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# Dysfunction of the NAc-mPFC circuit in insomnia disorder

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ABSTRACT

*Background:* Insomnia disorder (ID) is a prevalent sleep disorder, which seriously affects people's daily life and was found to be associated with increased frequency of sleep stage shifts. Previous findings had revealed the critical role of the nucleus accumbens (NAc) in sleep-wake transition. However, the neuroimaging studies of the NAc in patients with ID have been rare. We hypothesized that structural and functional abnormalities of the NAc would be implicated in ID.

*Methods:* Twenty-six ID patients and 36 matched healthy controls (HC) were included in the current study. The volumes and corresponding resting-state functional connectivity (RSFC) of the bilateral NAc were compared between the two groups. The abnormal RSFC in ID were then correlated with Pittsburgh Sleep Quality Index (PSQI).

*Results:* Compared with HC, ID patients showed significantly increased volume of right NAc. Several brain regions showed increased RSFC with the NAc in ID patients, such as medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), caudate and putamen. Meanwhile, the occipital gyrus and temporal gyrus showed decreased RSFC with the NAc. Additionally, the increased RSFC strength between bilateral NAc and left mPFC was significant correlated with PSQI scores in ID patients.

*Conclusion:* Dysfunctions of the NAc-mPFC circuit were found in ID patients, which were associated with sleep quality measured by PSQI. The two patterns of increase and decrease of RSFC in ID patients observed in our study may reflect the state of hyperarousal and potential impairment of cognitive function in the patients, respectively. It is hoped that our study focusing on NAc-mPFC circuits could provide new insights for the neural mechanisms of ID and potential novel therapeutic targets for treatment of ID patients.

## 1. Introduction

According to the Healthy China (2019–2030) initiative, a latest report released by a promotional committee on healthcare, the prevalence of insomnia in China in 2016 was 15%, and the number of insomniacs is increasing year by year (http://www.nhc.gov.cn/guihuaxxs/s3585u/201907/e9275fb95d5b4295be8308415d4cd1b2.shtml). In the United States, studies estimated that the rate of insomnia was 23.2% (Kessler et al., 2011). Insomnia is not only a very prevalent sleep disorder, but also has been shown to have the functional consequences of reduced productivity, increased absenteeism, and increased health care costs (Kessler et al., 2011; Sarsour et al., 2011). As an important type of sleep disorder, insomnia disorder (ID) is characterized by difficulties in falling asleep, maintaining sleep, and early morning awakening for at least 3 times per week over a period of 3 months, as well as coupling with at least one related daytime impairment (American Psychiatric Association, 2013). Unfortunately, the neurobiological mechanisms of ID have remained unclear. It is urgent to explore the neural mechanisms of insomnia, which could provide new ideas for the treatment of insomnia in the future.

Previous studies using polysomnography found that the patients with insomnia had increased frequency of sleep stage shifts (Riemann et al., 2015) and a particular vulnerability of stage N2 made higher empirical probabilities to the transition from stage N2 to the lighter sleep stage N1 or wakefulness (Wei et al., 2017). A meta- analysis investigating PSG in insomnia patients also found other anomalies such as reduced slow wave

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sleep and REM sleep (Baglioni et al., 2014). These findings indicated an abnormal sleep pattern in insomniacs, in particular in the sleep-wake transitions. Dopamine and adenosine, two important neurotransmitters involved in the regulation of sleep-wake, are both expressed on nucleus accumbens (NAc) (Oishi and Lazarus, 2017). A fact that injecting $D_2$ receptor agonist quinelorane directly into NAc increases wakefulness in rats whereas injecting $D_2$ receptor antagonist into this same region induces sleep indicates the wake-promoting function of NAc (Barik and Beaurepaire, 2005). Besides, adenosine was thought to regulate sleep by acting through the $A_1$ receptor and $A_{2A}$ receptor (Basheer et al., 2004; Huang et al., 2007). Moreover, recent studies found that optogenetic and chemogenetic activation of certain excitatory adenosine $A_{2A}$ receptor-expressing neurons in the core region of the NAc strongly induces slow-wave sleep (Oishi et al., 2017). Taken together, these animal studies aforementioned suggests that NAc is an important brain region implicated in the sleep-wake transition process. In addition, numerous human neuroimaging studies contributed to exploring the neural mechanism of insomnia disorder (Tahmasian et al., 2018). A previous study found that patients with ID showed a smaller task-elicited BOLD response than controls selectively in the head of the left caudate nucleus in a similar level of task performance, which was further associated with hyperarousal and confirmed to be predicted by the orbitofrontal gray matter volume (Stoffers et al., 2014). Another study used probabilistic tractography found that people with ID showed structural hyperconnectivity within a subnetwork that spread over frontal, parietal, temporal and subcortical regions, and the right angular gyrus is a hub of stronger structural connectivity (Wei et al., 2019). However, although great process had been made for the involvement of the striatum in reward (Yuan et al., 2016, 2017a, 2017b, 2018a, 2018b), few neuroimaging studies focused on the implication of striatum, especially the NAc, in ID patients. The phenomenon that the significant implications of the NAc in animal sleep researches and few concerns of neuroimaging studies on NAc in ID patients drives us to investigate the neuroimaging abnormalities of NAc in patients with ID.

