Evaluation of brain default network fMRI of Insomnia with Depression patients at Resting state

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Abstract: Research Purpose: By conducting fMRI research on insomniacs with depression in resting state, this experiment reveals the abnormality in the patient's DMN and its neural pathogenesis, and different degrees of depression's impact on the neural networks causing weakened cognitive function. Consequently, it offers objective imageological basis for clinical cognitive impairment treatment and evaluation of such treatment. Method: a group of 40 cases are selected as the insomniac group, consisting of 20 as mild depression group and 20 as moderate depression group. And another 40 cases are selected as the HC group. All the testees take PSQI, HAMD, 3.0T routine MRI examination and fMRI, and cases with abnormal brain structures are excluded. Then on the basis of PCC as the seed point, comparisons are made between the insomniac group and HC group, between mild and moderate depression group in terms of their DMN differences. Result: Depressive Insomniac Group have stronger functional connection with PCC/pC: bilateral superior frontal gyri and bilateral middle cingulate gyri; the following regions have weaker functional connection: left occipital lobe lingual gyrus/ parahippocampal gyrus/ fusiform gyrus, right superior temporal gyrus/temporal pole, right middle temporal gyrus/middle occipital gyrus, and left occipital lobe/middle temporal gyrus. Compared with Mildly Depressive Group, the following encephalic regions of Moderately Depressive Insomniac Group have stronger functional connection with PCC/pC: right middle cingulate cortex and right frontal gyrus; the following regions have weaker functional connection: left parahippocampal gyrus. Conclusion: There is abnormity in the brain default mode network of insomniacs with depressive symptoms. The depression degree of insomniacs varies. There are differences in the brain default mode network. It is suggested that there is a positive correlation between the middle cingulate gyrus and insomnia and depression, this is also shown between the activated degree of the middle frontal gyrus and insomnia and depression. There is a negative correlation between the activated degree of the parahippocampal gyrus and insomnia and depression. This research also suggested that there is a cognitive disorder and a neutral network mechanism of emotion regulation disorder among depressive insomniacs.
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1. Introduction

Insomnia is a common and frequently-occurring clinical disease and the most common sleep disorder, causing severe problems to people's physical and mental health, as well as affecting the well-being of their livelihood. Surveys show that about 50% of adults around the world suffer from chronic insomnia[1]. This disease causes not only damages to body functions such as declining immunity, endocrine disorder and weakened cardiac function[2], but also emotional disorders such as anxiety and depression, as well as other problems[3]. Therefore, the long-term insomnia's harm to people has drawn increasing attention. At present, the incidences of insomnia are on the rise year by year, making it a public health issue of widespread concern[4].

As emotions and sleep are closely related, negative emotional cognition plays a major role in the formation of insomnia. Insomniacs are prone to feeling down or depressed, as studies show 41% of insomnia cases before depression, 29% for cases of insomnia and depression happening simultaneously and 29% for cases of insomnia after depression which reveals that insomnia is more likely to cause depression than the other way around. Having trouble sleeping by anxiety from long-term insomnia, insomniacs may develop depressive feelings, as studies show that depression occurs in 17% of primary insomniacs within 6 years after they are diagnosed with insomnia[5]. Therefore, insomnia with depression today has emerged as a hot spot for medical studies but researchers have not yet found its pathogenesis. In a resting state, neurons in the human brain are performing functional activities spontaneously and continuously, indicating there is a default mode network (DMN) [6], covering the areas of

