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Plasma luteinizing hormone level affects the brain activity of patients with polycystic ovary syndrome

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ABSTRACT

Objective: Cognitive function has been reported to be impaired in women with polycystic ovary syndrome (PCOS). This study aimed to investigate the effect of PCOS on brain activity and explore the relationship between brain activity and sex hormone levels in women with PCOS (WPCOS).
Methods: Twenty-one women aged 18–45 years old with new-diagnosed PCOS were enrolled. Plasma levels of six sex hormones including luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were tested during the 2–5 days of their menstrual periods. Twenty-seven healthy controls (HC) were recruited. Every subject underwent a resting-state functional magnetic resonance imaging (fMRI). The amplitude of low-frequency fluctuation (ALFF) of the whole brain was evaluated followed by the functional connectivity (FC) analysis. Finally, the correlation between the ALFF, FC of the significant areas and the plasma hormone levels were analyzed.
Results: The patients showed increased ALFF value in the left inferior temporal gyrus (ITG.L) and decreased ALFF value in the left inferior occipital gyrus (IOG.L) as well as the superior frontal gyrus (SFG.R, $P < 0.005$). For the FC analysis, patients showed decreased FC in SFG.R with the right middle frontal gyrus (MFG.R, $P < 0.05$). The FC between SFG.R and MFG.R was negatively correlated with LH level ($R = -0.594$, $P = 0.005$) and with the LH/FSH ratio ($R = -0.521$, $P = 0.015$).
Conclusion: PCOS can induce changes in activities of brain regions responsible for visuospatial working memory, face processing and episodic memory. The reduced functional connectivity within the right frontal lobe is related with the high LH level in WPCOS.

1. Introduction

Polycystic ovarian syndrome (PCOS), characterized by chronic oligo- or anovulation, polycystic ovaries and hyperandrogenism, is one of the most frequent endocrine disorders in women of reproductive age with a prevalence rate of 5–20% in this population (Azziz et al., 2016; Diamanti-Kandarakis and Dunaif, 2012; March et al., 2010; Norman et al., 2007). PCOS is not only the major cause of anovulatory infertility, but also a risk factor for type 2 diabetes mellitus, obstetrical complications, ovarian cancer, endometrial cancer, depression and cognition (Azziz et al., 2016). Although not all women, nearly 70% of the WPCOS suffer from clinical/biochemical features of hyperandrogenism (Soleman et al., 2016). Especially, anovulatory infertility resulted from PCOS has caused the economic impacts over 4 billion

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dollars in the United States alone without regard to T2DM and other disorders in 2004 (Azziz et al., 2016, 2005).

To date, the etiology of PCOS has multiple suspected factors covering metabolism, genetics, and epigenetic modifications and is still unclear, although the neuroendocrine impairments involved hypothalamic-pituitary-gonadal (HPG) axis in PCOS is widely acknowledged (Moore and Campbell, 2017). The increased frequency of gonadotropin-releasing hormone (GnRH) pulses from the hypothalamus leads to the high luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, which may ultimately cause ovulary dysfunction and hyperandrogenism (Moore and Campbell, 2017). Previous researches mainly focused on the effects of hyperandrogenism on skin manifestations (hirsutism and acne) and reproductive system (infertility) in WPCOS. However, brain is not only the regulating center of neuroendocrine axis and ovarian function but also the target organ of peripheral gonadal hormones (Moore and Campbell, 2017). Evidence shows that PCOS is also associated with psychiatric and neurological disorders such as depression, anxiety, eating disorders and epilepsy (Dokras, 2012; Herzog et al., 1984; Hollinrake et al., 2007; Kalinin and Zheleznova, 2007; Rassi et al., 2010).

There is abundant proof that sex hormones have widely effects on the brain activity (Arelin et al., 2015; Engman et al., 2016; Heany et al., 2018; Lisofsky et al., 2015; Syan et al., 2017), and the results of some studies suggested that the cognitive function was impaired in WPCOS, which was related to testosterone (T) level, although without imaging data (Barnard et al., 2007; Schattmann and Sherwin, 2007). A few studies investigated the brain structure and activity in WPCOS using brain imaging. In young adults with PCOS, cognitive performance is associated with the altered white matter microstructure (Rees et al., 2016). The limited results of functional magnetic resonance (fMRI) also demonstrated that WPCOS showed more activation in the right superior parietal lobe and the inferior parietal lobe than healthy women during a working memory task (Soleman et al., 2016).

