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Characteristics of locus coeruleus functional connectivity network in patients with comorbid migraine and insomnia

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Abstract

Background Migraine and insomnia are prevalent conditions that often co-occur, each exacerbating the other and substantially impacting the quality of life. The locus coeruleus (LC), a brainstem region responsible for norepinephrine synthesis, participates in pain modulation, sleep/wake cycles, and emotional regulation, rendering it a potential nexus in the comorbidity of migraine and insomnia. Disruptions in the LC-noradrenergic system have been hypothesized to contribute to the comorbidities of migraine and insomnia, although neuroimaging evidence in humans remains scarce. In this study, we aimed to investigate the intrinsic functional connectivity (FC) network of the LC in patients with comorbid migraine and subjective chronic insomnia and patients with migraine with no insomnia (MnI) using resting-state functional magnetic resonance imaging (rs-fMRI) and seed-based FC analyses.

Methods In this cross-sectional study, 30 patients with comorbid migraine and chronic insomnia (MI), 30 patients with MnI, and 30 healthy controls (HCs) were enrolled. Participants underwent neuropsychological testing and rs-fMRI. The LC-FC network was constructed using seed-based voxel-wise FC analysis. To identify group differences in LC-FC networks, voxel-wise covariance analysis was conducted with sex and age as covariates. Subsequently, a partial correlation analysis was conducted to probe the clinical relevance of aberrant LC-FC in patients with MI and MnI.

Results Except for the insomnia score, no other significant difference was detected in demographic characteristics and behavioral performance between the MI and MnI groups. Compared with HCs, patients with MI exhibited altered LC-FC in several brain regions, including the dorsomedial prefrontal cortex (DMPFC), anterior cerebellum, dorsolateral prefrontal cortex (DLPFC), thalamus, and parahippocampal gyrus (PHG). Lower FC between the LC and DLPFC was associated with greater insomnia severity, whereas higher FC between the LC and DMPFC was linked to longer migraine attack duration in the MI group.

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Conclusion Our findings reveal the presence of aberrant LC-FC networks in patients with MI, providing neuroimaging evidence of the interplay between these conditions. The identified LC-FC alterations may serve as potential targets for therapeutic interventions and highlight the importance of considering the LC-noradrenergic system in the management of MI.

Keywords Migraine, Insomnia, Locus coeruleus, Functional connectivity

Background

Migraine, a prevalent neurological disorder characterized by recurrent episodes of severe headaches, affects approximately 10–20% of the global population [1]. Insomnia, a common sleep disorder, is characterized by difficulties in initiating or maintaining sleep and affects roughly the same proportion of individuals [2]. The comorbidity of migraine and insomnia is not merely coincidental; epidemiological studies have consistently shown that these two conditions are intricately linked, with each exacerbating the other and considerably burdening an individual's quality of life and socioeconomic status [3, 4].

The relationship between migraine and insomnia suggests a shared neuroimaging underpinning, where sleep disturbances can trigger migraine attacks, and individuals with migraine often report poor sleep quality [4]. Recent neuroimaging studies have highlighted the intricate interplay between these two conditions. For instance, research using resting-state functional magnetic resonance imaging (rs-fMRI) has demonstrated alterations in the default mode network (DMN), a brain network previously linked to both migraine and insomnia pathophysiology [5]. Additionally, a structural covariance network analysis revealed changes in the postcentral gyrus in patients with comorbid migraine and insomnia [6]. This accumulating evidence indicates a complex interconnection between migraine and insomnia, suggesting the potential for shared neuroanatomical substrates that can be targeted for therapeutic interventions.

Continuing with this line of inquiry, the locus coeruleus (LC) is a region in the brainstem primarily responsible for the synthesis of norepinephrine (NE). The LC receives afferent signals from nociceptive neurons of the trigeminovascular complex and paraventricular hypothalamic nuclei [7, 8]. The LC-NE system has been implicated in pain modulation, sleep/wake cycle, emotional regulation, and stress-induced anxiety, positioning it as a potential nexus in the pathophysiology of migraine and insomnia [9]. Our previous study identified dysfunctional LC-NE functional connectivity (FC) in patients with chronic insomnia disorder, with these alterations linked to anxiety symptoms [10]. Additionally, altered FC between the LC and hypothalamus has been observed in patients with migraine [11]. These findings suggest a potential common pathway in individuals with MI. Furthermore, a recent animal study revealed that acute sleep deprivation could exacerbate migraine-like headaches and that activating NE neurons in the LC reduces pain thresholds and increases sleep latency, with inhibition of these neurons producing the opposite effects [12]. Despite these insights, neuroimaging evidence confirming disruptions in the LC-NE system as a contributing factor to the comorbidities of migraine and insomnia in humans remains limited.

Therefore, in the current study, we aimed to examine the intrinsic LC-FC network in patients with MI and those with migraine with no insomnia (MnI) using rs-fMRI data and seed-based FC analysis. We hypothesized that patients with MI exhibit abnormal LC-FC networks in the fronto-parietal control, default mode, and somatomotor networks. Furthermore, we postulated that these aberrant LC-FC networks correlate with key clinical features, such as insomnia severity and headache characteristics, specifically in the MI group. Our goal was to provide a neuroimaging basis for the observed comorbidity between migraine and insomnia while also refining the focus of the analysis to the most relevant correlations based on prior hypotheses.

