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ORIGINAL RESEARCH

Abnormalities of thalamus volume and resting state functional connectivity in primary insomnia patients

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Abstract

Primary insomnia (PI) is associated with deteriorating attention, memory, physical and mood complaints. Based on the extensive literature demonstrating the critical roles of the thalamus in sleep regulation, we hypothesized that insomnia would be associated with functional and structural changes of the thalamus. This information is needed to better understand the neural mechanisms of insomnia, and would be useful for informing future attempts to alleviate or treat insomnia symptoms. Twenty-seven PI patients and 39 matched healthy controls were included in the present study. Subcortical volume and resting state functional connectivity (RSFC) of thalamus were compared between groups, and the relationships between neuroimaging differences and clinical features, including the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index Scale (ISI), the Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS), also be explored. Compared with the control group, the PI group showed significantly reduced volume of thalamus. In addition, several brain regions showed reduced RSFC with thalamus in PI patients, such as anterior cingulate cortex (ACC), orbitofrontal cortex, hippocampus, caudate and putamen. Correlation analyses revealed that, several of these RSFC patterns were negatively correlated with PSQI score among PI patients, including thalamic connections with the putamen, caudate, hippocampus. Negative correlation was also observed between the RSFC strength of right thalamus–right ACC and SDS score in PI patients. This work demonstrates the structural and functional abnormalities of the thalamus in PI patients that were associated with key clinical features of insomnia. These data further highlight the important role of the thalamus in sleep and PI.

Keywords Insomnia · Thalamus · Resting state functional connectivity · Pittsburgh sleep quality index

Introduction

Primary insomnia is defined by difficulties in falling asleep, maintaining sleep or early morning awakening for at least 1 month that cannot be attributed to medical, psychiatric or environmental factors (Ancoli-Israel and Roth 1999; Kyle et al. 2010a). A series of symptoms has been associated with primary insomnia, such as deteriorating attention, memory decline, and mood disturbances (Fortier-Brochu et al. 2012; Kyle et al. 2010b; Ma et al. 2015). Unfortunately, neurobiological mechanisms underlying primary insomnia have remained enigmatic, hampering the development of effective treatments. Accordingly, there is an urgent need to determine the neural mechanisms of insomnia, which would inform future attempts to alleviate or treat insomnia symptoms.

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Previous studies have demonstrated that thalamic neurons are associated with the generation of sleep spindles (Steriade et al. 1985) and the regulation of sleep and wakefulness (Saper et al. 2005). In addition, the thalamus selects information to be projected to the cortex while the cortex is asleep to protect sleep from external perturbations (Del Felice et al. 2012). Patients with degenerative, vascular and surgical lesions of the thalamus have serious insomnia and isolated suppression of spindle waves (Bricolo 1967; Schott et al. 1972; Lugaresi et al. 1986). Taken together, these findings demonstrate that the thalamus plays a crucial role in diverse sleep related physiological phenomenon and that thalamus dysfunction might contribute to the neurobiological mechanisms underlying insomnia.

Several prior neuroimaging studies have investigated functional or structural brain changes in primary insomnia. Previous structural studies mainly typically employed voxel-based morphometry (VBM) revealed reduced grey matter volume/density in several brain regions, e.g., orbitofrontal cortex (OFC) (Altena et al. 2010), anterior cingulate cortex (ACC) (Winkelman et al. 2013), and hippocampus (Riemann et al. 2007). However, researchers have obtained contradictory results for the thalamus, some see decreases whereas others find no significant differences (Altena et al. 2010; Winkelman et al. 2013; Riemann et al. 2007; Koo et al. 2017). The conflicting structural findings may be due to the subjects included in the studies, e.g., sample size, varying age ranges and gender ratios, etc. Therefore, in the current study, we enrolled a larger sample of patients with primary insomnia to investigate thalamus volume differences between primary insomnia patients and matched controls using surface-based morphometry, which had been proved to be more sensitive than VBM.