prefrontal lobe, happocampi, thalamus, superior parietal lobule, precuneus and temporal cortex of both sides. The DMN maintains the most basic cognitive activities of the human brain in a resting state, including perceiving the outside world and monitoring mental conditions for their behaviors, etc.[7-10]. It is widely applied to mental disease research because it can conduct intuitive comparisons between case groups on brain functions such as cognitive functions. A large amount of research has found that the DMN has changed in patients with Alzheimer's disease, infantile autism and schizophrenia. Ye Enmao et al.[11] applied fMRI in a resting state to investigate sleep deprivation's impact on the DMN and discovered that the longer sleep is deprived, the slower the activity of anterior cingulate cortex (ACC) is, with manifestations like a decline in attention and executing capabilities. The study suggests that the functional connection in the DMN is enhanced after sleep is deprived while the thalamus is over-activated, as maintaining a sober state is prioritized over fulfilling tasks when sleep is deprived. Evidence shows that fMRI has discovered that there are abnormalities in insomniacs' brain structure and functions that spread into many areas of the brain, mainly involving neural circuits related to emotion processing, sleep generation and regulation. So far, there are no systematic researches on different degrees of insomnia's impact on the fMRI neural network of specific damaged areas in an insomniac's brain. Further research should be done to find out where the damaged areas are in the brain of an insomniac with depression due to the inconsistent findings in medical imaging research. Therefore, such imageological research on insomnia with depression will continue in the years to come. By conducting fMRI research on insomniacs with depression in resting state, this experiment reveals the abnormality in the patient's DMN and its neural pathogenesis, and different degrees of depression's impact on the neural networks causing weakened cognitive function. Consequently, it offers objective imageological basis for clinical cognitive impairment treatment and evaluation of such treatment.

2. Materials and Method

The experiment design adheres to medical ethics and is approved by Zhengzhou University Ethics Committee.

2.1Target group

A group of 40 people are selected as the insomniac group, consisting of 28 women and 12 men aged between 23 and 47, with an average age of (38.5 ± 8.57). They are patients with normal brain structures (abnormal cases in routine tests are excluded in advance), who passed all the grouping criteria for insomniac groups and were treated in the neurology department of Henan Provincial People's Hospital from July, 2012 to December, 2013. Another 40 cases are also selected as the healthy control group, consisting of the same number of men and women as the insomniac group. They have normal brain structures (abnormal cases in routine tests excluded in advance), who passed all the grouping criteria for a healthy control group. They are between 21 and 54 years old, with an average age of (35.4 ± 10.41) so there is no significant statistical difference in the age of the test group. All subjects are dextral. They have been informed of the experiment details and signed consent before the experiment.

2.2 Grouping criteria

2.2.1 Grouping criteria for insomniac group

1) PSQI＞7, HAMD＜24;

2) No other mental diseases or whole-body organic diseases;

3) Aged between 18 and 55;

4) No anti-anxiety, anti-depression and sleeping pills taken within recent two weeks.

2.2.2 Grouping criteria for a healthy control group:

1) No familial diseases or whole-body organic diseases;

2) No habits of drinking or smoking;

3) PSQI＜5, HAMD＜7;

4) No staying up late within the last two weeks;

5) Aged between 18 and 55.

2.2.3 Clinical scale evaluation:

Two senior neurologists conduct one-to-one clinical scale evaluation of PSQI and HAMD to all subjects. The criteria are as follows: 1) Pittsburgh Sleep Quality Index (PSQI): formulated in 1993 by Buysse Dj, a sleep expert in Sleep and Biological Rhythm Research Center, Department of Psychiatry, Medical Center of University of Pittsburgh. It has a score range from 0 to 21. The higher the score is, the worse the sleep is and a score no less than 7 is seen as an indicator of insomnia. 2) Hamilton Depression Scale (HAMD) (see Appendix D): Formulated by Hamilton in 1960, it is used for scaling the degree of depression in clinics. The full score is 52, among which less than 7 is normal, 7-16 is mild depression, 17-24 is moderate depression and over 24 is severe depression.

2.3 fMRI parameters

All selected subjects arrive at the fMRI room half an hour before taking the test. They are given instructions by two graduate students in the research team on how the test will be done before signing the consent for the experiment. Then they have a 10-minute break before the test and a silent break with eyes closed is suggested. Siemens Tim Trio 3.0T

superconductive MRI scanner is used for data collection. The subjects wear a 12-channel coil to have their brain structures and resting-state functions scanned. Those subjects with abnormal structures or unqualified data for the brain functions will be excluded from the case groups. While scanning, foam is used to secure the subjects' head while cotton balls and earplugs are usedto alleviate noise.

