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Sleep Deficits Inter-Link Lower Basal Forebrain–Posterior Cingulate Connectivity and Perceived Stress and Anxiety Bidirectionally in Young Men

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Abstract

Background: The basal nucleus of Meynert (BNM), a primary source of cholinergic projections to the cortex, plays key roles in regulating the sleep-wake cycle and attention. Sleep deficit is associated with impairment in cognitive and emotional functions. However, whether or how cholinergic circuit, sleep, and cognitive/emotional dysfunction are inter-related remains unclear.

Methods: We curated the Human Connectome Project data and explored BNM resting state functional connectivities (rsFC) in relation to sleep deficit, based on the Pittsburgh Sleep Quality Index (PSQI), cognitive performance, and subjective reports of emotional states in 687 young adults (342 women). Imaging data were processed with published routines and evaluated at a corrected threshold. We assessed the correlation between BNM rsFC, PSQI, and clinical measurements with Pearson regressions and their inter-relationships with mediation analyses.

Results: In whole-brain regressions with age and alcohol use severity as covariates, men showed lower BNM rsFC with the posterior cingulate cortex (PCC) in correlation with PSQI score. No clusters were identified in women at the same threshold. Both BNM-PCC rsFC and PSQI score were significantly correlated with anxiety, perceived stress, and neuroticism scores in men. Moreover, mediation analyses showed that PSQI score mediated the relationship between BNM-PCC rsFC and these measures of negative emotions bidirectionally in men.

Conclusions: Sleep deficit is associated with negative emotions and lower BNM rsFC with the PCC. Negative emotional states and BNM-PCC rsFC are bidirectionally related through poor sleep quality. These findings are specific to men, suggesting potential sex differences in the neural circuits regulating sleep and emotional states.

Keywords: PSQI, anxiety, rsFC, basal nucleus of Meynert, posterior cingulate cortex, fMRI

Significance Statement

Basal nucleus of Meynert (BNM) circuit dysfunction has been implicated in sleep deficit. We investigated the roles of resting-state functional connectivity (rsFC) of the BNM in sleep deficit and negative emotion. In 687 young adults (342 women), we showed lower BNM rsFC with the posterior cingulate cortex (PCC) in association with more severe sleep deficit in men only. Both BNM-PCC rsFC and sleep deficit were significantly correlated with anxiety, perceived stress, and neuroticism scores in men. Mediation analyses showed that sleep deficit mediated the relationship between BNM-PCC rsFC and these measures of negative emotions bidirectionally. These findings are specific to men, suggesting potential sex differences in the neural circuits regulating sleep and emotional states.

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INTRODUCTION

Basal Nucleus of Meynert (BNM) and Sleep

As the primary source of cholinergic projections to the cortex, the BNM supports wakefulness and attention (Qi et al., 2021). Though accounting only for approximately 5% of the neuronal populations in the basal forebrain, the cholinergic neurons play a central role in modulating sleep-wake homeostasis (Gritti et al., 2006; Nikonova et al., 2017), increasing and decreasing in activities during attentive wakefulness/REM sleep and non-REM sleep, respectively (Xu et al., 2015). Human studies associated BNM neuronal loss with premortem sleep deficits (Kasanuki et al., 2018) and lower BNM connectivity with left visual cortices in patients with sleep disorder and mild cognitive impairment (Byun et al., 2022). In rodent studies, 36 hours of total sleep deprivation, compared with rested wakefulness, led to higher BNM-thalamus/cingulate cortex and lower BNM-right superior parietal lobule connectivity, with BNM-cingulate cortex connectivity negatively correlated with attention performance following total sleep deprivation (Qi et al., 2021). Contributing to altered physiological responses as well as cognitive and emotional problems (Irwin, 2019), sleep deficit is noted in individuals with many different neuropsychiatric conditions, including anxiety and other mood disorders (Nutt et al., 2008). However, how the BNM circuits are implicated in sleep deficit and its comorbidities in humans remains under-investigated.