On the other hand, to our knowledge, there is no examinations thalamic resting state functional connectivity (RSFC) in primary insomnia thus far. This is important because the thalamus is not a unitary structure, but is strongly interconnected with the neocortex via radiating thalamic neuronal fibers (Sherman 2016). Recently, RSFC have allowed whole-brain analyses to identify the temporal correlation across brain regions. Consequently, we employed seed-based RSFC analysis to investigate the different thalamocortical connections between primary insomnia patients and healthy matched controls with normal sleep behavior. We hypothesized that thalamic volume and thalamocortical FC would be different between patients with primary insomnia and healthy controls.

Methods and materials

Ethics statement

This study was approved by the Ethics Committee of medical research in First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China. All primary insomnia patients were recruited from the First Affiliated Hospital of Baotou Medical College. Informed written contents were obtained from all participants.

Participants

Twenty-seven right-handed adults with primary insomnia (9 males, 18 females; mean ± standard deviation age = 42.11 ± 9.39 years) and thirty-nine age-, gender-, education-matched controls with healthy sleep patterns (16 males, 23 females; mean ± standard deviation age = 41.08 ± 9.17 years) were included in the present study. Inclusion criteria for primary insomnia patients were as follows: (1) the primary insomnia patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (Cooper 2001); (2) at least 1 month complaining of difficulty falling asleep, maintaining sleep or early awakening; (3) absence of other sleep disorders such as parasomnia, hypersomnia, sleep-related movement disorder, or other psychiatric disorders; (4) right-handedness as measured by the Edinburgh Handedness Inventory (Oldfield 1971). All matched controls satisfied the following criteria: (1) good sleep quality and good sleep onset and/or maintenance, lower score of Pittsburgh Sleep Quality Index (PSQI) than five (Buysse et al. 1989); (2) at least 3 months without consumption of any stimulants, medications, cigarettes, alcohol or coffee before the current study; (3) right-handedness.

Exclusion criteria for all participants were as follows: (1) pregnancy, currently nursing or menstruating (for females); (2) insomnia caused by organic disease or severe mental disease secondary to depression or generalized anxiety; (3) history of neurological or other physical diseases such as respiratory, cardiac, renal, hepatic and endocrinal diseases; (4) any medication that might affect sleep or cerebral function within 2 weeks; (5) addiction disorder.

Approximately 20–40% of people with insomnia experiencing a co-occurring psychiatric illness, anxiety and depression are the most common comorbidity with insomnia(Ford and Kamerow 2016). Insomnia is a strong predictive risk factor for the development of depression and anxiety disorders (Batterham et al. 2012; Neckelmann et al. 2002). Meanwhile, insomnia increases depression risk (Breslau et al. 1996) complicates depression treatment, and increases suicide risk in depressed patients. All participants were administered the Pittsburgh Sleep Quality Index (PSQI), the Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) to assess sleep patterns and mental status prior to MRI scanning. In addition, primary insomnia patients also completed the Insomnia Severity Index Scale (ISI).

MRI data acquisition

The participants underwent MRI scanning after completing all the questionnaires. Meanwhile, MRI scanning was carried out by a professional doctor to control the MRI acquisition time. The experiment was implemented on a 3 T Philips scanner (Achieva; Philips Medical Systems, Best, The Netherlands) at the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China. Foam pads were used, along with an eight-channel phase-array head coil to restrict head motion and diminish scanner noise. The scanning session for each participant included high-resolution structural image and resting-state functional images. Structural image were obtained using a volumetric three-dimensional spoiled gradient echo sequence with the following parameters: repetition time (TR) = 8.5 ms; echo time (TE) = 3.4 ms; flip angle (FA) = 12°;in-plane matrix size = 240×240; slices = 140; field of view (FOV) = 240×240mm^2; slices thickness = 1 mm; voxel size = 1mm^3. Then, resting-state functional images were acquired with an echo planar-imaging sequence with parameters: TR = 2000 ms; TE = 30 ms; FA = 90°; FOV = 240 × 240mm^2; data matrix =64 × 64; slices = 30; slice thickness = 5 mm and without slice gap; total volumes = 185. Subjects were recommended to keep their eyes closed, keep awake and not to think about anything during the functional scan. Subsequently, participants were asked how they felt during the scan to eliminate the effect of anxiety on the resting state of fMRI.