2.3.1 Routine MRI scanning:

First, all subjects take a routine brain structure scanning and those subjects with abnormal structures will be excluded from the case groups. The scanning sequence includes axial T1WI, T2WI, FLAIR and DWI.

2.3.2 Sequence and parameters for fMRI of DMN in resting state:

The subjects are told to lie down and rest themselves with their eyes closed, and suggested to clear their mind and think about nothing. Siemens ep2d_BOLD fMRI sequence: TR/TE: 3000ms/30ms, a 64*64 matrix; 5mm thick; 0.5mm spacing; 36 layers and a 320*320 view, 140 volumes. High-definition T1 3D-MPRAGE sequence: TR/TE 1950ms/2.30ms, TI 900ms, a 248*256 matrix; 1mm thick; no spacing, a 244*252 view and a seven-minute scanning.

2.4 Data processing after fMRI of the cases in resting state

2.4.1 Pre-processing:

First Mricron is used for DICOM Data Conversion and then SPM8 is applied to pre-process the data. The major procedures in pre-processing include: first, slice the time of and realign the EPI image of every subject and remove those data with 3DPAN over 1.5mm or 3D Rotation over 1.5°. Second, remove TR in the first 10 time points of resting state data. Next, resign, co-register, normalize and smooth data. This experiment found out no subjects' realignment goes beyond the normal range.

2.4.2 Take PCC/pC (BA23/31/7) for seed point connectivity analysis:

The DMN is often selected as a default network seed point because PCC/pC (BA23/31/7) is found connected to other areas of DMN. Then, a WFU_PickAtlas tool is used to generate seed points and then samples are recollected. This experiment found that the data matches these samples. Next, REST is used for statistical analysis, drawing the average value of PCC/pC time sequence, analyzing the time sequence with other voxels in the brain and charting the Z value of every subject after Fisher Z conversion; single sample t-tests are conducted to the mild and moderate depression group respectively, with significant threshold value set as $P<0.001$ and voxel cluster≥6 voxels (adjusted threshold value is set according to AlphaSim); then a comparison and two-sample t-test are conducted between the groups, with significant threshold value set as $P<0.01$ and cluster size ≥20 voxels (adjusted threshold value is set according to AlphaSim). Then the BrainNet Viewer is used to produce a 3D image, and xjview to identify the brain areas with abnormal functional connection.

2.5. Statistical processing

The statistical threshold is set as $P<0.01$ to make it statiscally significant. two-sample t-test is used to conduct statistical comparison between the insomniac group and the healthy control group in terms of age, PSQI, HAMD, and DMN.

3. Result

3.1 The Comparison of the Clinical Material of PSQI and HAMD of Depressive Insomniac Group with that of HC Group

3.1.1 See the comparison between Depressive Insomniac Group and HC Group on age, PSQI and HAMD in Table 1.

3.1.2 See the comparison between Mildly Depressive insomniac Group and Moderately Depressive insomniac Group on HAMD in Table 2.

Table 1. The Comparison between Depressive Insomniac Group and HC Group on age, PSQI and HAMD

	Healthy Control Group	Depressive Insomniac Group	Value t	*p*
Case Number	40	40		
Gender	28/12(female/male)	28/12(female/male)		
Age	36.15±8.61	39.36±8.53	-1.630	0.107
PSQI	2.52±1.41	12.72±3.97	-15.198	0.000
HAMD	1.93±1.91	15.53±3.86	-19.770	0.000

Note: When $p<0.01$, there is statistical difference.

Compared with HC Group, PSQI and HAMD of Depressive Insomniac Group are both higher and also have the statistical difference ($p<0.01$), while the two groups don't have statistical difference in age ($p>0.01$).

