



Sleep discrepancy is associated with alterations in the salience network in patients with insomnia disorder: An EEG-fMRI study

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ABSTRACT

Background: Positron emission tomography – computed tomography (PET-CT) research has shown that sleep discrepancy recorded by self-report and polysomnography (PSG) may be related to the altered metabolic rate of the anterior insula (aINS) during non-rapid eye movement (NREM) sleep in patients with insomnia disorder. We aim to explore the functional connectivity of aINS across wake and NREM sleep in the patients and to reveal the association between aINS connectivity and sleep discrepancy.

Methods: Patients with insomnia disorder ($n = 33$) and healthy controls ($n = 31$) underwent simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI) during nighttime sleep, and aINS-based connectivity was calculated across wake and NREM sleep. A linear mixed-effects model was used to assess the main effect of group and group-by-stage (wake, NREM stages 1–3) interaction effect on aINS connectivity. Similar mixed models were used to assess the potential correlation between aINS connectivity and the sleep misperception index (MI).

Results: A significant group-by-stage interaction effect on aINS-based connectivity was observed in the bilateral frontal gyrus, right inferior temporal gyrus, bilateral middle occipital gyrus and right postcentral gyrus ($p < 0.05$, corrected). There was also a significant group-by-MI interaction effect on aINS connectivity with the putamen and thalamus during wakefulness ($p < 0.05$ corrected); MI was significantly associated with aINS–putamen/thalamus connectivity in the control group, whereas the association was weak or even nonsignificant in the patient group. There was no significant main effect of group.

Conclusion: The waking activity of a neural pathway containing the aINS, putamen, and thalamus may underlie sleep perception, potentially providing important perspectives to reveal complex mechanisms of sleep discrepancy between self-report and PSG.

1. Introduction

Insomnia disorder is characterized by difficulty in initiating or

maintaining sleep and is associated with daytime cognitive impairment; this disorder is very common, with a prevalence of approximately 10% among adults in most countries. (Ohayon, 2002; Roth et al., 2011) The

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diagnosis of insomnia disorder depends on the subjective complaints of the patient, rather than the report of sleep electroencephalography (EEG) monitoring by polysomnography (PSG). However, there is often a mismatch between the sleep complaints and PSG reports. Most patients with insomnia disorder tend to report shorter total sleep time (TST) or longer sleep onset latency (SOL) than are recorded by PSG (Harvey and Tang, 2012) or actigraphy (Te Lindert et al., 2020), but good sleepers tend to report the same or longer TST/shorter SOL than that are recorded by PSG (Trajanovic et al., 2007). The mismatch between self-report and PSG reports is so-called paradoxical insomnia or sleep misperception. Because the mismatch widely exists in insomnia patients, and the definition of paradoxical insomnia is controversial, the misperception index (Manconi et al., 2010) was often used to determine the degree of discrepancy recorded by self-report and PSG.

The mechanisms of sleep discrepancy in patients with insomnia disorder are still unclear, but it has been proposed that altered central nervous system activation, specifically, hyperarousal (Hsiao et al., 2018; Riemann et al., 2010), impaired inhibitory processes, or insufficient local sleep, may be the underlying explanation (Drummond et al., 2004; Harvey and Tang, 2012; Kay et al., 2017; Kay et al., 2016; Levenson et al., 2015). A recent high-density EEG study showed spatially widespread high-frequency power was inversely related to self-reported sleep depth in NREM sleep (Stephan et al., 2021). Increased high-frequency EEG activity (Corsi-Cabrera et al., 2012b; Hsiao et al., 2018; Maes et al., 2014; Stephan et al., 2021) with heightened alpha, beta, and gamma power has been consistently observed in insomnia patients with sleep discrepancy, indicating a connection between EEG hyperactivity and sleep discrepancy. Reduced delta, theta, and alpha power might be a signature of modified rapid eye movement (REM) sleep associated with a high level of perceived wakefulness, which suggests that spectral power in REM sleep is also linked to sleep discrepancy (Benz et al., 2020; Stephan et al., 2021). Previous studies showed that patients with sleep discrepancy often verbally reported heightened cognitive activation (Gokce et al., 2020; Harvey, 2002; Takano et al., 2016), such as awareness of environmental stimuli and mental activity (intrusive thoughts, rumination, or worry), while attempting to fall asleep or during sleep; this increased cognitive activity may be the behavioral performance of sleep discrepancy, but its brain mechanism is not clear.

Previous neuroimaging studies have shown that the anterior insula (aINS) is a very important target to consider when exploring the causes of sleep discrepancy. Using positron emission tomography-computed tomography, Kay et al. found that an altered relative regional rate of glucose metabolism in the right aINS, left anterior cingulate cortex, and middle/posterior cingulate cortex during NREM sleep may be involved in sleep onset latency discrepancy in patients with insomnia disorder (Kay et al., 2017). Chen et al., using simultaneous EEG-fMRI, found that patients with insomnia disorder had increased coactivation between the bilateral aINS and salience networks in terms of blood oxygenation level-dependent (BOLD) signal while the patients were trying to fall asleep, this increased involvement of the insula within salience networks was positively associated with alertness and negative affect; on this basis, Chen et al. proposed that increased aINS coactivation with salience networks may contribute specifically to the misperception of sleep quality and subjective distress in insomnia (Chen et al., 2014). Our previous study (Zou et al., 2021) showed that thalamic connectivity in the subcortical cluster and the right temporal cluster in sleep stage N1 was significantly correlated with the misperception index. In general, conclusions from previous studies regarding the brain regions involved in sleep discrepancy are rare and inconsistent. The salience network (Seeley et al., 2007) responds to environmental stimuli and may be involved in conscious awareness of feelings (Corsi-Cabrera et al., 2012a). The aINS is the key node of the salience network, and it has been proposed to integrate a variety of information, including interoceptive stimuli, awareness of body movement, time perception, emotional awareness, self-recognition, cognitive control and performance monitoring, (Craig, 2009) some of which have been proposed to play an

important role in sleep perception (Harvey and Tang, 2012). Therefore, we aimed to explore the brain connectivity of the aINS in relation to sleep discrepancy between self-report and PSG among patients with insomnia disorder.

With simultaneous EEG and neuroimaging techniques, we can investigate the dynamic functional changes in the brain across the sleep-wake cycle, which provides an appropriate and advantageous strategy to reveal the functional basis of insomnia disorder, (Spiegelhalder et al., 2013) but this type of research in the patients with insomnia disorder is difficult and rare. Using synchronous EEG-fMRI recording during wakefulness and sleep, this study aimed to investigate the brain functional connectivity of the aINS related to sleep discrepancy between self-report and PSG in patients with insomnia disorder. We hypothesize that the functional connectivity of the aINS in patients with insomnia disorder would be altered during the progression from wakefulness to NREM sleep and that the altered connectivity of the aINS would be associated with sleep discrepancy.

2. Material and methods

2.1. Participants

A total of 63 participants, including 33 patients with insomnia disorder and 31 healthy controls, were enrolled. All participants were recruited from outpatients at the sleep center in Peking University Sixth Hospital, or in the local community. They were all Chinese Han population and right-handed. Patients with insomnia disorder were diagnosed using a structured clinical interview according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American-Psychiatric-Association, 2013); and insomnia symptoms persisted for more than 3 months; healthy controls completed the same interview to ensure that they had no insomnia and fit the inclusion criteria of normal sleep (Beattie et al., 2015) and a Pittsburgh Sleep Quality Index (PSQI) score <7. The two groups were matched for age, sex and years of education. This study was approved by the Institutional Review Board of Peking University Sixth Hospital (2015–9). Participants signed informed consent before enrollment and were compensated for their participation.

Participants in both the insomnia and control groups met the following criteria: (1) age 18–60 years, (2) Mini-Mental State Examination (MMSE) score ≥ 26 , (3) length of education ≥ 8 years, (4) no major past or present medical or psychiatric conditions and no self-reported sleep disorders (other than insomnia for the insomnia group), and (5) no past or present drug or alcohol use disorder. The exclusion criteria were as follows: (1) self-reported left-handedness, (2) use of prescribed or over-the-counter medicines that might affect sleep within the 2 weeks before participation, (3) ineligibility for MRI scanning (any type of metal implant), (4) periodic limb movement index (PLMI) $\geq 20/h$, (5) apnea-hypopnea index (AHI) ≥ 5 , and (6) shift work.

