**ORIGINAL STUDY**

Brain functional changes in perimenopausal women: an amplitude of low-frequency fluctuation study

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**Abstract**

**Objective:** To evaluate the effects of sex hormones on amplitude of low-frequency fluctuation (ALFF) in brain regions related to cognition in perimenopausal women.

**Methods:** This cross-sectional study involved 25 perimenopausal women and 25 premenopausal women who underwent behavioral evaluations, sex hormone level measurements, and functional magnetic resonance imaging (fMRI). All data and ALFF analyses were preprocessed using the Data Processing Assistant for Resting-State fMRI. Statistical analyses were performed using the Resting-State fMRI Data Analysis Toolkit to explore the differences in ALFF between perimenopausal and premenopausal women. The gray matter volume (GMV) values extracted from brain regions (regions of interest) with significantly different ALFF values between the perimenopausal and premenopausal groups were compared. We analyzed the correlations of the ALFF and GMV values of these regions of interest with the results of behavioral evaluations and sex hormone levels in the two groups.

**Results:** Compared with the premenopausal group, the perimenopausal group showed significant ALFF increase in the left gyrus rectus. Regions with decreased ALFF in the perimenopausal group included the left superior temporal gyrus, left inferior frontal gyrus, and left insula. The GMV values of the left gyrus rectus and left superior temporal gyrus were reduced in perimenopausal women. Furthermore, the estradiol level was negatively correlated with the ALFF value of the left gyrus rectus in perimenopausal women.

**Conclusions:** The ALFF and GMV values of certain brain regions related to cognitive function were changed in perimenopausal women. Such functional brain alterations may provide more information regarding the mechanism of cognitive dysfunction in perimenopausal women.

**Key Words:** Amplitude of low-frequency fluctuation – Cognitive function – Functional magnetic resonance imaging – Gray matter volume – Perimenopausal – Sex hormones.

Perimenopause is a transitional period of ovarian function prior to menopause, and is accompanied by endocrine, metabolic, and other internal biological changes. 1 Depressive symptoms, vasomotor dysfunction, and sleep disorders are widely observed during this transition. 2,3 In addition, cognitive dysfunction, 4 and learning disabilities and memory decline 5 have been reported in menopausal women. 18F-Fluorodeoxyglucose positron-emission tomography analysis has revealed that during menopause, low metabolism is present in brain regions associated with learning and memory function. 6 Compared with postmenopausal women who were estrogen users, postmenopausal women who were non-estrogen users showed significantly lower metabolism in the hippocampus, parahippocampal gyrus, temporal lobe, medial prefrontal cortex, and posterior cingulate cortex over a 2-year observation period. 6 Estrogen replacement therapy could prevent the metabolic decline in these brain regions and preserve

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N.L. designed the study and wrote the manuscript, Y.Z. and S.L. collected data, and X.Z. and H.L. revised the manuscript. All authors read and approved the final manuscript.

Ethical approval was obtained from the local institutional review board (ethics committee of Tianjin Medical University Second Hospital).

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memory function. A study evaluating local cerebral blood flow found that postmenopausal women who received estrogen therapy showed increased resting-state cerebral blood flow.

In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) has attracted increasing attention. As a noninvasive and advanced neuroimaging measurement technology, rs-fMRI has been used to study the pathophysiology of nervous system diseases and mental illness. The amplitude of low-frequency fluctuation (ALFF) is an indicator used to measure the intensity of spontaneous fluctuations in the blood oxygen level-dependent signal on rs-fMRI and to locate spontaneous neural activity and physiological states in specific areas of the brain. Electrophysiological studies have shown that low-frequency oscillations may be caused by spontaneous neuronal activity and have physiological significance; they manifest as rhythmic activity of brain regions and information interaction between connected brain regions. Thus, ALFF can reflect brain characteristics. ALFF studies have shown that intrinsic resting-state activity promotes or allows specific brain circuits to participate in cognitive tasks, while the resting state predicts subsequent task-induced brain responses and behavioral performance. ALFF measures brain activity without cognitive load, and cognition-related brain abnormalities in this state may be the basis for cognitive impairment in perimenopausal women. Therefore, ALFF is a suitable marker for studying cognitive dysfunction in perimenopausal women.