Methods

Participants

In this cross-sectional study, we recruited all participants from the outpatient department of the Third Affiliated Hospital of Anhui Medical University to investigate the LC-FC network in patients with MI and those with MnI. The sample comprised 30 patients with MI, 30 patients with MnI, and 30 age-, sex-, and education-matched healthy controls (HC). All participants underwent various neuropsychological tests and rs-fMRI scans. Additionally, a structured interview was conducted by trained researchers (CLW and CHX) to gather diagnostic information and detailed substance use histories from the participants. All participants were of Chinese Han descent and right-handed.

To qualify for the MI group, the participants fulfilled the diagnostic criteria for migraine without aura (MwoA) and insomnia disorder (ID). The MwoA diagnosis was based on the third edition of the International Classification of Headache Disorders (ICHD-3) [13] and confirmed when the following conditions were met: (A) the individual experienced at least five episodes that satisfied criteria B–D; (B) each headache episode lasted for a period of 4–72 h if left untreated or when treatment was

ineffective; (C) headaches with at least two of the following attributes: lateralized location, throbbing nature, moderate to severe intensity, and exacerbation by or leading to avoidance of routine physical activities, such as walking or climbing stairs; (D) presence of at least one of the following symptoms during a headache episode: nausea and/or vomiting and sensitivity to light and sound; and (E) headaches could not be explained more accurately by another ICHD-3 classification. In our study, migraine diagnosis was based on a combination of diaries and recall. ID diagnosis was based on the following criteria set out in the third version of the International Classification of Sleep Disorders [14]: (A) difficulty initiating or maintaining sleep or early-morning awakening with inability to return to sleep; (B) sleep disturbance causing substantial distress or impairment in social, occupational, or other important areas of functioning; (C) sleep difficulty occurring at least 3 times per week and present for at least 3 months. (D) sleep difficulty not attributable to another sleep disorder; and (E) a Pittsburgh Sleep Quality Index (PSQI) score>7 indicates patients with insomnia symptoms [15, 16]. Additional eligibility requirements for the MI group were (1) abstaining from analgesics, sedatives, or antidepressants for 3 days prior to neuropsychological testing and MRI scanning and (2) participant age range from 18 to 55 years. Exclusion criteria were: (1) history of other neuropsychiatric conditions; (2) history of substance misuse involving caffeine, nicotine, or alcohol; (3) history of other neurological or psychiatric illnesses such as convulsions, head trauma, cerebrovascular accidents, or transient ischemic episodes; and (4) contraindications for MRI. The inclusion criteria for the MnI group were the same as those for the MI group but with a PSQI score of ≤7. Inclusion criteria for the HC group were good sleep patterns, emotional stability, and normal cognitive abilities; exclusion criteria were the same as those for the MI and MnI groups: (1) a history of other neuropsychiatric conditions; (2) a history of substance misuse involving caffeine, nicotine, or alcohol; (3) a history of other neurological or psychiatric illnesses, convulsions, head trauma, cerebrovascular accidents, or transient ischemic episodes; and (4) contraindications for MRI. No participants had signs of brain abnormalities on standard T2-weighted MRI scans.

Five participants, two with MI, two with MnI, and one HC, were excluded from the study owing to excessive head motion artifacts exceeding 2 mm or 2°. The final analysis included 28 patients with MI, 28 patients with MnI, and 29 HCs. This study was approved by the Institutional Review Board of the Third Affiliated Hospital of Anhui Medical University (Approval Number 2023-044-01). All participants provided written informed consent for participation in this study.

Neuropsychological test

To assess the severity of headaches over the preceding 3 months, the visual analog scale (VAS) was used [17]. The six-item Headache Impact Test (HIT-6) was employed to measure the impact of headaches on day-to-day functioning [18]. Subjective assessments of sleep quality and insomnia severity were conducted using the PSQI [15, 19]. A PSQI score>7 indicates that patients were experiencing substantial insomnia symptoms [15, 20]. Symptoms of depression and anxiety were evaluated using the Zung Self-Rating Depression Scale (SDS) and Zung Self-Rating Anxiety Scale (SAS) [21, 22]. All neuropsychological assessments were conducted prior to the imaging procedures.

Imaging data

The imaging procedures were conducted at the Third Affiliated Hospital of Anhui Medical University using a Siemens Verio 3.0-Tesla MRI scanner (Siemens Corporation, Erlangen, Germany). Based on the availability of the imaging equipment, the scanning sessions for all participants were scheduled from 16:00 to 22:00. The MRI scanning times are detailed in Table S1. A chi-square test revealed a significant difference in scanning times across the groups ($\chi^2 = 10.81$, $p=0.03$). To account for this variability, we included scanning time as a covariate in the imaging analysis. High-resolution structural images were captured using a spoiled gradient-recalled echo sequence, with the following technical settings: repetition time to echo time ratio, 1,900/2.52 ms; flip angle, 9°; acquisition matrix, 256×256; field-of-view, 240×240 mm; slice thickness, 1.0 mm with no gap between slices; and 192 slices per acquisition, with a single excitation. Rs-fMRI data were collected over an 8-min period using a gradient-recalled echo-planar imaging sequence, with parameters set at a TR/TE of 2,000/35 ms, 90° flip angle, 64×64 acquisition matrix, 3.5 mm slice thickness, 33 slices, and 240 time points. Participants were instructed to remain relaxed with their eyes closed throughout the scanning process, and head stabilizers were used to minimize movement. Vigilance was confirmed after scanning, verifying that all participants remained conscious throughout the examination.