Table 2. The Comparison between Mildly Depressive insomniac Group and Moderately Depressive insomniac Group on HAMD

	Mildly Depressive Insomniac Group	Moderately Depressive Insomniac Group	Value t	*p*
Case Number	20	20		
HAMD	12.75±2.05	19.00±2.50	-8.258	0.000

Note: When $p<0.01$, HAMD<7 indicates normality, 7≤HAMD≤16 mild depression, while 17≤HAMD≤24 moderate depression. The comparison between the mildly depressed insomniac group and the moderately depressed insomniac group shows that there is obvious difference between the two groups' HAMD.

3.2 The fMRI of Default Mode Network in Resting State:

3.2.1 The Comparison of the Default Mode Network of Depressive Insomniac Group with that of HC Group: compared with HC Group, the following encephalic regions of the Depressive Insomniac Group have stronger functional connection with PCC/pC: bilateral superior frontal gyri and bilateral middle cingulate gyri; the following regions have weaker functional connection: left occipital lobe lingual gyrus/ parahippocampal gyrus/ fusiform gyrus, right superior temporal gyrus/temporal pole, right middle temporal gyrus/middle occipital gyrus, and left occipital lobe/middle temporal gyrus. (See Table 3, 4 and Figure 1).

Table 3. Compared with HC Group, Depressive Insomniac Group's Regions with Stronger Functional Connection with PCC/pC

	BA	clusters	MNI coordinate			t-values	*p*
			X	Y	Z		
Right superior frontal gyrus	10	52	21	54	24	5.0442	<0.01
Left superior frontal gyrus		24	-15	48	27	6.5559	<0.01
Bilateral middle cingulate gyri	23	59	3	-27	33	5.4483	<0.01

$p<0.01$, cluster size≥20voxels. Note: BA means Brodmann's compartmental location; x, y and z indicates the center coordinates of the maximum activated encephalic regions; and t value refers to the maximum activating strength of the same interested region.

Table 4. Compared with HC Group, Depressive Insomniac Group's Regions with Weaker Functional Connection with PCC/pC

	BA	clusters	MNI coordinate			t-values	*p*
			X	Y	Z		
Left occipital lobe lingual gyrus/ parahippocampal gyrus/ fusiform gyrus		30	-30	-54	-6	-5.6358	<0.01
Right superior temporal gyrus/temporal pole	22	33	51	9	-3	-4.2511	<0.01
Right middle temporal gyrus/middle occipital gyrus		47	39	-66	15	-4.7524	<0.01
Left occipital lobe/middle temporal gyrus		46	-42	-75	21	-4.7291	<0.01

$p<0.01$, cluster size≥20voxels. Note: BA means Brodmann's compartmental location; x, y and z indicates the center coordinates of the maximum activated encephalic regions; and t value refers to the maximum activating strength of the same interested region.

