Acta Neurophysiologica

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Research Article *Volume 4 Issue 7*

Altered Brain Activity in the Frontal Hub Brain Regions of Patients with Primary Insomnia: A Resting-State Functional Magnetic Resonance Imaging Study

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Received Date: August 09, 2023; **Published Date:** September 08, 2023

Abstract

Objective: To investigate the functional connectivity of frontal hub brain regions important for primary insomnia (PI).

Materials and Methods: Enrolled 20 the patients of PI (15 females and 5 males) and 20 normal people (15 females and 5 males), matching age, sex and education in this stud, all participants were right-Handed. Each participant was administered Pittsburgh Sleep Quality Index (PSQI), Self-rating Anxiety Scale, and Self-rating Depression Scale (SDS) questionnaires for the evaluation of neuropsychological performance. Using resting-state functional magnetic resonance imaging (fMRI) and Voxal-mirrored homotopic connectivity (VMHC) to analyze the abnormal changes of functional connectivity in frontal lobe of patients with PI. The Pearson correlation test was employed to examine the correlations between the clinical rating scales and the abnormal VMHC brain area in patients.

Results: In comparison with normal peoples, abnormal functional connectivity regions were mainly concentrated in the superior frontal gyrus of orbital part (L/R), middle frontal gyrus of orbital part (L/R), inferior frontal gyrus of orbital part (L) and inferior frontal gyrus of opercular part part (L)($p < 0.05$), and abnormal functional connectivity was found in middle frontal gyrus of orbital part (GFR correction, voxel $P < 0.01$, cluster $P < 0.025$) in patients with PI. There were no significant relationship between clinical rating scales and the abnormal VMHC brain area in patients ($P>0.05$).

Conclusion: Our study identified abnormal functional connectivity, which were mainly located in the orbitofrontal gyrus and the inferior frontal gyrus of opercular part, in the frontal lobe of patients with insomnia by resting-state functional connectivity imaging. This area are related to the impairment of decision making, value judging, reward and hedonism processing emotional processing, language function, Which is more helpful to understand the abnormal neural activity mechanism in the frontal lobe of insomnia, and provide a relatively accurate brain region basis for future prevention, diagnosis and treatment.

Keywords: Primary Insomnia; Resting-State Functional Magnetic Resonance Imaging; Functional Connectivity

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; SDS: Self-Rating Depression Scale; FMRI: Functional Magnetic Resonance Imaging; VMHC: Voxal-Mirrored Homotopic Connectivity; BOLD: Blood Oxygen Level Dependent; FC: Functional Connectivity; EPI: Echo-Planar Imaging.

Introduction

PI is one of the most common sleep disorders. Insomnia is defined as dissatisfaction with the duration or quality of sleep, which can be manifested as difficultly falling asleep, easily waking up at night and/or waking up early [1], usually accompanied with daytime cognitive impairment and memory consolidation impairment during sleep [2]. The prevalence of insomnia is 6%-10%, and the incidence rate is 4% per year [3], which is significantly higher in women than in men, and the prevalence increases with age [4]. Insomnia seriously affects the mood and quality of life of patients, easily leading to negative emotions such as depression and anxiety. At present, the diagnosis of insomnia is mainly based on subjective sleep difficulties, and it is still necessary to find objective neurobiological markers. At the same time, the neuropathological mechanism of insomnia also needs to be further studied, so that we can figure out the more superior treatment methods. Functional magnetic resonance (fMRI) measurement is an indirect and non-invasive measurement of brain activity by blood oxygen level dependent (BOLD) contrast, which has the characteristics of high spatial resolution. FMRI technology provides a new imaging method for the study of neuropsychiatric diseases including insomnia [5].