Rs-fMRI data underwent comprehensive preprocessing using the Statistical Parametric Mapping software package, version 12, and the Data Processing & Analysis of Brain Imaging (DPABI) toolbox, version 6.0 [23]. These tools were integrated into MATLAB 8.0 (MathWorks, Inc, Natick, MA, USA). The initial five volumes from the rs-fMRI time series were discarded to mitigate the effects of magnetization equilibrium and environmental adaptation. Subsequently, 235 images underwent slice-timing correction, reorientation to the anterior commissure-posterior commissure plane, realignment for motion

correction, and co-registration with T1-weighted structural images. Structural images were segmented using the DARTEL algorithm [24]. All images were normalized to the standard Montreal Neurological Institute space, followed by smoothing with a Gaussian kernel set to a full width at the half maximum of 6 mm. The voxel time series were detrended and bandpass filtered within the frequency range of 0.01–0.1 Hz to minimize low-frequency drift and high-frequency noise. Variance normalization of each time series was performed to account for signal intensity fluctuations. In the context of potential confounders, regression analysis was applied to remove noise related to global signals, white matter, cerebrospinal fluid, and covariates associated with head motion, with a total of 24 parameters. Framewise displacement, an indicator of head motion, was assessed, and no significant differences were detected between the groups ($p>0.05$); thus, motion artifacts were adequately controlled in the preprocessing stage.

LC-FC network construction

The bilateral LC was identified as the seed for charting the LC-NE functional network and was delineated independently. These regions were extracted from the Automated Anatomical Labelling Atlas 3 [25]. Given that the left and right LC reportedly exhibit distinct FC patterns [10, 26, 27], we used the left LC and right LC separately as seeds. The DPABI toolbox facilitated the construction of the LC-FC network through a seed-based voxel-wise FC analysis. The process began by extracting the average time course from the LC and establishing it as a seed time series, followed by a calculation of the correlation with all other brain voxels using Pearson's correlation. To normalize the correlation values, Fisher's Z-transformation was implemented ($Z=0.5\ln[(1+CC)/(1-CC)]$). Consequently, the individual LC-FC networks were used for further analyses.

Statistical analysis

Initially, demographic and neuropsychological data were compared among the three groups using analysis of variance (ANOVA) and chi-square tests, with Bonferroni analysis performed for post hoc analysis. Two-sample t-tests were used to compare headache-related features between the two migraine groups. Pearson's correlation analyses were performed to examine the relationships between clinical characteristics and neuropsychological measures, with adjustments for age, sex, and education in the pooled migraine groups, MI group, and MnI group, respectively. Additionally, between-group comparisons of Fisher's z-transformed correlation coefficients were performed to determine whether the strength of these correlations differed significantly between the MI and MnI groups, providing further specificity to the correlational findings. Data analyses were performed using the SPSS Statistics for Windows, version 24.0 (SPSS Inc., Armonk, NY, USA). Statistical significance was set at $p<0.05$. Additionally, the false discovery rate (FDR) correction was applied to adjust for multiple comparisons, with statistical significance set at FDR $q<0.05$.

Next, voxel-wise ANOVA was performed with sex, age, SAS, and SDS scores as covariates to identify group differences in bilateral LC-FC networks. The significance levels were set at $p<0.005$ for individual voxels and $p<0.05$ for clusters, with a minimum cluster size of 35 voxels. Gaussian Random Field (GRF) correction was applied to adjust for multiple comparisons. This correction method was implemented using the DPABI Viewer tool, which required a minimum cluster size of 19 voxels. To enhance result stability and align with previous research practices, we used a cluster size threshold of 35 voxels.

Finally, to assess the clinical relevance of aberrant LC-FC in patients with migraine, a partial correlation analysis was performed. Regional values were extracted using the DPABI toolbox extract signal tool, which calculates the average signal within each cluster. The objective of this analysis was to explore the relationship between LC-FC alterations and various clinical and neuropsychological variables—including disease duration, frequency, attack duration, VAS, HIT-6, PSQI, SDS, and SAS—while controlling for age, sex, and disease duration. SDS and SAS were also included as covariates in correlations with insomnia-related features such as PSQI. The significance threshold was set at $p<0.05$; the FDR correction was also applied to adjust for multiple comparisons, with statistical significance set at FDR $q<0.05$. In addition, between-group comparisons of Fisher's z-transformed correlation coefficients were performed for the MI and MnI groups.

Results

Demographic and behavioral information

The demographic data and behavioral performance of the three groups are shown in Table 1. There were no significant differences in sex, age, or years of education between the groups. The headache-related features, including duration, frequency, attack duration, VAS, HIT score, and depression (SDS) score, did not differ significantly between the two migraine groups ($p>0.05$). The two migraine groups had higher SAS and SDS scores than the HC group ($p<0.001$, FDR-$q<0.01$). The insomnia scores (PSQI) were higher in the MI group than those in the MnI group and HC group ($p<0.001$, FDR-$q<0.01$). However, the SAS and SDS scores did not differ significantly between the MI and MnI groups ($p>0.05$).

The correlations between clinical features and neuropsychological tests in the pooled migraine patients and individual MI and MnI groups are shown in Fig. 1.