However, the studies containing brain imaging were all small-sample researches, with different medication history in each patient, and most importantly, none of them discovered any relationship between the brain activity and the plasma hormones level in WPCOS. In the present study, we aimed to perform a rest-state functional MRI in new-diagnosed WPCOS and HC to identify the functional manifestations in the brain of WPCOS. In the meanwhile, we hoped to investigate whether sex hormone levels are associated with the activity of the brain in WPCOS. We hypothesized that these women would exhibit impaired activity in specific regions of the brain, which would be resulted from the changes of their hormone levels.

2. Materials and methods

2.1. Ethical aspects

Ethical approval was granted by West China Hospital of Sichuan University Biomedical Research Ethics Committee and all participants provided the written informed consent.

2.2. Participants

We enrolled twenty-four women of child-bearing age (18–45 years old) with new-diagnosed PCOS in West China Hospital and West China Second Hospital between October 2016 and October 2018. All women attended a routine examination in the gynecological or endocrine outpatient clinic and were screened for clinical features or past medical history of PCOS. The diagnosis of PCOS was based on the 2003 Rotterdam criteria (Rotterdam, 2004) which defined as below (2 out of 3):1. oligo-ovulation (fewer than 8 menses per year) and/or anovulation; 2. clinical and/or biochemical signs of hyperandrogenism; 3. polycystic ovaries (≥12 follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume > 10 ml) by ultrasonography and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome). The exclusion criteria included: 1. Other gynecological diseases; 2. Current or recent (last three months) hormonal treatment. 3. History of head trauma or other neurological disorders; 4. Left-handedness; 5. Pregnancy or breastfeeding; 6. history of psychiatric diseases, diabetes, hyperlipidemia, hypertension; 7. Current or recent (last three months) substance or alcohol abuse; 8. Diagnosis of prolactinoma. Among twenty-four WPCOS who underwent MRI examination, three women were excluded because of the head movement (> 3) and a total of 21 WPCOS were finally included for analysis.

HC (n = 27) were recruited by advertisement among staff and students within the West China hospital of Sichuan University. All controls were between 18 and 45 years old and were required to have normal menstrual cycles (28 ± 2 days), normal ultrasonographic appearance of the ovaries and no signs of hirsutism. Furthermore, controls with personal history of diabetes or family history of PCOS were excluded. Their health status was determined by medical history and physical examination.

2.3. Data acquisition and image preprocessing

All participants were performed a 3.0 T scanning (GE Discovery MR750, Milwaukee, WI) at the MRI research center of University of Electronic Science and Technology of China. Axial anatomical T1-weighted images were also acquired with a 3D fast-spoiled gradient echo sequence, and the parameters were as follows: TR/TE, 6.008/1.984 ms; flip angle = 90°; matrix size = 256 × 256; field of view = 25.6 × 25.6 cm^2; slice thickness (no gap) = 1 mm. The resting-state functional images were gathered via a echo-planar imaging sequence. The scan parameters were also as follows: repetition time/echo time (TR/TE), 2000/30 ms; flip angle, 90°; matrix size, 64 × 64; field of view, 24 × 24 cm^2; and thickness/gap, 4/0.4 mm. A total of 205 volumes (32 slices per volume) were obtained over a 410-second period. During the scan, all participants were required to close their eyes and relax without thinking of anything.

2.4. ALFF analysis and ROI determination

The amplitude of low-frequency fluctuation (ALFF) maps was computed via the REST software (http://www.restfmri.net/forum/REST). First, the time series of each voxel was transformed into a frequency domain via fast Fourier transform, so the square root of the power spectrum was calculated. Secondly, the mean square root of the power across 0.01–0.08 Hz was obtained as the ALFF. Then, the ALFF of each voxel was divided by their own mean ALFF for each subject within the brain mask for standardization as modified ALFF (mALFF). The mALFF value were compared between PCOS group and healthy control using two-sample t-test. Finally, three regions of interest (ROIs) were screened out when the significance was set at P < 0.005 (clusters > 600mm3).