Most fMRI studies on changes in cognitive function and brain activation in perimenopausal women have focused on the differences before and after estrogen therapy; however, the dose and duration of administration of estrogen may influence cognitive function in perimenopausal women. Few studies have concentrated on the effects of serum sex hormone levels on brain function. We hypothesized that compared with premenopausal women, perimenopausal women may show changes in the activity of cortical brain regions, which may affect cognitive function. Therefore, in this study, we assessed ALFF on rs-fMRI to evaluate neuronal activity in the cortical brain regions associated with cognitive function, and analyzed the correlation between ALFF values and sex hormone levels.

**METHODS**

**Ethics statement**

This cross-sectional study was approved by the ethics committee of our hospital, and all participants provided informed consent and participated in the experiment voluntarily.

**Participants**

The inclusion criteria were as follows: (a) women aged 45 to 55 years, (b) right-handedness, (c) education for more than 12 years; and (d) a diagnosis of perimenopause based on the Stages of Reproductive Aging Workshop (STRAW)+10: menstrual cycle change longer than 7 days repeated for 10 menstrual cycles or amenorrhea interval ≥60 days, and follicle-stimulating hormone (FSH) levels of 11 to 45 IU/L. In addition, we recruited premenopausal women who did not meet the above STRAW+10 criteria, and had a regular ovulation day based on the rhythm method and an FSH level < 11 IU/L.

The exclusion criteria were as follows: (a) history of neoplasm of the female genital organs, hysterectomy, or oophorectomy; (b) presence of neurological or psychiatric disorders or a history of brain trauma, smoking or alcohol dependence, or other diseases that may affect brain structure and function; (c) presence of a mood disorder (such as depression or anxiety disorders); (d) history of hormone administration; (e) colorblindness; or (f) contraindications to MRI.

**Sex hormone level measurement**

All participants underwent tests for the measurement of sex hormones, including FSH, luteinizing hormone (LH), estradiol (E2), progesterone (P), testosterone (T), and prolactin (PRL). Blood samples for the sex hormone measurements were collected from an elbow vein at 8:00 to 9:00 AM within 3 days of the start of menstruation (in the early follicular phase). The collected venous blood was tested using chemiluminescence analysis, and the concentrations of the above six sex hormones were determined. Participants with an abnormal menstrual cycle or amenorrhea completed the blood sex hormone testing at 8:00 to 9:00 AM on the day of the experiment.

**Behavioral evaluations**

All participants completed full-scale tests, including the Menopause Rating Scale (MRS) and Patient Health Questionnaire (PHQ)-9, to evaluate menopausal and depressive symptoms (ie, vascular symptoms, joint problems, urinary problems, sexual interests, loss of pleasure, sleep disorders, and low self-evaluation). Then, all participants performed a computer-based Stroop color-word test, in which incongruent color-words were displayed in the center of a computer monitor, and the participants were required to choose from four matching color-words according to the ink color of the color-word in the center.

**MRI acquisition**

All participants underwent conventional MRI examination and rs-fMRI scans, which were performed using a 3.0-T MR scanner (Discovery MR 750, GE, Milwaukee) with an eight-channel head coil. The participants underwent fMRI scanning within 3 days of the start of menstruation. For participants with amenorrhea, there was no such time restriction. MRI scanning was performed using the three-dimensional brain volume sequence with the following parameters: repetition time/echo time = 8.1/3.1 ms, flip angle = 13°, field of view = 256 mm × 256 mm, matrix = 256 × 256, 176 slices, and slice thickness = 1 mm. For the rs-fMRI scans, a single-shot gradient echo planar imaging sequence was used: repetition time/echo time = 2,000/30 ms, field of view = 220 mm × 220 mm, matrix = 64 × 64, 32 slices, slice thickness = 3 mm, slice gap = 0.9 mm. Prior to the MRI scanning, sponge pads were placed on both sides of the participants’ ears to keep the head fixed, and the participant was told to keep their eyes closed, and stay quiet and awake during the scanning.
fMRI preprocessing

