years, all right-handed with the completion of at least 9 years of education) made up of 21 postpartum women and 21 nulliparous women were included through community health screening and newspaper advertisements. No subject was subsequently excluded because of the exceeded limits for head motion during scanning. All the women were medication free and had delivered a healthy and full-term infant in the preceding 3 months. None of the women experienced any complications during pregnancy or delivery, such as hypertension, diabetes, eclampsia, heart disease, or postpartum hemorrhage. Among them, 11 women had natural childbirth, and the other 10 chose cesarean section. Fifteen women were breastfeeding and the other 6 women were mixing feeding.

Women were excluded from the study if they had severe smoking, alcoholism, stroke, Alzheimer’s disease, Parkinson’s disease, major depression, neuropsychic disorders that could affect cognitive function, major medical illness (e.g., anemia, thyroid dysfunction, and cancer), MRI contraindications, or were currently pregnant. None of the postpartum women had symptoms of postnatal depression according to the Edinburgh Postnatal Depression Scale (EPDS, overall scores < 12).[23] The characteristics of the postpartum women and nulliparous women are summarized in Table 1. This study was approved by the Research Ethics Committee of the Nanjing Medical University. All individuals provided written informed consent before their participation in the study protocol.

2.2. Neuropsychological assessment

All subjects underwent a battery of neuropsychological tests that covered related cognitive domains. The neuropsychological status of the participants was established using the Mini Mental State Exam (MMSE),[24] Montreal Cognitive Assessment (MoCA),[25] Auditory Verbal Learning Test (AVLT),[26] complex figure test (CFT),[27] digit span test (DST),[28] trail-making test (TMT) A and B,[29] clock-drawing test (CDT),[30] verbal fluency test (VFT),[31] and digit symbol substitution test (DSST).[32] The tests assessed general cognitive function, episodic verbal and visual memory, semantic memory, attention, psychomotor speed, executive function, and visuospatial skills. It took ~60 min for each individual to complete all of the tests in a fixed order.

![Table 1](image)

| Demographics, clinical, and cognitive characteristics of the postpartum and nulliparous women. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Postpartum women (n = 21) | Nulliparous women (n = 21) | P     | Cohen’s d |
| Age (year) | 29.00 ± 2.59 | 29.05 ± 2.56 | .961 | 0.016 |
| Education levels (years) | 17.00 ± 1.76 | 17.52 ± 3.11 | .508 | 0.206 |
| MMSE | 28.71 ± 1.23 | 28.67 ± 1.39 | .907 | 0.030 |
| MoCA | 25.62 ± 1.77 | 25.52 ± 1.86 | .866 | 0.055 |
| AVLT | 34.19 ± 9.06 | 33.29 ± 7.18 | .722 | 0.110 |
| AVLT-delayed recall | 6.86 ± 2.83 | 6.43 ± 1.91 | .569 | 0.178 |
| CFT | 34.55 ± 1.60 | 34.17 ± 1.95 | .493 | 0.213 |
| CFT-delayed recall | 14.52 ± 3.99 | 16.71 ± 3.24 | .013 | 0.815 |
| DST | 11.14 ± 1.46 | 11.57 ± 1.94 | .423 | 0.250 |
| TMT-A | 71.81 ± 21.75 | 69.86 ± 21.82 | .773 | 0.090 |
| TMT-B | 160.76 ± 56.70 | 159.14 ± 52.86 | .924 | 0.030 |
| CDT | 3.05 ± 0.59 | 3.57 ± 0.51 | .004 | 0.943 |
| VFT | 13.33 ± 4.54 | 14.21 ± 3.52 | .486 | 0.217 |
| DSST | 70.76 ± 8.87 | 67.95 ± 9.43 | .326 | 0.307 |
| EPDS | 4.29 ± 2.53 | – | – |

Data are represented as mean ± SD. *P < .05.