Roles of the BNM in Cognition and Emotion

In humans, the BNM extends from the medial septum and diagonal band of Broca rostrally to the most caudal area of the global pallidus (Hofman and Swaab, 2004), and, with endogenous acetylcholine, the BNM supports a wide array of cognitive and affective functions (Li et al., 2017). Many studies have associated BNM with cognitive impairment in neurological illnesses. Patients with Parkinson disease showed improved cognition after bilateral subthalamic stimulation, with the outcomes in positive correlation with BNM volume (Kübler et al., 2022). Patients with Alzheimer disease demonstrated significant losses of cholinergic neurons in the BNM in postmortem studies (Whitehouse et al., 1982; Hampel et al., 2019). Relative to controls, patients with multiple sclerosis showed higher mean diffusivity—which describes the extent of water diffusion in non-axial directions, an index of the severity of loss of white matter integrity—of the BNM and poorer cognitive performance (Hildesheim et al., 2021). With myelin imaging and magnetic resonance spectroscopy, a recent study reported a significant correlation between left BNM qT1—an index of myelin integrity—and magnetic resonance spectroscopy–based dorsal anterior cingulate choline in healthy individuals, a relationship disrupted in first-episode psychosis (Park et al., 2022). In rodents, administration of corticotropin releasing factor in the BNM disrupted local synthesis of glutamate and led to attention deficits (Eck et al., 2022). Thus, a substantial body of evidence supports the role of the BNM circuits in cognitive and affective functioning. As the great majority of mental illnesses involve sleep as well as cognitive and emotional problems, it would advance our knowledge to understand the roles of BNM circuit dysfunction in inter-relating altered sleep, cognition, and emotion.

Resting-State Connectivities and Functional Brain Organization

In magnetic resonance imaging (MRI), functional organization of the brain can be characterized by how blood oxygenation–level dependent (BOLD) signals are correlated temporally across brain regions (Lee et al., 2013). By quantifying how BOLD signals of individual brain areas are correlated, investigators define large-scale, including motor, executive control, and default mode, circuits (van den Heuvel and Hulshoff Pol, 2010) or fine-map subregional connectivities of a brain area (Zhang et al., 2012; Zhang and Li, 2012, 2014; Zhang and Li, 2017). These "connectomes" can also be employed to predict individual differences in clinical characteristics (Manza et al., 2015; Kann et al., 2016; Zhang et al., 2016; Li et al., 2017; Hu et al., 2018b; Li et al., 2018) and cognitive performance (Yoo et al., 2018; Fong et al., 2019) and serve as biomarkers of neuropsychiatric illnesses (Manza et al., 2016; Canario et al., 2021) as well as the effects of pharmacological interventions (Farr et al., 2014; Kline et al., 2016; Carhart-Harris et al., 2017). Thus, investigating BNM rsFC represents a feasible approach to understanding the potential roles of BNM circuit dysfunction in impaired sleep, cognition, and emotion.

We previously reported whole-brain rsFCs of the BNM (Li et al., 2014; Zhang et al., 2017; Wan et al., 2019). The BNM showed a distinct pattern of cortical and subcortical connectivity. Compared with a spatially adjacent structure, the ventral striatum, the BNM showed stronger positive connectivity with the putamen, pallidum, thalamus, amygdala, and midbrain, as well as the anterior cingulate cortex and supplementary and presupplementary motor areas, in support of arousal, saliency responses, and cognitive motor control (Li et al., 2014). Another study combining EEG and fMRI showed an increase in BNM-visual cortical rsFC when participants transitioned from eyes-closed to eyes-open resting, in association with desynchronization of the alpha rhythm (8–12 Hz) (Wan et al., 2019). The findings support a potentially pervasive role of the BNM circuit in regulating arousal and cognitive function. In studies of clinical populations, female but not male smokers vs nonsmokers demonstrated higher positive BNM rsFC with supplementary motor area, bilateral anterior insula, and right superior temporal/supramarginal gyri as well as higher negative rsFC with the posterior cingulate cortex (PCC) and precuneus. Further, BNM rsFC with the supplementary motor area is negatively correlated with the severity of nicotine dependence in male but not female smokers (Zhang et al., 2017). The latter findings suggest BNM circuit dysfunction as a potentially sex-specific etiological marker of nicotine misuse, which is known to affect sleep and cognitive performance. Together, these studies support the premise of investigating BNM rsFC to understand the potential roles of BNM circuit dysfunction in impaired sleep, cognition, and emotion.

The Present Study

Here, we investigated whether BNM rsFCs are altered in relation to sleep deficit and its cognitive and emotional comorbidities. We curated the Human Connectome Project (HCP) data and employed whole-brain regression of BNM rsFC against the Pittsburgh Sleep Quality Index (PSQI)—an index of sleep quality—in a cohort of over 600 participants. We identified the BNM rsFC correlates and tested the inter-relationship between the rsFC and cognitive/emotional measures available from the HCP. Finally, we performed mediation analyses to characterize the inter-relationship among PSQI score, BNM rsFC, and those cognitive and emotional measures that were correlated with the rsFC. Because men and women may show differences in the severity of negative emotional states and sleep dysfunction, we conducted the analyses for men and women both in combination and separately.