Table 1 Participants' demographic and clinical traits

Characteristic	MI ($n=28$)	MnI ($n=28$)	HC ($n=29$)	F/T/X^2	*p*-value
Age	34.86 ± 9.65	33.82 ± 5.94	36.86 ± 8.93	0.98	0.38
Sex (M/F)	9/19	10/18	11/18	0.21	0.89
Education (Years)	11.39 ± 1.79	11.61 ± 2.64	11.55 ± 2.31	0.06	0.94
Duration (Years)	4.14 ± 2.72	5.39 ± 2.45	-	1.81	0.08
Frequency (Days/Month)	4.89 ± 5.51	3.32 ± 1.86	-	1.43	0.16
Attack duration (Hours/Time)	9.18 ± 5.63	8.75 ± 5.26	-	0.29	0.77
VAS	6.39 ± 1.64	6.25 ± 1.79	-	0.31	0.76
HIT-6	60.86 ± 7.78	59.82 ± 8.42	-	0.48	0.63
PSQI	10.71 ± 2.8	3.84 ± 1.09	3.45 ± 1.66	120.56	< 0.001
SDS	53.50 ± 9.62	52.86 ± 9.00	43.76 ± 9.96	9.35	< 0.001
SAS	48.61 ± 10.48	43.46 ± 10.23	36.17 ± 5.92	13.48	< 0.001

[a], significant difference from the MI ($p<0.05$)

Abbreviations: MI: patients with comorbid migraine and insomnia; MnI: patients with migraine with no insomnia; HC: health controls; VAS: Visual Analogue Scale; HIT-6: Headache Impact Test six; PSQI: Pittsburgh Sleep Quality Index; SDS: Zung self-depression scale; SAS: Zung self-anxiety scale

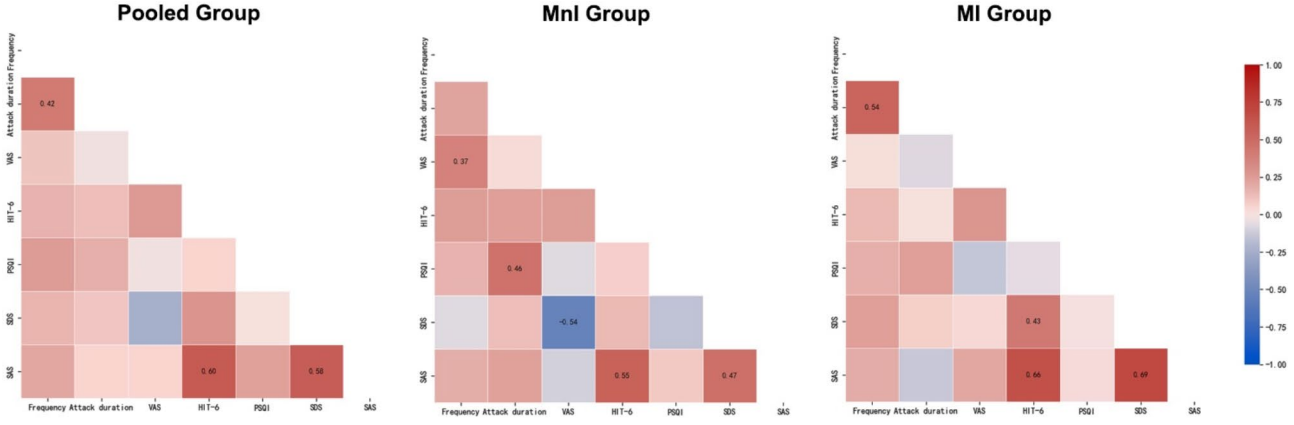

Fig. 1 Correlation matrix of clinical features and behavioral assessment in pooled migraine, MnI, and MI groups. Abbreviations: MnI: patients with migraine with no insomnia; MI: patients with comorbid migraine and insomnia; Duration: duration of disease; Frequency: frequency of disease; Attack duration: attack duration of each migraine; VAS: mean Visual Analogue Scale; HIT-6: Headache Impact Test six; PSQI: Pittsburgh Sleep Quality Index; SDS: Zung self-depression scale; SAS: Zung self-anxiety scale

Specifically, for the pooled migraine groups, the attack duration was positively associated with headache frequency ($r=0.42$, $p=0.001$, FDR-q=0.008); the HIT-6 score was positively associated with SAS score ($r=0.60$, $p=1.19*10^{-6}$, FDR-q=$2.51*10^{-5}$); and SDS score was positively associated with SAS score ($r=0.58$, $p=3.11*10^{-6}$, FDR-q=$3.27*10^{-5}$). Considering the MnI group, headache frequency was positively associated with mean VAS score ($r=0.38$, $p=0.048$, FDR-q=0.21); the mean VAS score was negatively associated with SDS score (r = -0.54, $p=0.003$, FDR-q=0.03); and the SAS score was positively associated with HIT-6 score ($r=0.55$, $p=0.002$, FDR-q=0.03). Considering the MI group, headache frequency was positively correlated with attack duration ($r=0.54$, $p=0.003$, FDR-q=0.02), while HIT-6 score was positively correlated with SDS ($r=0.43$, $p=0.022$, FDR-q=0.12) and SAS ($r=0.66$, $p=1.52*10-4$, FDR-q=0.002) scores. Fisher's z-transformed correlation coefficients are presented in Table S2.