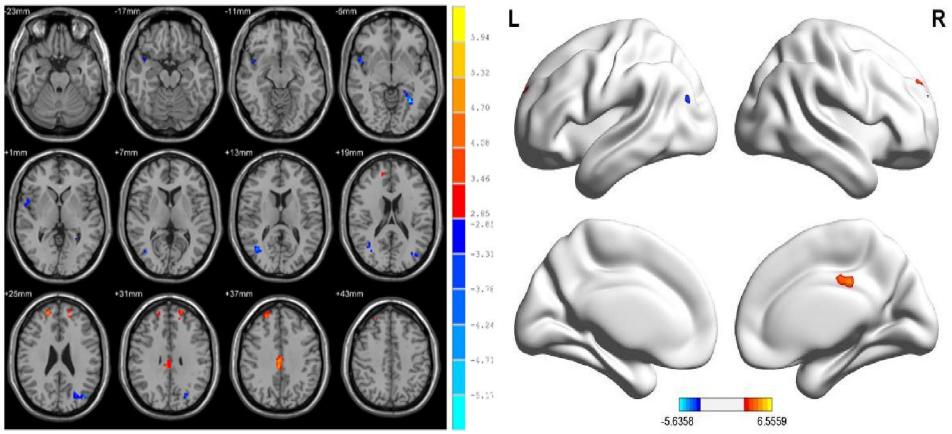

Figure 1. The brain function diagram of the PI group and PCC/pCfunctional connection, compared with the HC group. Enhanced encephalic regions of the PI group and PCC/pC functional connection: the right and the left superior frontal gyrus and the middle cingulate gyrus; decreased encephalic regions of the PI group and PCC/pC functional connection: the left occipital lobe, gyrus lingualis, the parahippocampal gyrus, the fusiform gyrus, the right gyrus temporalis superior, the temporal pole, the gyrus temporalis medius, middle occipital gyrus. The obvious threshold value is set as $p<0.01$, the cluster size≥20 voxels (with the revised threshold value set according to AlphaSim, and with the color red representing the enhanced regions, and the color blue the decreased ones.

3.2.2 The Comparison of the Default Mode Network of Mildly Depressive Insomniac Group with that of Moderately Depressive Insomniac Group: Compared with Mildly Depressive Group, the following encephalic regions of Moderately Depressive Insomniac Group have stronger functional connection with PCC/pC: right middle cingulate cortex and right frontal gyrus; the following regions have weaker functional connection: left parahippocampal gyrus. (See Table 5 and Figure 2).

Table 5: Compared with Mildly Depressive Insomniac Group, Moderately Depressive Insomniac Group's Regions with Abnormal Functional Connection with PCC/pC

Cortical region	BA	clusters	MNI coordinate			t-values	*p*
			X	Y	Z		
Left parahippocampal gyrus		69	-15	-33	-9	-5.032	<0.01
Right Middle cingulate cortex	31	22	12	-42	36	4.1171	<0.01
Right middle frontal gyrus		22	30	30	39	3.4495	<0.01

p<0.01, cluster size≥20 voxels Note: BA means Brodmann's compartmental location; x, y and z indicate the center coordinates of the maximum activated encephalic regions; and t value refers to the maximum difference of functional connection with the interested region.

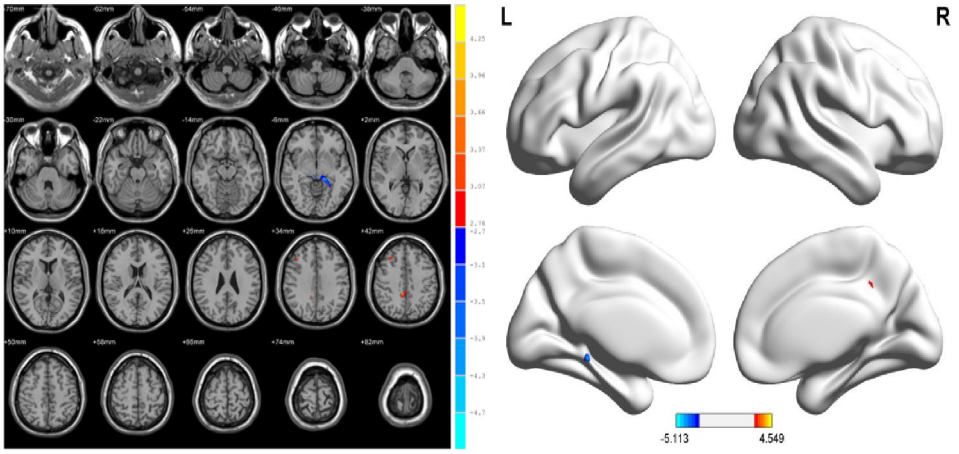

Figure 2. The enhanced and decreased brain function diagram of the PI mild depression group and PCC/pC binding, compared with the PI mild depression group and the middle depression group. Enhanced encephalic regions of the PI mild depression group and the posterior cingulate cortex (PCC/pC) functional connection: the right middle frontal gyrus and the right central cingulate gyrus. Decreased encephalic regions of the PI mild depression group and PCC/pC binding: the left parahippocampal gyrus. The obvious threshold value is set as $p<0.01$, the cluster size≥20 voxels (with the revised threshold value set according to AlphaSim, and with the color red representing the enhanced regions, and the color blue the decreased ones.