2.2. Procedures

Participants were screened through validated clinician-administered interviews and a package of questionnaires to assess current sleep and mood states. Then, they were asked to follow a regular sleep schedule for 2 weeks, and their habitual sleep patterns were monitored by actigraphy and sleep diaries. After this, two consecutive overnight PSG recordings (Compumedics, Grael, Australia) and sleep diary entries were collected to evaluate sleep structure and to exclude participants with other sleep disorders. The PSG recordings were performed at Peking University Sixth Hospital. After these initial records were collected, simultaneous EEG (64 channels, Brain Products, Germany) and fMRI (3T Prisma Scanner, Siemens Healthineers, Erlangen, Germany) recordings were conducted at the Center for MRI Research, Peking University, as the participants attempted to fall asleep in an MRI scanner at their usual bedtime. Before the EEG-fMRI data were collected, patients were

allotted one session to adapt to our MR scanner in order to promote sleep and reduce the first-night effect.

2.3. Clinical interview

In addition to insomnia-related information, current and past psychiatric disorders were assessed by a physician according to the criteria of the Mini-International Neuropsychiatric Interview (MINI) version 5.0 (Sheehan et al., 1998). Participants in both groups were free of psychiatric disorders (including current or past depression disorder and anxiety disorder) and had no family history of mental disorders. Current mood state was assessed with the Self-Rating Depression Scale (SDS) (Lee et al., 1994) and the Self-Rating Anxiety Scale (SAS). A cutoff score of 53 was used to identify depression, and a cutoff of 50 was used for anxiety. Although none of the participants had a current psychiatric diagnosis, the scores of two patients in the insomnia group were above the cutoff score, suggesting they had mild symptoms of depression and anxiety. Such symptoms were not present in any of the controls.

2.4. Sleep measurements

2.4.1. Questionnaire

Sleep quality was measured with the PSQI, which is a well-validated self-rated scale with good psychometric properties. This scale has nineteen individual items, and the total score can range from 0 to 21. A score greater than 7 indicates clinically significant poor sleep quality (Liu and Tang, 1996; Zheng et al., 2016). In addition, sleep reports were collected on the PSG nights using a table of sleep diary; the information gathered in these reports included awake time in bed, lights-off time, asleep time, awake time and time out of bed.

2.4.2. Polysomnography

All participants completed two consecutive overnight PSG sessions, including screening/adaptation and baseline recording. The first night of PSG, performed for screening and adaptation, was mainly used to screen for sleep apnea, periodic limb movement disorder and other sleep disorders; it also helped the participants adapt to the sleeping environment of the laboratory to prevent the first-night effect from interfering with later recordings. The second night of PSG was used as the baseline night. The sleep diary and PSG assessments were based on that night. The results of PSG were manually scored by two experienced technicians based on version 2.3 of the American Academy of Sleep Medicine criteria (Iber et al., 2007). The parameters include sleep latency, total sleep time, sleep efficiency, and the durations and ratio of NREM and REM sleep.

2.4.3. Sleep discrepancy between self-report and PSG

It is known that there is often a mismatch between sleep diary and PSG reports among patients with insomnia disorder. Manconi et al. introduced the misperception index (MI) to estimate the sleep discrepancy between self-report and PSG. (Manconi et al., 2010) The MI gives a reliable and immediate description of sleep discrepancy in both healthy individuals and those with insomnia. We used the total sleep time MI ((sleep diary TST – PSG TST)/PSG TST) to quantify sleep discrepancy.

Among these variables, PSG TST was obtained from the second night of PSG recording. The sleep diary TST was assessed during the same PSG night. Sleep diary TST can be obtained by direct or indirect queries. A direct query requires a time duration as a response, while an indirect query requires clock times, from which time durations are calculated. Because of the inconsistency of these two methods in obtaining TST estimates, the potential bias from indirect queries may be less than that from direct queries (Alameddine et al., 2015), the indirect method was used to obtain TST, which was calculated using several answers from sleep diaries: an outer boundary of time in bed (TIB) was first defined by the self-reported time of lights out and final awakening time, from which the self-reported sleep onset latency (SOL) and the wakefulness after

sleep onset (WASO) value were subtracted (Alameddine et al., 2015).

2.5. Simultaneous EEG-fMRI protocol

Simultaneous EEG-fMRI recordings were conducted after the PSG nights. At their usual bedtime, participants were instructed to lie in the MRI scanner wearing an MR-compatible EEG cap, close their eyes, relax and try to sleep in the scanner. The recording electrodes included the following: 57 EEG channels positioned according to the international 10/20 systems; two reference channels (A1, A2); two electrooculography (EOG) channels; one electrocardiography (ECG) channel; and two electromyography (EMG) channels. By using electrode paste (AbraLyt HiCl), the impedance of the reference channel and the ground channel was kept below 10 k Ω , whereas the impedance of other channels was maintained below 20 k Ω . The EEG signal was synchronized with the MR trigger and recorded using Brain Vision Recorder (Brain Products, Germany). The recording sampling rate was 5000 Hz, and the data were filtered with a lower bound of 10 s and an upper bound of 250 Hz. The resistance of all the channels was verified again before the start of MR scanning. The wires connecting the cap and the amplifiers were fixed in place to avoid any potential vibration during the MR scan.

For registration purposes, high-resolution T1-weighted anatomical images were acquired using a 3-dimensional magnetization-prepared rapid-acquisition gradient-echo sequence (repetition time (TR) = 2530 ms, echo time (TE) = 2.98 ms, inversion time = 1100 ms, flip angle (FA) = 7°, number of slices = 192, and voxel resolution = 0.5×0.5×1 mm³). The participants were asked to lie quietly in the scanner during data acquisition. The “sleep” session began after the participants were instructed to try to fall asleep. Sleep blood oxygenation level-dependent fMRI data sets were collected using a gradient-echo echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, FA = 90°, number of slices = 33, slice thickness = 3.5 mm, gap = 0.7 mm, matrix = 64×64, and in-plane resolution = 3.5×3.5 mm²). The “sleep” session ended when all 4096 volumes had been acquired, which would take 2 h 16 min; alternatively, if the participants failed to fall asleep, the session was ended.

2.6. Data analysis

2.6.1. EEG data preprocessing

EEG recording data were preprocessed using Brain Vision Analyzer 2.1 (Brain Products, Germany). We used the average artifact subtraction method to remove the MR gradient and cardiogram artifacts from the EEG records (Allen et al., 2000). EEG data were down sampled to 500 Hz and were re-referenced to the mean of the channels at the mastoids and temporally filtered (10–100 Hz for the EMG channels and 0.3–35 Hz for the other channels). Sleep stages were scored by two experienced technicians based on version 2.3 of the American Academy of Sleep Medicine criteria (Iber et al., 2007). Only 30-s epochs with consistent sleep stage scoring by the two technicians were used for further analysis.

2.6.2. fMRI data processing

There were 33 patients with insomnia disorder and 31 age- and sex-matched healthy controls who completed all the processes and had available fMRI data. fMRI data from continuous 5-min epochs of wakefulness and sleep stages N1, N2 and N3 were extracted. The insomnia group had 104 wakefulness epochs (17 subjects), 27 N1 epochs (13 subjects), 67 N2 epochs (20 subjects), and 20 N3 epochs (seven subjects); the healthy control group had 40 wakefulness epochs (13 subjects), 16 N1 epochs (11 subjects), 75 N2 epochs (21 subjects), and 91 N3 epochs (17 subjects). It has been shown that using 5-min data epochs is sufficient to estimate stable correlation strengths (Van Dijk et al., 2010). Even though increased epoch length can further improve reliability, it would result in fewer epochs available; thus, there was a tradeoff between epoch length and number of epochs (Birn et al., 2013). A 5-min epoch length was used in several previous studies of sleep (Hsiao et al., 2018; Mitra et al., 2016; Samann et al., 2011; Spooemaker

et al., 2010). Thus, we used data from 5-min epochs to perform the following analysis. The distribution of five-min epochs of fMRI data was showed in [supplementary material \(Table S1\)](#).

The fMRI data were preprocessed using the FMRIB Software Library (FSL, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>, version 5.0.9) tools, the Analysis of Functional NeuroImages software package (Cox, 1996) and MATLAB (MathWorks). The preprocessing steps included slice timing, motion correction, spatial normalization (voxel size, $2 \times 2 \times 2$ mm³), nuisance signal regression, linear detrending, temporal filtering (0.01–0.08 Hz) and spatial smoothing with a 6 mm Gaussian kernel. During nuisance signal regression, 30 regressors—including 24 head-motion-related regressors derived using a Volterra expansion (Friston et al., 1996; Power et al., 2014); 3 tissue-based average signals from cerebrospinal fluid, white matter, and the whole brain; and the first derivatives of tissue-based signals—were regressed out. The seeds for the bilateral aINS were selected based on Montreal Neurological Institute (MNI) coordinates (Seeley et al., 2007), as shown in the supplemental material (Fig. S1).