It is worth noting that a recent model proposed that adenosine and dopamine receptors in the NAc regulate sleep-wake behavior through cortical activation (Lazarus et al., 2012). Cortical hyperarousal measured by increased beta EEG power during sleep (Fernandezmendoza et al., 2016) and greater global cerebral glucose metabolism during sleep and while awake have been observed in insomnia (Nofzinger et al., 2004). However, the implications of the circuits between the NAc and cerebral cortex in insomnia has received surprisingly little attention. Therefore, the purposes of the current study were to (a) assess the NAc volume differences between ID patients and HCs; (b) detect the RSFC differences of the bilateral NAc between the two groups; (c) estimate the correlations between neuroimaging findings with sleep quality (i.e., PSQI). We hypothesized that there are significant neuroimaging differences in NAc and NAc-cortex pathway between patients with ID and HCs.

## 2. Materials and methods

### 2.1. 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. The experimental procedure was fully explained and informed written contents were obtained from all participants.

### 2.2. Participants

26 right-handed adults with ID (8 males, 18 females; age = 41.50 ± 9.01 years) and 36 healthy controls (18 males, 18 females; age = 41.28 ± 8.65 years) participated in this study. Detailed demographic and clinical characteristics were shown in Table 1. All the patients conformed to the standard of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and had difficulties in falling/maintaining sleep or early awakening at least for 1 month. And they did not suffer from any other psychiatric disorders and sleep disorders including hypersomnia, parasomnia, circadian rhythm sleep disorder, sleep-related movement disorder, and sleep-related breathing disorder. Also, no psychoactive medications were used at least 4 weeks prior to the study and during the whole procedure. The following criteria were used to screen healthy controls: (a) the total score of PSQI < 5, indicating in general a good sleep quality (Buysse et al., 1989); (b) at least 3 months without consumption of any stimulants, alcohol, coffee or cigarettes before the current study; (c) no history of psychiatric or neurologic diseases. In addition, assessing with the Edinburgh Handedness Inventory, all the participants were right handed (Oldfield, 1971).

**Table 1**
Demographic and clinical characteristics of all participants.

| Group | ID patient(n = 26) | Healthy control(n = 36) | $t/\chi^2$ | p-value |
|---|---|---|---|---|
| Age (years) | 41.50 ± 9.01 | 41.28 ± 8.65 | 0.098 | 0.922 |
| Gender (M/F) | 8/18 | 18/18 | 2.293[a] | 0.130 |
| Education (years) | 9.65 ± 3.73 | 13.11 ± 3.15 | −3.946 | < 0.001 |
| PSQI | 13.62 ± 3.56 | 3.89 ± 1.56 | 13.064 | < 0.001 |
| SAS | 53.04 ± 10.12 | 27.65 ± 5.29 | 11.691 | < 0.001 |
| SDS | 46.00 ± 9.61 | 15.31 ± 8.19 | 13.533 | < 0.001 |

Data are mean ± standard deviation (SD).
*PSQI* = Pittsburgh Sleep Quality Index.
*SAS* = Self-Rating Anxiety Scale, *SDS* = Self-Rating Depression Scale.

The following exclusion criteria were applied for all participants: (1) ID caused by organic disease or severe mental disease secondary to depression or generalized anxiety; (2) history of neurological or other physical diseases such ascardiac, hepatic, renal, endocrinal and respiratory diseases; (3) addiction disorder (including substance addictions and behavioral addiction); (4) any medication that might affect sleep or cerebral function (e.g. hypnotics) within 4 weeks before the scans; (5) women who were pregnant, nursing, or menstruating.

All participants in this study were required to complete the PSQI to assess sleep patterns prior to the MRI scanning. The participants were also asked to fill in the Self-Rating Anxiety Scale (SAS) (Zung, 1971) and Self-Rating Depression Scale (SDS) (Zung, 1965) for the assessment of depression and anxiety.

### 2.3. MRI data acquisition

Image acquisition was carried out at the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China.

