Magnetic resonance study on the brain structure and resting-state brain functional connectivity in primary insomnia patients

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Abstract
The aim of the study was to study the changes in brain structure and functional connectivity in primary insomnia (PI) patients, as well as to explore the biological characteristics of PI abnormality and the pathophysiological mechanism underlying the brain structure and the abnormal functional connectivity under depression.

Voxel-based morphometry (VBM) technique and resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) techniques were used to investigate the brain structure and rs-fc in PI and light-moderate primary insomnia with depression (PID) patients; healthy individuals were used as the normal control (NC) group. The differences between the 3 groups, the correlation between the brain network connection of the anterior cingulate cortex (ACC), and clinical information were compared.

Compared with the NC group, patients in PI and PID groups showed changes in brain structure and brain functional connectivity, which might be related to the pathophysiological mechanism of primary insomnia. PI patients had enhanced connections in the left anterior cingulate cortex/insula, left posterior cingulate, and the right limbic lobe/cingulate gyrus/paracingulate gyrus with ACC. Compared with PI patients, PID patients had weaker brain functional connectivity in the left corpus callosum/posterior cingulate with ACC and enhanced functional connectivity in the frontal and limbic lobes with ACC, suggesting that PI patients with depression had abnormal brain network connection.

Primary insomnia has abnormalities in intracephalic multisystem structure and neural network connection. The interaction and influence between depression and insomnia aggravate the cognitive function damage. This study provided the theoretical basis for exploring the neuropathology underlying the PID disorder and cognitive function.

Abbreviations: ACC = anterior cingulate cortex, BA = Brodmann area, BOLD = blood oxygenation level-dependent signal, DMN = default mode network, DSM-IV = diagnostic and statistical manual, DWI = diffusion-weighted imaging, EPI = echo planar imaging, Fc = functional connectivity, FLAIR = fluid-attenuated inversion recovery, fMRI = functional magnetic resonance imaging, fourth edition, FOV = field of view, FWHM = full width at half maximum, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, MMPI = Minnesota Multiphasic Personality Inventory, MNI = Montreal Neurological Institute, PI = primary insomnia, PID = primary insomnia with depression, PSQI = Pittsburgh Sleep Quality Index, RCFT = Rey Complex Figure Test, ROI = region of interest, rs-fMRI = resting state functional magnetic resonance imaging, SPM = statistical parametric mapping, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging, TI = inversion time, TR/TE = repetition time/echo time, VBM = Voxel-based morphometry.

Keywords: anterior cingulate cortex, cognitive function, depressive disorder, functional magnetic resonance, primary insomnia, resting-state functional connectivity, voxel-based morphometry
1. Introduction

Insomnia is a common risk factor for the attack of other mental diseases. It is divided into primary and secondary insomnia. Primary insomnia (PI) refers to the difficulty in falling asleep, maintaining sleep, or refreshing after sleep for at least 1 month, rather than secondary to other sleep disorders, excluding causatives such as drug or other mental disorders.\(^3\) The morbidity rate is 3% to 5%,\(^2\) accounting for 25% of chronic insomnia. PI can increase the risk of suffering from cardiovascular diseases and diabetes in the middle-aged and elderly individuals.\(^3\) The slow disease course causes a decrease in functional activities during the daytime, severely influencing the normal physiological activities and the quality of life. Thus, the neurobiological investigations on PI can provide effective imaging evidence for diagnosing the disease and evaluating the therapy.

Chronic insomnia is one of the risk factors for the attack of cardiovascular diseases as well as death. This attack might be correlated with hyperarousal, a disorder of circadian rhythm, and endocrine disequilibrium.\(^3\) PI possesses several characteristics, such as easy and early awakening, decreased sleep quality, and difficulty in sleep initiation and maintenance, accompanied by significant daytime functional injury. PI is often accompanied by hyperarousal status.\(^4\) Such patients are under overreaction and stress with respect to mental state, physiology, emotion, and cognition; the level of hormone increases and the overall basal metabolic level also increases, along with the physiological arousal. In addition, they often present circadian dysregulation and abnormality in the sleep-awakening mechanism that causes emotional disorder and greatly influences the health. Clinically, PI patients are often accompanied by anxiety and depression disorder in different degrees, and also present habitual anxiety.\(^5\)

Insomnia is an independent risk factor for depression, with a complicated relationship. The quality of sleep interplays with an emotional disorder, and the disorder of sleep-awakening regulation aggravates the emotional symptoms. Long-term vicious circle leads to damage of the cognitive function, subjective sensation, or mental disorder. Shekleton et al\(^6\) found that PI patients presented cognitive function damages in different degrees. Furthermore, only a few studies based on magnetic resonance were carried out on PI. Harper et al\(^7\) reported that the pathogenesis of PI might be closely related to the arousal system (reticular structure ascending activating system and hypothalamus), emotional regulation system (hippocampus, amygdala, and anterior cingulate cortex), and cognitive system (prefrontal cortex), which provides the basis for magnetic resonance on the neuropathological mechanism of PI.

Recently, magnetic resonance has been developed rapidly in neurosciences, which is divided into structural and functional types, and widely applied in various investigations of nerve and mental disorders, such as schizophrenia,\(^8\) Alzheimer’s disease (AD),\(^9\) and epilepsy.\(^10\) Using these magnetic resonance techniques in PI is useful for further exploring the disease as well as clinical application. Voxel-based morphometry (VBM) indicates the morphological and biological characteristics of brain tissues, and hence we used this technique to analyze the morphological changes in the gray matter structure of the brain in PI patients and those with depression (PDD). Functional magnetic resonance imaging (fMRI) can indicate the status of brain tissue and neural activity; it is divided into resting-state and task-state. Resting-state fMRI (rs-fMRI) is based on the blood oxygenation level-dependent (BOLD) signal that is generated to maintain the activity of the brain without any specific tasks or clear external/internal stimuli. The functional connectivity (fc) analysis based on rs-fMRI (rs-fcMRI) can analyze the network connections of brain function, in order to prospectively investigate the regulation of nerve function connection of PI. The anterior cingulate cortex (ACC) plays critical roles in the human brain function, such as cognitive function, automatic control, and emotion processing. Carter et al\(^11\) found that with a prolonged sleep deprivation, the functional activities of ACC were decreased, thereby leading to reduced attention and executive function. Herein, the bilateral ACC has been considered as the seed point, and rs-fcMRI analysis is performed to explore the abnormality of ACC network connection in PI and PDD patients. We also explored the influences of cognitive impairment and emotional disorder on the brain neural network in resting-state.

Moreover, whether the brain structure and brain function of PI would change? Whether the depressive disorder has influences on the brain structure and functional connectivity of PI? Whether the changed brain region would cause changes in the brain function? Whether the clinical scores Pittsburgh Sleep Quality Index (PSQI) and Hamilton Depression Scale (HAMD) have a correlation with the brain region under abnormal functional connectivity? Only a limited number of current studies are available of the above issues. Therefore, using normal control group as reference, we explored the brain structure and rs-fcMRI in PI and PDD patients and compared and analyzed the differences among them, as well as the correlations between the ACC brain network connection and clinical information, which could aid in the early-stage diagnosis and treatment of PI patients.