We calculated the value of Pearson's correlation coefficient between the seed time series and every other voxel in the brain and transformed the correlation coefficient values into z values using Fisher's r-to-z transformation. Functional connectivity with the bilateral aINS in both groups during wakefulness is shown in Fig. S2.

2.6.3. Statistical analysis

All clinical data were tested for normality using the Kolmogorov–Smirnov test. The demographic, clinical, and sleep parameters of the two groups were compared using independent t tests, Mann–Whitney U tests, or chi-square tests. These analyses were conducted in IBM SPSS 24 (IBM Corp., Armonk, NY, USA) or SAS version 9.3 (SAS Institute, Cary, NC).

For fMRI data, a linear mixed-effects model was used to assess the interaction effect of group (insomnia vs. control) and stage (wakefulness, N1, N2, N3) and the main effect of group on the seed-based functional connectivity. Age, sex, and years of education were added as covariates of no interest. We used the autocorrelation function (ACF) modeling approach combined with a voxelwise threshold of $p < 0.001$ to correct for multiple comparisons (Cox, 1996; Eklund et al., 2016). The ACF was developed and implemented into the 3dClustSim tool to determine the cluster-size threshold to use for a given voxelwise threshold. ACF was estimated using the 3dFWHMx tool based on the preprocessed fMRI data prior to functional connectivity calculations. Correspondingly, a corrected significance level of $p < 0.05$ for the resulting statistical maps was obtained using clusters with a minimum number of 247 voxels at an uncorrected individual voxel height threshold of $p < 0.001$.

To assess the potential correlation between seed-based functional connectivity and the sleep misperception index (MI, (sleep diary TST – PSG TST)/PSG TST), similar mixed-effects models were used. Motivated by Kay and colleagues' work (Kay et al., 2017; Kay et al., 2016), we investigated the interaction effect of MI and group as well as the main effect of MI on functional connectivity during each of the four stages.

3. Results

3.1. Demographic and clinical characteristics

Thirty-three patients with chronic insomnia disorder and thirty-one healthy controls participated in this study. The demographic, sleep diary and PSG characteristics of both groups are presented in [Table 1](#). There was no significant difference in demographic characteristics between the two groups. The PSQI, SDS, and SAS scores of the patients were significantly higher than those of the controls. The patients had worse self-reported sleep, longer SOL and shorter TST than controls, while there was no significant difference in PSG-measured SOL. Both PSG-measured and sleep-diary-measured TST values were significantly

Table 1
Demographic and clinical characteristics of the participants.

Variable	Insomnia (n = 33) Mean (SD)	Control (n = 31) Mean (SD)	t	p value
Age (years)	39.18 (9.42)	35.06 (8.55)	1.83	0.072
Male/female	14/19	15/16	$\chi^2 = 0.23$	0.632
Years of education	16.82 (2.93)	16.61 (2.16)	0.32	0.752
PSQI	11.45 (3.26)	2.32 (1.25)	14.61	<0.001***
SOL of sleep diary (min) ¹	54.28 (55.28)	19.41 (22.09)	3.27	0.002**
TST of sleep diary (min) ¹	347.66 (103.93)	451.90 (50.44)	-4.90	<0.001***
SOL of PSG (min)	14.79 (23.65)	6.73 (5.76)	1.85	0.070
TST of PSG (min)	400.23 (63.69)	447.34 (40.15)	-3.51	<0.001***
Misperception index ¹	-0.14 (0.19)	0.01 (0.09)	-4.07	<0.001***
TIB (min)	462.73 (64.68)	481.53 (31.64)	-1.44	0.154
SE (%)	86.84 (8.89)	92.85 (5.24)	-3.27	0.002**
WASO (min)	42.21 (37.80)	24.74 (21.11)	2.30	0.026*
N1 (min)	36.52 (14.14)	36.94 (11.58)	-0.13	0.897
N2 (min)	212.79 (44.57)	238.94 (27.60)	-2.80	0.007**
N3 (min)	69.50 (29.13)	71.68 (27.90)	-0.31	0.761
REM (min)	81.42 (21.48)	99.79 (21.39)	-3.43	0.001**
Arousal index (/h)	6.29 (3.12)	4.88 (1.87)	2.17	0.033*
AHI (/h)	1.33 (1.24)	0.91 (0.87)	1.59	0.118
PLMI (/h)	3.02 (4.47)	2.65 (3.66)	0.36	0.717
SDS	40.76 (8.30)	30.32 (4.74)	6.12	<0.001***
SAS	38.33 (6.87)	28.39 (4.81)	6.67	<0.001***

Notes: Mean (SD) values of variables are reported, along with t-statistics and p values. Significant main effects are in bold. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Misperception index: (Sleep diary TST – PSG TST)/PSG TST.

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time; TIB, time in bed; SOL, sleep onset latency; SE, sleep efficiency (PSG TST/TIB); WASO, wakefulness after sleep onset; REM, rapid eye movement; AHI, apnea–hypopnea index; PLMI, periodic limb movement index; SDS, Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale.

¹ The number of participants used to calculate these terms was 32 for the insomnia group and 29 for the control group because the sleep diaries of 3 participants from the night of the PSG recording were lost.

shorter in the patient group than in the control group, while the discrepancy between PSG-measured and sleep-diary-measured sleep was significantly greater in the patients than in the healthy controls. There was a significant difference in MI values between the two groups. Additionally, as measured by PSG, the insomnia group showed significantly lower sleep efficiency and shorter N2 and REM sleep durations than the control group.

3.2. Functional connectivity of the aINS

A group (insomnia vs. control)-by-stage (wakefulness, N1, N2, N3) interaction of functional connectivity with the left aINS was mainly observed in five clusters, located in the left middle occipital/right inferior temporal gyrus, right middle occipital gyrus, bilateral superior frontal gyrus, right inferior temporal gyrus and right postcentral gyrus ($p < 0.05$ corrected, [Fig. 1, Table 2](#)).

Post hoc analysis showed that the functional connectivity in those areas was significantly changed across all four stages in the insomnia group compared to the control group. The connectivity of the aINS with the bilateral superior frontal gyrus, bilateral middle occipital gyrus, right inferior temporal gyrus and right postcentral gyrus was significantly lower in the patients than in the controls during wakefulness. With the transition from wakefulness to NREM sleep, the functional