Structural MRI data analysis

Subcortical volumetric segmentation of the whole brain on structural image was performed by FreeSurfer 5.0 software (http://surfer.nmr.mgh.harvard.edu) as described in our previous studies (Yuan et al. 2016; Cai et al. 2016; Li et al. 2015; Yuan et al. 2013). The processing procedure consisted of (1) brain extraction; (2) automated Talairach transformation; (3) segmentation of the subcortical white matter and deep gray matter volumetric structures; (4) intensity normalization; (5) tessellation of the gray matter/white matter boundary; (6) automated topology correction;(7) surface deformation; (8) registration of the subjects' brains to a common spherical atlas.

The volumes of the bilateral thalamus structures and intracranial volume (ICV) were extracted and imported into SPSS 20.0 software (SPSS Statistics, IBM, Armonk, NY). For each structure, a general linear model was accorded with volume as the dependent variable, diagnosis (primary insomnia patients and healthy controls) as categorical predictors, ICV as covariates. Bonferroni procedure was employed to correct for multiple comparisons. All tests were 2-tailed, and p values of less than 0.025 ($p < 0.05/2$) were considered significant.

Resting-state MRI data analysis

For each participant's resting-state functional image, the preprocessing procedure was completed by Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/) and FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/). The data preprocessing session included core image processing and denoising. Core image processing consists of: (1) discarded the first 5 volumes; (2) slice timing correction; (3) rigid-body head motion correction (3-mm displacements and 3° rotations); (4) obliquity transformed to the structural image; (5) affine co-registration to the skull-stripped structural image; (6) standard spatial transform to the MNI152 template; (7) spatial smoothing (4-mm full width at half maximum); (8) intensity normalization to a whole-brain median of 1000. Previous studies suggested that nuisance regression and bandpass filtering alone are often inadequate to control head motion induced noise (Patel et al. 2014; Power et al. 2012). Accordingly, wavelet despiking was applied in the present study for the resting-state functional connectivity analyses (Patel et al. 2014). Denoising steps included the following steps: (9) time series despiking (wavelet domain); (10) nuisance signal regression including the 6 motion parameters estimated in (3), their first order temporal derivatives, white matter and ventricular cerebrospinal fluid (CSF) signal (14-parameters regression); (11) a temporal Fourier filter (0.009–0.10 Hz). We chose the regions of bilateral thalamus, which were labeled using the Harvard-subcortical structural atlas (http://www.cma.mgh.harvard.edu/), as our seeds in the functional connectivity analysis. The averaged resting-state fMRI time series for all voxels within each region at each time point in the preprocessed data was extracted as reference time series for each region of interest (ROI). To investigate the strength of resting state functional connectivity between average time series of each ROI and the time series of each voxel within the brain, Pearson correlation was carried out respectively for left thalamus and right thalamus. A Fisher's r-to-z transformation was employed to account for the non-normality of Pearson correlations (Berry and Mielke 2000). Permutation-based non-parametric testing with 5000 random permutations was used to investigate the group comparisons of functional connectivity. To control for multiple comparisons, threshold-free cluster-enhancement (TFCE) was used, and the significance threshold was set to $p < 0.05$, familywise-error (FWE) corrected in line with current reporting guidelines (Eklund et al. 2016).