MATERIALS AND METHODS

Dataset and Demographics

We employed the HCP 1200 Subjects Release data, collected from 2012 to 2015, in the current study. A total of 1096 young adults completed a resting-state fMRI scan and, after exclusion of participants missing physiological data (n = 80) or not meeting the scrubbing criteria (n = 146; details in "2.3 Imaging protocol and preprocessing"), 870 were retained. Of the 1096 participants, 998 completed fMRI scans of the 7 behavioral tasks (Barch et al., 2013), and 833 of them showed good image quality across all scans. Because we would evaluate the impact of sleep on cognitive performance, we took the intersection of the samples of 870 and 833 to arrive at a pool of 687 participants (345 men) to include in this study. Note that task-related imaging data were not analyzed in the current study. All participants were physically healthy with no severe neurodevelopmental, neuropsychiatric, or neurological disorders. Individuals may use alcohol to varying extents, which is known to influence brain structure and function (Hahn et al., 2022; Zhu et al., 2022). HCP evaluated alcohol use with multiple questions and, as in our earlier work (Li et al., 2021; Li et al., 2022), we conducted a principal component analysis of all drinking-related measures and identified a single, principal component (PC1) with an eigenvalue (7.22) > 1 and explaining 48.16% of the variance. Thus, age, sex, and drinking PC1 were included as covariates in the analyses of all participants, and age and PC1 were included as covariates in the analyses of men and women separately. The HCP study was approved by the Washington University Institutional Review Board (IRB #201204036).

Clinical and Cognitive Measures

The HCP data comprised 15 drinking metrics to assess the severity of alcohol use. Supplementary Table 1 shows the mean ± SD of the metrics and PC1 identified from principal component analysis of the metrics. All participants were assessed with the Achenbach Adult DSM-Oriented Scales. The anxiety problems subscale comprises 6 items, each scored from 0 to 2, with a higher score indicating more anxiety problems (supplementary Methods). All participants were evaluated with the NIH-Toolbox Emotion Measures 18+ battery, which consists of 4 subdomains: negative affect, psychological well-being, stress and self-efficacy, and social relationships. There are 10 items in perceived stress subscale each scored from 1 to 5 or 5 to 1 (reverse scored), so the raw score sums to 10–50 (T-score ranges from 25.4 to 88.8), with a higher score indicating higher perceived stress. Participants were also assessed with the 5-factor model of personality: neuroticism, extroversion, agreeableness, openness, and conscientiousness (Heine and Buchtel, 2009). The neuroticism subscale comprises 12 items, each scored from 0 to 4 or 4 to 0 (reverse scored), with a higher score indicating the individual's tendency to experience negative emotions and emotional instability.

Participants were evaluated with the PSQI (Buysse et al., 1989), which contains 19 self-rated questions. The 19 self-rated items are combined to 7 component scores, each of which ranged from 0 (no difficulty with sleep) to 3 (severe difficulty). Thus, individuals ranged from 0 to 21 in PSQI score, with a higher score representing worse sleep quality.

Table 1 shows age, years of education, drinking PC1, PSQI, anxiety, perceived stress, and neuroticism scores of men and women separately.

The 7 HCP behavioral tasks included (1) working memory task: images of places, tools, faces, and body parts were shown in separate blocks, half with 2- and half with 0-back trials; (2) gambling task: participants guessed if a mystery card (with a number 1–9) was higher or lower than 5 to win money, with feedback of win, loss, or even (when the number is "5") provided; (3) motor task: participants tapped fingers, squeezed toes, or moved their tongue following cues; (4) language task: participants listened to a story and selected an appropriate topic of the story or arithmetic operations and chose the answer; (5) social cognition task: participants viewed video clips of moving objects and judged whether they interacted "socially" or moved randomly; (6) relational processing task: participants viewed visual stimuli of 6 different shapes and 6 different textures and judged whether a bottom pair of stimuli differed in the same feature dimension (shape or texture) from the top pair; (7) emotional processing task: participants selected from 2 faces the one that expressed the same emotion (angry, fearful, neutral) as the one at the bottom and did the same with shape stimuli in shape blocks. The 7 behavioral tasks are described in detail by Barch et al. (Barch et al., 2013). Supplementary Table 2 shows the performance measures in these tasks for men and women separately.