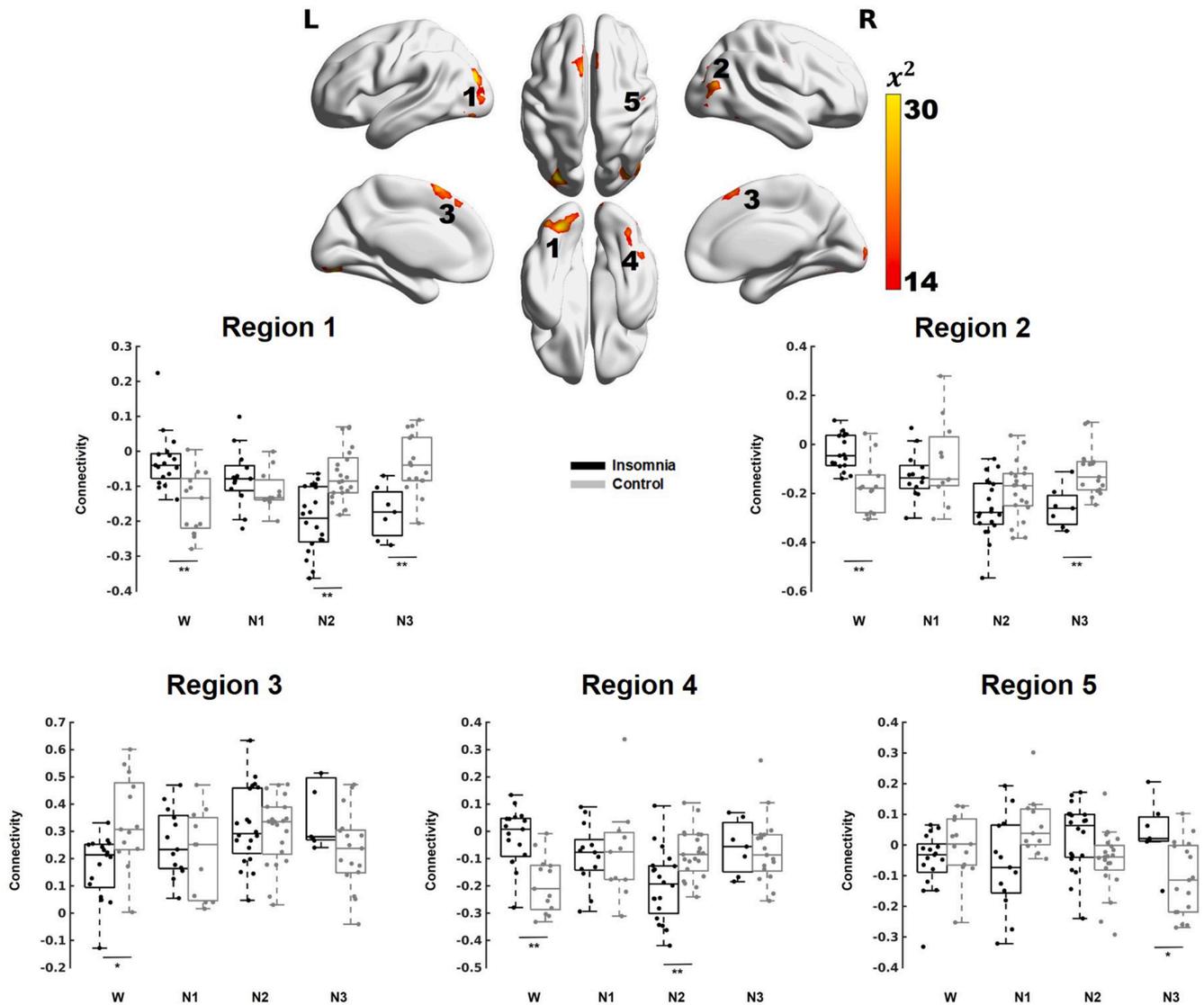


Fig. 1. Group-by-stage interaction effect on the connectivity of the left aINS. (N=33 for the patients, N=31 for the controls. $p < 0.001$ and clusterwise corrected $p < 0.05$). Average Fisher-transformed z scores (mean \pm SEM) in the clusters for the interaction (post hoc two-sample t tests between the two groups, $**p < 0.01$). Region 1, left middle occipital gyrus/right inferior temporal gyrus; Region 2, right middle occipital gyrus; Region 3, bilateral superior frontal gyrus; Region 4, right inferior temporal gyrus; Region 5, right postcentral gyrus.

Table 2
Altered connectivity with the left aINS in patients with insomnia disorder compared with healthy controls.

Brain region ¹	MNI coordinates (x, y, z)	Number of voxels	χ^2	Post-hoc p values			
				Wake	N1	N2	N3
<i>Group-by-stage interaction</i>							
Occipital_Mid_L/Temporal_Inf_R	(-30, -84, 22)	2190	41.11	0.0021	0.96	0.0001	0.0034
Occipital_Mid_R	(34, -74, 20)	841	33.83	0.0007	1.00	0.22	0.0081
Frontal_Sup_B	(-8, 14, 62)	663	32.30	0.013	1.00	1.00	0.10
Temporal_Inf_R	(36, -72, -14)	404	24.48	0.0004	1.00	0.0062	1.00
Postcentral_R	(48, -16, 34)	322	28.33	0.69	0.11	0.085	0.039
<i>Group effect</i>							
None							

¹ N = 33 for the patients, N = 31 for the controls; **Abbreviations:** Mid, middle; L, left; Inf, inferior; R, right; Sup, superior; B, bilateral; MNI, Montreal Neurological Institute. p values are corrected by Bonferroni correction.

connectivity of these regions gradually increased in the patients but decreased in the healthy controls.

Two clusters showed a significant group-by-stage interaction in right aINS-based functional connectivity, including the left middle occipital gyrus and superior medial frontal gyrus ($p < 0.05$ corrected, Fig. 2,

Table 3). Post hoc analysis showed that compared with controls, the functional connectivity between right aINS and left middle occipital and superior medial frontal regions in the patient group was significantly altered across wake and NREM sleep.

Notably, there was no significant main effect of group on aINS-based

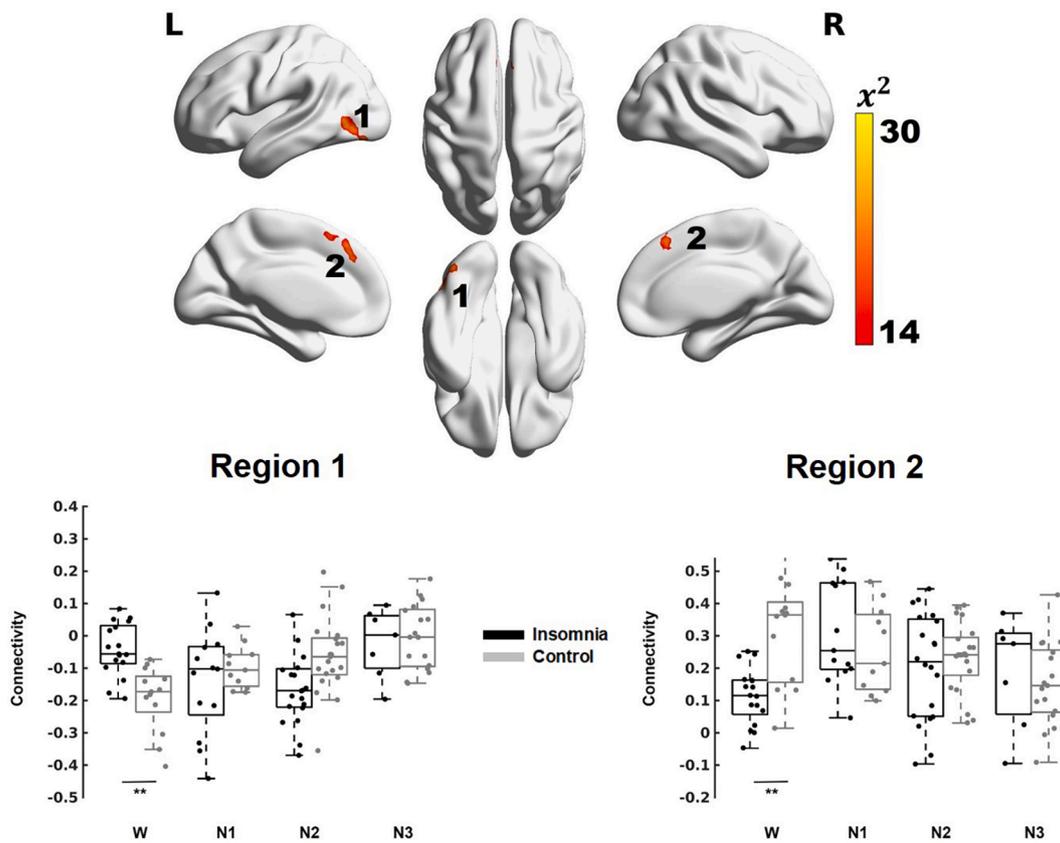


Fig. 2. Group-by-stage interaction effect on the connectivity of the right aINS. (N=33 for the patients, N=31 for the controls. $p < 0.001$ and clusterwise corrected $p < 0.05$). Average Fisher-transformed z scores (mean \pm SEM) in the clusters for the interaction (post hoc two-sample t tests between the two groups, $**p < 0.01$). Region 1, left middle occipital gyrus; Region 2, superior medial frontal gyrus.

Table 3
Altered connectivity with the right aINS in patients with insomnia disorder compared with healthy controls.

Brain regions ¹	MNI coordinates (x, y, z)	Number of voxels	χ^2	Post-hoc p values			
<i>Group-by-stage interaction</i>				Wake	N1	N2	N3
Occipital_Mid.L	(-40, -72, -6)	473	25.74	0.0004	1.00	0.20	1.00
Frontal_Sup_Med	(-2, 32, 44)	365	24.05	0.0006	1.00	1.00	1.00
<i>Group effect</i>				None			

¹ N = 33 for the patients, N = 31 for the controls; **Abbreviations:** Mid, middle; L, left; Sup, superior; Med, medial; MNI, Montreal Neurological Institute. p values are corrected by Bonferroni correction.

functional connectivity.

3.3. Exploratory correlation analysis between functional connectivity and sleep discrepancy

Group (insomnia vs. control)-by-MI interaction analysis of bilateral aINS-based functional connectivity during each of the four stages (wakefulness, N1, N2, N3) was conducted. A significant interaction effect on connectivity between aINS and the putamen/thalamus was observed during wakefulness, as shown in Fig. 3 and Table 4. In healthy controls, the correlation between MI and left aINS-left putamen/thalamus connectivity was significantly positive during wakefulness, i.e., as the subjects attempted to fall asleep ($r = 0.90, p < 0.001$), but patients with insomnia disorder showed no significant correlation. Similarly, a significant interaction effect was observed on right aINS-right putamen/thalamus connectivity during wakefulness. Healthy controls also showed a significant positive correlation between MI and right aINS connectivity, but the insomnia group showed a significant negative

correlation (Fig. 4, Table 4).