LC-FC network difference among the three groups

The bilateral LC-FC network patterns for each group are presented in Figure S1. As shown in Figure S1, differences in the left and right LC-FC patterns were observed between the groups. Inter-group differences in the bilateral LC-FC networks are shown in Table 2; Fig. 2. Brain region networks were defined based on the Yeo seven networks functional atlas (Yeo et al., 2011; 7-network parcellation) [31], as presented in Figure S2. Subcortical and cerebellar networks, which are not part of the Yeo seven networks, were defined separately. Inter-group differences in the left LC-FC network were observed in the bilateral anterior cerebellum lobe (aCbm), the right parahippocampal gyrus (PHG), the left superior/middle temporal gyrus (STG/MTG), the right supplementary motor area (SMA), and the right dorsolateral prefrontal cortex (DLPFC). Post-hoc analyses revealed that the MI group showed higher LC-FC in the aCbm and lower LC-FC in the STG/MTG, PHG, and DLPFC than the other two groups. The MnI group had lower LC-FC in the SMA

Table 2 Group differences in the bilateral LC-FC network (GRF correction, Voxel level $p < 0.005$, cluster level $p < 0.05$, cluster size > 35)

Brain region	BA	Cluster size	MNI coordinates (RAI)			Peak F Score
			x	y	z	
Left LC - FC network						
Right PHG	34	90	20	3	-30	11.07
Left STG/MTG	48/20	90	-48	-9	-6	7.71
Right SMA	32	45	2	18	48	8.15
Right DLPFC	9/10	103	36	42	24	8.19
aCbm	-	53	-3	-57	-3	7.43
Right LC - FC network						
Bilateral thalamus	-	44	-9	-18	6	9.27
Right MOG	18	68	30	-90	-3	7.51
Right Caudate	25	41	9	21	-9	7.33
Left DMPFC	9	44	-3	48	39	7.00

Abbreviations: LC: locus coeruleus; FC: functional connectivity; BA: Brodmann's area; PHG: parahippocampal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; SMA: supplementary motor area; DLPFC: dorsolateral prefrontal cortex; MOG: middle occipital gyrus; DMPFC: dorsomedial prefrontal cortex

than the HC group, but not the MI group. Inter-group differences in the right LC-FC network were observed in the right caudate, the right middle occipital gyrus, and the bilateral thalamus. Post-hoc analysis revealed that the MI group showed higher LC-FC in the DMPFC and caudate and lower LC-FC in the thalamus than the other two groups. The MnI group had higher LC-FC in the MOG than the HC group, but not the MI group.

Clinical significance of the altered LC-FC network in the MI group

As shown in Fig. 3, for the pooled migraine groups, the PSQI score was negatively associated with the left LC-FC in the right PHG (Fig. 3A, r = -0.45, p=0.0006, FDR-q=0.008) and the STG/MTG (Fig. 3B, r = -0.42, p=0.0014, FDR-q=0.008), while positively associated with the right LC-FC in the caudate (Fig. 3C, r=0.29, p=0.03, FDR-q=0.10). The disease duration was negatively associated with the right LC-FC in the caudate (Fig. 3E, r = -0.38, p=0.005, FDR-q=0.07). However, these associations were not significant in the MI or MnI groups, respectively. In the MI group, the PSQI score was positively associated with the left LC-FC in the right DLPFC (Fig. 3D, r=0.52, p=0.006, FDR-q=0.24), while attack duration was positively associated with the right LC-FC in the left DMPFC (Fig. 3F, r = -0.41, p=0.036, FDR-q=0.42). Fisher's z-transformed correlation coefficients are presented in Table S3. There was no significant association between altered LC-FC strength and clinical or neuropsychological features in the MnI group (all p>0.05).

Discussion

In the current study, we examined the intrinsic LC-FC network in patients with MI and MnI. First, we found that the patients with MI exhibited intrinsic LC-FC changes in the DMPFC, DLPFC, PHG, STG/MTG, aCbm, thalamus, and caudate compared with HCs and patients with MnI. Alterations in the LC-FC network were primarily observed in regions of the DMN (the DMPFC) [28], frontoparietal network (FPN; DLPFC) [29], limbic network (LMB; PHG, and MTG), subcortical network (caudate and thalamus) [30], and cerebellum network of patients with MI [31, 32]. Second, patients with MnI exhibited alterations in the LC-FC network in the visual network (VN, MOG) and ventral attention network (VAN, SMA) [31]. Third, alteration in the LC-FC network was associated with insomnia features in the pooled migraine groups. Importantly, the lower LC-FC in the left DLPFC was associated with greater insomnia severity, whereas higher LC-FC in the right DMPFC was associated with a longer duration of migraine attacks. Overall, these findings offer novel perspectives on the neuroimaging mechanisms underlying MI.

The demographic and behavioral results indicated no significant differences in age, sex, or education levels across the three groups, indicating that the observed clinical differences are not influenced by these factors. Consistent with previous reports, both migraine groups (MI and MnI) showed substantially higher anxiety (SAS) and depression (SDS) scores compared with the HC group, underscoring the well-documented comorbidity between migraines and emotional disturbances [33, 34]. However, the lack of significant differences in SAS and SDS scores between the MI and MnI groups suggests that insomnia may not further exacerbate these emotional factors beyond the presence of migraine alone. The MI group exhibited markedly higher insomnia (PSQI) scores compared with both the MnI and HC groups, reinforcing the link between migraine and sleep disturbances.

Correlation analyses revealed notable relationships between clinical features and neuropsychological measures. In the pooled migraine group, headache severity and frequency were strongly linked to emotional distress.