Previous functional magnetic resonance imaging studies have linked insomnia disorder to cortical dysfunction. Studies have found abnormal brain activity or functional connectivity were in the prefrontal cortex, insular cortex, amygdala, precuneus, and caudate nucleus in PI, as well as abnormal functional connectivity were in the default mode network, including the anterior and posterior cingulate cortex, inferior parietal lobule, ventromedial prefrontal gyrus, posterior splenium cortex, Precuneus, and hippocampus [6]. A recent animal experiment has also shown that prefrontal dysfunction may be related to neural fatigue of locus coeruleus neurons projecting to the prefrontal cortex under chronic sleep deprivation [7]. The prefrontal cortex and its relationship with other cortex play a key role in the pattern of sleep-wake. Many functional magnetic resonance imaging (fMRI) studies of insomnia have involved the abnormalities of the frontal lobe, but the researches on the divisions of the frontal lobe are not consistent, and the interaction between the brain activities of the internal regions of the frontal lobe is also unknown. Functional connectivity (FC) methods in functional magnetic resonance imaging (fMRI) can identify the spatiotemporal association patterns of the brain at rest or while performing tasks. These association patterns are a measure of co-activation in time series of functional connectivity between anatomically distinct brain regions [8]. Voxal-mirrored homotopic connectivity (VMHC) is an RS-fMRI method that analyses synchronized activity between the two cerebral hemispheres. That is the time series correlation between each voxel in one hemisphere and its allelic voxel (in the other hemisphere) [9]. In this study, using functional connectivity and voxel-mirrored homotopic functional connectivity methods to study the abnormal brain activity changes in the frontal lobe may be helpful to study the mechanism of insomnia or find more accurate neurobiological markers related to the frontal lobe.

Materials and Methods

Subjects were recruited from the Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University. A total of 40 participants were enrolled. 20 patients with PI(5 males, 15females; mean ± standard deviation 49.10 ±11.37 years) and 20 normal peoples (5 males, 15 females; mean ± standard deviation 50 ±11.44 years)matched age, dominant hand, and gender were recruited as the control group, of those most are women(75%), this is consistent with the fact that insomnia occurs more commonly in women than in men. Patients with PI were included in this study according to the following criteria :(i) patients met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; (ii) a history of difficultly falling asleep or maintaining sleep or waking up early for at least 1 month; (iii) Pittsburgh Sleep Quality Index (PSQI)≥7; (iv) right-handed patients as assessed by the Edinburgh Handedness Scale (EHI), and (v) patients <65 years of age.

The exclusion criteria are as follows: (i) Patients with serious primary diseases, such as cancer, diseases of the heart, liver, lung, kidney, hematopoietic system, and other diseases; (ii) Medication or substance abuse, such as alcohol, nicotine, or other drugs;(iii) Patients with abnormal signals on routine T1 or T2 fluid-attenuated inversion recovery MRI; (iv) Insomnia patients with psychiatric disorders, or other sleep disorders (including hypersomnia, parasomnia, sleep-disordered breathing, sleep-related dyskinesia, or circadian rhythm sleep disorders); (v) Metallic implants in the body; (vi) Moderate body size and weight (body mass index < 18.5, body mass index > 28).

All normal peoples met the following criteria: (i) Good sleep status, PSQI score <5; (ii) No stimulant or drug use for ≥3 months before enrollment; All normal peoples met the above exclusion criteria. The purpose and benefits of the study were informed to each subject. Participants provided written informed consent. This study was approved by the Research Ethics Committee of Beijing Hospital of Traditional Chinese

Medicine, Capital Medical University (reference: 2021BL02-061-02).

Assessment of Sleep Complaints

Sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, hypnotics use and daytime dysfunction in the past month were measured by PSQI. A total scores ≥7 indicates poor sleep quality. SAS can evaluate the severity of anxiety symptoms. It contains 20 items that reflect the subjective feeling of anxiety. Each item is divided into 4 grades according to the frequency of symptoms. SDS can reflect depressive mood, physical symptoms, psychomotor behavior and psychological symptom experience. It includes 20 items and is divided into 4 grades.

MRI, Data Acquisition

A Magnetom Skyra 3.0T scanner (Siemens AG, England) was used with the subject in the supine position and head movement was controlled using foam pads. During the scan, subjects were instructed to close their eyes and remain still. Resting-state fMRI scans were performed parallel to the anterior skull base and anteroposterior symphysis, using echo-planar imaging (EPI) sequence. The scan parameters were repetition time of 3000ms, echo time of 30ms, field view of 220mm×220mm, turn Angle of 90o, slice thickness of 3.0mm. The number of slices was 40, the voxel size was 2.3mm×2.3mm×3.0mm, and the scan was interleaved. T1-weighted 3D magnetization preparation gradient echo sequence repetition time of 2300ms, echo time of 2.32ms, matrix of 256×256, field view of 240mm×240mm, flip Angle of 8o. Conventional T2-weighted images were acquired to exclude other lesions.