2. Materials and methods

2.1. Study subjects

The present study consisted of 3 groups: normal control (NC), PI, and PDD (light and moderate depression) groups. The study protocol was approved by the Ethics Committees of Henan Provincial People’s Hospital. All patients signed the informed consent.

The inclusion criteria for participation in the study were as follows: neither physical and mental diseases nor family history of neuronal and mental disease; no history of alcohol and psychotropic drug abuse; education ≥26 years (above elementary school); age 20 to 50 years; Han nationality and right-handedness; no contraindications of magnetic resonance examination in the body, and no organic diseases found in the brain; all participation do not have MRI contraindications, such as metallic implants, claustrophobia, or devices in the body.

2.1.1. Patients group. All the patients were from the Department of Neurology (outpatient and inpatient). A total of 36 patients with PI from January 2013 to November 2014 were included, and finally, 30 patients complying with the inclusion criteria were enrolled. The cohort comprised of 15 patients with PI (6 males and 9 females), aged between 22 and 50 years (average, 37.13 ± 2.53 years), and education of 11.53 ± 1.125 years. Another 15 patients presented light and moderate depression (7 males and 8 females) were aged between 28 and 50 years (average, 40.53 ± 1.919 years), and education of 11.40 ± 0.753 years.

2.1.1.1. Inclusion criteria.

1. Complying with the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) of PI: A duration of insomnia of ≥1 year with sleep difficulty occurring at least 3 nights per week.
2. Patients who never received clinical intervention therapy;

3. Inclusion criteria for PID: PSQI score ≥ 7, Hamilton anxiety scale (HAMA) score < 14, HAMD in PI group < 7, PID group 7 ≤ HAMD ≤ 24.

2.1.2. NC group. Fifteen healthy individuals (7 males and 8 females), age- and sex-matched were enrolled in the NC, aged 21 to 49 years (average, 32.60 ± 2.541 years), education of 32.60 ± 2.541 years, PSQI score < 7, HAMD score < 7, and HAMA < 7 score. The control group neither presented any diseases in the past 2 weeks nor received any drugs. Smoking, drinking, and staying up late, as well as ingesting stimulating foods were not allowed within 3 days before scanning.

2.2. Study methods

2.2.1. Clinical evaluation. Two experienced neurological physicians graded the clinical scales and graphs, including PSQI, HAMD, HAMA, and Rey Complex Figure Test (RCFT). The parameters for the scales were as follows: PSQI total score 0 to 21, high value indicates poor sleep quality, PSQI ≥ 7 is insomnia; HAMD: total score 52, < 7 is normal, 7 to 16 is light depression, 17 to 24 is moderate depression, > 24 is severe depression; HAMA: < 7 is not anxiety, 14 is boundary value, and > 14 is anxiety disorder. Intraclass correlation coefficient (ICC) was used to evaluate the consistency of PSQI scores (ICC=0.98), and weighted Kappa value was used to assess the consistency of HAMD, HAMA, and RCFT scores from the 2 physicians. Kappa value > 0.75 indicates a good consistency of the score as assessed by the 2 physicians.

2.2.2. Magnetic resonance examination. Siemens Trio Tim 3.0 T magnetic resonance imaging system (Siemens, Erlangen, Germany) was used, as well as 12 head channels phased the array coil. All the subjects underwent whole brain 3D high-resolution T1WI structure imaging and rs-fcMRI scanning of the whole brain.

The whole brain structure imaging was conducted by 3D high-resolution magnetization for preparing fast gradient echo imaging (3D MPRAGE) sequence and sagittal encompassing the whole brain scanning. Scanning parameters: TR/TE = 2300/2.98 ms, reversing time TI = 900 ms, flip angle 9°, slice thickness 1.2 mm, visual field FOV = 240 × 236 mm², matrix 256 × 256, number of excitation NEX 1, voxel 1 × 1 × 1.2 mm³, and scanning time total 9’14″.

rs-fcMRI: The subjects should be told to keep quiet, relax, eyes closed, and placed down on the examination table. Gradient echo combined with single excitation EPI technique was used. Scanning parameters: TR/TE = 3000/30 ms, visual field FOV 1200 × 1200 mm², matrix 64 × 64, slice thickness: 3 mm, slice gap 0.5 mm, totally 36 layers, scanning time 7’06″.

The criteria before scanning were as follows: do not drink stimulants, such as alcoholic beverage, strong tea, and coffee at the scanning day; women should not be in pregnancy or menstrual period; onlookers are forbidden; the scanning time should not be later than 9:00 AM; the patients should come to the waiting area before 30 minutes.

2.2.3. Data processing. The original DICOM (digital imaging and communications in medicine) data were transferred by MRicero software, analyzed, and processed using SPM8 (statistical parametric maps) and VBM tools in MATLAB R2009b software. REST software of MATLAB r2009b was used to remove the concomitant variables, such as head motion parameter, whole brain signal, white matter signal, and cerebrospinal fluid signal (CSF).

2.2.4. rs-fcMRI images processing. SPM8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and REST1.8 (resting-state data analysis toolkit, http://www.restfmri.net/forum/REST) in MATLAB R2009b software were used to reprocess the fMRI imaging data of the subjects. To eliminate the interference of the surrounding environment and instability of the magnetic field, the images of the initial 10 time points were excluded. All functional runs were expressed relative to the first values in each run. We set a movement threshold of 1.5 mm and 1.5° for the 3 linear and 3 axial coordinates to eliminate subjects with excessive head movement. However, none of the subjects had head movements that exceeded threshold. All functional runs were normalized to Montreal Neurological Institute (MNI) space with voxel resampling to 3 × 3 × 3 mm³. After spatial normalization, we used REST to extract the linear changes over time within the 0.01 to 0.08 Hz bandwidth. The resulting time series were then spatially smoothed with a 4-mm full width at half maximum (FWHM) Gaussian kernel.

2.2.5. Functional connectivity of rs-fcMRI. WFU_pick Atlas software (http://www.ansir.wfubmc.edu) was used to select the bilateral ACC as the region of interest (ROI) in automatic anatomical labelling (AAL), generating seed points, and extracting the average reference time series of bilateral ACC. Voxels within the seed region were averaged to generate reference time series. Firstly, all the time series of the voxel of the whole brain were processed by correlation analysis to obtain a figure relevant to functional connectivity. The correlation coefficient “r” was transferred by Fisher “Z” to make the data comply with a normal distribution, followed by calculating the functional connectivity between bilateral ACC and whole brain. The T value indicated the correlation of functional connectivity; a higher T value indicated superior correlation.

2.2.6. Statistical analysis. Statistics for general information: SPSS17.0 was used to analyze the data. ANOVA was used to compare the differences in sex, age, and level of education among the 3 groups. P < .05 was termed as statistical significance.

VBM data analysis: Single sample t test was used to compare the differences in the gray matter volume in each brain region among NC, PI, and PID groups. P < .001 served as the test threshold, and cluster > 50 voxels. The brain region images with a statistical difference were overlapped on the 3D structure of MNI provided by SPM8, localized by MN coordinates, and Brodmann (BA) partition. The regions were observed and recorded. T value indicated the decrease in the degree of gray matter volume; the higher T value indicated the greater reduction in the degree.