Correlation analysis

Pearson correlation was applied between the absolute volumes of bilateral thalamus and clinical variables (i.e. PSQI, ISI, SAS, SDS). All tests were 2-tailed, to correct for multiple comparisons of correlation analysis, the Bonferroni correction

was also used in this part ($p < 0.00625$ (0.05/8)). Similarly, Pearson analysis was implemented to investigate the association between the RSFC and clinical variables in the primary insomnia patients. Bonferroni correction was conducted to examine the Pearson correlations ($p < 0.05/40$ (0.00125)).

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of all participants in the current study are shown in Table 1. There were no significant differences in gender, age, education (all $p > 0.05$) between the primary insomnia and control groups. However, the primary insomnia patients showed higher PSQI, SDS and SAS scores than controls, as expected in Table 1.

Subcortical volume results

The primary insomnia patients showed significantly lower ICV than healthy controls. Further analysis revealed that primary insomnia patients showed significantly lower volume in both the left and the right thalamus ($p < 0.001$, Bonferroni correction) relative to matched controls, after controlling for ICV as the covariates (Table 2, Fig. 1).

Functional connectivity results

One sample t-tests result showed that, for both groups, the left and right thalamus have significant positive RSFC with several regions, such as ACC, OFC, caudate, putamen, hippocampus (Fig. 2, FWE corrected, $p < 0.05$). Next, we investigated group differences in thalamic RSFC between the patients and controls. Two-sample t-tests revealed significantly lower RSFC between left thalamus and several regions in primary insomnia group relative to the control group (Fig. 3a, FWE corrected, $p < 0.05$), i.e., left caudate, left putamen, bilateral ACC and OFC. In addition, the right thalamus exhibited decreased RSFC with left caudate, left putamen, left hippocampus and bilateral ACC and OFC in primary insomnia group (Fig. 3b, FWE corrected, $p < 0.05$).

Table 1 Demographics and clinical characteristics of all participants

Clinical details	Insomnia($N = 27$) Mean ± SD (range)	Control($N = 39$) Mean ± SD (range)	p value
Gender(M/F)	9/18	16/23	0.526[a]
Age(years)	42.11±9.39(18–58)	41.08±9.17(31–60)	0.526[a]
Education(years)	12.51±3.72(9–18)	13.21±2.89(9–18)	0.402[b]
PSQI	13.67±3.50(6–20)	3.54±1.37(1–e5)	<0.001[b]*
SAS	53.15±9.94(28–73)	27.20±5.18(15–30)	<0.001[b]*
SDS	46.08±9.43(23–63)	12.97±7.87(1–30)	<0.001[b]*
ISI	17.30±6.44(2–28)	–	–

Values = mean±standard deviation(SD). * $p < 0.05$. N = Participants

a = The p-value was obtained using a chi-square test

b = The p-value was obtained using a two-sided two-sample t-test

PSQI = Pittsburgh Sleep Quality Index

SAS = Self-Rating Anxiety Scale

SDS = Self-Rating Depression Scale

ISI = Insomnia Severity Index Scale

Correlation analysis results

In primary insomnia patients, no significant correlation was found between bilateral thalamus volume and clinical variables (i.e. PSQI, ISI, SAS, SDS). The RSFC of the left thalamus and the left putamen (Fig. 3c, $p = 0.0144$), right thalamus and left caudate (Fig. 3d, $p = 0.0174$), right thalamus and left hippocampus (Fig. 3d, $p = 0.0286$) in primary insomnia patients showed negative correlation with the total score of the PSQI. Similarly, the negative correlation was also observed between right thalamus–right ACC RSFC and SDS score (Fig. 3c, $p = 0.0190$) in primary insomnia patients. This is an exploratory analysis section since it's not strictly corrected for.