AVLT = auditory verbal learning test, CDT = clock drawing test, CFT = complex figure test, DST = digit span test, DSST = digit symbol substitution test, EPDS = Edinburgh Postnatal Depression Scale, MMSE = Mini Mental State Exam, MoCA = Montreal Cognitive Assessment, TMT-A = trail making test-part A, TMT-B = trail making test-part B, VFT = verbal fluency test.
2.3. MRI data acquisition

MRI data were acquired using a 3.0T MRI scanner (Ingenia, Philips Medical Systems, Netherlands) with an 8-channel receiver array head coil. Head motion and scanner noise were alleviated using foam padding and earplugs. Subjects were instructed to lie quietly with their eyes closed, remain awake, not think about anything in particular, and avoid any head motion during the scan. Functional images were obtained axially using a gradient echo-planar imaging sequence as follows: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; slices = 36; thickness = 4 mm; gap = 0 mm; field of view (FOV) = 240 mm × 240 mm; acquisition matrix = 64 × 64; and flip angle (FA) = 90°. The fMRI sequence was obtained in 8 min and 8 s. Structural images were acquired with a three-dimensional turbo fast echo (3D-TFE) T1WI sequence with high resolution as follows: TR = 8.1 ms; TE = 3.7 ms; slices = 170; thickness = 1 mm; gap = 0 mm; FA = 8°; acquisition matrix = 256 × 256; FOV = 256 mm × 256 mm. The structural sequence was obtained in 5 min and 29 s.

2.4. Functional data preprocessing

fMRI data preprocessing was performed using Data Processing and Analysis for (Resting-State) Brain Imaging (DPABI_V2.3_170105)[33] with the following stages. The first 10 volumes were removed from each time series to account for the time it took participants to adapt to the scanning environment. Slice timing and realignment for head-motion correction were then performed for the remaining 230 images. Participant data exhibiting head motion >2.0mm translation or >2.0° rotation were excluded from analysis. The remaining dataset was spatially normalized to the Montreal Neurological Institute template (resampling voxel size = 3 × 3 × 3 mm³). In addition, smoothing with an isotropic Gaussian kernel (full width at half maximum [FWHM] = 6 mm), detrending and filtering (0.01–0.08 Hz) were performed in order.

2.5. Functional data analysis

The seed regions of interest (ROI) of the PCC were generated from Brodmann template using the WFU_PickAtlas software.[34] Briefly, the mean time series of the PCC was obtained for the reference time course. Then, Pearson’s correlation coefficients were calculated between the mean signal change of the PCC and the time series of each voxel. Finally, a Fisher’s z-transform was used to improve the normality of the correlation coefficients.[35] Six head motion parameters and mean time courses of global, WM and CSF signals were included in the regression analysis. Since small head movements from volume to volume can influence the FC, framewise displacement (FD) values were computed for each subject to reflect the temporal derivative of the motion parameters.

Between-group analyses were conducted to analyze FC differences between the postpartum women and nulliparous women using a whole-brain mask. Age, education level, and FD value were added as the nuisance covariates. Multiple comparison corrections were performed using a false discovery rate (FDR) criterion and set at P < .01.

2.6. Statistical analysis

Independent t tests and χ²-tests were calculated to investigate the differences in the demographic variables, and cognitive performance scores between postpartum women and nulliparous women. Briefly, the mean Z-values of each brain region that showed significant differences were extracted within each subject. Then we performed Pearson’s correlation analyses between the mean Z-values and each variable using SPSS (SPSS 19.0, Inc, Chicago, IL). Partial correlations were analyzed using age, education level, and FD value as covariates. P < .05 was considered to indicate a statistically significant difference.

3. Results

3.1. Demographic and neuropsychological characteristics

The demographic and neuropsychological results of the postpartum women and the nulliparous women were summarized in Table 1. The postpartum women had significantly poorer CFT-delay and CDT scores than the nulliparous women (all P < .05). The other neuropsychological tests showed no significant differences between postpartum women and nulliparous women.

3.2. Functional analysis

The PCC exhibited strong FC to several DMN regions, including the medial prefrontal cortex (mPFC), inferior parietal lobule (IPL), and precuneus in both postpartum women and nulliparous women (Fig. 1). Compared with the nulliparous women, postpartum women showed a significantly decreased FC between the PCC and the left mPFC (Fig. 2A and Table 2). In addition, no FC differences were found between women with natural childbirth and cesarean section.

3.3. Correlation analysis

After correcting for age, education, and motion parameter, postpartum women showed reduced FC of the PCC to the left mPFC, which was positively correlated with the poorer CDT scores (r = 0.742, P < .001) (Fig. 2B). Moreover, we did not find the correlation between the CDT score and the time of postpartum. None of the reduced FC was correlated with other cognitive performances.

4. Discussion

This study found abnormal FC within the DMN associated with cognitive impairment in postpartum women without depression. Decreased FC of the PCC was primarily detected in the prefrontal cortex. Moreover, significantly decreased FC in the left mPFC was positively correlated with the impaired CDT scores in postpartum women compared with nulliparous women. These neural cognition associations may play a critical role in postpartum-related cognitive dysfunction.