4. Discussion

4.1 A Discussion on Comparison and Contrast of Insomniacs in Depression Group and Those in HC Group in Resting State on Default Mode Network with PCC/pC (BA23/32/7) as Seed Point

According to Beck's Negative Thinking Theory[11], if an insomniac pays excessive attention to insomnia, such a negative cognitive disorder will not only lead to pre-insomniac anxiety, but will also make it more difficult for the patient to fall asleep. Beck also thinks that long-term insomnia and anxiety will trigger depression. The result of this experiment shows that compared with HC Group, Depressive Insomniac Group's bilateral superior frontal gyri and middle cingulate gyrus have stronger functional connection with PCC/pC. As an important part of the brain, prefrontal lobe is involved in the brain's integration of the inner and outer environmental information, the emotional integration and the extraction of episodic memory, but also cooperates with other encephalic regions to keep the brain's fundamental functions in the resting state. According

to fMRI, prefrontal lobe's inside and dorsal part are closely connected with self-awareness and therefore where the brain produces self-awareness and introspection. Some or all parts of the cognitive forming process of self-awareness take place in these regions and more activities here indicate a depressive insomniac's excessive self-awareness and his cognitive disorders such as abnormal emotional adjustment. As the excessive activation of middle cingulate gyrus is regarded as the symbol of severe depression in the existing research[10], Depressive Insomniac Group's enhanced functional connection with PCC/pC showed in this experiment, as middle cingulate gyrus is related to depression, keeps consistent with previous study[12].

This research shows that Depressive Insomniac's following encephalic regions have weaker functional connection with PCC/pC: left occipital lobe lingual gyrus, parahippocampalgyrus, fusiform gyrus, right temporal lobe (superior temporal gyrus, temporal pole, middle temporal gyrus) and middle occipital gyrus. As the visual center, occipital lobe is mainly in charge of processing visual information and also deals with some parts of language, action and other abstract concepts. Patients with impaired occipital lobe will have a visual disorder and also other symptoms such as memory decline and motion perception disorder. The research of Bilo L and other scholars shows that patients with asymptomatic occipital lobe epilepsy will not only have an obvious visual and space cognitive disorder, but also have weaker executive function[13]. This further demonstrates the occipital lobe's function. In this experiment, the left occipital lobe lingual gyrus has a weaker functional connection with PCC/PC, which indicates that some parts of a depressive insomniac's encephalic regions, in charge of short-term memory and social communication, become abnormal and therefore the patient may have a weaker daily social communication. Hippocampi, as well as its perimeter zone and adjacent cortex (such as temporal point, insular lobe and occipital lobe dentate gyrus), belongs to the limbic system and receives the information of frontal lobe, parietal lobe and occipital lobe. As the memory center, the limbic system is also in charge of emotional adjustment. According to the research, a healthy person with deprived sleep will also have an impaired psychomotor system, such as impaired memory, slow reaction and declining alertness[14]; as hippocampi is responsible for memory storage and enhancement, a long-term insomniac will have an obviously weaker daily declarative memory[15]. All this shows that insomnia will lead to the impairment of hippocampi, parahippocampalgyrus and amygdaloid body, and the connection between hippocampi and other regions will also be changed. During the input of memory and other information, hippocampi is also related to HPA's arousal and adjusting function. According to this research, the left parahippocampalgyrus has a weaker connection with PCC/pC, possibly because a long-term insomniac with depression is always over stressed, then HPA's hyperfunction is produced. Then the insomniac may have cognitive disorders such as memory impairment and declining executive function, and also clinical features such as declining memory, anxiety and depression adjusting disorder. All these manifestations all keep consistent with higher HAMA of Insomniac Group than that of HC Group recorded in the clinical material.