Analysis of Functional Magnetic Resonance Data

Using SPM8 toolkit (http://www.fil.ion.ucl.ac.uk/spm/) for image preprocessing. For each participant, the first 10 time points were discarded due to signal balancing and participant adaptation to scanning noise. To minimize the effects of head motion, we first excluded subjects with > 2 mm maximum displacement and 2° angular motion in any dimension throughout the fMRI session. Slice timing, head motion correction, and spatial normalization were performed in sequence using statistical parametric mapping (spm8) and resampled to 3mm×3mm×3mm. In order to eliminate the influence of extremely low frequency drift and physiological high frequency respiratory and cardiac noise, all data were filtered by linear trend of time course and time bandpass (bandpass frequency 0.01-0.08 Hz). The REST software was used to set the AAL (Anatomical Automatic Labeling) template 18 brain regions of frontal lobe as nodes, and the time series of the corresponding nodes were extracted for each participant, and then the Pearson correlation coefficients between the time series of all nodes were obtained to form the FC matrix of nodes. Fisher transformation was used to convert the FC matrix into Z scores. Then two-sample T test ($P<0.05$) was performed by DPABI Net software. The Pearson correlation coefficient of BOLD signals between each pair of left and right symmetrical voxels in the brain was calculated by the VMHC module of REST software, and then the correlation coefficient was converted to Z score by Fisher Z transformation.

Statistical Analysis

Two-sample t test was used for age, PSQI, SAS and SDS of the subjects using SPSS software. The statistical module of DPABI Net software was used to perform a two-sample T test on the FC matrix maps between patients and normal peoples. $p<0.05$ for functional connectivity module and $P<0.01$ for voxel and $P<0.025$ for cluster (GFR corrected) for Voxal-mirrored homotopic connectivity were considered statistically significant.

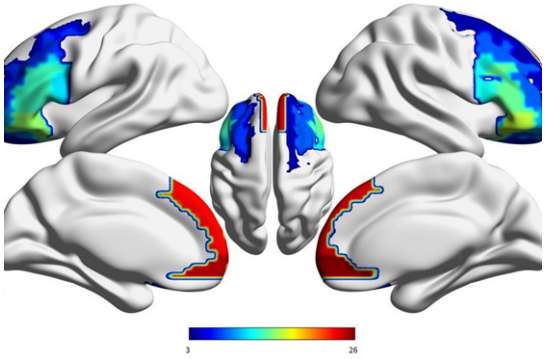
Results

Demographic and Clinical Outcomes

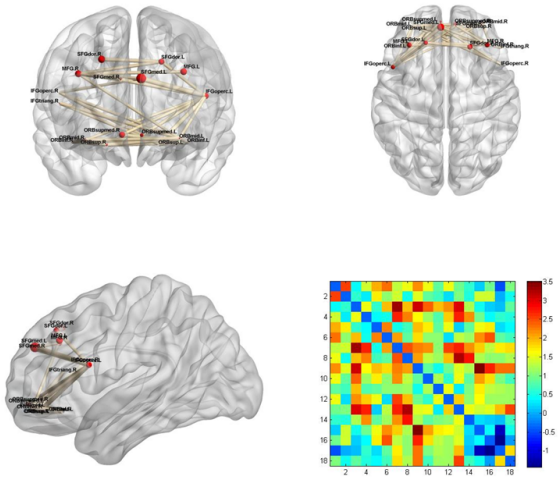
There were no significant differences in age, gender, but were significant differences in PSQI, SAS and SDS between insomnia group and normal control group (Table 1).