Rs-fcMRI data analysis: Double sample t test in REST 1.8 software was used to compare the differences among the NC, PI, and PID groups. P < .01 served as the significant activation threshold, and activated voxels ranged > 52 voxels (corrected by AlphaSim). The 3D images were generated using BrainNet Viewer, and xjView software was used to automatically identify the abnormal brain region, such that the functional connectivity between each brain region and ACC of each patient could be well understood, as along with the connection changes under resting-state.

Correlation analysis: REST1.8 software was used for extracting the functional connectivity strength, that is, the Z value of
each ROI from the brain regions with abnormal functional connectivity in the 3 groups. Pearson’s correlation in the SPSS17.0 software was used to analyze the correlation between Z values and scores in each scale. P < .05 was considered as statistical significance.

3. Results

3.1. Baseline data

No statistically significant differences were observed with respect to sex, age, and the level of education among the 3 groups (P > .05) (Table 1).

### Table 1

| Group      | NC group (n = 15) | PI group (n = 15) | PID group (n = 15) |
|------------|-------------------|-------------------|-------------------|
| Age, y     | 32.60±2.541       | 37.13±2.530       | 40.53±1.919       |
| Sex (male/female) | 7/8               | 6/9               | 7/8               |
| Education degree, y | 14.40±1.041     | 14.53±1.125       | 14.40±0.755       |
| PSQI score | 1.13±0.165        | 12.13±1.222       | 13.73±0.727       |
| HAMD score | 0.60±0.190        | 12.27±0.521       | 18.67±0.386       |
| RCFT score | 43.60±0.935       | 33.53±1.594       | 33.93±1.462       |
| HAMA score | 0.60±0.190        | 11.67±0.513       | 12.27±0.411       |

HAMA = Hamilton Anxiety Scale; HAMD = Hamilton Depression Scale; PSQI = Pittsburgh Sleep Quality Index; RCFT = Rey Complex Figure Test.

3.2. VBM

Compared with the NC group, the volumes of brain structure in multiple sites decreased in PI patients; however, the volume of the left middle temporal gyrus increased (P < .001, cluster size >50 voxels) (Tables 2 and 3; Figs. 1 and 2).

Compared with the NC group, the volumes of multiple sites in the PID group decreased, and the volumes of multiple sites increased (P < .001, cluster >50 voxels) (Tables 4 and 5, Figs. 3 and 4).

Compared with the PI group, the volumes of multiple sites in the PID group decreased, and the volumes of multiple sites increased (P < .001, cluster >50 voxels) (Tables 6 and 7; Figs. 5 and 6).

3.3. Rs-fcMRI

#### 3.3.1. Brain functional connectivity analysis considers bilateral ACC as a seed point

In the brain functional connectivity neural networks of the NC group, multiple sites showed a positive correlation with ACC, and multiple sites exhibited a negative correlation with the anterior cingulate cortex (P < .01, cluster >20 voxels) (Table 8 and Fig. 7).

In the neural networks of the abnormal brain functional connectivity of PI patients, multiple sites showed a negative correlation with ACC, and multiple sites were positively correlated with ACC (P < .01, cluster >20 voxels) (Table 9 and Fig. 8).

In the abnormal brain functional connectivity neural networks in PID patients, multiple sites were negatively correlated with each ROI from the brain regions with abnormal functional connectivity in the 3 groups. Pearson’s correlation in the SPSS17.0 software was used to analyze the correlation between Z values and scores in each scale. P < .05 was considered as statistical significance.

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HAMA = Hamilton Anxiety Scale; HAMD = Hamilton Depression Scale; PSQI = Pittsburgh Sleep Quality Index; RCFT = Rey Complex Figure Test.

### Table 2

| Brain region | L/R | Brodmann’s area | MINI coordinates (X, Y, Z) | Mass volume | T |
|--------------|-----|-----------------|---------------------------|-------------|---|
| Middle temporal gyrus/inferior temporal gyrus/superior temporal gyrus | R | BA 21 | 63 | −3 | −15 | 1751 | 4.4695 |
| Middle temporal gyrus/inferior temporal gyrus/fusiform gyrus/superior temporal gyrus | L | BA 20 | −51 | −4.5 | −28.5 | 2672 | 4.652 |
| Fusiform gyrus/inferior temporal gyrus R (aal) | R | — | 49.5 | −21 | −30 | 128 | 3.3648 |
| Parahippocampal/superior temporal gyrus/hippocampus | L | — | −37.5 | 12 | −24 | 277 | 3.5518 |
| Frontal lobe/rolandic gyrus | L | — | −3 | 36 | 27 | 189 | 3.7499 |
| Inferior occipital gyrus | L | — | −34.5 | −85.5 | −24 | 29 | 2.9352 |
| Inferior frontal gyrus/frontal middle orbital | L | — | −21 | 31.5 | −22.5 | 50 | 3.1264 |
| Medial frontal gyrus/anterior cingulate | R | — | 9 | 27 | −13.5 | 388 | 3.4392 |
| Anterior cingulated/caudate/ventromedial nucleus | L | — | −9 | 22.5 | −1.5 | 582 | 4.2889 |
| Frontal medial orbital | L | — | 0 | 42 | −7.5 | 24 | 3.0505 |
| Temporal middle | R | — | 69 | −45 | −6 | 28 | 2.9832 |
| Superior frontal gyrus/frONTAL superior orbital/middle frontal gyrus | L | — | −24 | 54 | −4.5 | 75 | 3.1490 |
| Inferior frontal gyrus | R | — | 34.5 | 31.5 | 1.5 | 27 | 2.9689 |
| Superior frontal gyrus/superior frontal/superior frontal superior medial/medial frontal gyrus | R | BA 10 | 28.5 | 61.5 | 7.5 | 483 | 4.0256 |

aal = anatomical automatic labeling.
ACC, in addition multiple sites showed a positive correlation with ACC ($P < .01$, cluster $> 20$ voxels) (Table 10 and Fig. 9).

Compared with the NC, the brain region was negatively correlated with the ACC functional connectivity in PI patients, including the right inferior temporal gyrus, right superior parietal gyrus/superior parietal lobule/inferior parietal lobule, and left limbic lobe/cingulate gyrus. The region that was positively correlated with ACC functional connectivity included the left cerebellum anterior lobe/culmen/lingual gyrus ($P < .01$, cluster $> 20$ voxels) (Table 11 and Fig. 10).

Compared with the NC group, the brain region negatively correlated with the ACC functional connectivity of PID patients, including brainstem/midbrain, left middle temporal gyrus, and left posterior cerebellar lobe/cerebellum Crus1 area. The region positively correlated with the ACC functional connectivity included the left parietal lobe/subgyrus/Rolandic operculum, left parietal lobe/subgyrus/pars triangularis inferior frontal gyrus, right parietal lobe/middle occipital gyrus, and right superior parietal gyrus ($P < .01$, cluster $> 20$ voxels) (Table 12 and Fig. 11).