2.5. FC analysis

The preprocessed images were further processed for functional connectivity (FC) analysis using spatial smoothing (Gaussian kernel with a 6 mm FWHM) and nuisance signal regression (24 head motion parameters, white matter, cerebrospinal fluid and global signals). To define the FC map for each ROI, Pearson's correlation coefficients were calculated between the average time course of each ROI and that of each voxel in the whole brain after filtering (0.01–0.08 Hz). The resulting correlation coefficients were Fisher-Z-transformed. Two-sample t-tests were used to assess the differences in the FC maps between the two groups within the masks, which resulted from the union of the one-sample tests of the FC maps of the two groups, controlling for age and gender effects (clusters > 600mm3). Significance was set at P < 0.005

(uncorrected) or $P < 0.05$ (FDR corrected).

2.6. Correlations between functional properties and sex hormone levels

To investigate whether PCOS influences the brain activities through hormone changes, we tested the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), estradiol (E2), progesterone (P) and testosterone (T) of the 21 WPCOS. After an overnight fasting on days 2–5 day (early follicular phase) of the spontaneous menstrual cycle, venous blood samples were collected for assessment of the hormone levels above. Then, we analyzed the relevance of each hormone level to the altered resting-state FC of each ROI using Pearson's correlation analysis. The significance was set at $P < 0.05$.

3. Results

3.1. Demographic characteristics

Three patients were excluded due to excessive motion. Twenty-one WPCOS and 27 HC were included in the final analysis. Demographic characteristics of all participants and the hormone levels of the 21 WPCOS were shown in Table 1.

3.2. Seed-based FC analysis

Compared with the controls, the patients exhibited increased ALFF value in the left inferior temporal gyrus (ITG.L, Brodmann area 20-BA 20) as well as decreased ALFF value in the left inferior occipital gyrus (IOG.L, BA19) and the right superior frontal gyrus (SFG.R, BA 10), which were defined as the three ROIs (Fig. 1. $P < 0.005$, uncorrected). The peak values of the ROIs were shown in Supplemental Table 1.

To assess the effect of PCOS on intrinsic FC of the brain, a seed-based FC analysis was conducted for each ROI. The analysis revealed the alteration of FC in all of the three ROIs (Fig. 2 and Supplemental Table 2). For the seed at ITG.L, patients showed increased FC with the left parahippocampal gyrus (PHG.L, BA 34, $P < 0.005$, uncorrected). For the seed at IOG.L, patients showed decreased FC with the right inferior temporal gyrus (ITG.R, BA 20, $P < 0.005$, uncorrected). For the seed at SFG.R, patients also showed decreased FC with the right middle frontal gyrus (MFG.R, BA 9, $P < 0.05$, FDR corrected).

3.3. Correlations between functional properties and plasma hormone levels

Pearson's correlation analysis showed negative correlation of the plasma LH level with the FC between SFG.R and MFG.R ($R = -0.594$, $P = 0.005$). The LH/FSH ratio was also negatively correlated with the FC between SFG.R and MFG.R ($R = -0.521$, $P = 0.015$). No significant correlations were identified between the remaining hormone levels and ALFF value or FC (Fig. 3).

Table 1
Demographic characteristics and hormone levels of the study sample.

Characteristic	PCOS (N = 21)	Control (N = 27)	*P* value
Age, y (SD)	25.0 (5.0)	21.8 (2.1)	0.010
BMI, kg/m^2 (SD)	24.1 (5.6)	21.6 (3.2)	0.083
Education, y (SD)	14.4 (2.5)	15.4 (1.8)	0.097
Right handedness (%)	100%	100%	–
Hormone levels (SD)			
P (ng/ml)	0.71 (0.77)	–	–
E_2 (pg/ml)	68.35 (40.46)	–	–
T (ng/ml)	0.63 (0.17)	–	–
LH (mIU/ml)	12.36 (8.75)	–	–
FSH (mIU/ml)	5.86 (2.15)	–	–
PRL (ng/ml)	15.96 (14.47)	–	–

Note: PCOS, polycystic ovary syndrome; BMI, body mass index; P, progesterone; E2, estradiol; T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin.

4. Discussion

This is the first study using rest-state fMRI to explore the brain activity and its relevance to serum hormone levels in women with new-diagnosed PCOS. We found that the mean mALFF value was higher in ITG.L and lower in IOG.L and SFG.R of the patients compared with the healthy controls. Through further calculation, we found an increased FC in ITG.L with PHG.L as well as decreased FC both in IOG.L with ITG.R and in SFG.R with MFG.R of the patients. More importantly, we discovered a negative correlation between the serum LH level and the FC in SFG.R with MFG.R, indicating that the brain functional changes might be resulted from the internal hormone shift in WPCOS.