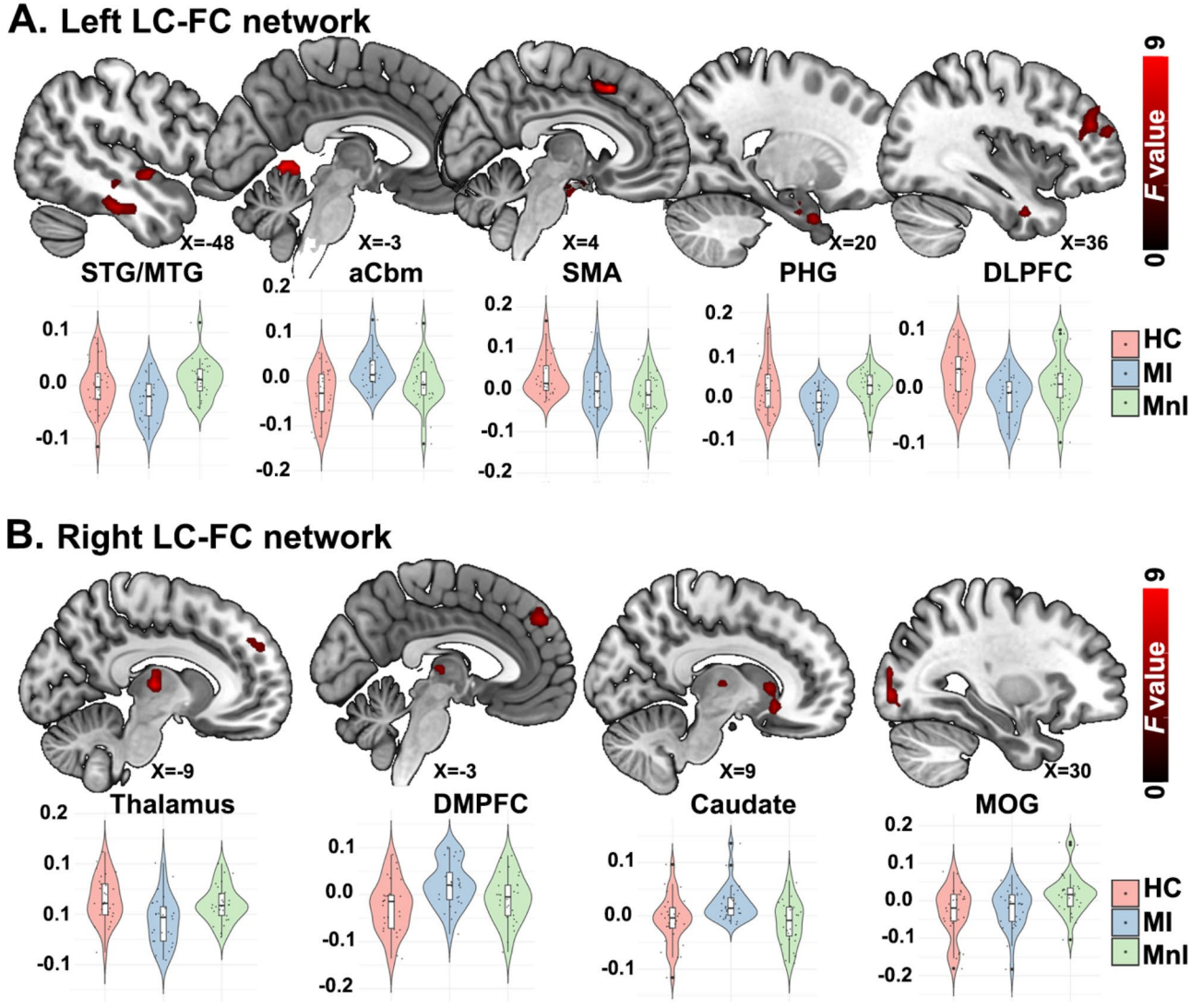

Fig. 2 Group differences in LC-FC network among three groups (GRF correction, Voxel level $p < 0.005$, cluster level $p < 0.05$, cluster size > 35). **A**. the group difference brain regions in left LC-FC network. **B**. the group difference brain regions in the right LF-FC network. Abbreviations: GRF: Gaussian Random Field; LC-FC: locus coeruleus functional connectivity; HC: healthy control; MnI: patients with migraine with no insomnia; MI: patients with comorbid migraine and insomnia; STG: superior temporal gyrus; MTG: middle temporal gyrus; aCbm: anterior cerebellum lobe; SMA: supplementary motor area; PHG: parahippocampal gyrus; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex; MOG: middle occipital gyrus

These findings suggest that emotional distress may play a key role in the severity and frequency of headaches, potentially serving as both a consequence and exacerbating factor of migraine symptoms [35]. In the MI group, the strong correlation between headache frequency and attack duration, as well as the positive associations between HIT-6 and emotional distress scores (SAS and SDS), highlight the compounding burden of emotional and sleep disturbances in patients with MI [36]. These results underscore the importance of addressing both emotional and sleep-related symptoms in the clinical management of patients with migraine, particularly those with comorbid insomnia. Early identification and treatment of insomnia and emotional symptoms can potentially improve outcomes in patients with migraines by reducing the overall disease burden.