Compared with the PI patients, the left corpus callosum/posterior cingulate in the PI patients was negatively correlated with ACC functional connectivity, whereas the midbrain was positively correlated ($P < .01$, cluster $> 20$ voxels) (Table 13 and Fig. 12).

3.3.2. Correlation analysis. Abnormal areas in brain functional connectivity in PI patients and NC group: left cingulate gyrus, left lingual, right inferior temporal gyrus, and right superior parietal gyrus were not significantly associated with the PSQI score ($P > .05$) (Fig. 13).

Abnormal areas in brain functional connectivity in PID patients and NC group: midbrain, left middle temporal gyrus, and left cerebellum Crus1 area were negatively correlated with the PSQI score ($P < .05$), and the left Rolandic operculum, left pars triangularis inferior frontal, right middle occipital gyrus, and right superior parietal gyrus were not significantly associated with the PSQI score ($P > .05$). The other abnormal areas of brain functional connectivity were not significantly associated with the HAMD score ($P > .05$), except the right pars triangularis inferior frontal region that was positively correlation with the HAMD score ($P < .05$) (Figs. 14–17).

The abnormal areas in brain functional connectivity in PID and PI patients: left posterior cingulate showed a positive correlation with the HAMD score ($P < .05$), whereas the midbrain was not associated similarly ($P > .05$) (Fig. 18).

Table 3

| Brain region          | L/R | Brodmann's area | MINI coordinates (X, Y, Z) | Mass volume | T   |
|-----------------------|-----|-----------------|---------------------------|-------------|-----|
| Middle temporal gyrus | L   | —               | $-36$                     | $-63$       | 19.5| 71  | 4.3265 |

Figure 1. Compared with the NC group, brain region showed decreased gray matter volume in the PI group; $P < .001$, cluster $> 50$ voxels.
4. Discussion

4.1. Investigation of VBM

The concept of magnetic resonance of brain structure based on voxel was proposed by Wright et al.[12] in 1995. VBM has been widely applied in the diseases of the central nervous system, such as AD,[13] epilepsy,[14] schizophrenia,[15] and depression.[16] Only a few studies are available in the brain structure of PI patients, and the influence of depressive disorder on the changes in PI brain morphology is a prospective investigation.

TABLE 4

| Brain region with decreased gray matter volume in PI patients as compared with the PID group. |
|-----------------------------------------------|
| Brain region | L/R | Brodmann's area | MINI coordinates (X, Y, Z) | Mass volume | T   |
|----------------|-----|-----------------|-----------------------------|-------------|-----|
| Cerebelum 8/cerebellum posterior lobe         | L   | —               | −34.5                     | −60         | −61.5| 68   | 3.0305|
| Cerebellum posterior lobe/cerebellar tonsil/cerebelum 8 | R   | —               | 27                          | −46.5       | −46.5| 306  | 3.551 |
| Inferior temporal gyrus/temporal pole middle/fusiform gyrus | L   | —               | −49.5                      | 15          | −34.5| 685  | 4.248 |
| Middle temporal gyrus/superior temporal gyrus/temporal inferior | R   | —               | 48                         | 15          | −39  | 385  | 4.8165|
| Fusiform gyrus/temporal inferior/temporal middle | L   | BA 20           | −54                        | −31.5       | −24  | 767  | 5.5243|
| Cerebelum anterior lobe | L   | —               | −15                       | −57         | −28.5| 82   | 3.2864|
| Temporal middle/inferior temporal gyrus | L   | BA 21           | −58.5                     | −9          | 21   | 24   | 2.9228|
| Inferior occipital gyrus/middle occipital gyrus/fusiform gyrus | L   | —               | −40.5                    | −85.5       | −18  | 183  | 3.6905|
| Limbic lobe/anterior cingulate | R   | —               | 9                          | 24          | −9   | 97   | 3.2291|
| Middle temporal gyrus/temporal superior | L   | —               | −60                        | −13.5       | −7.5 | 149  | 3.4031|
| Limbic lobe/anterior cingulate | L   | BA 32           | −1.5                      | 37.5        | −4.5 | 72   | 3.1984|
| Temporal inferior | R   | BA 37           | 46.5                      | −70.5       | −3   | 29   | 2.9838|
| Occipital superior/precentral | L   | —               | −21                       | −70.5       | 21   | 179  | 3.3652|
| Precentral | L   | —               | 13.5                      | −55.5       | 24   | 22   | 3.0418|
| Angular/supramarginal gyrus | R   | —               | 40.5                      | −57         | 33   | 67   | 4.1199|
| Middle frontal gyrus/inferior frontal oper | R   | BA 9            | 13.5                      | 21          | 63   | 364  | 4.0939|
| Superior frontal gyrus/supple motor area/frontal superior medial | R   | BA 6            | 13.5                      | 21          | 63   | 364  | 4.0939|
| Superior frontal gyrus/supple motor area | L   | —               | −9                        | −7.5        | 75   | 244  | 4.4963|

Figure 2. Compared with the NC group, brain region showed increased gray matter volume in the PI group; P<.001, cluster >50 voxels.
that the depression negatively influences the development of the disease in PI patients, an abnormal connection in the brain functional network is observed, and the brain structure will exhibit morphological changes. Therefore, PI patients were divided into 2 groups and compared with the NC group to evaluate the changes in brain structure in PI and PID patients.

The results were deduced as follows:

1. Compared with the NC group, the volumes of brain structure in multiple sites decreased in PI patients; however, the volume of the left middle temporal gyrus increased. This phenomenon was consistent with most of the results from the study by Joo et al.\[17\] except the increased volume of the left middle temporal gyrus. Recently, the volume of rostral cingulate zone increased as compared with the control group, and the severity of insomnia was relevant to the rostral cingulate zone volume, which might be caused by the compensatory reaction of the brain chronic insomnia.\[18\] Thus, we deduced that the increase in the volume of middle temporal gyrus in insomnia patients was an adaptation to the long-term excessive brain response and remodeling of the brain structure. The middle temporal gyrus is time-efficient in the extraction of new memories and consolidation of the long-term memory. The activity of middle temporal gyrus significantly decreases with age under the memory task status.\[19\] The abnormality in the occipital cortex area is correlated with the loss of cognitive function (such as visual attention and memory) during chronic persistent disease course. The structural abnormality of the frontal and temporal lobes leads to a decrease in cognitive level, thereby severely influencing the quality of life in PI patients. The decrease in the

Table 5

| Brain region                      | L/R | Brodmann’s area | MINI coordinates (X, Y, Z) | Mass volume | T    |
|----------------------------------|-----|-----------------|-----------------------------|-------------|------|
| Left brainstem/midbrain          | L   |                 | −4.5, −34.5, −10.5          | 52          | 2.9473|
| Temporal lobe/subgyrus           | R   |                 | 28.5, −46.5, −1.5           | 12          | 3.6491|
| Occipital lobe/lingual           | R   |                 | 25.5, −61.5, −1.4           | 2           | 2.8255|
| Limbic lobe/parahippocampal gyrus| R   |                 | 25.5, −45, 1.5              | 1           | 2.8643|
| Precentral gyrus/postcentral     | L   | BA 43           | −57, −6, 13.5               | 20          | 2.97  |
| Frontal middle/precentral        | L   |                 | −40.5, 12, 45               | 110         | 3.2547|
| Parietal lobe                    | R   | BA 7            | 3, −67.5, 49.5              | 126         | 4.1599|
| Parietal lobe/postcentral        | R   |                 | 39, −33, 52.5               | 181         | 4.4098|
| Parietal lobe/postcentral        | L   | BA 5            | −16.5, −40.5, 76.5          | 11          | 2.9609|