Discussion

Primary insomnia is a prevalent disorder that affects 6–20% of the general population and is associated with impaired function and an array of physiological dysfunctions, such as anxiety and depression (Fernandez-Mendoza et al. 2012; Morin et al. 2006; Ohayon 2002; Roth et al. 2011; Sivertsen et al. 2009). Based on the crucial roles of thalamus in sleep rhythms, it is important to identify possible morphological changes and connectivity abnormities of the thalamus in primary insomnia. The major findings of this study are as follows: (1) primary insomnia patients had significantly lower thalamus volume relative to matched controls; (2) the left caudate, left putamen, left hippocampus, ACC and OFC showed decreased functional connectivity with the thalamus in primary insomnia patients relative to matched controls; (3) the RSFC of the thalamus with putamen, caudate and hippocampus were associated with PSQI and the connectivity of thalamus with ACC were associated with SDS in primary insomnia patients. Our findings implicate the thalamus in the neurobiological mechanisms underlying primary insomnia, specifically for sleep quality and depression.

Reduced volume of bilateral thalamus in primary insomnia patients

There were many previous studies of the gray volume of the brain in primary insomnia patients, but few studies have found

Table 2 Subcortical volumes of bilateral thalamus comparison between primary insomnia patients and healthy controls

Region	Subcortical Volume (mean±SD)		T/F Value	p Value
	Insomnia(N = 27)	Control(*N* = 39)		
ICV	891,253.91 ±150,522.75	1,138,305.86 ±272,496.74	11.435	0.001*
Left Thalamus	6053.26±836.13	7448.49±796.72	28.812	<0.001*
Right Thalamus	5740.93±861.49	7487.64±733.45	49.596	<0.001*

Values = mean ± standard deviation(SD). * $p < 0.025$

ICV = intracranial volume

Bonferroni procedure was employed to correct for multiple comparisons. All tests were 2-tailed, and p values of less than 0.025 ($p < 0.05/2$) were considered significant

the difference in the thalamus volume between primary insomnia patients and healthy controls (Altena et al. 2010; Winkelman et al. 2013; Riemann et al. 2007; Koo et al. 2017). In this study, we have demonstrated smaller volumes of the bilateral thalamus in primary insomnia patients (Fig. 1). Furthermore, potential confounders such as ICV did not account for differences between patients with primary insomnia and good sleeper groups, and all patients were medication free and cautiously screened to be free of present and lifetime psychiatric disease. The hyperarousal theory is the most widely accepted model of the pathophysiology of primary insomnia, which indicates that global increases in cortical and physiological arousal across the sleep–wake cycle would reduce difficulties with initiating and/or maintaining sleep (Perlis et al. 1997). Mounting evidence demonstrated that thalamus plays an indispensable role in arousal function (Coenen et al. 2012). Sleep onset and maintenance is regulated through a delicate balance of inhibition and activation of the thalamus (Altena et al. 2016; Pace-Schott and Hobson 2002). Taken together, the decreased volume of bilateral thalamus provided morphometric evidence for the role of thalamus in primary insomnia patients.

Reduced RSFC of thalamus and ACC in primary insomnia patients

We discovered that, compared to good sleepers, primary insomnia patients showed decreased RSFC between thalamus and ACC. Notably, decreased left thalamus-right ACC RSFC was correlated with SDS scores, indicating a possible link between the RSFC of thalamus-ACC and depression, which might aid in elucidating the biobehavioral marker for depression vulnerability. Moreover, the ACC is a core brain area of the emotional processing brain network (Altena et al. 2016; Bush et al. 2000). Abnormalities in the ACC in emotion disorders have been demonstrated using functional neuroimaging (Drevets et al. 2008), and deep brain stimulation of the ACC may lead to remission of depressive symptoms (Holtzheimer and Mayberg 2011).The increased volume of ACC and reduced RSFC may relate to emotional dysregulation in primary insomnia (Baglioni et al. 2010). In summary, these data may highlight a neurobiological substrate of impaired emotional processing in primary insomnia patients. Future longitudinal studies will be needed to identify whether this is a predisposing factor for insomnia or if it is a consequence of long-term sleep deprivation.