First, a 3 T Philips scanner (Achieva; Philips Medical Systems, Best, The Netherlands) was used to obtain the individual T1-weighted images, with an eight-channel phase-array head coil to restrict head motion and diminish scanner noise. The parameters were as follows: repetition time (TR) = 8.5 ms; echo time (TE) = 3.4 ms; flip angle = 12°; data matrix = 240 × 240; slices = 140; field of view (FOV) = 240 × 240 $mm^2$; slice thickness = 1 mm. Second, the resting-state functional images were acquired with an echo-planar imaging (EPI), using the following parameters: TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 240 × 240 $mm^2$; slice thickness = 5 mm; slices = 30; matrix size = 64 × 64; and total volumes = 185. During the 6 min 10 s functional scan, participants were required to stay awake with their eyes closing and to think about nothing. After the data acquisition, participants were asked whether or not they kept awake during the whole procedure.

### 2.4. Structural MRI data analysis

The subcortical regional brain volumes and the intracranial volume

(ICV) were both acquired by using the FreeSurfer 5.0 (http://surfer.nmr.mgh.harvard.edu) processing pipeline on the T1-weighted images as described in our previous studies (Cai et al., 2016; Li et al., 2015; Yuan et al., 2013). Eight main processes were included: (1) removal of non-brain tissue; (2) automated Talairach transformation; (3) segmentation of the deep gray matter volumetric structures and subcortical white matter; (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. It should be noted that subcortical segmentation was corrupted for one patient. So only 25 patients and 36 controls were used for the structural comparison in subsequent statistical analysis.

### 2.5. Resting-state MRI data analysis

AFNI (http://afni.nimh.nih.gov/) and FMRIB's Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/) were used in the processing of the functional neuroimages. As described in our previous study (Yuan et al., 2016, 2017b), the preprocessing consists of eight sections as follows: (1) dropping the first 5 volumes; (2) slice timing correction; (3) rigid-body motion correction; (4) removal skull; (5) spatial smoothing; (6) affine registration to the skull-stripped structural image; (7) spatially normalized into MNI152 template; (8) intensity normalization. Using nuisance regression and bandpass filtering only is usually insufficient to control the noise of head movement (Patel et al., 2014). Thus, wavelet despiking was used for the RSFC analyses (Patel et al., 2014). The denoising steps were as follows: (1) time series despiking (wavelet domain); (2) nuisance signal regression (14-paremeters regression); (3) a temporal Fourier filter (0.009–0.10 Hz). Both the left and right NAc, which were labeled according to Harvard-subcortical structural atlas (http://www.cma.mgh.harvard.edu/), were chosen as our seeds. The regional resting-state fMRI time series was extracted for the bilateral NAc by using the average functional time series of all voxels within each region. Pearson correlation was used to investigate the RSFC between each ROI and the whole-brain regions, and then a Fisher's r-to-z transform was employed.

### 2.6. Statistical analysis

The demographic and clinical characteristics, the volumes of bilateral NAc and intracranial volume (ICV) were imported into the SPSS 25.0 (SPSS Statistics, IBM, Armonk, NY) for comparisons between ID and HC groups. The demographic and clinical characteristics were compared by independent t-tests which were two tailed, and the level of significance was $p < 0.05$. Univariate analyses of variance for both left and right NAc volumes were performed separately to assess the differences between patients with ID and healthy controls while using ICV as a covariate. The tests were two-tailed, and the level of significance was $p < 0.025$ (0.05/2) due to the Bonferroni correction.

Then, two-sample t tests were applied to compare z value maps between the patients with ID and HC. To investigate the group comparisons of functional connectivity, permutation-based nonparametric testing with 5000 random permutations was used. Threshold-free cluster-enhancement (TFCE) with a family-wise error (FWE) correction was used for comparisons, and the significance threshold was set to $p < 0.05$ (Eklund et al., 2016). Finally, the correlations between the neuroimaging findings (i.e., the bilateral NAc RSFC) and clinical variables (i.e. PSQI) were assessed by regression analysis.

## 3. Results

### 3.1. Demographic and clinical characteristics

The detailed demographic and clinical characteristics of the participants were shown in Table 1. There were no significant differences in age and gender between the two groups. The analysis revealed that ID patients had higher PSQI scores than HC both in total ($t = 13.064$, $p < 0.001$) and in each subdivision (Fig. 1). Additionally, ID also exhibited higher scores in self-rating of anxiety ($t = 11.691$, $p < 0.001$) and self-rating of depression ($t = 13.533$, $p < 0.001$) compared with controls.

### 3.2. NAc volume differences

Significant ICV difference ($t = -5.576$, $p < 0.001$) between ID patients ($882{,}724 \pm 151{,}095$ mm$^3$) and healthy controls ($1{,}204{,}029 \pm 294{,}360$ mm$^3$) was detected. The increased volumes of right NAc ($F = 5.357$, $p = 0.024$, Fig. 2C) in patients with ID were observed ($656.08 \pm 113.62$) compared with healthy controls ($600.19 \pm 100.70$), controlling ICV as the covariates (Bonferroni corrected). The volume of the left NAc showed similar changes in ID ($F = 5.090$, $p = 0.028$), which didn't survive the Bonferroni correction (Fig. 2B).