PCOS has already been reported to change the brain function, which was thought to be associated with the high internal T level. Barnarda et al. found that WPCOS demonstrated worse performance on reaction time and word recognition tasks than the controls and WPCOS receiving AA treatment made less errors in these tasks than WPCOS with no AA treatment (Barnard et al., 2007). Schattmann et al. also found WPCOS had higher free androgen index (FAI) and performed worse in cognition tests including verbal fluency, verbal memory, manual dexterity and visuospatial working memory than the healthy women. FAI values were significantly and negatively correlated with the total scores of Purdue Pegboard Test (used to evaluate the hand function (Gonzalez et al., 2017)). Nevertheless, WPCOS in a recent study reached a higher average score on a three-dimensional mental rotation task than the controls and the scores of WPCOS were significantly positively associated with their circulating testosterone level, while negatively correlated with their estradiol level (Barry et al., 2013). These studies respectively suggested that hormone levels can affect verbal, motor and visual-spatial ability in WPCOS, no matter negatively or positively. However, none of these studies detected the brain activity changes of the patients and therefore, which part of the brain involved in the changes remains unknown.

Our patients showed decreased ALFF value in SFG.R (BA 10) and poorer FC in SFG.R with MFG.R (BA 9), which means the prefrontal associational integration were impacted in WPCOS. The prefrontal cortex (PFC) has been testified to participate in emotional, social, motivational, perceptual, and other processes, indicating a central role of these regions in cognitive functions including working memory and decision-making (Carlen, 2017). The same as other parts of the brain, PFC activity exhibits right lateralization in visuospatial memory tasks and left lateralization in verbal memory tasks. Therefore, the right PFC has been thought to play an important role in active processing within visuospatial working memory (VSWM) (Owen et al., 2005; Smith and Jonides, 1999; Wager and Smith, 2003). Then by using Pearson's correlation we found the FC between SFG.R and MFG.R was negatively associated with the plasma LH level, as well as the LH/FSH ratio. Evidence is sufficient for the elevated LH/FSH ratio in WPCOS (usually two to three), which is only one in normal women (Krishnan and Muthusami, 2017). This change in LH/FSH ratio is enough to disrupt ovulation and even elevate androgen production in WPCOS since LH induces androgen biosynthesis by theca interna cells while FSH stimulates aromatase activity by granulosa cells (Krishnan and Muthusami, 2017). However, we did not observe any significant relationship between T level and the functional activity. Therefore, the correlation between LH level (or the LH/FSH ratio) and the FC should be resulted from the LH itself. LH and its receptor are found in the brain of both human and rats. The receptors were distributed in the whole brain including hippocampus, cerebral cortex, cerebellum, hypothalamus, anterior pituitary, and brain stem (Lei et al., 1993; Rao, 2017). LH is also related to some specific neurological disorder such as Alzheimer's Disease (AD) (Casadesus et al., 2006; Rao, 2017) and the possible mechanisms of LH-induced cognitive impairment include that LH can increase the Aβ level or impact the GABA neurotransmission in