In this study, the PCC was selected as seed region to detect the abnormal activity within the DMN. Significant hypoconnectivity was observed in DMN regions including the mPFC and was positively correlated with impaired CDT scores. As the central hub of the DMN, the PCC performs diverse cognitive functions including visuospatial memory and processing of emotional and non-emotional information.[19] Moreover, the postpartum women had significantly poorer CFT-delay score than the nulliparous women, which was used to assess the visuospatial memory and visuospatial skills.[21,27] In addition, the PCC is also recognized for its role in self-referential processing and social cognition.[37] Thus, our results suggest that decreased FC of the PCC may be responsible for the impaired visuospatial memory.
and self-referential processing in postpartum women. Furthermore, previous studies also revealed that pregnancy was associated with impaired visuospatial memory and self-referential processing.\textsuperscript{[15,38–40]} Postpartum women with depression mainly showed reduced FC patterns between the amygdala and other brain regions,\textsuperscript{[15–18]} such as PCC and dorsal mPFC, which were different from the FC patterns in postpartum women without depression, since the amygdala involves in the onset and course of depression.\textsuperscript{[41]} In one recent study, the dorsal mPFC had greater connectivity with the rest of the DMN in postpartum depression,\textsuperscript{[14]} which was in contrast to our current results probably partly due to the effect of the depression.

Furthermore, the prefrontal cortex is mainly responsible for executive and cognitive functions.\textsuperscript{[42]} In the present study, neural abnormalities in the mPFC were linked to impaired cognitive performance on CDT tests in postpartum women, which indicated the dysfunction of executive abilities. Only CDT scores were found to be associated with FC between PCC and left mPFC. CDT score is a neurocognitive test that reflects the function of the mPFC, and it has been commonly used to define cognitive impairments, especially the executive dysfunction.\textsuperscript{[10]} Using neuropsychological assessment, previous studies have confirmed disrupted executive function as one of the main cognitive impairments in postpartum women.\textsuperscript{[6,43]} Thus, we

![Figure 1. Significant FC patterns of the PCC in postpartum women (A) and nulliparous women (B). Significant thresholds were corrected using FDR criterion and set at $P < .01$. Note that the left side corresponds to the right hemisphere.](image1)

![Figure 2. (A) Compared with the nulliparous women, postpartum women exhibited decreased FC between the PCC and the left mPFC; (B) positive correlations between reduced FC between the PCC and the left mPFC and poorer CDT scores in postpartum women ($r = 0.742$, $P < .001$).](image2)
speculate that this region-specific neural cognition relationship supports our hypothesis that executive dysfunction caused by PCC-mPFC connectivity abnormalities may play a pivotal role in postpartum women without depression. In addition, decreased glutamatergic levels in the dorsolateral prefrontal cortex were observed in depressed postpartum women by proton magnetic resonance spectroscopy (MRS).[44] A study using fMRI showed that the neural activity of the prefrontal cortex during a response inhibition task was decreased in postpartum women.[43] Our study shows that reduced neural activity in the prefrontal cortex may play a critical role in postpartum-related executive dysfunction.

Nonetheless, there still exist several limitations in this study. First, we admit that it is difficult to make direct causal inferences regarding the relationships between the decreased FC and cognitive impairment in postpartum women, given the cross-sectional nature of our experimental design and limited sample size. Thus, further longitudinal studies involving a larger sample size are needed to confirm the present conclusions. Despite it, we think that our research is still meaningful in providing direction for future study in this field. Second, there are currently no diagnostic criteria for postpartum cognitive impairment that may limit the interpretation of our results. Moreover, we only selected the PCC as the seed region to investigate the intrinsic FC patterns of DMN in postpartum women. The current seed-based approach could be extended to other DMN regions. Moreover, we did not select the seeds from executive network in our initial experimental design, such as the mPFC and anterior cingulate cortex (ACC). The role of the executive network will be considered in our future study. Finally, in addition to functional disruptions, more researches are needed to demonstrate the possibility of structural connectivity within the DMN, which can be detected using the diffusion tensor imaging (DTI) approach.

5. Conclusions

Despite these limitations, this study mainly demonstrated decreased resting-state FC patterns within the DMN regions, which were associated with impaired cognitive function in postpartum women without depression. These findings illustrate the potential role of the DMN in postpartum women that will enhance our understanding of the neurobiological mechanisms in postpartum period.

Author contributions

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