### 3.3. RSFC differences

The analysis revealed increased RSFC between left NAc and several regions in patients with ID, that is, left insula, some subregions of striatum (bilateral caudate, left putamen, left pallidum),bilateral mPFC, bilateral olfactory cortex, bilateral ACC and paracingulate cortex, ($p < 0.05$, FWE corrected, Fig. 3A). Decreased RSFC was also found between left NAc and some regions, that is, right occipital gyrus, right temporal gyrus and right lingual gyrus ($p < 0.05$, FWE corrected, Fig. 3C).

In addition, increased RSFC was found between right NAc and several regions, i.e., right caudate, right putamen, right olfactory cortex and bilateral mPFC, bilateral ACC and paracingulate cortex ($p < 0.05$, FWE corrected, Fig. 3B).And the right NAc showed reduced RSFC with left occipital gyrus, left temporal gyrus, left lingual gyrus and left fusiform gyrus ($p < 0.05$, FWE corrected, Fig. 3D).

### 3.4. Correlation analysis results

Pearson correlation showed that the RSFC between bilateral NAc and left mPFC were negatively correlated with PSQI scores in ID patients (Fig. 4B-C). It is worth mentioning that the negative correlation between the RSFC of bilateral NAc-right mPFC and PSQI scores in ID patients was no longer significant after Bonferroni correction (Fig. 4D-E). The detailed correlation analysis results were shown in Fig. 4. In addition, we found that the RSFC between right NAc and right mPFC were negatively correlated with PSQI scores in HC (Fig. S1). No other significant correlations were found.

## 4. Discussion

We extended the implications of the NAc in sleep-wake regulation from animals to patients with ID. The current study revealed the enlarged volume of right NAc and abnormal RSFC between bilateral NAc and caudate, putamen, pallidum, occipital gyrus, temporal gyrus, medial prefrontal cortex, olfactory cortex, anterior cingulate cortex in ID patients (Fig. 3). Besides, the increased RSFC between bilateral NAc and left mPFC in ID have significant correlations with PSQI scores (Fig. 4B-C). Particularly, the potential role of NAc-mPFC pathway in ID might be reflected by the abnormal RSFC between the two regions and the related correlation analysis.

### 4.1. Increased RSFC of NAc in insomnia disorder

In the current study, our results were partially consistent with hyperarousal model by showing the enhanced RSFC between NAc and mPFC in ID patients. We considered that such increased RSFC might indicate the cortical overactivation. In fact, a number of studies have shown the potential relationship between mPFC and NAc and insomnia. A previous study revealed that subjects with injury in the left mPFC suffered moderate-to-severe insomnia, which indicated that left mPFC

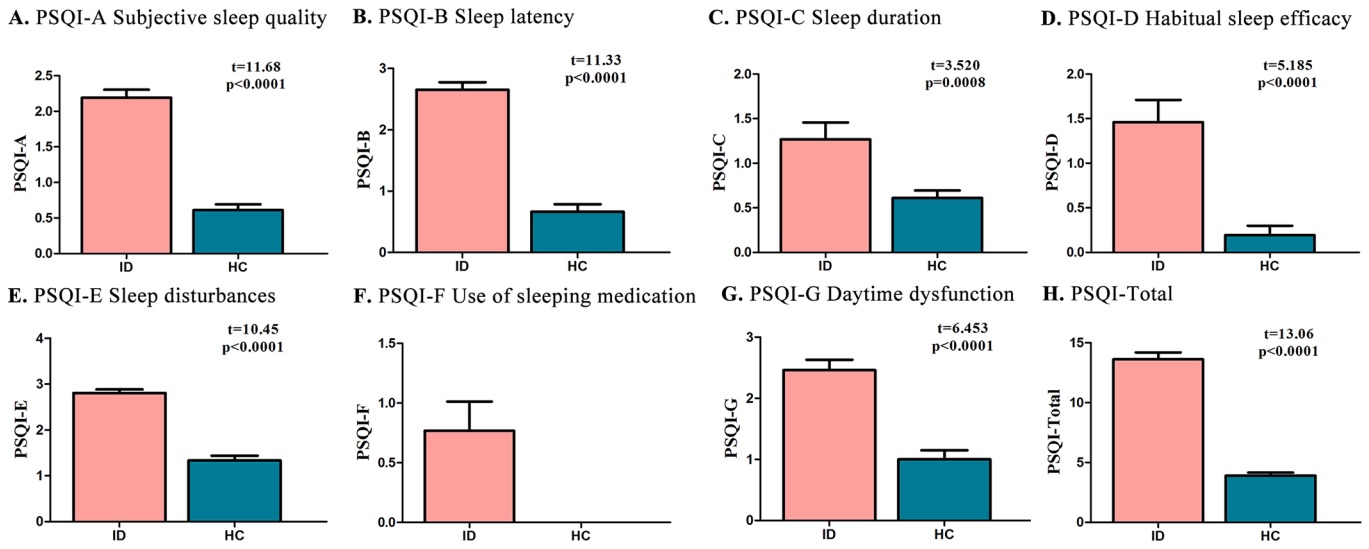


**Fig. 1.** (a-h) PSQI scores in ID patients and HCs. ID patients committed higher scores in each subdivision of PSQI compared to HCs.