Imaging Protocol and Preprocessing

Imaging protocols and data preprocessing are described in supplementary Methods. Participants completed 7 task and 2 resting-state scans on 2 separate days.

Resting-State Functional Connectivity (rsFC) of BNM

The mask of the BNM was obtained from the Automated Anatomic Labeling atlas (Tzourio-Mazoyer et al., 2002) and was used as the seed region. Whole-brain voxel-wise analyses were conducted to compute the rsFC of BNM. The BOLD time courses of individual

Table 1. Demographics and Clinical Measures of the Participants[a]

Characteristic	Men (n = 345)	Women (n = 342)	*t*	*P* value[b]
Age, y	27.6 ± 3.6	29.3 ± 3.6	−6.24	<.001
Education, y	15.0 ± 1.7	15.2 ± 1.7	−1.82	.069
Drinking PC1	0.33 ± 1.07	−0.34 ± 0.80	9.30	<.001
PSQI score	4.6 ± 2.5	4.7 ± 2.9	−1.87	.062[c]
Anxiety score	3.4 ± 2.5	4.2 ± 2.8	−4.24	<.001[c]
Perceived stress	47.8 ± 9.3	48.4 ± 8.9	−1.26	.207[c]
Neuroticism	15.6 ± 7.7	17.3 ± 7.1	−3.23	.001[c]

Abbreviations: Drinking PC1, first principal component obtained of principal component analyses of all drinking measures; PSQI, Pittsburgh Sleep Quality Index.
[a]Values are mean ± SD.
[b]2-sample *t* test.
[c]2-sample *t* test with age and PC1 as covariates.

voxels of the BNM seed were averaged, and the correlation coefficient was computed between the average time course of the BNM and the time courses of all other voxels of the brain for individual participants.

In group analyses, a whole-brain regression of seed-based BNM rsFC against PSQI score was conducted in men and women combined, with age, sex, and drinking PC1 as covariates, as well as separately, with age and PC1 as covariates. The results were evaluated at voxel $P<.001$, uncorrected, in combination with a cluster $P<.05$, corrected for family-wise error of multiple comparisons, based on Gaussian random field theory, as implemented in SPM, following current reporting standards.

For the regions of interest (ROI) identified from linear regressions, we used MarsBar (http://marsbar.sourceforge.net/) to derive for individual participants the β estimates of the rsFCs. We then tested sex differences in the regressions using slope tests, with age and PC1 as covariates (Zar, 1999). Note that the slope tests of sex differences were not "double-dipping" (Dhingra et al., 2020; Ide et al., 2020), as the regression maps were identified with a threshold and a cluster showing correlation in men could also show a correlation in women that just missed the threshold to be identified from whole-brain regression, and vice versa. Thus, direct tests of the slopes were needed to confirm sex differences.

Mediation Analyses

We performed mediation analyses following published routines, as detailed earlier (Ide et al., 2017; Hu et al., 2018a; Zhornitsky et al., 2019) (supplementary Methods), to evaluate the relationships between neural markers, perceived stress/anxiety/neuroticism, and PSQI scores in men (see Results). Note that the results of mediation analyses did not imply causality. Rather, the findings served to clarify the inter-relationships of multiple, correlating variables.

RESULTS

Clinical Measures

PSQI and perceived stress scores showed no significant difference between men and women ($t=-1.87$, $P=.062$; $t=-1.26$, $P=.207$, respectively). Men showed significantly lower anxiety and neuroticism scores than women ($t=-4.24$, $P<.001$; $t=-3.23$, $P=.001$, respectively). supplementary Table 3 shows the results of sex differences on all Achenbach Adult Self-Report DSM-oriented measures.

PSQI score showed a significant correlation with anxiety score (all: $r=0.277$, $P<.001$; men: $r=0.339$, $P<.001$; women: $r=0.222$, $P<.001$), perceived stress score (all: $r=0.267$, $P<.001$; men: $r=0.298$, $P<.001$; women: $r=0.227$, $P<.001$), and neuroticism score (all: $r=0.239$, $P<.001$; men: $r=0.253$, $P<.001$; women: $r=0.205$, $P<.001$) in linear regressions with age and drinking PC1 as covariates. In a slope test men and women did not differ in the slopes of regressions ($Z=1.66$, $P=.097$, **Figure 1A**; $Z=1.00$, $P=.317$, **Figure 1B**; $Z=0.66$, $P=.509$; **Figure 1C**, respectively) (supplementary Table 4 shows the results of correlation of PSQI score and all Achenbach Adult Self-Report measures).