4.2 A Discussion on Comparison and Contrast of Insomniacs in the Mild Depression Group with Those in the Moderate Depression Group in a Resting State in a Default Mode Network with PCC/pC (BA23/31/7) as a Seed Point

It was discovered by Kales and other researchers that long-term insomniacs have an internal emotional mechanism, which tends to deal with the pressure from long-term insomnia and consequently puts the brain in a persistent excited state. This emotional disorder, in turn, brings about abnormal changes to the organism and its functions. When the changes appear, insomniacs pay more attention to the distressing experience associated with insomnia, which causes a vicious circle of anxious and negative emotions, and makes it harder for them to sleep. The result from this experiment shows that when compared with insomniacs in the mild depression group and those in the moderate depression group, the following encephalic regions are enhanced in the latter group with PCC/pC functional connection: the middle cingulate gyrus and the right middle frontal gyrus. The cingulate gyrus belongs to the limbic system, mainly playing a role in human cognitive control, learning reinforcement and functional regulation like pain and emotion. It is suggested by many existing research on brain function imaging that the sign of a major depressive disorder is the over activation in the middle cingulate gyrus[16], that there is an over enhanced state in the mild depressive insomniac group with PCC/pC functional connection, and that the middle cingulate gyrus belongs to the encephalic region associated with depression, and has a positive correlation with the depression degree. It is indicated by research that damage on the vigilance system and the memory function is found in long-term insomniacs[13]. In this research, the functional connection of the mild depressive insomniac group PCC/pC and the middlefrontalgyrus is enhanced, which suggests that with the deepening of depression in insomniacs, the cognitive function of the prefrontal lobe decreases

and the relatively long-term activated state of the emotional integration system increases, causing more obvious damage on the functions of relevant encephalic regions, and having a positive correlation with the depression degree.

It is indicated by results from this experiment that the following encephalic region decreases in the mild depressive insomniac group with PCC/pC functional connection: left parahippocampal gyrus, which belongs to a part of the limbic system. Structures like the hippocampi, the parahippocampal gyrus and the amygdaloid body are closely related to functions like human learning and memory[17]. Riemann[18] and many other researches analyze encephalic regions' volume changes of eight primary insomniacs and eight healthy controls by using 1.5T MRI. It is discovered that the hippocampal volume of the primary insomniacs reduces noticeably while there is no obvious change in the amygdaloid body, the anterior cingulate cortex, the orbitofrontal region and the forehead dorsolateral prefrontal region. 4.0T MRI is used by Neylan[19] to measure the CA3 area of hippocampus, and it is found out that insomnia severity is associated with the reduction of the CA3 area of hippocampus, because sleeping brings nutrition to nerves and insomnia reduces the CA3 area of hippocampus. The hippocampal volume is associated with human behavior, cognitive and executive capability, and memory which may be taken as the anatomic study for the loss of learning ability and memory after insomnia. This experiment discovered that with the increasing degree of depressive insomnia, the functional connection of parahippocampal gyrus and PCC/pC is reduced. It is also suggested that insomnia gets worse with depression deepening, and the functions of memory and cognition deteriorate observably, and that insomnia has a negative correlation with the depression degree caused by insomnia.

In short, insomniacs suffer from noticeable depressive moods, which lead to low spirits and a decline in cognitive ability such as learning, memory, vigilance and attention. Negative emotions, in turn, adversely affect the metabolism of the brain and the neutral network, and further deteriorate insomnia. Therefore, when it comes to the treatment of insomniacs, their sleeping quality should be improved; more importantly, their depressive emotional disorder should be more focused, as it treats insomnia fundamentally and may have better therapeutic effects. The magnetic resonance imaging in the resting state on the default mode network of the brain function provides objective images for clinical insomniacs with depression symptoms. It is hoped that it can provide objective and scientific images for the therapeutic evaluation of clinical pretherapy and post-treatment of insomniacs in the future.

5. Conclusion

There is abnormity in the brain default mode network of insomniacs with depressive symptoms. The depression degree of insomniacs varies. There are differences in the brain default mode network. It is suggested that there is a positive correlation between the middle cingulate gyrus and insomnia and depression, this is also shown between the activated degree of the middle frontal gyrus and insomnia and depression. There is a negative correlation between the activated degree of the parahippocampal gyrus and insomnia and depression. This research also suggested that there is a cognitive disorder and a neutral network mechanism of emotion regulation disorder among depressive insomniacs.

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