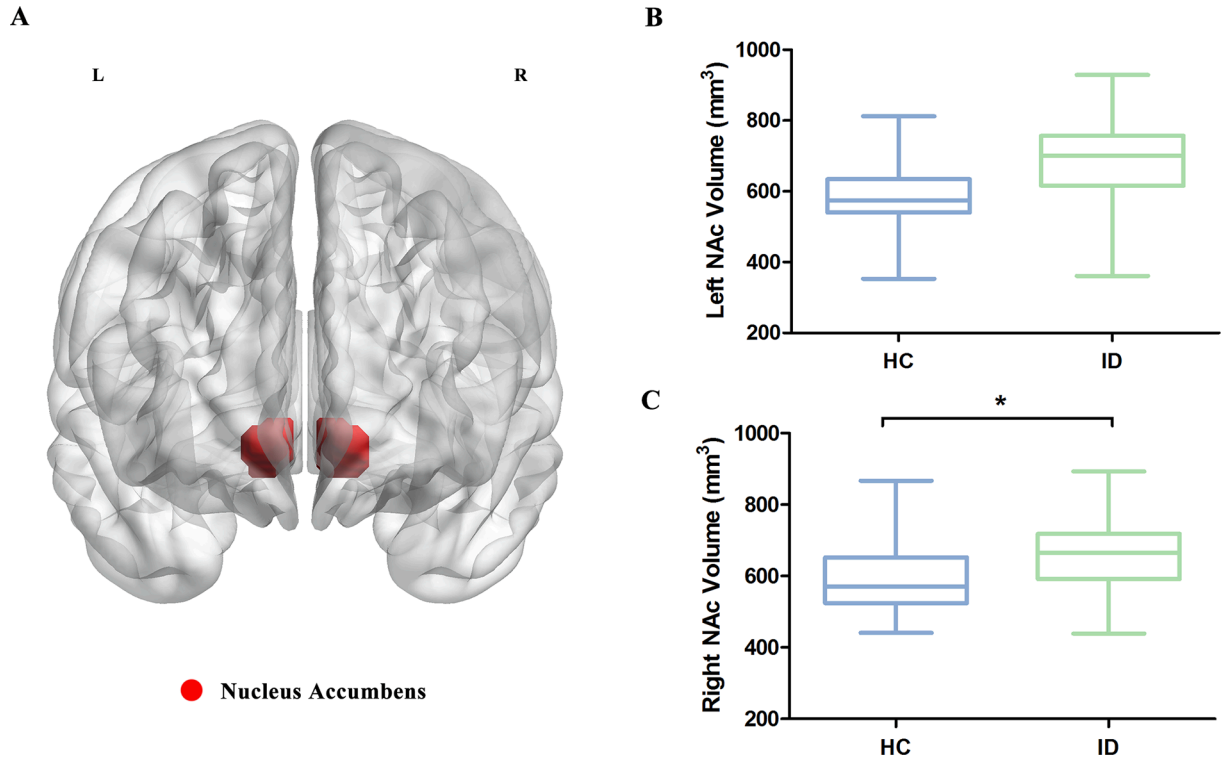


**Fig. 2.** (A) A sketch map of bilateral NAc and comparisons of the (B) left NAc volume and (C) right NAc volume between ID and HC. The increased volume of right NAc ($F = 5.357$, $p = 0.024$) in ID patients was observed as compared with HC (Bonferroni corrected).

damage is associated with insomnia (Koenigs et al., 2010). Functional abnormalities related to mPFC were also found to be correlated with sleep impairments in one of our previous study (Liu et al., 2019). Besides, the heuristic model in which the NAc is an integral part of the sleep-wake regulation network predicted that dopamine acting on inhibitory $D_2$ receptors and working opposite to the excitatory adenosine-$A_{2A}$ receptor system, modulates the activity of medium spiny projection neurons in the NAc, thereby inhibiting arousal, and the model also proposed the existence of the excitatory synapses from mPFC to NAc (Lazarus et al., 2012). Moreover, another study showed high extracellular dopamine levels during wakefulness and REM sleep in NAc and mPFC, while significantly lower during NREM sleep (Lena et al., 2005). Such synchronous changes might reveal the implication of NAc-mPFC pathway in the sleep-wake regulation. The increased RSFC between NAc and mPFC in ID patients observed in our study provides more evidence for the potential role of the NAc-mPFC pathway in sleep-wake transition.