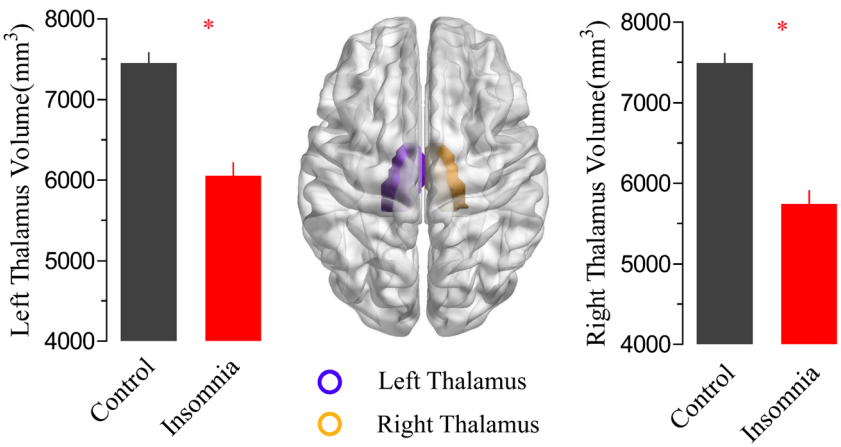

Fig. 1 Subcortical volume results. Relative to healthy controls, primary insomnia patients showed lower volume in bilateral thalamus (left: F = 28.812, $p < 0.001$; right: F = 49.596, $p < 0.001$, Bonferroni-corrected), after controlling for intracranial volume (ICV)

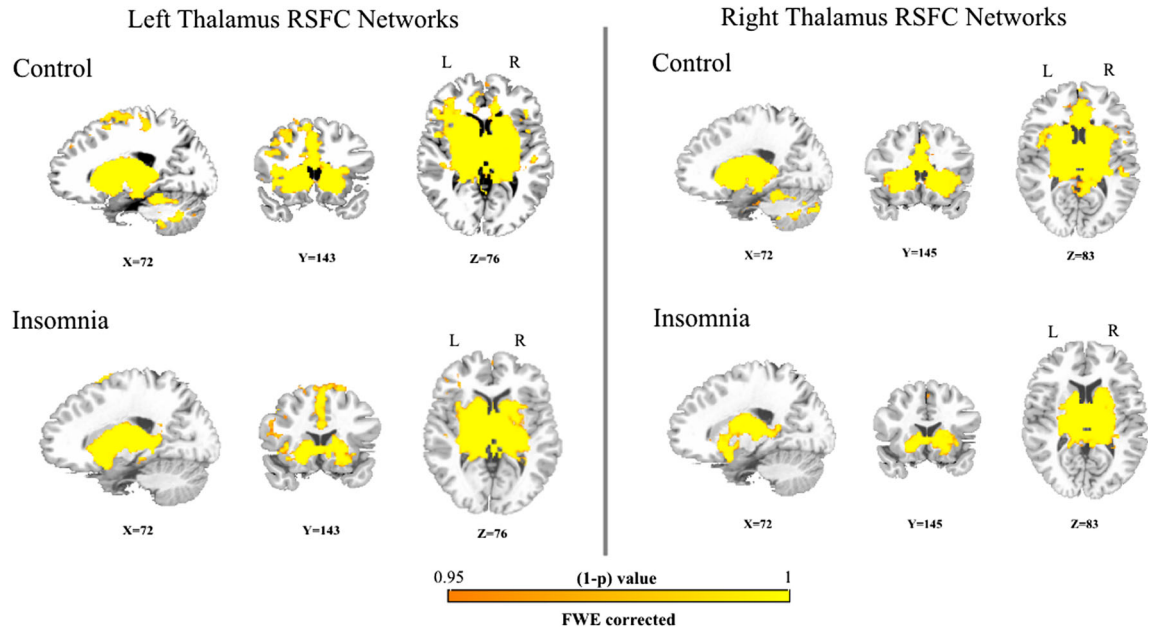

Fig. 2 Thalamus resting-state functional connectivity (RSFC) networks. RSFC analysis generated similar thalamus networks in primary insomnia patients and controls with good sleep quality, such as anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), caudate, putamen, hippocampus