Figure 3. Compared with the NC group, brain region showed decreased gray matter volume in the PID group; \( P < .001 \), cluster>50 voxels.
Figure 4. Compared with the NC group, brain region showed increased gray matter volume in the PID group; $P < .001$, cluster $> 50$ voxels.

| Table 6 |
|----------------------------------|
| Brain region with decreased gray matter volume in PID patients as compared with the PI patients. |
| Brain region | L/R | Brodmann’s area | MINI coordinates ($X$, $Y$, $Z$) | Mass volume $T$ |
|--------------|-----|-----------------|-------------------------------|----------------|
| Cerebellum 10 | L | — | $-19.5$ | $-34.5$ | $-45$ | 69 | 3.2468 |
| Cerebellum posterior lobe/cerebellum 6 | L | — | $-12$ | $-61.5$ | $-24$ | 82 | 3.1097 |
| Temporal inferior | L | BA 20 | $-34$ | $-31.5$ | $-21$ | 1 | 2.7924 |
| Subgranular temporal lobe/subgyrus | R | — | $31.5$ | $-64.5$ | $-6$ | 1 | 2.8769 |
| Inferior frontal gyrus/frontal inferior trigonal | R | — | $49.5$ | $28.5$ | $25$ | 25 | 3.1533 |
| Angular/superior temporal gyrus | R | — | $40.5$ | $-57$ | $25.5$ | 63 | 3.0687 |
| Frontal inferior trigonal | L | — | $-34.5$ | $20.5$ | $25.5$ | 2 | 2.8248 |
| Superior frontal gyrus/supplemental motor area | R | — | $12$ | $7.5$ | $67.5$ | 44 | 3.0487 |

| Table 7 |
|----------------------------------|
| Brain region with increased gray matter volume in PID patients as compared with the PI patients. |
| Brain region | L/R | Brodmann’s area | MINI coordinates ($X$, $Y$, $Z$) | Mass volume $T$ |
|--------------|-----|-----------------|-------------------------------|----------------|
| Cerebellum posterior lobe/cerebellum 8 | L | — | $-34.5$ | $-60$ | $-61.5$ | 68 | 3.0365 |
| Cerebellum posterior lobe/cerebellum 8 | R | — | $27$ | $-46.5$ | $-46.5$ | 306 | 3.551 |
| Temporal inferior/temporal pole middle/superior temporal gyrus | L | — | $-49.5$ | $15$ | $-34.5$ | 685 | 4.344 |
| Temporal pole middle/superior temporal gyrus/temporal inferior | R | — | $48$ | $15$ | $-39$ | 385 | 4.8165 |
| Fusiform gyrus/temporal inferior gyrus/temporal middle gyrus | L | BA 20 | $-54$ | $-31.5$ | $-24$ | 767 | 5.5243 |
| Cerebellum anterior lobe | L | — | $-15$ | $-57$ | $-28.5$ | 62 | 3.2864 |
| Inferior temporal gyrus/temporal middle | L | BA 21 | $-58.5$ | $-9$ | $-21$ | 24 | 2.6228 |
| Inferior occipital gyrus/middle occipital gyrus/fusiform gyrus | L | — | $-40.5$ | $-85.5$ | $-18$ | 183 | 3.6906 |
| Limbic lobe/paracingulate/medial frontal gyrus | R | — | $9$ | $24$ | $-9$ | 97 | 3.2291 |
| Temporal middle/temporal superior | L | — | $-60$ | $-13.5$ | $-7.5$ | 149 | 3.4031 |
| Anterior cingulate gyrus/parscingulate gyrus | L | BA 32 | $-1.5$ | $37.5$ | $-4.5$ | 72 | 3.1984 |
| Temporal inferior | R | BA 37 | $46.5$ | $-70.5$ | $-3$ | 29 | 2.9638 |
| Occipital superior/precuneus | L | — | $-21$ | $-70.5$ | $21$ | 179 | 3.3652 |
| Precuneus | R | — | $13.5$ | $-55.5$ | $24$ | 22 | 3.0418 |
| Angular/supramarginal gyrus | R | — | $40.5$ | $-57$ | $33$ | 67 | 4.1199 |
| Middle frontal gyrus/frontal inferior opercular | R | BA 9 | $51$ | $15$ | $33$ | 20 | 3.4945 |
| Superior frontal gyrus/supplemental motor area | R | BA 6 | $13.5$ | $21$ | $63$ | 634 | 4.0039 |
| Paracentral/superior frontal gyrus/supplemental motor area | L | — | $-9$ | $-7.5$ | $75$ | 244 | 4.4963 |
volume of anterior prefrontal cortex area influences the emotional and social function, thereby leading to a damage in cognitive function. The decrease in the volume of visual association cortex area is closely related to the cognitive function disorder in PI patients. The decrease in the volume of the right fusiform gyrus was correlated with the abnormality in self-awareness. The morphological abnormality of the paracentral lobule may influence the attention and the ability to problem solving, working memory, and self-cognition capacity. Cingulate gyrus plays a pivotal role in cognitive function and emotional memory. The high RCFT and HAMD values in PI patients were in agreement with our results. Thus, it was deduced that the decrease in the volume of brain region formed the basis for the cognitive pathological changes,
thereby becoming a risk condition accompanied by emotional disorder in insomnia patients. Pillay et al\(^2\) reported that the volumes of caudate nucleus and lenticular nucleus were negatively correlated with the degree of depression. The results of our study also indicated that the abnormality in this area could increase the morbidity of depression. The structural abnormality in the left cerebellum will cause damage to the cognitive function in different degrees, especially spatial abstraction generalization and concept formation ability. Moreover, the long-term hyperarousal status is related to the