In addition, our results revealed a negative correlation trend between the bilateral mPFC-NAc RSFC strength and PSQI score in ID patients (Fig. 4B-E). However, it should be noted that the area where the mPFC of ID patients had significant increased RSFC did not overlap with the area where there was a significant correlation in the correlation analysis. In fact, mPFC can be divided into several sub-regions with different functions. Previous studies revealed less activation in the dorsomedial

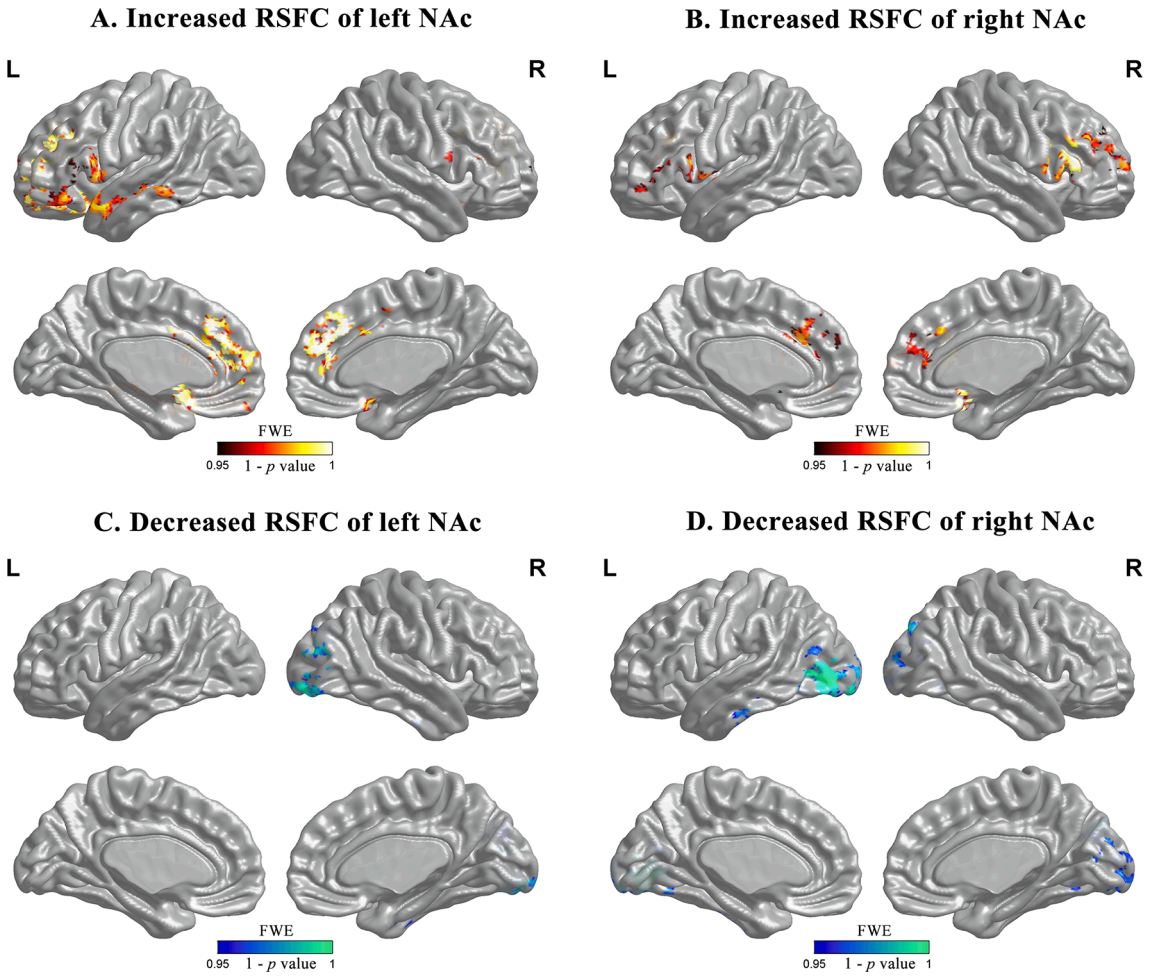


**Fig. 3.** The increased/decreased RSFC of bilateral NAc between ID patients and HCs, respectively.

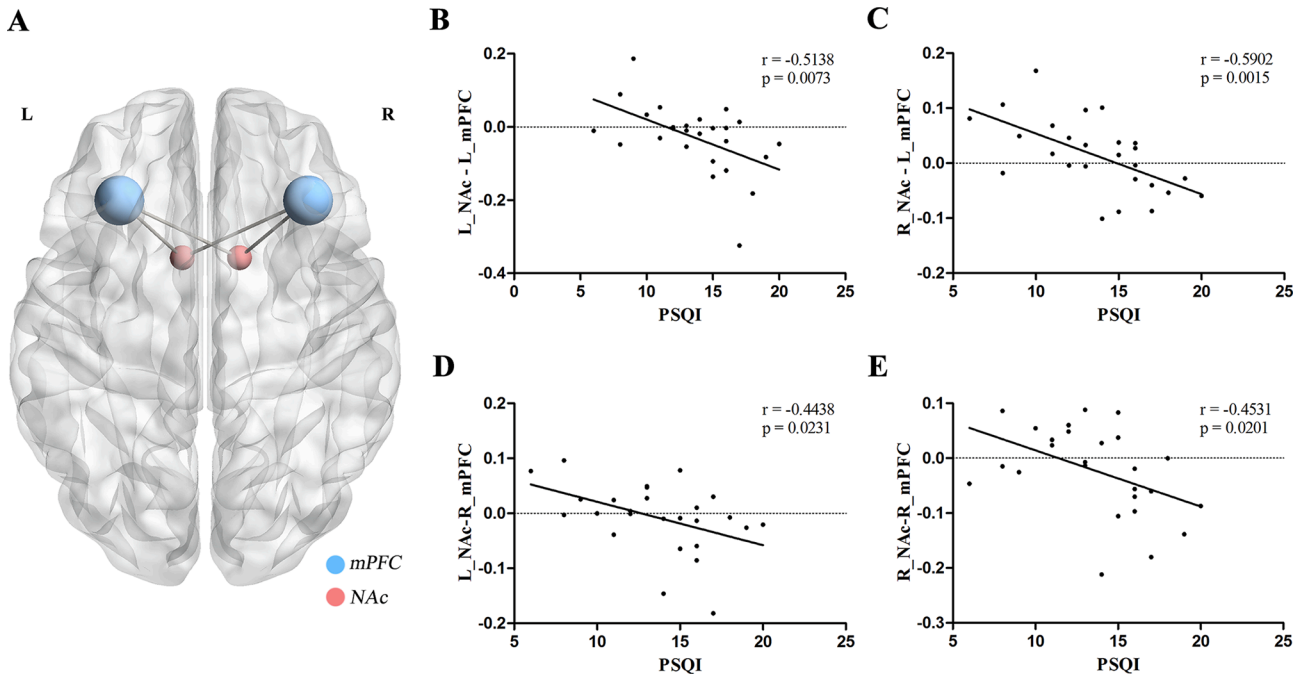


**Fig. 4.** (A) A sketch map of bilateral NAc and mPFC. (B-E) The correlation between NAc-mPFC RSFC strength and PSQI scores in ID patients. Significant negative correlation was observed between the (B) left NAc-left mPFC ($r = -0.5138$, $p = 0.0073$), (C) right NAc-left mPFC ($r = -0.5902$, $p = 0.0015$) RSFC strength and PSQI scores (Bonferroni corrected, $p < 0.0125$).

prefrontal cortex (dmPFC) during cognitive reappraisal in ID patients (Minkel et al., 2012). In another study, researchers found that goal-directed learning mainly recruited the ventromedial prefrontal cortex (vmPFC), the activation of which was less pronounced during goal-directed learning after sleep deprivation (Chen et al., 2017). The multiple functional differences of mPFC sub-regions implied the complex possibilities of the correlation analysis results. Thus, the phenomenon that the RSFC between other part of mPFC and NAc showed negative correlation with PSQI drove us to further investigate the roles of different sub-regions of mPFC in insomnia disorders.

Cortical excitability reflects a balance between excitation and inhibition, and GABA is a main inhibitory neurotransmitter in the cortex (Petroff, 2002). It has been proposed that the NAc had GABAergic projections to a wide range of targets (Lazarus et al., 2012) and was thought to induce sleep via its inhibitory projections to the waking systems (Luppi et al., 2017). More importantly, previous studies have found that ID patients had significantly lower GABA relative to total creatine (GABA/Cr) in ACC than the healthy sleepers (Plante et al., 2012), which would lead to the hyperarousal. Increased voxel-mirrored homotopic connectivity (VMHC) in the ACC bilaterally was also to be found in ID patients in a recent study (Yan et al., 2018). These findings indicate the important roles of ACC in ID, and it might be further supported by the increased RSFC between NAc and ACC in ID patients observed in our study.