The significant group-by-MI interaction effect on the functional connectivity of the aINS suggests that functional connectivity between the aINS and the putamen/thalamus may be the key neural pathway correlated with sleep perception in healthy controls; patients with insomnia disorder show abnormal functional connectivity in this circuit, potentially representing sleep discrepancy.

4. Discussion

Using simultaneous EEG-fMRI, this study explored the aINS-based brain functional networks across wakefulness and all NREM stages to clarify the functional connectivity of the aINS and its association with sleep discrepancy between self-report and PSG in patients with insomnia disorder. We identified altered aINS-based connectivity across wakefulness and all NREM stages, and we noted a neural pathway during wakefulness that may characterize sleep perception, which may provide clues regarding the pathological mechanism of insomnia disorder and

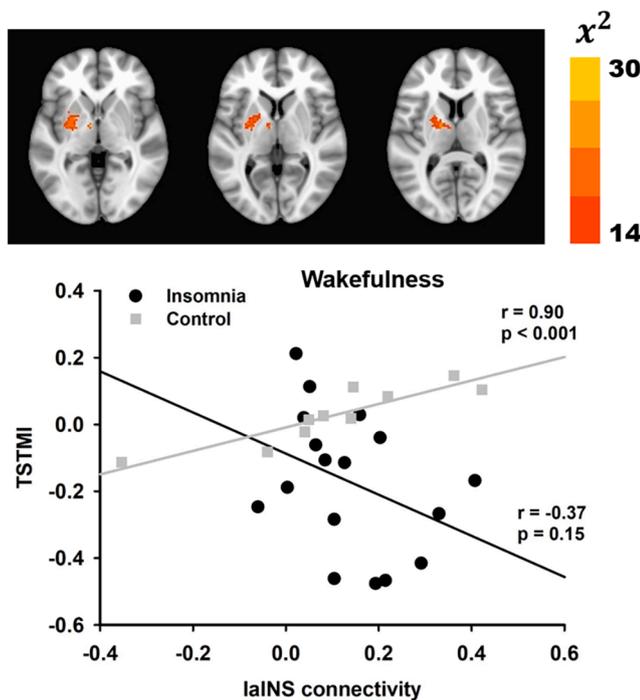


Fig. 3. MI-by-group interaction effect on the connectivity of the left aINS during wakefulness. (N=17 for the patients, N=10 for the controls). Colored brain region: left putamen/ thalamus. TSTMI, total sleep time misperception index ((sleep diary TST - PSG TST) / PSG TST); laINS, left anterior insula.

Table 4

MI-by-group interaction effect on aINS connectivity during wakefulness.

Brain regions ¹	MNI ordinates (x, y, z)	No. of voxels	χ^2
<i>Connectivity with the left anterior insula</i>			
Put_L/Tha_L	-8 -6 0	512	27.10
<i>Connectivity with the right anterior insula</i>			
Put_R/Tha_R	28 8 -10	875	39.22

¹ N = 17 for the patients, N = 10 for the controls; **Abbreviations:** Put, putamen; L, left; Tha, thalamus; R, right; MNI, Montreal Neurological Institute.

reveal the underlying neural circuitry of sleep discrepancy.

Altered connectivity between the insula and various cortical regions in insomnia across all four stages may shed new light on the pathophysiology of insomnia, including the “hyperarousal” theory and other neurobiological models. The findings of our simultaneous EEG-fMRI study are consistent with the results of a positron emission tomography-computed tomography study (Kay et al., 2016), in which Kay et al. found altered patterns of relative glucose metabolism across wakefulness and NREM sleep in brain regions involved in cognition (left frontoparietal), self-referential processes (precuneus/posterior cingulate), and affect (left middle frontal, fusiform/lingual gyri) in patients with insomnia disorder. We found that the same brain regions, such as the superior frontal and inferior temporal regions, had altered functional connectivity with the insula across all four stages. We also found altered connectivity with the middle occipital gyrus and right postcentral gyrus. The connectivity of the aINS with the gyri of the frontal, temporal and occipital lobes in insomnia patients gradually increased after the onset of N2, in contrast to a gradual decrease among healthy controls. Increased connectivity of the frontal and temporal regions with the aINS during N2 and N3 is in agreement with our previous study (Zou et al.,

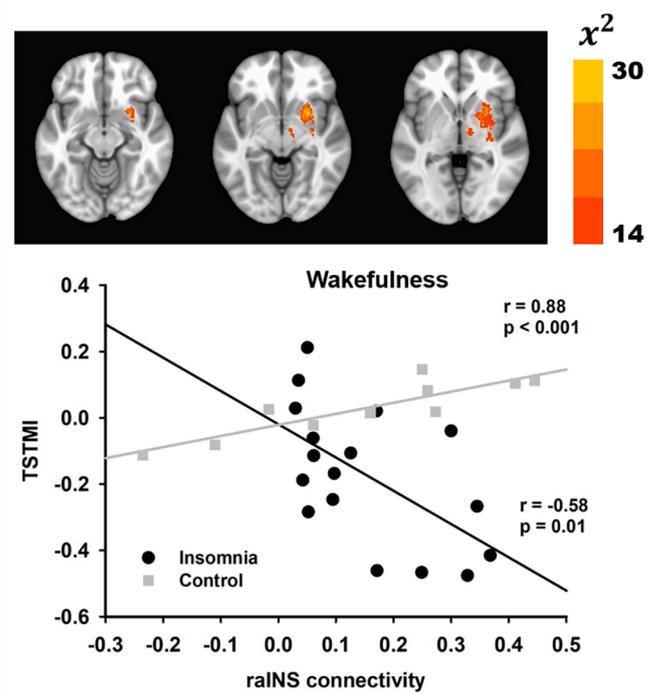


Fig. 4. MI-by-group interaction effect on the connectivity of the right aINS during wakefulness. (N=17 for the patients, N=10 for the controls). Colored brain region: right putamen/ thalamus. TSTMI, total sleep time misperception index ((sleep diary TST - PSG TST) / PSG TST); raINS, right anterior insula.

2021), which demonstrated elevated thalamo-frontal and thalamo-temporal connectivity. Those cortical regions with increased connectivity are involved in higher cognitive processes, inwardly directed attention, and conscious awareness of insomnia disorder in NREM sleep, which may be related to the patients’ main complaints regarding sleep, such as an active struggle to control sleep (Espie et al., 2006), uncontrollable intrusive thoughts (Lichstein and Rosenthal, 1980), awareness of their surroundings (Yang and Lo, 2007), and overactive sensory information processing. Unfortunately, we found no significant correlation between the altered connectivity and the MI. The increased connectivity of specific brain regions with the aINS during stable sleep may provide new insights into hyperarousal and inhibition deficits in insomnia disorder and help elucidate the pathophysiological mechanisms and neurobehavioral consequences of chronic insomnia.

The functional connectivity between the aINS and the putamen/thalamus during wakefulness may be an important pathway underlying sleep perception. We found a significant and stable positive correlation between MI and aINS connectivity during wakefulness in good sleepers, while there was a negative correlation between MI and right aINS connectivity during wakefulness in patients with insomnia disorder; there was no correlation after the onset of sleep in either insomnia patients or controls. This finding suggests that this neural pathway can effectively characterize sleep perception among good sleepers. The neural connectivity of aINS and the putamen/thalamus during wakefulness may be an important pathway to explain the neural mechanism of sleep discrepancy.

The aINS is the major node of the salience network, which is involved in the conscious awareness of exteroceptive and interoceptive stimuli, such as time perception and self-recognition. Results from both Kay (Kay et al., 2017) and Chen (Chen et al., 2014) have indicated that the aINS may be an important brain region related to sleep discrepancy in patients with insomnia.