| Brain region | L/R | Brodmann's area | MINI coordinates (X, Y, Z) | Mass volume | T  |
|--------------|-----|----------------|---------------------------|------------|----|
| Cerebellum posterior lobe/pyramis/cerebellum 7b | L | — | −12 −72 −39 | 95 | −7.6253 |
| Cerebellum 8 L | — | — | — | — | — |
| Middle temporal gyrus/inferior temporal gyrus | L | BA21 | −45 3 −39 | 108 | 7.6715 |
| Middle temporal gyrus/inferior temporal gyrus/temporal pole/superior temporal Gyrus/fusiform gyrus | R | — | 54 3 −30 | 126 | 9.8582 |
| Occipital lobe/fusiform gyrus/lingual gyrus/inferior temporal gyrus/middle temporal gyrus | R | BA19 | 30 −75 −18 | 287 | −9.6034 |
| Medial superior frontal gyrus/dorsolateral superior frontal gyrus/inferior frontal gyrus/middle frontal gyrus/superior temporal gyrus/caudate/insula/frontal inferior orbital/lentiform nucleus/anterior cingulate gyrus | L | — | −6 36 6 | 3183 | 14.7236 |
| Limbic lobe/parahippocampal gyrus/fusiform gyrus/Middle temporal gyrus/inferior temporal gyrus/fusiform gyrus/middle occipital gyrus | L | BA36 | −30 −30 −21 | 52 | 6.3867 |
| Limbic lobe/precuneus/cingulate gyrus | R | — | 9 −51 27 | 642 | 11.4972 |
| Inferior frontal gyrus/frontal middle gyrus | L | BA46 | −45 48 0 | 292 | −11.1311 |
| Middle frontal gyrus | R | — | 51 42 18 | 61 | −7.4556 |
| Parietal lobe/angular gyrus/middle temporal gyrus | L | BA39 | −54 −69 36 | 179 | 11.9337 |
| Parietal lobe/angular gyrus/supramarginal gyrus/superior temporal gyrus | R | — | 54 −63 30 | 115 | 11.5599 |
| Inferior parietal lobule/superior parietal lobule/parietal superior/parietal inferior/precuneus/angular/middle occipital gyrus/supramarginal gyrus/superior occipital gyrus | R | — | 12 −72 60 | 2191 | −15.4929 |
| Interhemispheric/middle cingulum gyrus | L | — | 0 −18 39 | 112 | 8.744 |
| Middle frontal gyrus/dorsolateral superior frontal gyrus | R | — | 30 3 63 | 131 | −8.1905 |
| Middle frontal gyrus/dorsolateral superior frontal gyrus/frontal superior | L | BA6 | −30 3 63 | 146 | −9.0515 |

Figure 7. Brain functional connectivity in NC considering bilateral ACC as a seed point. The significant threshold was set at \(P < .01\), cluster >20 voxels. Red indicates the area with the enhanced connection; blue indicates the area with the weakened connection.
**Table 9**

Abnormal brain functional connectivity in PI group considered as the bilateral ACC (seed point).

| Brain region                                                                 | L/R | Brodmann's area | MINI coordinates (X, Y, Z) | Mass volume | T     |
|------------------------------------------------------------------------------|-----|-----------------|---------------------------|-------------|-------|
| Cerebellum posterior lobe/inferior semilunar lobule/cerebellum               | R   | ----            | 15, −78, −57             | 97          | −7.1324 |
| Crus2/cerebellum 7b                                                         |     |                 |                          |             |       |
| Inferior temporal gyrus/middle temporal gyrus                                | R   | BA21            | 60, −3, −21              | 74          | 7.7562 |
| Inferior temporal gyrus/occipital inferior/middle occipital gyrus            |     |                 |                          |             |       |
| Anterior cingulate/superior frontal gyrus/medial superior frontal gyrus/     | L   | BA37            | −48, −57, −15            | 79          | −6.1939 |
| frontal gyrus/caudate/entorhinal nucleus/middle                               |     |                 |                          |             |       |
| Parietal lobe/inferior frontal orbital/insula                               | L   | −9, −57, 33     | 375                      | 10.4338     |       |
| Parietal lobe/angular                                                        | L   | −51, −66, 36    | 88                       | 10.3376     |       |
| Limbic lobe/cingulate gyrus/middle cingulum gyrus                           | R   | BA23            | 3, −18, 30               | 155         | 9.229  |
| Parietal inferior/parietal lobule/superior parietal lobule/precuneus         | L   | BA40            | −42, −39, 48             | 457         | −11.0643 |
| Frontal lobe/middle frontal gyrus                                            | L   | −18, −6, 57     | 57                       | 7.6686      |       |
| Parietal superior/superior parietal lobule/precuneus                        | R   | −27, −63, 54    | 321                      | −8.5371     |       |

**Table 10**

Abnormal brain functional connectivity in PID group, bilateral ACC considered as a seed point.

| Brain region                                                                 | L/R | Brodmann's area | MINI coordinates (X, Y, Z) | Mass volume | T     |
|------------------------------------------------------------------------------|-----|-----------------|---------------------------|-------------|-------|
| Cerebellum posterior lobe/inferior semilunar lobule/cerebellum               | R   | ----            | 33, −75, −51             | 75          | −6.5307 |
| Crus2/cerebellum 7b                                                         |     |                 |                          |             |       |
| Middle occipital gyrus/inferior temporal gyrus                              | L   | −54, −63, −12   | 86                       | −8.0949     |       |
| Medial frontal gyrus/anterior cingulate/superior frontal gyrus/             | L   | BA24            | −3, 30, −6               | 2251        | 20.6422 |
| cingulum anterior/medial superior frontal/middle cingulum gyrus/paracentral|     |                 |                          |             |       |
| Lobule                                                                      |     |                 |                          |             |       |
| Caudate head/caudate                                                        | R   | 9, 12, −3       | 223                      | 8.4671      |       |
| Posterior cingulate/precuneus                                               | L   | −9, −51, 21     | 162                      | 7.3576      |       |
| Parietal lobe/angular gyrus/supramarginal gyrus                            | L   | −39, −81, 42    | 56                       | 6.7332      |       |
| Middle frontal gyrus/precunean                                              | L   | BA9             | −45, 9, 30               | 50          | −7.343 |
| Parietal superior/superior parietal lobule/parietal inferior/precuneus      | L   | −15, −69, 60    | 329                      | −9.5575     |       |
| Superior parietal lobule/parietal inferior/parietal superior                 | R   | BA7             | 21, −63, 57              | 219         | −7.1975 |

Figure 8. Abnormal brain functional connectivity in PI patients, considering bilateral ACC as a seed point. The significant threshold was set at $P < .01$, cluster $>20$ voxels. Red indicates the area with the enhanced connection; blue indicates the area with the weakened connection.
excessive activities of ascending reticular activation pathway, hypothalamus–pituitary gland–adrenal cortex, and sympathetic–adrenal medulla system.\textsuperscript{[2,4]} Therefore, the glucocorticoids and adrenaline increase, melatonin decreases, the brain regions with distribution of hormone receptor are influenced, the neuron is inhibited and missing, and the brain structure is altered. Hippocampus, prefrontal lobe, interior orbital lobe, ACC, and amygdala are all located in the regions widely distributed with glucocorticoids receptors.\textsuperscript{[21]} Therefore, the missing regional neuron might be related to the increased adrenal cortisol in patients with insomnia.