According to the hyperarousal theory of insomnia, increased physiological arousal could result in difficulty in initiating or maintaining sleep and make individuals in a cycle of hyperarousal and increased sensitivity to sensory stimulation (Perlis et al., 1997). As reviewed in another article, such arousal is expressed in terms of somatic, cognitive and cortical activation (Riemann et al., 2010). On the one hand, the NAc has been considered as a key structure that mediates various kinds of neurobiological behaviors including cognition (Salgado and Kaplitt, 2015). On the other hand, previous studies have revealed that both difficulty in falling asleep and maintaining sleep were found to be associated with increased functional connectivity related to the olfactory cortex, a sensory region (Killgore et al., 2013). Thus, the increased RSFC between NAc and olfactory cortex in ID patients might consistently indicate the increased physiological arousal, in accordance with the theory of hyperarousal.

### 4.2. Decreased RSFC of NAc in insomnia disorder

Studies have found cognitive impairment in individuals with insomnia, that is, insomniacs had poorer global cognitive performance compared with normal sleepers (Fortierbrochu and Morin, 2013). In another study, insomnia patients were found to exhibit deficit in high level neurobehavioral functioning, which indicated that neurobehavioral deficits in insomnia are due to neurobiological alterations (Shekleton et al., 2014). These studies made a strong link between insomnia and cognitive dysfunction.

More importantly, a recent study found cognitive impairment-related gray matter volume decreases in bilateral occipital and temporal cortices among Parkinson's disease patients (Chen et al., 2019). Besides, a review showed that the fMRI and event-related potentials (ERP) face-selective responses in the right occipital-temporal cortex are strongly associated with three well-established behavioral face-selective measures, which indicated that right occipital-temporal cortex is closely involved in the cognition (Yovel, 2016). Since NAc is thought to be closely related to cognitive function (Floresco, 2015; Salgado and Kaplitt, 2015), we suspected that the decreased RSFC between NAc and occipital-temporal cortex is associated with the potential cognitive impairment in ID patients. In fact, although not directly investigating cognitive function, we tested the correlation between the RSFC and PSQI-G scores (i.e. daytime dysfunction). Significant negative correlation was observed between left NAc-left occipital cortex RSFC strength and PSQI-G scores in ID patients (Fig. S2, $r = -0.3962$, $p = 0.0451$, uncorrected).

### 4.3. Limitations

In the current study, we assessed the sleep quality of ID patients only by subjective measures (i.e. PSQI). Other specific questionnaire for insomnia severity, and objective measures, such as polysomnography, should be added to investigate the association between abnormal brain function and sleep quality. We used DSM-IV for insomnia diagnosis, and the diagnostic criteria are a little different from the latest version (DSM-5). The different sample size of patients and controls was also a limitation. We did not investigate the cognitive function of the subjects specifically so that we could not give a more accurate explanation for the partial results. We did not give an exact explanation for the results of correlation analysis which seemed counterintuitive to our theoretical framework. Because mPFC is a large brain region that can be divided into several sub-regions with different functions, more targeted experiments and analysis are needed in the future to interpret the results. Besides, the NAc is a complex region. Firstly, the different NAc subregions (core and shell) presented connectivity to specific cell types, suggesting that different NAc subregions may differ in function (Li et al., 2018). Secondly, based on in vivo electrophysiologic recordings, previous findings indicate that sleep-active and wake-active neurons are intermingled in the NAc region in rats (Callaway and Henriksen, 1992; Oishi and Lazarus, 2017; Osaka and Matsumura, 1995; Tellez et al., 2012). The method based on neuroimaging used in the current study could not differentiate between NAc subregions and heterogeneous neurons in the NAc. More subtle templates could be applied to evaluate the role of different subregions of NAc in the brain. In future studies, experiments at the molecular level could be conducted to assess the functional differences of different types of neurons in NAc.

## 5. Conclusion

We revealed enlarged right NAc volume, increased RSFC between NAc and mPFC, ACC, olfactory cortex, and decreased RSFC between NAc and occipital-temporal cortex in ID patients. The abnormal RSFC in ID patients showed two patterns of increase and decrease. We thought that the increased RSFC reflected that the ID patients was in a state of hyperarousal, which could cause difficulty in initiating or maintaining sleep. The decreased RSFC might reflect the cognitive impairment caused by ID. Additionally, the increased RSFC between bilateral NAc and left mPFC have significant correlations with PSQI scores. It is hoped that our study focusing on NAc-mPFC circuits could provide new insights for the neural mechanisms of ID. This study may inspire new therapeutic ideas for patients with ID.

## CRediT authorship contribution statement

**Ziqiang Shao:** Software, Formal analysis, Investigation, Writing - original draft, Visualization. **Yan Xu:** Investigation, Writing - review & editing. **Longmao Chen:** Validation. **Shicong Wang:** Formal analysis. **Min Zhang:** Visualization. **Shuang Liu:** Software. **Xinwen Wen:** Data curation. **Dahua Yu:** Conceptualization, Methodology, Supervision. **Kai Yuan:** Conceptualization, Methodology, Resources, Supervision, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102474.

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