The fMRI data were analyzed using the Data Processing Assistant for Resting-State fMRI (DPARSF http://restfmri.net/forum/DPARSF) toolbox based on the Matrix Laboratory platform (MATLAB R2012a; MathWorks, Cambridge, MA). For each participant, the first 10 time points were discarded to reach signal equilibrium and adapt to the scanning noise. The remaining 170 time points were preprocessed by slicing time, realigned, normalized to the Montreal Neurological Institute space, and smoothed with a Gaussian kernel of $4 \times 4 \times 4$ mm$^3$ full width at half maximum (FWHM). We also corrected for head movements, and images with translation $\geq 2$ mm and rotation $\geq 2^\circ$ were excluded. No participants were excluded due to obvious head movements in this experiment.

ALFF analysis

ALFF analysis was performed using the DPARSF toolbox. ALFF represents the intensity of the spontaneous activity of each individual voxel, and was defined as the average value of the amplitude of a 0.01 to 0.08 Hz frequency band at all frequency points. This method can reflect the level of the spontaneous activity of each individual voxel in the resting state from the perspective of energy. The specific calculation steps were as follows: (a) The time series of each voxel was transformed into the frequency range through Fourier change, and the power spectrum was obtained. (b) The square root of the power spectrum at each frequency was calculated. (c) The average square root of the power spectrum at all frequencies was deemed the ALFF value. (d) The ALFF of each voxel was segmented by the global average ALFF within the brain tissue mask for standardization. The normalized ALFF value for each voxel should be approximately 1. (e) Finally, the normalized ALFF maps of each subject were smoothed using an isotropic Gaussian kernel of $4 \times 4 \times 4$ mm$^3$ FWHM.

Structural MRI preprocessing

Structural MRI data were analyzed using voxel-based morphometry and the Statistical Parametric Mapping (SPM12, London, UK) software. The data preprocessing steps included segmenting into gray matter (GM), white matter, and cerebrospinal fluid, and registering of the GM DARTEL template to the tissue probability map in the Montreal Neurological Institute space. We obtained the gray matter volume (GMV) of each voxel by multiplying the GM concentration map by the nonlinear determinants derived from the spatial normalization step. The GMV represents the probability that each voxel is genetically modified for individual brain sizes. Finally, the GMV maps were smoothed with a Gaussian kernel of $4 \times 4 \times 4$ mm$^3$ FWHM. After smoothing, the GMV maps were used for statistical analysis.

Statistical analysis

All statistical analyses were performed using SPSS v20.0 software (SPSS Inc, Chicago, IL). The independent two-sample $t$ test was used to compare the age, years of education, MRS score, PHQ-9 score, the accuracy rate and reaction time of the Stroop color-word test, and sex hormone levels between the two groups. $P < 0.05$ indicated statistically significant differences.

The statistical analysis module of Matlab-based SPM12 was used to analyze differences in ALFF between the perimenopausal and premenopausal groups. Two-sample $t$ tests were performed on individual normalized ALFF in a voxel-by-voxel manner. Age and years of education were controlled for as covariates, as they may affect the results. For multiple-comparison correction, the correction standard was determined by Monte Carlo simulations applied with the Resting-State fMRI Data Analysis Toolkit (REST, http://restfmri.net/forum/REST_V1.8) of the AlphaSim program (parameters: individual voxel $P$ value = 0.05, 5,000 simulations, FWHM = 4 mm, $r = 5$ mm, with the group GM mask). The AlphaSim correction was applied with a corrected level of $P < 0.05$ and obtained for a minimum volume of 74 voxels. Brain regions with significantly different ALFF between the two groups were considered as regions of interest (ROIs). The ALFF and GMV values of each ROI were extracted using the REST software and compared between the two groups by using the two-sample $t$ test and SPSS v20.0 software. $P < 0.05$ indicated statistically significant differences.

Age effect

To assess the effect of age on the GMV, we performed correlation analysis between the GMV values of the ROIs and age in the perimenopausal and premenopausal groups. Correlation analysis was also performed between the serum sex hormone levels and age in the two groups.