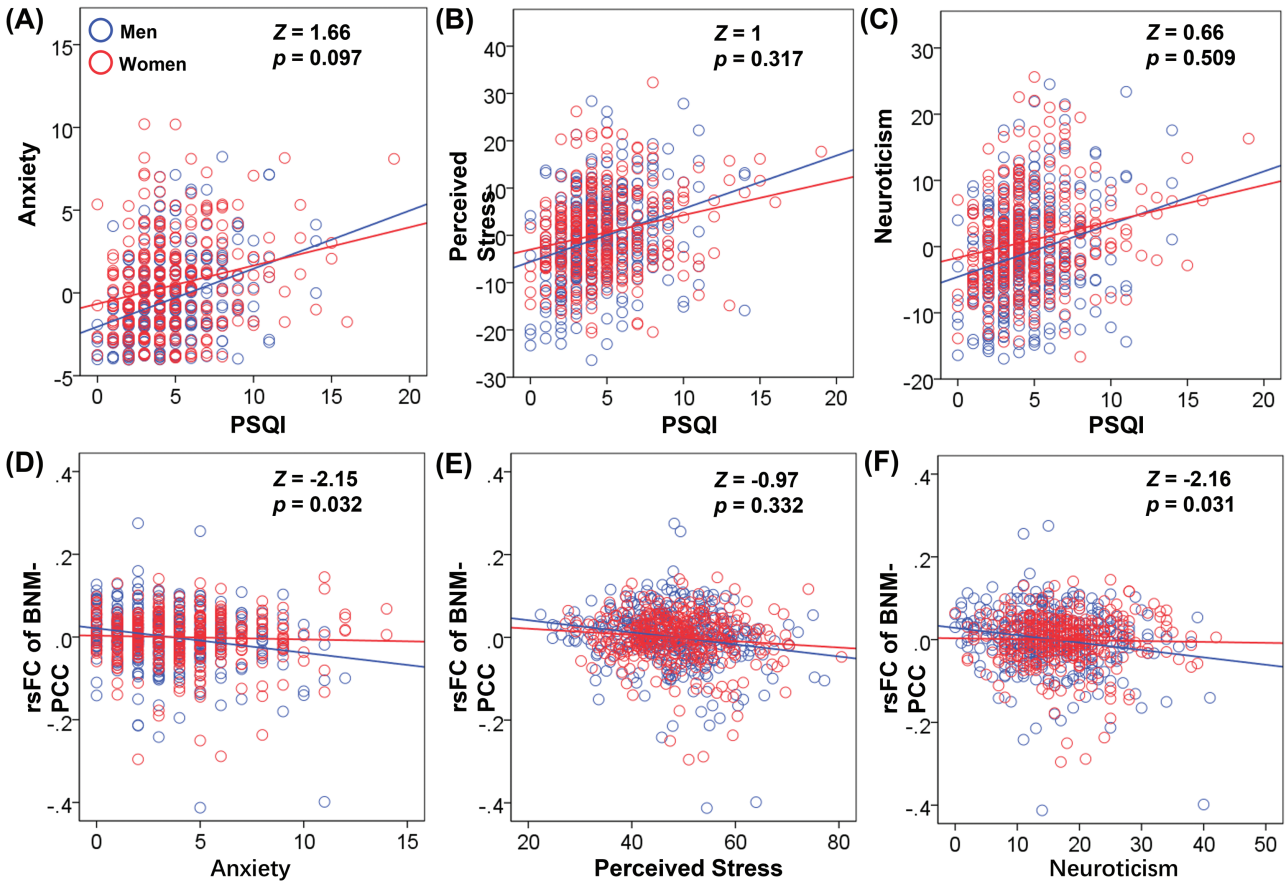

Figure 1. Linear regression of: (A) anxiety, (B) perceived stress, and (C) neuroticism vs PSQI score in men (blue) and women (red) subjects; linear regression of BNM-PCC rsFC vs (D) anxiety, (E) perceived stress, and (F) neuroticism score. The Z and P values reflect slope test of sex differences in the regressions. Note that the residuals are plotted here with age and PC1 accounted for in all regressions.