The putamen is a component of the striatum, a subcortical structure that forms part of the basal ganglia. The putamen is involved in learning, motor control, reward, cognitive functioning and addiction (Ghandili

and Munakomi, 2022). Lu et al. found that aberrant salience network topology and frontostriatal connectivity may be linked to the severity of insomnia and proposed that aberrant connectivity could serve as an important biomarker for insomnia. (Lu et al., 2017) Previous studies have found altered resting-state functional connectivity between the putamen and other regions in patients with insomnia disorder, such as the thalamus (Li et al., 2019), dorsolateral prefrontal cortex (Zhou et al., 2020), and nucleus accumbens (Shao et al., 2020), which may be correlated with the severity of insomnia (Li et al., 2019; Lu et al., 2017; Motomura et al., 2021). Li et al. found that the resting-state functional connectivity between the thalamus and the putamen, caudate, and hippocampus was negatively correlated with PSQI scores among patients with insomnia disorder (Li et al., 2019). After 36 h of total sleep deprivation, the functional connectivity between the putamen and the bilateral precentral gyrus, bilateral postcentral gyrus, bilateral temporal lobe, and left caudate nucleus was significantly reduced (Wang et al., 2021). Another study showed that after cognitive-behavioral therapy for insomnia, patients with insomnia disorder exhibited decreased functional connectivity between the putamen and motor cortex and between the thalamus and parietal cortex (Lee et al., 2018). These studies suggest that the putamen may be the key brain region associated with the severity of insomnia in patients with insomnia disorder. The thalamus is an important part of the ascending reticular activating system. Thalamic function has been closely linked to vigilance levels, transitions between sleep and wakefulness, and arousals from NREM sleep (Zou et al., 2020). A previous study showed that thalamic connectivity with subcortical and right temporal regions during N1 sleep was correlated with the MI (Zou et al., 2021). The thalamus may be the key brain area in the sleep-wake transition, and this function of the thalamus may be related to sleep discrepancy in patients with insomnia. Thus, the neural pathway linking the aINS to the putamen and thalamus may be a characteristic pathway of sleep discrepancy in insomnia disorder.

The combination of fMRI and EEG can provide distinctive insights within specific sleep stages, (Spiegelhalder et al., 2013) it is necessary to explore brain activity during sleep stages. Using simultaneous EEG-fMRI, we find that wakefulness and the wake-sleep transition state may be important states for sleep discrepancy in patients with insomnia disorder. There was a significant correlation between MI and aINS connectivity during wakefulness; the wakefulness epochs were selected from rest periods as subjects attempted to fall asleep, and according to the instructions, they were asked to close their eyes and try to sleep, or from waking periods interspersed with sleep, so the wakefulness was the state with eyes closed and trying to sleep at night. Our finding is consistent with previous studies. Chen found that it was during rest and trying to fall asleep that patients with insomnia disorder had increased involvement of the aINS with salience networks (Chen et al., 2014). Another study showed enhanced synchronized frontoparietal activation during the wake-sleep transition in patients with primary insomnia disorder (Corsi-Cabrera et al., 2012a), and the persistence of network activation during the wake-sleep transition period may help explain sleep discrepancy in insomnia patients with lighter, poorer sleep. Recently, another study showed that patients with insomnia, particularly those with sleep discrepancy, need longer continuous sleep bouts than healthy controls in order to perceive sleep onset. (Hermans et al., 2020) Insomnia patients showed difficulties disengaging from wakeful processes and some inability to initiate normal sleep processes at sleep onset compared to good sleepers (Bastien et al., 2008). Taken together, these researches suggest that the period of rest preceding sleep and periods of wakefulness interrupting sleep may be very important periods to clarify the underlying mechanisms of sleep discrepancy in patients with insomnia disorder. Previous studies have found a possible correlation between altered brain activity and sleep discrepancy in N1 (Schinkelshoek et al., 2020; Zou et al., 2021), REM (Feige et al., 2008; Feige et al., 2021), or NREM sleep (Kay et al., 2017; Maes et al., 2014) in patients with insomnia disorder. Therefore, these findings suggest that

sleep discrepancy in insomnia may have multiple, complex pathological mechanisms, which may involve wakefulness and different sleep stages.

This study not only provides the basis of brain functional changes, but also has clinical significance of treatment for sleep discrepancy. The neural pathways connecting the right aINS with the right putamen and thalamus may constitute a new, therapeutically meaningful neural circuit for sleep discrepancy; and wakefulness before sleep onset may be an important physiological state to target with interventions. Mindfulness meditation or relaxation training before sleep are generally advised to improve subjective sleep quality, and this study provides some theoretical evidence for these intervention strategies. In the future, therapeutic interventions targeting the aINS-putamen/thalamus neural circuit during the waking state can be explored as a new method to help improve sleep discrepancy.

There are some limitations to this study. First, the nighttime EEG-fMRI scans were not always successful. Although participants completed an adaptation session to promote sleep in the scanner, some of the patients with insomnia disorder still could not fall asleep in the uncomfortable scanning environment, the sample size is limited. Second, a stringent standard (consistency between two raters) was applied to ensure the accuracy of sleep stage scoring, which left some subjects with only one 5-min epoch in certain NREM stages; the scarcity of data for some sleep stages may have influenced the reliability of the functional connectivity analysis. (Noble et al., 2019) It may be beneficial to obtain more stable sleep periods by prolonging the scanning time to a certain extent (Moehlman et al., 2019). Third, some covariates were not well controlled. Although insomnia patients with past or present depression or anxiety were excluded at the time of enrollment, the mean SDS and SAS scores of patients with insomnia disorder were still higher than that of healthy controls, which may be related to the common pathway of insomnia and emotion in patients with insomnia disorder, as many studies showed (Bagherzadeh-Azbari et al., 2019; Baglioni et al., 2010; Vandekerckhove and Cluydts, 2010); if the covariates of SDS and SAS were fully controlled, the apparent difference in sleep discrepancy might be diminished somewhat. Finally, sleep diary was not computed on the night of the actual fMRI-EEG scan. Sleep diary on the EEG-fMRI night were only acquired from one third of the participants. The sample size was too small for correlation analysis. Meanwhile, PSG-diary sleep discrepancy can still reflect the discrepancy. Sleep discrepancy has been found to be consistent in younger adults, and older adults with sleep complaints exhibited night-to-night variability in sleep discrepancy (Kay et al., 2013). The participants in the current study are middle-aged people, whose sleep discrepancies are more stable than that of the elderly.

5. Conclusion

The aINS-based brain functional network and its correlation with sleep discrepancy between self-report and PSG were explored in patients with insomnia disorder across wakefulness and all NREM stages using simultaneous EEG-fMRI. Increased connectivity in the aINS-cortical network during stable NREM sleep may provide new evidence for hyperarousal and inhibitory deficits in patients with insomnia disorder. A new neural pathway connecting the aINS to the putamen and thalamus during wakefulness may underlie the sleep perception of healthy people, which may provide clues regarding the complex waking-state neural mechanisms of sleep discrepancy in insomnia disorder; this pathway may also suggest regions and physiological states that would be meaningful therapeutic targets for sleep discrepancy.

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.2022.103111>.