The higher FC between the left LC and aCbm and between the right LC and DMPFC, as well as the caudate in patients with MI, are particularly noteworthy. The cerebellum has traditionally been associated with motor control [37]; however, recent studies have highlighted its role in trigeminal nociception in pain processing and sleep regulation [38]. The observed enhanced functional connectivity between the LC and cerebellum may suggest alterations in trigeminal nociceptive processing and pain modulation within the LC in patients with MI. However, further research is needed to confirm these potential mechanisms. The DMPFC, as the anterior hub region

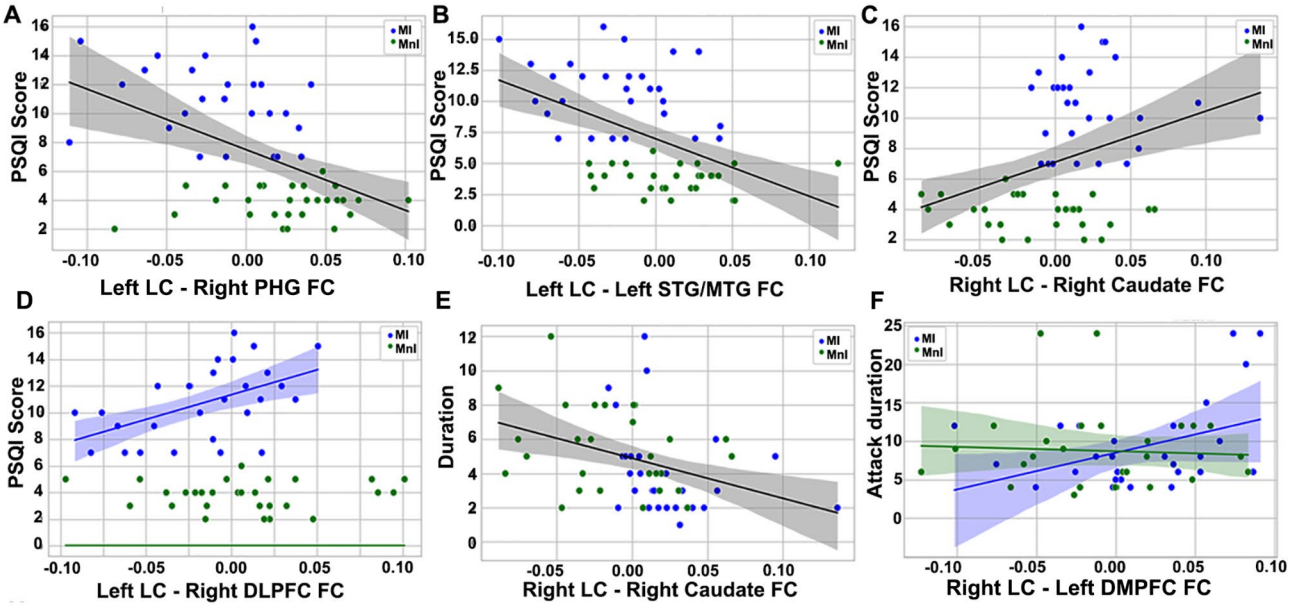

Fig. 3 Relationship between altered LC-FC strength and behavioral features in pooled migraine, MI, and MnI groups. The PSQI score was negatively associated with the FC between the left LC and right PHG (**A**), left STG/MTG (**B**), right LC, and right caudate (**C**) in the pooled migraine groups. The PSQI score was positively associated with the FC between the left LC and right DLPFC in the MI but not the MnI group (**D**). The disease duration was negatively associated with the FC between the right LC and right caudate in the pooled migraine groups (**E**). The attack duration is positively associated with the FC between the right LC and the right DMPFC in the MI but not the MnI group (**F**). Abbreviations: LC-FC: locus coeruleus functional connectivity; MI: patients with comorbid migraine and insomnia; MnI: patients with migraine with no insomnia; PSQI: Pittsburgh Sleep Quality Index; PHG: parahippocampal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex

of the DMN [28], is substantially engaged in self-referential mental activities and emotional processing [39]. Imbalances in the anterior DMN (DMPFC) and posterior DMN (precuneus and angular gyrus) have also been identified in patients with primary insomnia [40]. More recently, Chou et al. found increased FC between the DMPFC and posterior cingulate cortex in both patients with migraine and insomnia [5]. The caudate also participates in pain modulation [41] and the hyper-arousal state in patients with insomnia [42], and an increased caudate volume has been detected in patients with chronic back pain [43]. Our study also found that higher FC between the LC and DMPFC was associated with longer migraine attack durations in the MI but not the MnI group, indicating that a dysfunctional LC system in the DMN is involved in persistent headaches, and the noninvasive brain stimulation target of the DMPFC with inhibitory stimulation may help decrease headache duration in patients with MI.

The lower FC between the LC and LMB and subcortical networks (the left PHG and bilateral thalamus for the left and right LC, respectively) is consistent with previous findings of abnormal ascending and descending headache pathways in chronic pain conditions [9]. The LC, PHG, and thalamus have direct and indirect connections with the trigeminocervical complex, which is the common secondary neuron of all types of primary headache and the key node of headache occurrence and development [44, 45]. The lower FC between the LC and PHG and the thalamus may indicate that an abnormal LC-NE system within the subcortical and LMB networks is linked to the interplay between insomnia and migraine during the pain-free phase.