Neural Correlates of PSQI: BNM rsFC

Whole-brain linear regression of the BNM (**Figure 2A**) rsFCs against PSQI score for women alone did not reveal any clusters at voxel $P<.001$, uncorrected in combination with cluster $P<.05$, family-wise error–corrected. In the entire sample, BNM rsFC with the left angular gyrus (lAG, x, y, z = –40, –82, 26; $Z=4.98$, 1144 mm^3; **Figure 2B**) and right middle occipital cortex (rMOC, x, y, z = 32, –86, –2; $Z=4.20$, 776 mm^3; **Figure 2B**) showed a significant positive and negative correlation with the PSQI score, respectively. In men, BNM rsFC with the right posterior insula (rPI, x, y, z = 38, –4, 6; $Z=4.28$, 1008 mm^3; **Figure 2D**) and PCC (x, y, z = 10, –46, 12; $Z=5.66$, 4784 mm^3; **Figure 2D**) showed a significant positive and negative correlation with the PSQI score, respectively.

Considering these clusters as ROI, we extracted the βs of the BNM-ROI rsFC for post hoc, including sex difference, analyses (please see Section 2.4 for reasons why these analyses did not represent "double-dipping"). The βs of BNM-lAG rsFC were significantly correlated with PSQI score (all: $r=0.189$, $P<.001$; men: $r=0.166$, $P=.002$; women: $r=0.210$, $P<.001$) in a linear regression with age and PC1 as covariates. In a slope test men and women did not differ significantly in the slope of regression ($Z=-0.6$, $P=.549$). The β estimate of the BNM-rMOC rsFC was significantly correlated with PSQI score (all: $r=-0.159$, $P<.001$; men: $r=-0.138$, $P=.010$; women: $r=-0.187$, $P=.001$) in a linear regression with age and PC1 as covariates. Men and women did not differ significantly in the slope of regression ($Z=0.66$, $P=.509$). The β estimate of the BNM-rPI rsFC was significantly correlated with PSQI score in all ($r=0.117$, $P=.002$) and men ($r=0.248$, $P<.001$), but not in women ($r=-0.028$, $P=.604$), in a linear regression with age and PC1 as covariates. In a slope test men and women differed significantly in the slope of regression ($Z=3.67$, $P<.001$). The β estimate of the BNM-PCC rsFC was significantly correlated with PSQI score in all ($r=-0.164$, $P<.001$) and in men ($r=-0.320$, $P<.001$), but not women ($r=-0.006$, $P=.918$), in a linear regression with age and PC1 as covariates. Men and women differed significantly in the slope of regression ($Z=-4.25$, $P<.001$).

We examined the correlation between the rsFC βs and anxiety, perceived stress, and neuroticism scores and evaluated the results at a corrected threshold **Table 2**. Only the β estimate of the BNM-PCC rsFC was significantly correlated with anxiety ($r=-0.205$, $P<.001$), perceived stress ($r=-0.186$, $P<.001$), and neuroticism ($r=-0.189$, $P<.001$) score in men in a linear regression with age and PC1 as covariates. None of the rsFC βs were significantly correlated with anxiety (all $Ps>.170$), perceived stress (all $Ps>.038$), or neuroticism (all $Ps>.254$) score in women. In slope tests men and women differed significantly in the slopes of regressions of BNM-PCC rsFC β against anxiety ($Z=-2.15$, $P=.032$; **Figure 1D**) and neuroticism ($Z=-2.16$, $P=.031$; **Figure 1F**) but not perceived stress ($Z=-0.97$, $P=.332$; **Figure 1E**).

With correction for multiple comparisons ($P=.05/12=.00416$), none of the performance measures in the cognitive tasks were significantly correlated with the PSQI score across all participants (all $Ps>.021$) or in men (all $Ps>.144$) or women (all $Ps>.052$) (supplementary Table 5). The findings remained the same with years of education included as an additional covariate: all (all $Ps>.051$), men (all $Ps>.177$), and women (all $Ps>.083$) (supplementary Table 6).