References

- Alameddine, Y., Ellenbogen, J.M., Bianchi, M.T., 2015. Sleep-wake time perception varies by direct or indirect query. *J Clin Sleep Med* 11, 123–129. <https://doi.org/10.5664/jcs.m.4456>.
- Allen, P.J., Josephs, O., Turner, R., 2000. A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage* 12, 230–239. <https://doi.org/10.1006/nimg.2000.0599>.
- American-Psychiatric-Association, 2013. *Diagnostic and statistical manual of mental disorders*, 5th ed. American Psychiatric Association, Washington, DC.
- Bagherzadeh-Azbari, S., Khazaie, H., Zarei, M., Spiegelhalter, K., Walter, M., Leerssen, J., Van Someren, E.J.W., Sepehry, A.A., Tahmasian, M., 2019. Neuroimaging insights into the link between depression and insomnia: A systematic review. *J Affect Disord* 258, 133–143. <https://doi.org/10.1016/j.jad.2019.07.089>.
- Baglioni, C., Spiegelhalter, K., Lombardo, C., Riemann, D., 2010. Sleep and emotions: a focus on insomnia. *Sleep Med Rev* 14, 227–238. <https://doi.org/10.1016/j.smrv.2009.10.007>.
- Bastien, C.H., St-Jean, G., Morin, C.M., Turcotte, I., Carrier, J., 2008. Chronic psychophysiological insomnia: hyperarousal and/or inhibition deficits? An ERPs investigation. *Sleep* 31, 887–898. <https://doi.org/10.1093/sleep/31.6.887>.
- Beattie, L., Espie, C.A., Kyle, S.D., Biello, S.M., 2015. How are normal sleeping controls selected? A systematic review of cross-sectional insomnia studies and a standardized method to select healthy controls for sleep research. *Sleep Medicine* 16, 669–677. <https://doi.org/10.1016/j.sleep.2015.01.010>.
- Benz, F., Riemann, D., Feige, B., 2020. Dreaming and Insomnia: Link between Physiological REM Parameters and Mentation Characteristics. *Brain Sci* 10. <https://doi.org/10.3390/brainsci10060378>.
- Birn, R.M., Molloy, E.K., Patriat, R., Parker, T., Meier, T.B., Kirk, G.R., Nair, V.A., Meyerand, M.E., Prabhakaran, V., 2013. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage* 83, 550–558. <https://doi.org/10.1016/j.neuroimage.2013.05.099>.
- Chen, M.C., Chang, C., Glover, G.H., Gotlib, I.H., 2014. Increased insula coactivation with salience networks in insomnia. *Biol Psychol* 97, 1–8. <https://doi.org/10.1016/j.biopsycho.2013.12.016>.
- Corsi-Cabrera, M., Figueredo-Rodríguez, P., del Río-Portilla, Y., Sanchez-Romero, J., Galán, L., Bosch-Bayard, J., 2012a. Enhanced frontoparietal synchronized activation during the wake-sleep transition in patients with primary insomnia. *Sleep* 35, 501–511. <https://doi.org/10.5665/sleep.1734>.
- Corsi-Cabrera, M., Figueredo-Rodríguez, P., del Río-Portilla, Y., Sánchez-Romero, J., Galán, L., Bosch-Bayard, J., 2012b. Enhanced frontoparietal synchronized activation during the wake-sleep transition in patients with primary insomnia. *Sleep* 35, 501–511. <https://doi.org/10.5665/sleep.1734>.
- Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29, 162–173. <https://doi.org/10.1006/cbmr.1996.0014>.
- Craig, A.D., 2009. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci* 10, 59–70. <https://doi.org/10.1038/nrn2555>.
- Drummond, S.P., Smith, M.T., Orff, H.J., Chengazi, V., Perlis, M.L., 2004. Functional imaging of the sleeping brain: review of findings and implications for the study of insomnia. *Sleep Med Rev* 8, 227–242. <https://doi.org/10.1016/j.smrv.2003.10.005>.
- Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A* 113, 7900–7905. <https://doi.org/10.1073/pnas.1602413113>.
- Espie, C.A., Broomfield, N.M., MacMahon, K.M., Macphee, L.M., Taylor, L.M., 2006. The attention-intention-effort pathway in the development of psychophysiological insomnia: a theoretical review. *Sleep Med Rev* 10, 215–245. <https://doi.org/10.1016/j.smrv.2006.03.002>.
- Feige, B., Al-Shajlawi, A., Nissen, C., Voderholzer, U., Hornyak, M., Spiegelhalter, K., Kloepfer, C., Perlis, M., Riemann, D., 2008. Does REM sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients. *J Sleep Res* 17, 180–190. <https://doi.org/10.1111/j.1365-2869.2008.00651.x>.
- Feige, B., Baglioni, C., Boehm, P., Heinrich, A., Trumm, S., Benz, F., Nissen, C., Domschke, K., Frase, L., Riemann, D., 2021. Event-related potentials in insomnia reflect altered perception of sleep. *Sleep* 44. <https://doi.org/10.1093/sleep/zsab137>.
- Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S., Turner, R., 1996. Movement-related effects in fMRI time-series. *Magn Reson Med* 35, 346–355. <https://doi.org/10.1002/mrm.1910350312>.
- Ghandili, M., Munakami, S., 2022. Neuroanatomy, Putamen. StatPearls. StatPearls Publishing.
- Gokce, F., Ehring, T., Werner, G.G., Takano, K., 2020. Misperception of sleep is associated with intrinsic motivation toward thinking about sleep. *J Behav Ther Exp Psychiatry* 69, 101591. <https://doi.org/10.1016/j.jbtep.2020.101591>.
- Harvey, A.G., 2002. A cognitive model of insomnia. *Behav Res Ther* 40, 869–893. [https://doi.org/10.1016/s0005-7967\(01\)00061-4](https://doi.org/10.1016/s0005-7967(01)00061-4).
- Harvey, A.G., Tang, N.K., 2012. (Mis)perception of sleep in insomnia: a puzzle and a resolution. *Psychol Bull* 138, 77–101. <https://doi.org/10.1037/a0025730>.
- Hermans, L.W.A., van Gilst, M.M., Regis, M., van den Heuvel, L.C.E., Langen, H., van Mierlo, P., Krijn, R., Hoondert, B., Maass, H., van Dijk, J.P., Leufkens, T.R.M., Overeem, S., 2020. Modeling sleep onset misperception in insomnia. *Sleep* 43. <https://doi.org/10.1093/sleep/zsaa014>.
- Hsiao, F.C., Tsai, P.J., Wu, C.W., Yang, C.M., Lane, T.J., Lee, H.C., Chen, L.C., Lee, W.K., Lu, L.H., Wu, Y.Z., 2018. The neurophysiological basis of the discrepancy between objective and subjective sleep during the sleep onset period: an EEG-fMRI study. *Sleep* 41. <https://doi.org/10.1093/sleep/zsy056>.
- Iber, C., Ancoli-Israel, S., Chesson, A.L., Quan, S., 2007. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, 1st ed. American Academy of Sleep Medicine, Westchester, IL.
- Kay, D.B., Dzierzewski, J.M., Rowe, M., McCrae, C.S., 2013. Greater night-to-night variability in sleep discrepancy among older adults with a sleep complaint compared to noncomplaining older adults. *Behav Sleep Med* 11, 76–90. <https://doi.org/10.1080/15402002.2011.602775>.
- Kay, D.B., Karim, H.T., Soehner, A.M., Hasler, B.P., James, J.A., Germain, A., Hall, M.H., Franzen, P.L., Price, J.C., Nofzinger, E.A., Buysse, D.J., 2017. Subjective-Objective Sleep Discrepancy Is Associated With Alterations in Regional Glucose Metabolism in Patients With Insomnia and Good Sleeper Controls. *Sleep* 40. <https://doi.org/10.1093/sleep/zsx155>.
- Kay, D.B., Karim, H.T., Soehner, A.M., Hasler, B.P., Wilckens, K.A., James, J.A., Aizenstein, H.J., Price, J.C., Rosario, B.L., Kupfer, D.J., Germain, A., Hall, M.H., Franzen, P.L., Nofzinger, E.A., Buysse, D.J., 2016. Sleep-Wake Differences in Relative Regional Cerebral Metabolic Rate for Glucose among Patients with Insomnia Compared with Good Sleepers. *Sleep* 39, 1779–1794. <https://doi.org/10.5665/sleep.6154>.
- Lee, H.C., Chiu, H.F., Wing, Y.K., Leung, C.M., Kwong, P.K., Chung, D.W., 1994. The Zung Self-rating Depression Scale: screening for depression among the Hong Kong Chinese elderly. *J Geriatr Psychiatry Neurol* 7, 216–220. <https://doi.org/10.1177/089198879400700404>.
- Lee, Y.G., Kim, S., Kim, N., Choi, J.W., Park, J., Kim, S.J., Gwak, A.R., Lee, Y.J., 2018. Changes in subcortical resting-state functional connectivity in patients with psychophysiological insomnia after cognitive-behavioral therapy: Changes in resting-state FC after CBT for insomnia patients. *Neuroimage Clin* 17, 115–123. <https://doi.org/10.1016/j.nicl.2017.10.013>.
- Levenson, J.C., Kay, D.B., Buysse, D.J., 2015. The pathophysiology of insomnia. *Chest* 147, 1179–1192. <https://doi.org/10.1378/chest.14-1617>.
- Li, M., Wang, R., Zhao, M., Zhai, J., Liu, B., Yu, D., Yuan, K., 2019. Abnormalities of thalamus volume and resting state functional connectivity in primary insomnia patients. *Brain Imaging Behav* 13, 1193–1201. <https://doi.org/10.1007/s11682-018-9932-y>.
- Lichstein, K.L., Rosenthal, T.L., 1980. Insomniacs' perceptions of cognitive versus somatic determinants of sleep disturbance. *J Abnorm Psychol* 89, 105–107. <https://doi.org/10.1037/0021-843x.89.1.105>.
- Liu, X.C., Tang, M.Q., 1996. Reliability and validity of the Pittsburgh Sleep Quality Index. *Chinese Journal of Psychiatry* 29, 29103–29107.
- Lu, F.M., Liu, C.H., Lu, S.L., Tang, L.R., Tie, C.L., Zhang, J., Yuan, Z., 2017. Disrupted Topology of Frontostriatal Circuits Is Linked to the Severity of Insomnia. *Front Neurosci* 11, 214. <https://doi.org/10.3389/fnins.2017.00214>.
- Maes, J., Verbraecken, J., Willems, M., De Volder, I., van Gastel, A., Michiels, N., Verbeek, I., Vandekerckhove, M., Wuyts, J., Haex, B., Willems, T., Exadaktylos, V., Bulckaert, A., Cluydts, R., 2014. Sleep misperception, EEG characteristics and autonomic nervous system activity in primary insomnia: a retrospective study on polysomnographic data. *Int J Psychophysiol* 91, 163–171. <https://doi.org/10.1016/j.ijpsycho.2013.10.012>.
- Manconi, M., Ferri, R., Sagrada, C., Punjabi, N.M., Tettamanzi, E., Zucconi, M., Oldani, A., Castronovo, V., Ferini-Strambi, L., 2010. Measuring the error in sleep estimation in normal subjects and in patients with insomnia. *J Sleep Res* 19, 478–486. <https://doi.org/10.1111/j.1365-2869.2009.00801.x>.
- Mitra, A., Snyder, A.Z., Hacker, C.D., Pahwa, M., Tagliazucchi, E., Laufs, H., Leuthardt, E.C., Raichle, M.E., 2016. Human cortical-hippocampal dialogue in wake and slow-wave sleep. *E6876 Proc Natl Acad Sci U S A* 113, E6868. <https://doi.org/10.1073/pnas.1607289113>.
- Moehlan, T.M., de Zwart, J.A., Chappel-Farley, M.G., Liu, X., McClain, I.B., Chang, C., Mandelkow, H., Ozbay, P.S., Johnson, N.L., Bieber, R.E., Fernandez, K.A., King, K.A., Zalewski, C.K., Brewer, C.C., van Gelderen, P., Duyn, J.H., Picchioni, D., 2019. All-night functional magnetic resonance imaging sleep studies. *J Neurosci Methods* 316, 83–98. <https://doi.org/10.1016/j.jneumeth.2018.09.019>.
- Motomura, Y., Katsunuma, R., Ayabe, N., Oba, K., Terasawa, Y., Kitamura, S., Moriguchi, Y., Hida, A., Kamei, Y., Mishima, K., 2021. Decreased activity in the reward network of chronic insomnia patients. *Sci Rep* 11, 3600. <https://doi.org/10.1038/s41598-020-79989-2>.