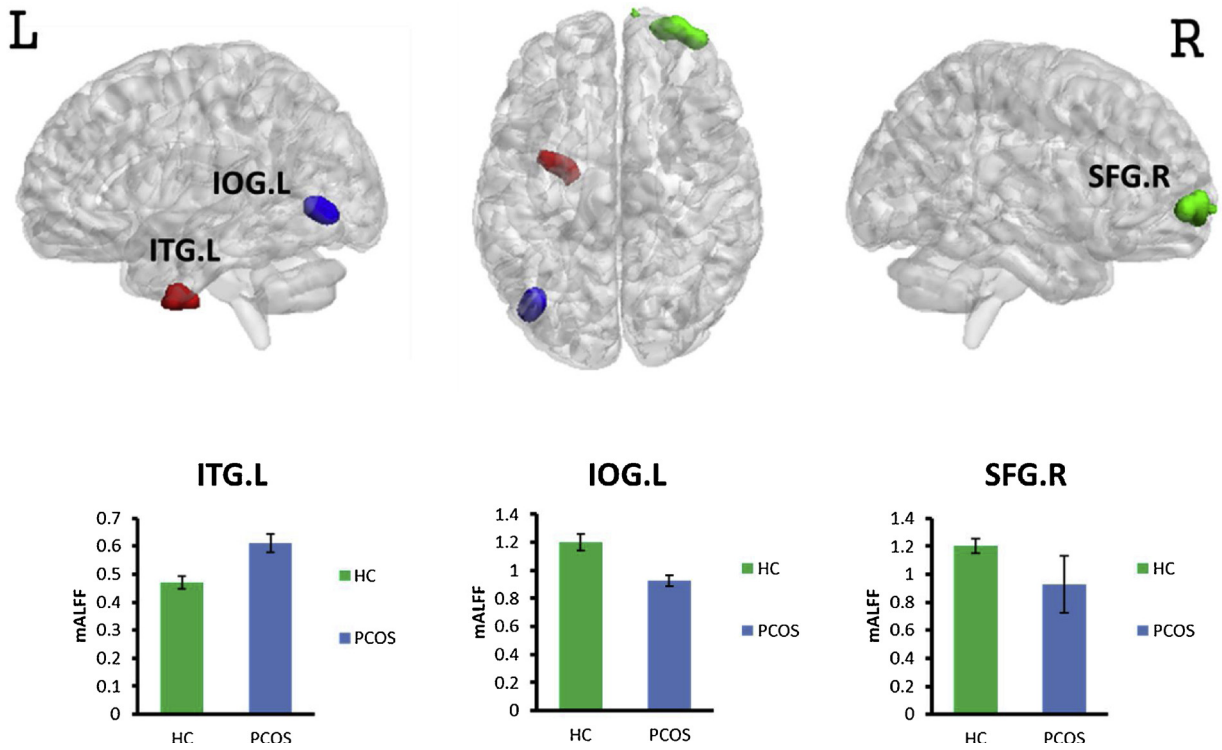

Fig. 1. Clusters with altered ALFF value in WPCOS compared with controls ($P < 0.005$, uncorrected). ITG.L, the left inferior temporal gyrus; IOG.L, the left inferior occipital gyrus; SFG.R, the right superior frontal gyrus; mALFF, modified amplitude of low-frequency fluctuation; PCOS, polycystic ovary syndrome; HC, healthy control.

hippocampus (Casadesus et al., 2006; Riordan et al., 2018; Wahjoepramono et al., 2011). However, we only observed a negative association between LH level and the FC in the right PFC of WPCOS, suggesting that LH level may also impact the VSWM function.

One study on fourteen WPCOS used task-state fMRI to investigate the brain activity in WPCOS during a working memory task and found that patients showed more activation in the right superior parietal lobe and the inferior parietal lobe than the healthy women. The difference in overall brain activity between the groups disappeared and accuracy in the high memory load condition of the task increased in WPCOS after antiandrogenic treatment (Soleman et al., 2016). In our study, we did not find any significant activity changes in the same regions as above. The reason may be that we performed a rest-state fMRI rather than a task-state fMRI. Also, we have a larger sample size of new-diagnosed patients who had never received any treatment for PCOS thus avoiding any possible effects of external hormone on brain activity.

Likewise, decreased ALFF value was also found in the IOG.L along with the reduced FC with the ITG.L in WPCOS. Many studies have showed that the IOG is involved in and may represents the first stage of face processing (Sato et al., 2016; Uono et al., 2017). Previous researchers have proposed that the IOG is the primary stage of a hierarchical brain network specific to face processing and represents facial parts in advance of subsequent configural processing in the fusiform gyrus (Haxby et al., 2000; Pitcher et al., 2011). Therefore, our results suggest that PCOS may affect the visual function, especially the face processing of patients. However, relevant task state fMRI should be performed in further studies.

Conversely, WPCOS exhibited higher ALFF value in ITG.L (BA 20) and increased FC in ITG.L with PHG.L (BA 34) but no correlation was observed with the sex hormone levels. It is worth mentioning that these regions belong to the mesial temporal lobe (MTL), which involves in the default-mode network (DMN). The DMN has been thought to take part in episodic memory function and reported to be impacted particularly by aging and AD(Andrews-Hanna et al., 2007; Buckner et al., 2005; Sperling et al., 2009). A recent study using resting-state MRI also indicated that the PHG was the primary hub of the DMN in the MTL (Ward et al., 2014). This result implied that WPCOS may show better episodic memory function than healthy women although the underlying mechanism remains unclear.