Inter-relationship of BNM-PCC rsFC, PSQI, and Anxiety/Perceived Stress/Neuroticism Scores

In men, individual PSQI score, anxiety score, and rsFC of BNM-PCC (BNM-PCC β) were correlated pairwise. We performed a mediation analysis to examine the inter-relationship among the PSQI, anxiety/perceived stress/neuroticism score, and BNM-PCC β, with age and PC1 as covariates. For each emotional measure, we considered all 6 models and employed a corrected P ($0.05/6/3=.00278$) to evaluate the mediation effects. For anxiety score, 2 models (anxiety score → PSQI score → BNM-PCC β; BNM-PCC β → PSQI score → anxiety score) showed significant and complete mediation (**Figure 3A**; statistics in supplementary Table 7). For perceived stress score, 2 models (perceived stress score → PSQI score → BNM-PCC β; BNM-PCC β → PSQI score → perceived stress score) showed significant mediation (**Figure 3B**; statistics in supplementary Table 8). For neuroticism score, 2 models (neuroticism score → PSQI score → BNM-PCC β; BNM-PCC β → PSQI score → neuroticism score) showed significant mediation (**Figure 3C**; statistics in supplementary Table 9).

We did not perform the mediation analyses in women as the BNM-PCC βs, and the emotional metrics were not significantly correlated.

DISCUSSION

We demonstrated that, in men, poor sleep, as reflected in higher PSQI score, was associated with lower BNM connectivity with PCC, a hub of the default mode network. PSQI score and β estimate of BNM-PCC rsFC were each positively and negatively correlated

Table 2. Correlation of BNM- rsFC and Measures of Negative Emotion[a]

Characteristic	Correlation coefficient	Anxiety	Perceived stress	Neuroticism
All (n = 687)				
BNM-lAG rsFC	*r*	0.02	–0.02	-0.02
	P	.616	.619	.657
BNM-rMOC rsFC	*r*	–0.09	–0.06	–0.05
	P	.024	.110	.187
Men (n = 345)				
BNM-rPI rsFC	*r*	0.08	0.07	0.07
	P	.122	.210	.213
BNM-PCC rsFC	*r*	–0.21	–0.19	–0.19
	P	<.001	<.001	<.001

[a]Correlation analyses with sex, age, and principal component 1 (PC1) as covariates in all participants, and with age and PC1 as covariates in men. BNM: basal nucleus of Meynert; rsFC: resting state functional connectivity; lAG: left angular gyrus; rMOC: right middle occipital cortex; rPI: right posterior insula; PCC: posterior cingulate cortex