- Noble, S., Scheinost, D., Constable, R.T., 2019. A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *Neuroimage* 203, 116157. <https://doi.org/10.1016/j.neuroimage.2019.116157>.
- Ohayon, M.M., 2002. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 6, 97–111. <https://doi.org/10.1053/smr.2002.0186>.
- Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84, 320–341. <https://doi.org/10.1016/j.neuroimage.2013.08.048>.
- Riemann, D., Spiegelhalter, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., Nissen, C., 2010. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 14, 19–31. <https://doi.org/10.1016/j.smr.2009.04.002>.
- Roth, T., Coulouvrat, C., Hajak, G., Lakoma, M.D., Sampson, N.A., Shahly, V., Shillington, A.C., Stephenson, J.J., Walsh, J.K., Kessler, R.C., 2011. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol Psychiatry* 69, 592–600. <https://doi.org/10.1016/j.biopsych.2010.10.023>.
- Samann, P.G., Wehrle, R., Hoehn, D., Spoormaker, V.I., Peters, H., Tully, C., Holsboer, F., Czisch, M., 2011. Development of the brain's default mode network from wakefulness to slow wave sleep. *Cereb Cortex* 21, 2082–2093. <https://doi.org/10.1093/cercor/bhq295>.
- Schinkelshoek, M.S., de Wit, K., Bruggink, V., Fronczek, R., Lammers, G.J., 2020. Daytime sleep state misperception in a tertiary sleep centre population. *Sleep Med* 69, 78–84. <https://doi.org/10.1016/j.sleep.2019.12.026>.
- Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27, 2349–2356. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>.
- Shao, Z., Xu, Y., Chen, L., Wang, S., Zhang, M., Liu, S., Wen, X., Yu, D., Yuan, K., 2020. Dysfunction of the NAc-mPFC circuit in insomnia disorder. *Neuroimage Clin* 28, 102474. <https://doi.org/10.1016/j.nicl.2020.102474>.
- D.V. Sheehan Y. Lecrubier K.H. Sheehan P. Amorim J. Janavs E. Weiller T. Hergueta R. Baker G.C. Dunbar The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10 *J Clin Psychiatry* 59 Suppl 20 1998 22–33;quiz 34–57.
- Spiegelhalter, K., Regen, W., Baglioni, C., Riemann, D., Winkelmann, J.W., 2013. Neuroimaging studies in insomnia. *Curr Psychiatry Rep* 15, 405. <https://doi.org/10.1007/s11920-013-0405-0>.
- Spoormaker, V.I., Schroter, M.S., Gleiser, P.M., Andrade, K.C., Dresler, M., Wehrle, R., Samann, P.G., Czisch, M., 2010. Development of a large-scale functional brain network during human non-rapid eye movement sleep. *J Neurosci* 30, 11379–11387. <https://doi.org/10.1523/JNEUROSCI.2015-10.2010>.
- Stephan, A.M., Lecci, S., Cataldi, J., Siclari, F., 2021. Conscious experiences and high-density EEG patterns predicting subjective sleep depth. *Current Biology* 31, 5487–+. <https://doi.org/10.1016/j.cub.2021.10.012>.
- Takano, K., Boddez, Y., Raes, F., 2016. I sleep with my Mind's eye open: Cognitive arousal and overgeneralization underpin the misperception of sleep. *J Behav Ther Exp Psychiatry* 52, 157–165. <https://doi.org/10.1016/j.jbtep.2016.04.007>.
- Te Lindert, B.H.W., Blanken, T.F., van der Meijden, W.P., Dekker, K., Wassing, R., van der Werf, Y.D., Ramautar, J.R., Van Someren, E.J.W., 2020. Actigraphic multi-night home-recorded sleep estimates reveal three types of sleep misperception in Insomnia Disorder and good sleepers. *J Sleep Res* 29, e12937. <https://doi.org/10.1111/jsr.12937>.
- Trajanovic, N.N., Radivojevic, V., Kaushansky, Y., Shapiro, C.M., 2007. Positive sleep state misperception – A new concept of sleep misperception. *Sleep Med* 8, 111–118. <https://doi.org/10.1016/j.sleep.2006.08.013>.
- Van Dijk, K.R., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *J Neurophysiol* 103, 297–321. <https://doi.org/10.1152/jn.00783.2009>.
- Vandekerckhove, M., Cluydts, R., 2010. The emotional brain and sleep: an intimate relationship. *Sleep Med Rev* 14, 219–226. <https://doi.org/10.1016/j.smr.2010.01.002>.
- Wang, H., Yu, K., Yang, T., Zeng, L., Li, J., Dai, C., Peng, Z., Shao, Y., Fu, W., Qi, J., 2021. Altered Functional Connectivity in the Resting State Neostriatum After Complete Sleep Deprivation: Impairment of Motor Control and Regulatory Network. *Front Neurosci* 15, 665687. <https://doi.org/10.3389/fnins.2021.665687>.
- Yang, C.M., Lo, H.S., 2007. ERP evidence of enhanced excitatory and reduced inhibitory processes of auditory stimuli during sleep in patients with primary insomnia. *Sleep* 30, 585–592. <https://doi.org/10.1093/sleep/30.5.585>.
- Zheng, B., Li, M., Wang, K.L., Lv, J., 2016. Analysis of the reliability and validity of the Chinese version of Pittsburgh sleep quality index among medical college students. *Beijing Da Xue Xue Bao Yi Xue Ban* 48, 424–428.
- Zhou, F., Zhu, Y., Zhu, Y., Huang, M., Jiang, J., He, L., Huang, S., Zeng, X., Gong, H., 2020. Altered long- and short-range functional connectivity density associated with poor sleep quality in patients with chronic insomnia disorder: A resting-state fMRI study. *Brain Behav* 10, e01844. <https://doi.org/10.1002/brb3.1844>.
- Zou, G., Li, Y., Liu, J., Zhou, S., Xu, J., Qin, L., Shao, Y., Yao, P., Sun, H., Zou, Q., Gao, J.H., 2021. Altered thalamic connectivity in insomnia disorder during wakefulness and sleep. *Hum Brain Mapp* 42, 259–270. <https://doi.org/10.1002/hbm.25221>.
- Zou, G., Xu, J., Zhou, S., Liu, J., Su, Z.H., Zou, Q., Gao, J.H., 2020. Functional MRI of arousals in nonrapid eye movement sleep. *Sleep* 43. <https://doi.org/10.1093/sleep/zsz218>.