Reduced RSFC of thalamus and OFC in primary insomnia patients

It has been validated that the OFC plays an essential role in decision-making, and problem-solving abilities (Bechara et al. 2000). In addition, because the thalamus transmit salient sensory information to the prefrontal cortex (Bruno and Sakmann 2006), it is not surprising that the thalamus has been implicated in variety of affective and cognitive functions, e.g. decision-making, and other goal-directed behaviors (Dichter et al. 2012). In particular, decision-making is hypersensitive to sleep deprivation (Venkatraman et al. 2007). Patients with insomnia are slower than good sleeper on a vigilance task, but only if decision-making is required (Altena et al. 2008).

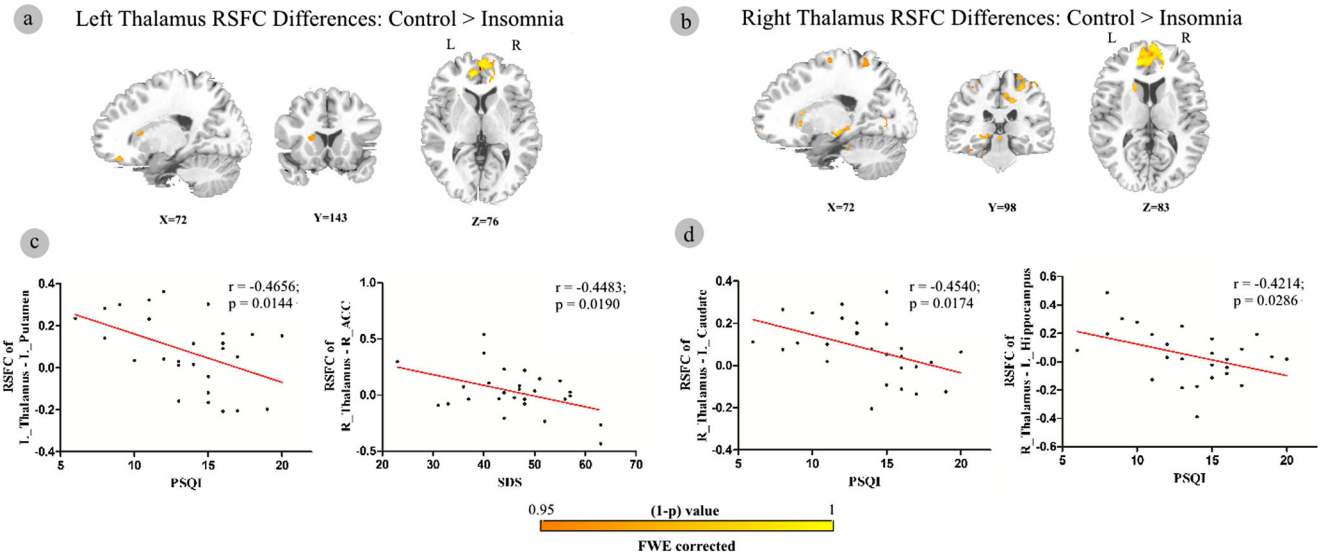

Fig. 3 Thalamic RSFC network patterns and association with insomnia-related clinical variables. We revealed significantly lower resting-state functional connectivity (RSFC) between left thalamus and several regions in the primary insomnia group (Fig. 3a, FWE corrected, $p < 0.05$), i.e., left caudate, left putamen, bilateral anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). In addition, the right thalamus exhibited decreased RSFC with left caudate, left putamen, left hippocampus and bilateral ACC and OFC in primary insomnia group (Fig. 3b, FWE corrected, $p < 0.05$). The RSFC of the left thalamus and the left putamen (Fig. 3c, $p = 0.0144$), right thalamus and left caudate (Fig. 3d, $p = 0.0174$), right thalamus and left hippocampus (Fig. 3d, $p = 0.0286$) in primary insomnia patients showed a negative correlation with the total score of the Pittsburgh Sleep Quality Index (PSQI). Similarly, a negative correlation was also observed between right thalamus–right ACC RSFC and Self-Rating Depression Scale (SDS) score (Fig. 3c, $p = 0.0190$) in primary insomnia patients

Deficits of decision-making might contribute to the lack of problem-solving abilities typical of insomnia (Wicklow and Espie 2000). Therefore, the decreased RSFC of thalamus-OFC may be associated with a decline in cognitive function of the primary insomnia patients.

Reduced RSFC of thalamus and striatum in primary insomnia patients

Findings have established that the dorsal striatum, consisting of caudate and putamen, is a key structural element for the regulation of sleep and wakefulness and is strongly interconnected with the thalamus (Lazarus et al. 2012). All output neurons of the striatum use GABA as a neurotransmitter and have inhibitory effects on their targets. The caudate and putamen project to the external globus pallidus (GPe) which in turn projects directly or via the thalamus to the cerebral cortex (Alexander et al. 1986). Therefore, activity of layer V pyramidal neurons and interneurons in the cerebral cortex is modulated through inhibition by GABAergic GPe neurons (Qiu et al. 2010; Vetrivelan et al. 2010).