Correlation analysis

Correlation analyses of the ALFF values with GMV values, MRS scores, PHQ-9 scores, the accuracy rate and reaction time of the Stroop color-word test, and sex hormone levels were conducted in the perimenopausal group. After group analysis, the regions showing significant changes in ALFF and GMV values between the two groups were identified, and the mean ALFF and GMV values of each of these brain regions were extracted in the perimenopausal group. Spearman partial correlation analyses were conducted to evaluate the relationships of the mean ALFF and GMV values of these regions with the MRS scores, PHQ-9 scores, the accuracy rate and reaction time of the Stroop color-word test, and sex hormone levels; age and years of education were considered nuisance covariates in this analysis.

RESULTS

Demographics, sex hormone levels, and behavioral data

A total of 50 participants met the requirements for the fMRI experiment, including 25 women in the perimenopausal group (average age, 53.19 ± 3.82 y) and 25 women in the premenopausal group (average age, 47.67 ± 3.48 y). The demographic characteristics and clinical scale scores of the two groups have been summarized in Table 1. There were significant between-group differences in age, MRS scores, $E_2$, FSH, and PRL levels, and reaction time of the Stroop test ($P < 0.01$), but no
significant differences in years of education, PHQ-9 scores, T, P, and LH levels, and the accuracy rate of the Stroop test ($P > 0.05$).

Changes in ALFF values

Compared with the premenopausal women, the perimenopausal women demonstrated a significant increase in the ALFF of the left gyrus rectus (Fig. 1). The regions with decreased ALFF in perimenopausal women included the left superior temporal gyrus, the left inferior frontal gyrus, and the left insula (Fig. 2). The ALFF results have been summarized in Table 2. We extracted the ALFF values of the above four brain regions in both groups, and found that the ALFF value of the left gyrus rectus was significantly higher in the perimenopausal group than in the premenopausal group ($P < 0.05$).

ROIs and changes in GMV values

GMV values were extracted for the four brain regions (ROIs) that showed significant differences in ALFF values between the perimenopausal and premenopausal groups. The GMV values of the left gyrus rectus and left superior temporal gyrus were significantly lower in the perimenopausal group than in the premenopausal group ($P < 0.05$).

Age effects

Spearman partial correlation analysis showed no significant correlations between the GMV values of the four ROIs and age in the perimenopausal and premenopausal groups. Moreover, no significant correlations were found between age and sex hormone levels in the two groups.

Correlation analysis

Spearman partial correlation analysis showed that in the perimenopausal group, the ALFF value of the left gyrus rectus was significantly and negatively correlated with the $E_2$ level (correlation coefficient: $-0.676, P < 0.001$; Fig. 3). The GMV values of the four ROIs showed no significant correlations with sex hormone levels or behavioral data.

DISCUSSION

Changes in ALFF values

The application of the ALFF method is helpful to understand changes in brain function and related neural networks in perimenopausal women. The results of this study showed that the brain regions with changes in ALFF values in perimenopausal women were mainly located in the frontal lobe, temporal lobe, and insula.

The frontal lobe, especially the prefrontal cortex, is associated with planning complex cognitive behaviors. The decline of memory and learning ability in perimenopausal

FIG. 1. Brain regions with increased ALFF values in the perimenopausal group as compared with the premenopausal group. ALFF, amplitude of low-frequency fluctuation.
women may be related to the decline of ovarian function and the fluctuation of estrogen levels. Some studies have found that estrogen therapy can improve executive function in perimenopausal and postmenopausal women. The regulation of cognitive function by estrogen is usually associated with the activation of the prefrontal cortex, which regulates the activation of cognition-related regions in the cerebral cortex. In this study, we found that the ALFF value of the left gyrus rectus was increased, whereas that of the left inferior frontal gyrus was decreased in perimenopausal women. Moreover, the GMV value of the left gyrus rectus decreased, its ALFF value may have increased to compensate for the structural loss leading to cognitive impairment. These changes may be attributable to the decrease in estrogen level in perimenopausal women, which may cause functional damage to the prefrontal cortex. Prefrontal cortex dysfunction is often observed in depression and schizophrenia with emotional and memory disorders. During the menopausal transition, fluctuating hormone levels and risk factors such as lack of sleep, age, and stress can lead to depressive symptoms. Freeman suggests that perimenopause opens a window of vulnerability for women. The changes in the ALFF values in the left gyrus rectus and left inferior frontal gyrus may reflect an increased risk of depression during the transition from premenopause to perimenopause.