The DLPFC is the brain hub of the FPN and plays a key role in the integration of cognition and emotion [46]. The projection between LC and DLPFC is the main top-down modulatory pathway in the NE system [47, 48]. Previous neuroimaging studies have documented hyperexcitability in the task and resting states in patients with insomnia [49], whereas inhibitory DLPFC stimulation is the most widely used target for noninvasive brain stimulation treatment of chronic insomnia [50]. Interestingly, previous neuroimaging studies have shown that patients with migraine exhibit lower resting and dynamic FC in the DLPFC during the interictal phase of migraines [51], whereas excitatory DLPFC stimulation was effective in reducing headache intensity in patients with migraines [52]. In our study, patients with MI exhibited lower FC between the LC and DLPFC than HCs and patients with MnI, and the decreased DLPFC FC was associated with higher insomnia severity in the MI but not the MnI group. This finding suggests that LC-DLPFC connectivity may be a potential biomarker of sleep disturbance in patients with MI. Furthermore, these results indicate that a dysfunctional LC system in the DLPFC plays an important role in insomnia symptoms, and excitatory

stimulation of the right DLPFC may help treat insomnia symptoms in patients with MI.

Only two regions (MOG and SMA), located within the VN and VAN, were identified as exhibiting altered LC-FC in the MnI group. These alterations were similar to those observed in the MI group, suggesting a common neurobiological substrate in patients with migraine. Furthermore, our study did not detect a direct association between the LC-FC alterations and migraine features in patients with MnI. Conversely, in the pooled migraine groups and MI group, alterations in LC-FC were correlated with features of insomnia. This discrepancy highlights the heterogeneity of migraine disorders, particularly when comorbid with insomnia [3, 9]. The differences observed in the LC-FC network between the MnI and MI groups may indicate that the underlying neurobiological mechanisms of migraine are influenced by the presence or absence of insomnia, highlighting the need for a nuanced approach to understanding and treating migraine disorders.

Although our study provides valuable preliminary evidence of altered LC intrinsic FC networks in patients with MI, some limitations need to be acknowledged. First, the cross-sectional design limited our ability to infer the causality or directionality of the observed FC changes. Longitudinal studies are needed to determine whether these FC alterations are consequences of or contributing factors to the development of MI. Second, although we applied FDR correction for multiple comparisons in this study, the relatively small sample size may still have limited the power to detect certain significant correlations, while some findings were rendered insignificant upon correction. Future studies with larger sample sizes and more rigorous statistical approaches are required to validate our findings and further reduce the risk of type I errors. Third, we conducted MRIs between 16:00 and 22:00. Given the potential influence of time of day, particularly among participants with insomnia, who may experience heightened hyperarousal and anxiety closer to their typical sleep time [53], this could have impacted the collected functional data. Although we included scanning time as a covariate in our analysis and detected no significant changes in the results, additional investigations are needed to explore the impact of scanning time on neuroimaging outcomes, especially in populations with sleep disorders, validating these findings using larger sample sizes. Fourth, future studies using objective measures of insomnia (such as polysomnography) may be more accurate in selecting patients with MI. Most patients with MI included in this study had episodic migraine with insomnia; therefore, the interpretation of the results is limited. Future investigations should explore the brain network mechanisms associated with chronic migraines accompanied by insomnia. Lastly, a key limitation of this study is the use of 3T fMRI, which lacks the resolution required for optimal imaging of small subcortical structures like the LC. Future studies using 7T MRI and advanced segmentation techniques may provide greater anatomical specificity and further validate our preliminary findings [54].

Conclusions

Our study revealed aberrant LC-FC networks in patients with MI, providing neuroimaging evidence of the interplay between migraine and insomnia. Furthermore, FC in the LC and DMPFC was associated with headache duration, whereas FC in the LC and DLPFC was associated with insomnia severity in patients with MI. These findings have important implications for the development of targeted interventions for specific symptoms in patients with MI.

Abbreviations

aCbm	Anterior cerebellum lobe
DARTEL	Diffeomorphic Anatomical Registration using Exponentiated Lie algebra
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DMPFC	Dorsomedial prefrontal cortex
DPABI	Data Processing & Analysis of Brain Imaging
FC	Functional connectivity
FDR	False discovery rate
FPN	Fronto-parietal network
GRF	Gaussian Random Field
HC	Healthy controls
HIT-6	Headache Impact Test-6
ID	Insomnia disorder
LC	Locus coeruleus
LC-FC	Locus coeruleus functional connectivity
LMB	Limbic network
MOG	Middle occipital gyrus
MnI	Patients with migraine with no insomnia
MI	Patients with comorbid migraine and insomnia
MRI	Magnetic resonance imaging
MwoA	Migraine without aura
NE	Norepinephrine
PHG	Parahippocampal gyrus
PSQI	Pittsburgh Sleep Quality Index
rs-fMRI	Resting-state functional magnetic resonance imaging
SAS	Zung Self-Rating Anxiety Scale
SDS	Zung Self-Rating Depression Scale
SMA	Supplementary motor area
SMN	Somatomotor network
STG/MTG	Superior/middle temporal gyrus
VAN	Ventral attention network
VAS	Visual analog scale
VN	Visual network

Supplementary Information

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Supplementary Material 1

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Author contributions
CLW, LG, CHX and YW were responsible for study design, statistical analyses, and manuscript preparation. CLW, SSC and LG analyzed the data and wrote a manuscript. CLW，SSC，ZHC, SYX，CJF and LY were responsible for the collection of participants. All authors reviewed the manuscript and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of the Third Affiliated Hospital of Anhui Medical University (Approval Number 2023-044-01). All participants provided written informed consent for participation in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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