Reduced RSFC of thalamus and Hippocampus in primary insomnia patients

Recent neuropsychological and memory studies indicate that patients with primary insomnia exhibit deficits of memory formation during sleep compared to good sleepers (Backhaus et al. 2006; Nissen et al. 2006; Boutin et al. 2017). This might be related to altered RSFC between thalamus and hippocampus since hippocampal–thalamic interconnections are crucial for human memory (Aggleton et al. 2010). Animal studies have shown that short-term sleep deprivation and sleep restriction have a negative impact on hippocampal neurogenesis (Kopp et al. 2006; Guzman-Marin et al. 2005; Mirescu et al. 2006; Hairston et al. 2005). The relationships between sleep and learning have received considerable attention in recent years. Sleep fosters nocturnal memory consolidation and prolonged wakefulness prevents this consolidation (Stickgold 2005). The fact that we observed significantly lower thalamic hippocampus RSFC in primary insomnia patients relative to controls, and that these abnormal RSFC patterns correlated with poor sleep quality as assessed by the PSQI, provide further evidence of potential neurobiological mechanisms for impaired memory processes in patients with primary insomnia.

Limitations

The present study still has several limitations. First, the cross-sectional nature of this study cannot make causal conclusions about insomnia and abnormities of thalamus structure and function. Longitudinal studies should be implemented in future to assess the longer-term effects on thalamus changes in primary insomnia patients. Second, the thalamus is a very complicated brain region and has distinctive sub regions with different function, accordingly the volume abnormalities and RSFC in distinctive sub regions of thalamus in PI could be taken into considerations in the future studies.

Conclusions

Primary insomnia symptoms were characterized by reduced thalamus volume and decreased RSFC of the thalamus with multiple brain regions. The reduced thalamus volume provides morphometric evidence for the role of thalamus in primary insomnia patients. The decreased functional connectivity of the thalamus with ACC, OFC, caudate, putamen and hippocampus demonstrates the dysfunction of emotional processing, decision-making and memory in primary insomnia patients. It is hoped that our findings may shed new insights into the neural mechanisms of insomnia. This study may provide new clues for the insomnia treatment in the future.

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Compliance with ethical standards

Ethical statements Informed consent was obtained from all individual participants included in the study.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors report no biomedical financial interests or potential conflicts of interest.

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