4.1. Strengths and limitations

A strength of our study is that the sample size of the WPCOS was larger than that in any other study on PCOS and brain imaging. Although previous studies investigated the brain function in WPCOS, this was the first study to investigate the brain FC and its association with plasma hormone levels in WPCOS and plasma LH level (or the LH/FSH ratio) was observed to be correlated with the brain FC in WPCOS for the first time. Moreover, all of our patients were new-diagnosed so that the interference of hormonal treatment could be eliminated. Nevertheless, our study still has limitations. First, clinical, MRI and hormone level data were only collected once before patients were treated in this cross-sectional observational study, so we were unable to compare the changes before and after treatment. Second, task-state fMRI involving visuospatial working memory, face processing and episodic memory should be performed in the further study to clarify the practical ability and monitor the brain activity of the patients in the real time.

5. Conclusion

Our results suggest that in WPCOS, the activities of regions responsible for visuospatial working memory and face processing are decreased, while activities in regions of episodic memory were increased. Furthermore, the plasma LH level and the LH/FSH ratio are negatively related to the FC in the brain regions of visuospatial working memory. Thus, we propose that PCOS can induce changes of brain activities and interfere with cognitive functions including visuospatial

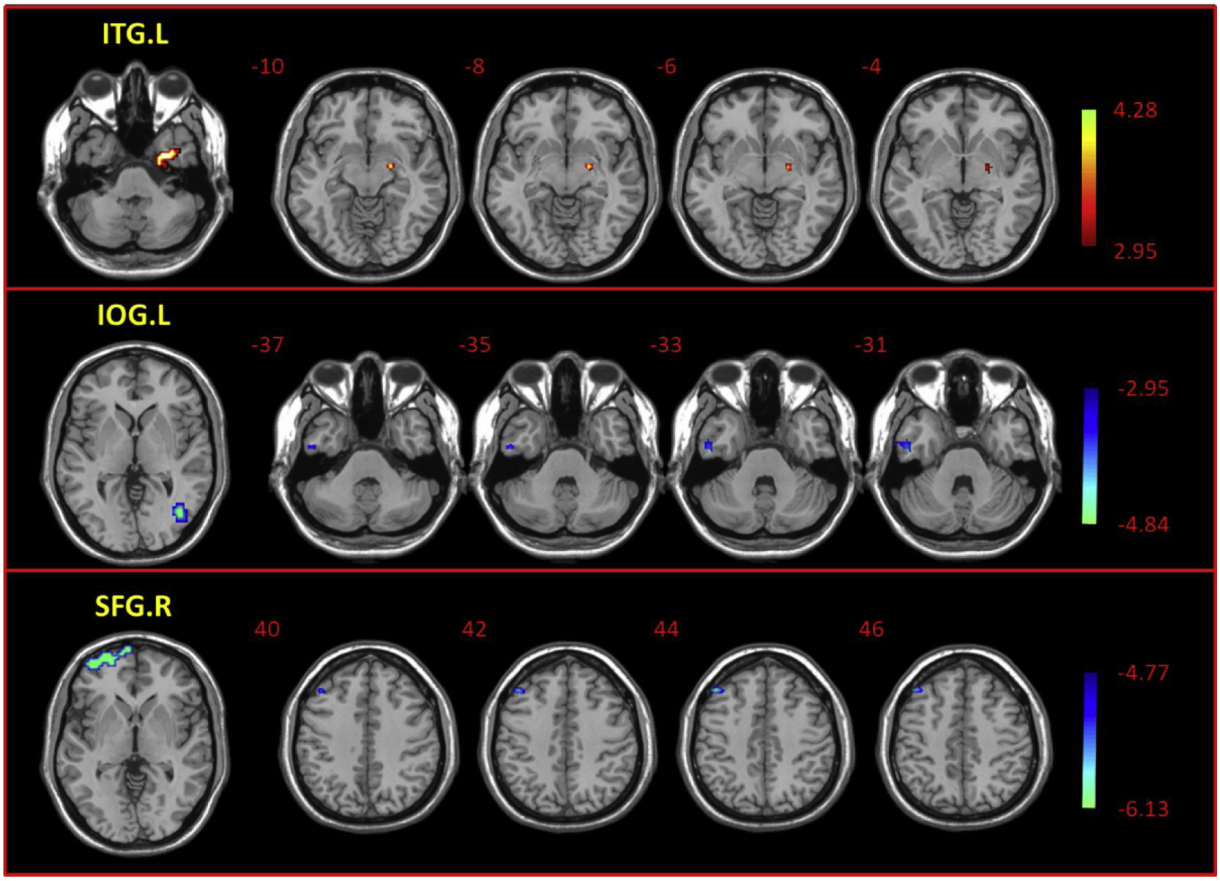