	PI group (n=20)	Normal control group (n=20)	P value
Gender	15F/5M	15F/5M	0.8
Education	13.06±3.87	12.11±4.05	0.492
Age	49.10 ±11.37	50 ±11.44	0.15
PSQI	15.73 ±2.70	3.05 ±1.15	0.004
SAS	40 (31-50)	31.65 ±5.50	0.001
SDS	47 (35 to 55)	35 ±7.42	0.017

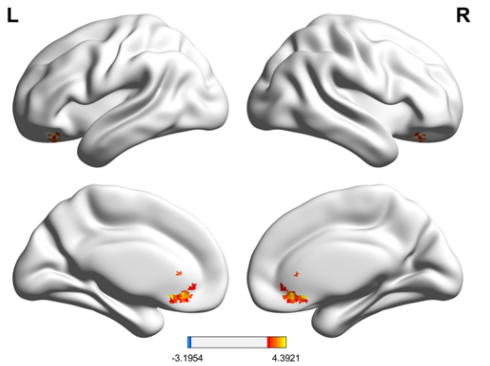
Table 1: Demographic and clinical outcomes.



Note: 18 frontal brain regions in the AAL template.



Note: Abnormal difference map of frontal functional connectivity maps between the insomniac and normal peoples, the abnormal functional connectivity areas were mainly concentrated in the superior frontal gyrus of orbital part (L/R), middle frontal gyrus of orbital part (L/R), inferior frontal gyrus of orbital part(L/R) inferior frontal gyrus of opercular part (L) ($p<0.05$)In the patients of PI .



Note: Map of mirrored homotopy abnormalities between insomniac and normal peoples, the abnormal functional connectivity area was in middle frontal gyrus of orbital part (GFR correction, voxel $P<0.01$, cluster $P<0.025$).

Functional Connectivity Results

The frontal lobe regions in the AAL template were selected as the template, a total of 18 brain regions: Frontal_Sup_L/R Frontal_Sup_Orb_L/R Frontal_Mid_L/R Frontal_Mid_Orb_L/R Frontal_Inf_Oper_L/R, Frontal_Inf_Tri_L/R, frontal_sup_orb_L /R frontal_mid_orb_L /R frontal_inf_tri_L /R, Frontal_Inf_Orb_L/R Frontal_Sup_Medial_L/R Frontal_Med_Orb_L/R (as shown in Figure 1). In the the patients of PI, we found that the abnormal functional connectivity areas were mainly concentrated in the superior frontal gyrus of orbital part (L/R), middle frontal gyrus of orbital part (L/R), inferior frontal gyrus of orbital part(L/R) inferior frontal gyrus of opercular part (L) ($p<0.05$), and the abnormal functional connectivity matrix results are shown in Figure 2. In the results of mirror homotopic connectivity, it was found that there was abnormal functional connectivity in middle frontal gyrus of orbital part (GFR correction, voxel $P<0.01$, cluster $P<0.025$), as shown in Figure 3.There were no significant relationship between clinical rating scales and the abnormal VMHC brain area in patients($P>0.05$).

Discussion

In this study, the abnormal functional connectivity within the frontal lobe was found to be concentrated in the frontal gyrus of orbital part and the inferior frontal gyrus of opercular part. The orbitofrontal gyrus has a unique role in acquiring primary and advanced sensory information and learning complex stimulus-outcome relationships and transmitting anticipatory signals of outcome, and which is considered to play an important role in learning complex stimulus-outcome relationships and transmitting expectant outcome signals [10,11]. it is also a key component in participating in value-based decision making [12]. Meantime, orbital prefrontal cortex is involved in value judgments formed in complex conditions. The prefrontal cortex is a large complex region that includes the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, orbitofrontal cortex, and frontopolar regions, which is involved in the ventral and dorsal attention network, salience network, frontoparietal executive network and default mode network [13]. The prominent clinical manifestations of disease occurring in the prefrontal area are psychiatric symptoms [14].

This area has many connections with the thalamus, striatum and hypothalamic autonomic nerve center. The prefrontal cortex also is known as visceral motor cortex, which can cause synchronous changes in respiratory, metabolic and cardiovascular functions [15]. For, example, Study show that stimulating the orbital gyrus of monkeys can reduce respiration, blood pressure and gastric peristalsis, and inhibit movement. Patients with insomnia are often accompanied by abnormal heart rate or digestive dysfunction. The ventromedial prefrontal lobe includes the ventral part of the medial prefrontal cortex and the medial part of the orbital surface ,The ventromedial and lateral prefrontal cortex as well as the orbital prefrontal cortex are to participate jointly the formation of value judgments under complex conditions. Orbitofrontal cortex usually encodes informations of the characteristics or identity of stimuli, such as food, odors, trinkets and so on. Studies have shown that insomniac does differ between the normal people on questions related to “wants” and “likes” which are two main distinguishable dimensions of reward and hedonism [16]. These findings suggest deficits in hedonism and reward processing in insomnia, nevertheless the orbitofrontal cortex is closely associated with hedonic assessment. The abnormal orbitofrontal functional connectivity in patients with insomnia indicate that participants have abnormal value judgment of things, which then affect the hedonic experience and abnormal reward processing [17].