2. Compared with NC, the brain structure volumes in multiple sites of PID patients were modified. A network connection is formed during the whole sleeping period, involving the frontal lobe, parietal lobe, temporal lobe, occipital lobe, limbic system and brainstem, and cerebellum, harboring a wide functional connectivity. The sleep mechanism of PID patients is not harmonious with awakening mechanisms. The PSQI of PID patients is relatively high, and the whole sleeping network structure is damaged. The result indicated that owing to the plasticity of brain, the volume of brain region is decreased; however, the adaptive volume of a part of the region is increased, which provided the basis for investigating the underlying regulatory mechanism. The structural changes in the frontal lobe, parietal lobe, temporal occipital lobe, and limbic system are related to the disorders of the cognitive function (e.g., spatial memory) in PI patients. The decrease in the volume of supplementary motor area can influence the subjective consciousness and cognitive function in patients. The brain region volumes of cerebellum, prefrontal cortex, and anterior cingulate cortex decrease in the PI patients with light and moderate depression, which might be associated with emotional factors. Peng et al.\textsuperscript{[22]} also found that the gray matter densities in the dorsolateral prefrontal lobe, dorsal medial prefrontal lobe, bilateral temporal pole, right superior temporal gyrus, bilateral insular lobe, left parahippocampal-gyrus, and cerebellar cortex were decreased; this phenomenon was similar to the findings of the present study. Thus, the depression might have influences on the structural changes in the brain of PI patients.

3. Compared with PI patients, the changes in the brain structure occurred in multiple sites in PID patients. The HAMD score in PID patients was higher than that of PI patients. According to the neurobiology, the functional disorder of sleep-awakening neural regulation mechanism may cause emotional reaction, which might disrupt the equilibrium between homeostasis and circadian rhythm and interact with brain functional area associated with sleep. Thus, we speculated that for PID patients with decreased brain gray matter volume, depression played a major role in the vicissitudes. The insomnia disorder played a secondary role and was also related to the neuropathological mechanism in PID patients. The neuroendocrine mechanism in depression patients is disordered, characterized by the hypothalamic–pituitary–adrenal hyperfunction. The neuron will degenerate and shrink by hormonal activities, neurotransmitters, or receptors, and the brain

Table 11

| Brain region                              | L/R  | Brodmann’s area | MINI coordinates (X, Y, Z) | Mass volume | T       |
|------------------------------------------|------|-----------------|---------------------------|-------------|---------|
| Temporal inferior                        | R    | BA20            | 51                        | –48 –15     | 20      | –4.2752 |
| Cerebellum anterior lobe/culmen/lingual | L    |                 | –9                        | –45 –3      | 20      | 3.8253  |
| Parietal superior/superior parietal lobule/inferior parietal lobule | R    |                 | 21                        | –75 54      | 119     | –4.2161 |
| Limbic lobe/cingulate gyrus              | L    |                 | –6                        | –3 30       | 29      | –4.5803 |
structure in depression patients will also change. The prefrontal cortex, hippocampus, anterior cingulate cortex, and basal nuclei have rich neurotransmitters and receptors that are the main regions for hormonal effects. Taki et al.[23] found that the volumes of brain gray matter in the frontal lobe, temporal lobe, precuneus, cingulate gyrus, amygdala, hippocampus, and parahippocampal gyrus decreased. This phenomenon was similar to our results, which proved that the area with decreased gray matter volume was associated with depression. The volume decrease in the bilateral inferior frontal gyrus and the superior frontal gyrus/supplementary motor area might form the structural basis for the depression symptom and cognitive impairment in PID patients. The missing volume of the temporal lobe gyrus is related to the damage in the short-term memory of PID patients. Cerebellum might be a crucial component associated with the neural circuits during mood disorders.[24] The decrease in the left cerebellum 8 and 10 area suggested an abnormality in the

Table 12

| Brain region | L/R | Brodmann’s area | MINI coordinates (X, Y, Z) | Mass volume | T     |
|--------------|-----|----------------|---------------------------|-------------|-------|
| Cerebellum posterior lobe/cerebellum Crus1 | L    | —              | -36 -81 27                | 38           | -3.9229 |
| Right brainstem/midbrain | R    | —              | 12 -24 -18                | 19           | -3.9072 |
| Parietal lobe/subgyrus/rolandic oper | L    | —              | -39 -30 21                | 44           | 4.4629  |
| Frontal lobe/subgyrus/frontal inferior trigonometric | L    | BA39           | -54 -72 24                | 21           | -3.5429 |
| Middle temporal gyrus | L    | BA19           | 36 -78 36                 | 29           | 4.0178  |
| Parietal lobe/precuneus/middle occipital | R    | BA19           | 36 -78 36                 | 29           | 4.0178  |
| Precuneus/parietal superior | R    | —              | -15 -75 54                | 52           | 4.2118  |
depression-related brain region in PI patients. Nevertheless, compared with the PI patients, the area with increased gray matter volume was more than that with the decreased volume, thereby indicating that the structural abnormality might be related to the pathogenesis in PID patients. To control the depression and strengthen the cognitive competence, the reaction of PI patients was enhanced, and the brain regional volumes of the related ACC, temporal lobe, parietal lobe, occipital lobe, and cerebellum increased.

4.2. Investigation of rs-fcMRI

ACC is a core component in cerebral limbic system, playing integrative roles in the regulation of behavior, cognition, and emotion. The lesion in ACC may generate a series of symptoms, including attention-deficit disorder, vegetative nervous function disturbances, and ahpithymia. A few studies are available describing the ACC network in PI. Thomas et al.[25] reported that the whole brain metabolism decreased in healthy subjects with sleep deprivation for >24 hours. The study used 18F-deoxyglucose (18FDG) PET scanning, especially in the frontal lobe, parietal lobe cortex, and thalamus, indicating that sleep is the restock of brain function of cognition-related thalamus cortex network, wherein the basal forebrain and ACC play crucial roles in regulating the awakening. Furthermore, we speculated that depression greatly influenced on the functional connectivity of ACC network in PI patients. Anand et al.[26,27] found that the regulatory function of ACC on the emotion circuit was

| Table 13 |
| --- |
| Brain functional connectivity analysis, bilateral ACC considered as a seed point for comparison between the PID and PI groups. |
| Brain region | L/R | Brodmann's area | MINI coordinates (X, Y, Z) | Mass volume | T |
| --- | --- | --- | --- | --- | --- |
| Midbrain | R | — | 12 | -24 | -21 | 21 | 4.5275 |
| Corpus callosum/post cingulum | L | — | -6 | -42 | 12 | 37 | -4.2996 |
weakened. After antidepression therapy, the regulatory effect of ACC was improved, and the remission of the depressive disorder symptoms was related to the enhanced regulatory effect. Our results also indicated that the volumes of ACC in PI and PID patients decreased, especially in PI patients. Thus, ACC was selected as the seed point to investigate the functional change in the brain region in ACC cognitive network in PI and PID patients and the neuromechanism underlying depressive disorder in PI patients.