Fig. 2. The differences of functional connectivity between groups. The first row shows the increased FC in ITG.L with the left parahippocampal gyrus ($p < 0.005$, uncorrected). The second row shows the decreased FC in IOG.L with the right inferior temporal gyrus ($p < 0.005$, uncorrected). The third row shows the decreased FC in SFG.R with the right middle frontal gyrus ($p < 0.05$, FDR corrected). ITG.L, the left inferior temporal gyrus; IOG.L, the left inferior occipital gyrus; SFG.R, the right superior frontal gyrus.

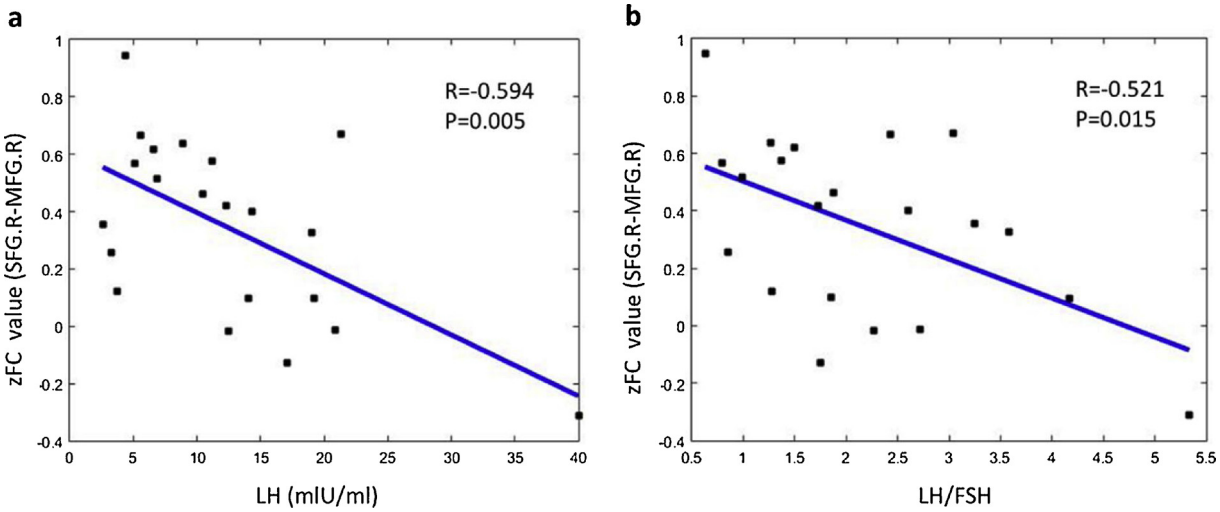

Fig. 3. Correlation between functional properties and plasma hormone levels. The zFC value between SFG.R and MFG.R was negatively correlated with the plasma LH level (a, $R = -0.594$, $P < 0.005$) and the LH to FSH ratio (b, $R = -0.521$, $P = 0.015$). zFC, Fisher-Z-transformed functional connectivity; SFG.R, the right superior frontal gyrus; MFG.R, the right middle frontal gyrus; LH, luteinizing hormone; FSH, follicle stimulating hormone.

working memory in women with PCOS by regulating the level of LH. As a result, gynecologists should pay more attention to WPCOS if they have high plasma LH level or exhibit neurological or psychiatric symptoms. Neurologists and psychiatrists should also advise their patients to see gynecologists if they have typical clinical manifestations or risk factors of PCOS, such as oligomenorrhea, hairiness, acne and obesity. At the same time, more intervention studies should be performed to further illustrate the connection between PCOS and brain cognitive function.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose. The authors have no financial relationships relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psyneuen.2019.104535.

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