Insomnia is associated with emotional regulation, and the risk of insomnia is associated with adverse childhood experiences, for instance, recent trauma, and major life events, such as the death or serious illness of relative or friend. Incidents of physical, sexual or emotional violence. Experiencing poor sleep in the face of stressful situations is known as “sleep reactivity.” People with high sleep reactivity are also more likely to develop depression and anxiety disorders [18]. The orbitofrontal cortex has been implicated in the down regulation and reappraisal of emotional distress. The orbitofrontal cortex is also a major part of limbic network, which plays a central role in cognitive and emotional processing, including conflict monitoring, emotional arousal, and attentional control in motivation and emotion regulation. Previous studies have shown that patients with insomnia have reduced functional network connectivity in the prefrontal lobe, and the complexity of brain network is significantly increased after sedative and hypnotic drug treatment [19]. Patients with insomnia showed stronger activation of the precentral gyrus and prefrontal cortex in response to sleep-related pictures, while this enhanced response was attenuated after cognitive behavioral therapy [20]. Studys based on fMRI showed spontaneous neural activity or disrupted functional connectivity in the insula, prefrontal and precuneus [13]. People with lower gray matter density in parts of the orbitofrontal cortex are prone to early morning arousal, fragmented sleep, and poor sleep quality. People with high gray matter density in the orbitofrontal cortex indicates sleep longer [21], and some sduies have found that sleep quality and duration correlate with fractional anisotropy and mean diffusivity of white matter in the anterior cingulate, orbitofrontal and insular regions, and the caudate. The study of function connective analysis also include impaired connectivity of the orbitofrontal-anterior

insula and anterior cingulate cortex in insomnia patients [22]. In this study, PI have significantly abnormal anxiety and depression emotional disorders contrasted to HC, which may be mediated by orbitofrontal cortex dysfunction in emotion regulation.

In the results of mirror homotopic connectivity, we also found that there was abnormal functional connectivity in middle frontal gyrus of orbital part. The middle frontal gyrus is involved in frontal parietal attention network and associative memory function [23]. During REM sleep, there are significant beta and θ oscillations in the middle frontal gyrus and suggest that this region may play a role in regulation of memory consolidation. In addition, the middle frontal gyrus belongs to the dorsolateral prefrontal cortex, which is involved in alertness, attention, and higher-order cognitive processes and all of which are disrupted in insomnia patients [24]. Therefore, the dysfunction of the middle frontal gyrus in PI patients may also be related to abnormal memory consolidation and impaired cognitive function. Previous studies have found that PI has decrease in the volume of gray matter in the middle frontal gyrus. Broca's gyrus includes the inferior frontal gyrus of opercular part region [25]. Since the production and development of language are closely related to hand move function, the dominant hemisphere of right-handedness is the left hemisphere, in the study, the dyfunction connectivity was found in the left hemisphere, this maybe signifies the dysfunction of memory and impaired cognitive and language function in PI. There are some deficiencies in our study, the study use two different kinds of data analysis tools. We hope to increase the sample size in the future. Moreover, the functional connectivity method only studies the abnormalities of the internal brain areas of the frontal lobe, and ignores the effects of other brain areas on the other lobe. In this study, the influencing factors of some patients who daily use of hypnotics were not excluded.

Conclusion

Frontal gyrus of orbital part and inferior frontal gyrus of opercular part are related to the impairment of decision making, value judging, reward and hedonism processing emotional processing, language function in patients with insomnia. This study is more helpful to reveal the neuropathological mechanism of patients with insomnia and to select more advantageous treatment methods for patients.

Funding

This research has been funded through Beijing Municipal Administration of Hospitals Incubating Program, code: PZ2020014.

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