Rs-fcMRI does not require the comparison between experimental conditions and basal level; the time series correlation of BOLD signal fluctuation is the primary factor in different brain regions distal to the observation space. Spontaneous, organized, and continuous functional activities exist under the no-task waking and resting states, which comprises the default mode network (DMN). DMN mainly includes the prefrontal cortex, parietal lobe cortex, and ACC, useful in maintaining the waking state, and is associated with the extraction of episodic memory, monitoring the surrounding environment and introspectiveness, as well as the interaction between continuous cognition and emotion. In this study, we proved that the brain function under resting-state had a DMN in normal individuals. DMN is still active under normal light sleep; however, an abnormality has been found after sleep deprivation. The extensive changes in DMN under resting-state occurs in the depressive disorder-related insomnia patients. The results showed that the brain functional connectivity of the frontal lobe, parietal lobe, occipital lobe, temporal cortex, and cerebellum area with ACC were weakened, and the enhanced area was mainly the limbic system. Under resting-state, DMN primarily remains as the waking-state of the brain; in the present study, the decreased activity of DMN function might be related to PI neuropathological changes. Recently, PI patients were reported to have abnormal consistency, mostly in the limbic system, which might be attributed to the long-term accumulation of negative emotion caused by insomnia. To adapt the changes of the inner emotional environment, the baseline activity level of the limbic system (especially anterior cingulate cortex) increased corresponding, which was in agreement with our result. This phenomenon suggested that the enhanced functional activity of the limbic system might be correlated with the emotional fluctuations in PI patients. The weakened area of ACC brain functional connectivity in PID patients.
Figure 13. The abnormal areas of brain functional connectivity in PI patients and NC group: left cingulate gyrus, left lingual gyrus, right inferior temporal gyrus, and right superior parietal gyrus were not significantly associated with the PSQI score ($P > .05$).

Figure 14. The abnormal areas of brain functional connectivity in PID patients and NC group: midbrain, left middle temporal gyrus, and left cerebellum Crus1 area showed significant negative correlations with the PSQI score ($r = -0.718, -0.556, -0.662$, respectively; $P < .05$).
patients primarily included the parietal lobe cortex, and the enhanced area was mainly in the frontal and limbic lobes. Under sleep deprivation, the functional activities of the parietal lobe cortex and ACC decreased, indicating a decrease in the cognitive functions (such as attention and execution). Our results also indicated that the cognitive function was damaged in PID patients. Hamilton et al.[33] reported that the functional connectivity of the prefrontal lobe and ACC in depression patients increased, and the results showed that the enhancement of functional connectivity of ACC with frontal lobe and limbic lobe was the underlying pathological mechanism for the emotional disorder in PI patients. The altered DMN in PI and PID patients, decrease in functional connectivity of the brain region, and imbalance of the DMN functional regulation indicated that both PI and PID patients exhibited damage in the regional function of the brain, and functional consistency disorder among neurons. The abnormality of ACC neural network might be the underlying pathological machinery for the changes in cognitive and emotional function in PI patients.

The bilateral ACC was considered as a seed point to compare the brain functional connectivity among the groups. Compared with the NC group, the right inferior temporal gyrus, right superior parietal gyrus/superior parietal lobule/inferior parietal lobule, and the left limbic lobe/cingulate gyrus had a negative
correlation with ACC, and left cerebellum anterior lobe/culmen/lingual gyrus had a positive correlation with the ACC functional connectivity. The brain region showing a weak negative correlation with the ACC functional connectivity showed that the results of VBM indicated a decreased volume in the related brain region. Frings et al\[34\] found that the damage to superior parietal lobule caused the disorders of topothesia, direction, and extremity spatial position. Therefore, the weakened functional connectivity of the right superior parietal gyrus/superior parietal lobule/inferior parietal lobule with ACC was closely related to the abnormality of attention control and lack of executive capacity in spatial memory of PI patients. The right inferior temporal gyrus and left limbic lobe/cingulate gyrus is one of the main regions of DMN, and the ACC functional connectivity was weakened; thus,
the cognitive function was damaged in PI patients. The enhanced ACC functional connectivity with the left cerebellum anterior lobe/culmen/lingual gyrus might be related to the functional abnormality of visual cortex in occipital lobe lingual gyrus and disorder of the cognitive function. The high RCFT score in the PI group corresponded to the relevant brain region with abnormal functional connectivity. Therefore, the abnormal regions of functional connectivity in PI patients and NC group did not show a significant correlation with the PSQI score. Thus, the abnormal region of functional connectivity in ACC and PI patients might be the underlying pathological mechanism for the cognitive function damage in PI patients.

Compared with the NC group, the brain region was negatively correlated with the ACC functional connectivity in PID patients, including brainstem/midbrain, left middle temporal gyrus, and the left posterior cerebellar lobe/cerebellum Crus I area. The region positively correlated with the ACC functional connectivity included left parietal lobe/subgyrus/Rolandic operculum, left parietal lobe/subgyrus/pars triangularis inferior frontal gyrus, right parietal lobe/middle occipital gyrus, and right superior parietal gyrus. The region with weakened ACC functional connectivity was consistent with the decreased volume in the related brain region. The weakened degree of functional connectivity in PID patients was negatively correlated with the PSQI score, among which the decrease in the degree of midbrain brain functional connectivity was strongly correlated with PSQI score. The network structure was closely related to the cerebellum, the loop formed between them affected the brain excitatory state and retention of the awake state. Thus, it was deduced that the weakened functional connectivity of these regions with ACC was closely related to the insomnia status and pathogenesis in PID patients. The left middle temporal gyrus and cerebellum Crus I area involved in the cognitive function process and the functional connectivity with ACC was weakened. The functional connectivity degree of the left inferior frontal gyrus was positively correlated with HAMD, suggesting that the vicious circle formed by PID patients’ sleep and emotional disorder influence the cognitive function. The brain regions positively correlated with the ACC functional connectivity mainly lie in the frontal parietal lobe. The adaptive compensatory effect of the enhanced functional connectivity indirectly proved the significance of the missing cognitive function in PI patients. The PSQI, HAMD, and RCFT scores in PID group were high, which also further improved the function in the relevant brain regions associated with sleep, emotion, and spatial memory.

Compared with PI patients, PID patients showed a negative correlation of the left corpus callosum/posterior cingulate with ACC functional connectivity, whereas the midbrain was positively correlated with the ACC functional connectivity. The occurrence of depression in PI patients might be related to the decrease in functional activity in brain region regulating the emotions. Reportedly, the abnormality of posterior cingulate in the depression patients is associated with persistent emotional burn. The present study, the decrease in the degree of functional connectivity of posterior cingulate was positively correlated with HAMD and the ACC functional connectivity with posterior cingulate was weakened, suggesting the onset of the neurological function in depressive disorder. The decrease in the corpus callosum and ACC functional connectivity indicated the damage in the cognitive function of PID patients. PID hyperarousal leads to dysfunction in a network system, changes in circadian rhythms, and no correlation between midbrain and the HAMD score. Thus, the functional connectivity between midbrain and ACC is enhanced, which is an adaptive response during chronic insomnia in PID patients.

Nonetheless, the brain structural connection and functional connectivity are interdependent. PI exhibits abnormality in intracerephal multisystem structure and neural network connection. The interaction and influence between depression and insomnia aggravate the damage to cognitive function. This study provides a theoretical basis for exploring the neuropathology of PID and cognitive function. It also indicates that VBM and rs-fcMRican effectively evaluate the changes in PI-associated brain structure and functional connectivity, which provides clinical value for the prospective investigation on neurocognition.

**Author contributions**

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Figure 18. The abnormal areas of brain functional connectivity in PID and PI patients. The left posterior cingulate was positively correlated with the HAMD score ($r = 541, P < .05$), whereas the midbrain was related significantly ($P > .05$).
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