Although considerable attention has been paid to the changes in the prefrontal cortex in perimenopausal women, the current study also found changes in the temporal lobe and insula. In addition to being involved in inner feelings and emotional activities, the insula is involved in cognitive function. The functional changes in the insula in perimenopausal women may reflect an increased risk of cognitive dysfunction during the transition from premenopause to perimenopause. In the temporal lobe, the ALFF and GMV values of the left superior temporal gyrus decreased in perimenopausal women. A literature review found that the superior temporal gyrus and its surrounding middle temporal gyrus, angular gyrus, and superior marginal gyrus may be critical for understanding. A study on quantitative lesion-deficit mapping showed that impairment of understanding was associated

FIG. 2. Brain regions with decreased ALFF values in the perimenopausal group as compared with the premenopausal group. ALFF, amplitude of low-frequency fluctuation.
with damage to several regions, including the angular gyrus, superior temporal gyrus, and left prefrontal cortex.29 The basic cognitive process may be closely related to the understanding of language meaning,28 and the changes in hormone levels in perimenopausal women may be the reason for the changes in cognitive function. In this study, the results of the Stroop color-word test showed that although the accuracy rate did not differ between the perimenopausal and premenopausal groups, the reaction time was significantly higher in the perimenopausal group than in the premenopausal group, which may be related to functional and structural changes in the left insula and left superior temporal gyrus.

**Correlation analyses**

Sex hormones act throughout the brain and are associated with the establishment of neuroendocrine phenomena and behavioral patterns, including cognition and emotion.30,31 Sex hormone receptors have been found to be expressed in the prefrontal cortex, amygdala, cerebellum, hypothalamus, and hippocampus.32 These receptors include the E2, LH, FSH, and PRL receptors.32,33 Studies have shown increased activity in the above brain regions after hormone treatment.34,35

In this study, we found a significant negative correlation between the ALFF value of the left gyrus rectus and the E2 level, which suggests that estrogen may affect specific brain regions or networks associated with cognitive function. In addition, some studies have found that age may be associated with GM atrophy.30 In this study, GMV values were not significantly correlated with age or sex hormone levels. This may be because the age difference between the perimenopausal and premenopausal groups was small, or because the sample size was small.

**CONCLUSION**

In this study, rs-fMRI was used to evaluate changes in the ALFF and GMV values of various brain regions in perimenopausal women and assess their relationship with cognitive function. Correlation analysis was applied to assess the relationship between sex hormone levels and brain function in perimenopausal women. Our study suggested that brain regions associated with cognition may be altered during perimenopause, which contributes to our understanding of the mechanism underlying the cognitive dysfunction that many perimenopausal women develop. Larger sample sizes and longitudinal studies are necessary to further investigate the relationship between sex hormone levels and cognitive function during menopause.

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**TABLE 2. Brain regions showing significant differences in ALFF values between the perimenopausal and premenopausal groups**

| Brain region                  | BA  | Cluster size (mm$^3$) | MNI coordinates ($x$, $y$, $z$) | Peak $t$ score |
|-------------------------------|-----|----------------------|---------------------------------|---------------|
| Left gyrus rectus             | 11  | 117                  | $-3, 21, -24$                   | 3.20          |
| Left superior temporal gyrus  | 38  | 106                  | $-36, 15, -24$                  | 3.68          |
| Left inferior frontal gyrus   | 6   | 119                  | $-51, 12, 0$                    | 3.58          |
| Left insula                   | 13  | 126                  | $-33, -30, 15$                  | 4.02          |

ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; MNI, Montreal Neurological Institute coordinate system or template; $x$, $y$, $z$, coordinates of primary peak locations in the MNI space.

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**FIG. 3.** Correlation analysis between the ALFF value of the left gyrus rectus and the estradiol level. ALFF, amplitude of low-frequency fluctuation; E2, estradiol.
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