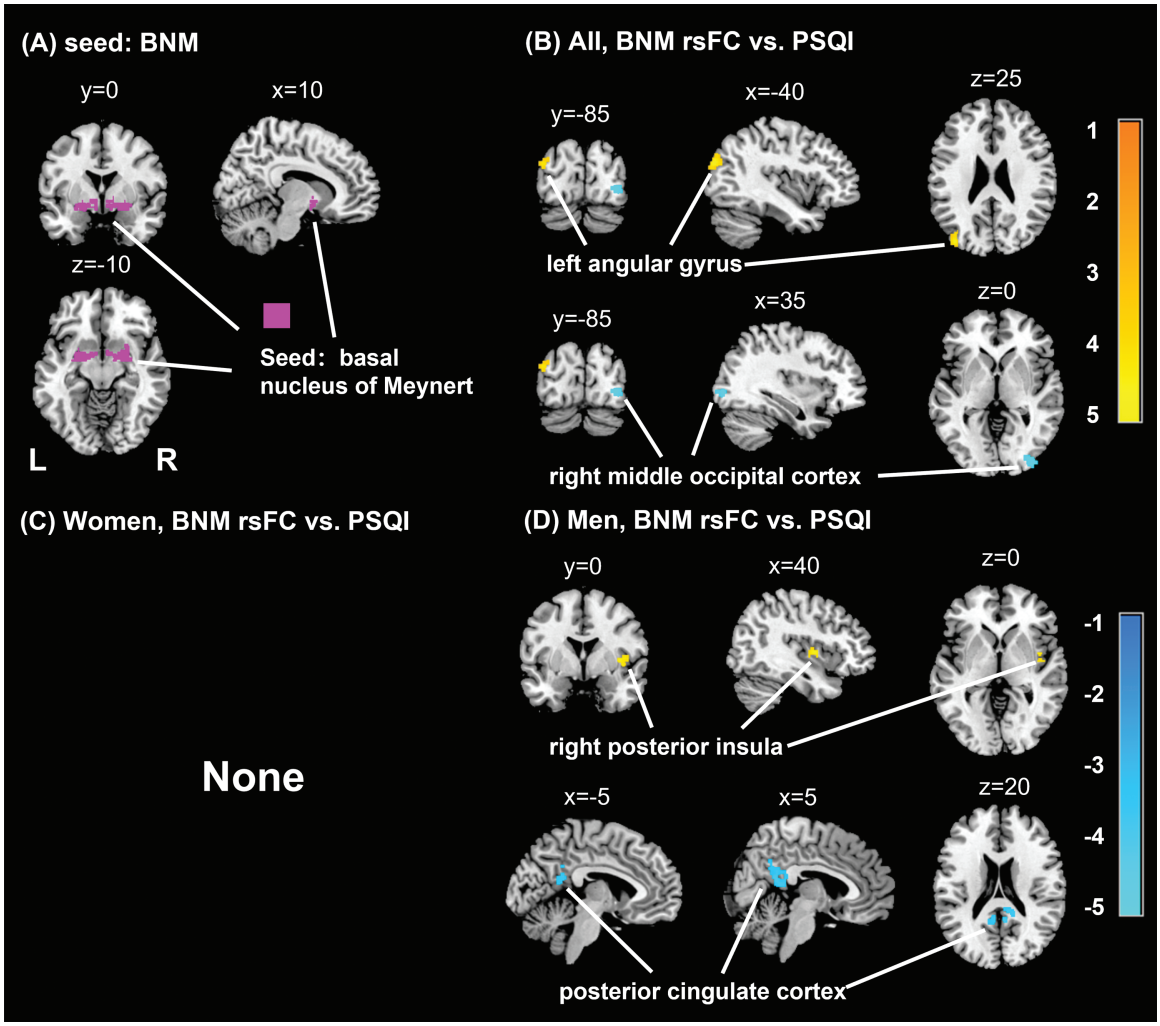

Figure 2. Brain regions showing BNM connectivity in correlation with PSQI. (A) BNM seed. BNM rsFC in correlation with the PSQI score for (B) the entire sample: left angular gyrus and right middle occipital cortex; for (C) women: none; and for (D) men: right posterior insula and posterior cingulate cortex. Color bars represent voxel T values. Abbreviations: L, left; R, right.

with the severity of anxiety, perceived stress, neuroticism ("negative emotions" henceforth) in men. Further, PSQI score mediated the relationship between BNM-PCC rsFC and negative emotions. Notably, although PSQI and anxiety and perceived stress scores were also significantly correlated, neither was associated with BNM-PCC rsFC in women, and the sex differences were confirmed by slope tests. Further, although sleep deficit was also associated with performance deficits in some of the cognitive tasks, BNM-PCC rsFC did not appear to play in role in supporting the deficits. Together, these findings implicate BNM-PCC rsFC in sleep disturbance and negative emotions and provide systems-level evidence for the impact of dysfunctional sleep on emotion in men.

BNM Connectivity With the PCC

A core region of the default mode network, the PCC supports the manifestation of memory/hippocampus-related emotional experiences and actions (Rolls, 2019). For instance, neurofeedback training to downregulate PCC response to negative emotional stimuli ameliorated distress in individuals with posttraumatic stress disorder (Nicholson et al., 2022). Imaging studies have also implicated the PCC in sleep deficits. Poor sleep quality, assessed by PSQI, significantly accelerated volume loss in the right PCC in otherwise-healthy elderly people (Liu et al., 2022). In young adults 29 ± 4.2 years of age, patients with nonrapid eye movement parasomnias vs controls showed lower gray matter volume in the left PCC and posterior midcingulate cortex (Heidbreder et al., 2017). Compared with controls, insomnia patients showed higher amplitude of low-frequency fluctuation in fMRI signals in the PCC and lower PCC rsFC with the prefrontal cortex (Zheng et al., 2023). A within-subject study recruited heathy men for rs-fMRI each following rested wakefulness and 72 hours of total sleep deprivation. Relative to rested wakefulness, sleep deprivation led to lower rsFC of the right inferior parietal lobule and left precuneus/PCC (Dai et al., 2015). Male patients with severe obstructive sleep apnea vs healthy controls showed lower PCC-hippocampus rsFC, and lower rsFC was associated with worse delayed memory score, as assessed by Montreal Cognitive Assessment in the patients (Li et al., 2016). Thus, a substantial body of literature implicates structural and functional alterations of the PCC in sleep deficits.

The findings of higher BNM connectivity with PCC in correlation with the PSQI and anxiety/perceived stress scores extend this literature and highlight a neural circuit that interlinks sleep deficit and negative emotions. The findings of sleep dysfunction bidirectionally mediating BNM-PCC connectivity and anxiety/stress support the mutual influences between sleep quality and emotional states. Notably, these findings were observed in men

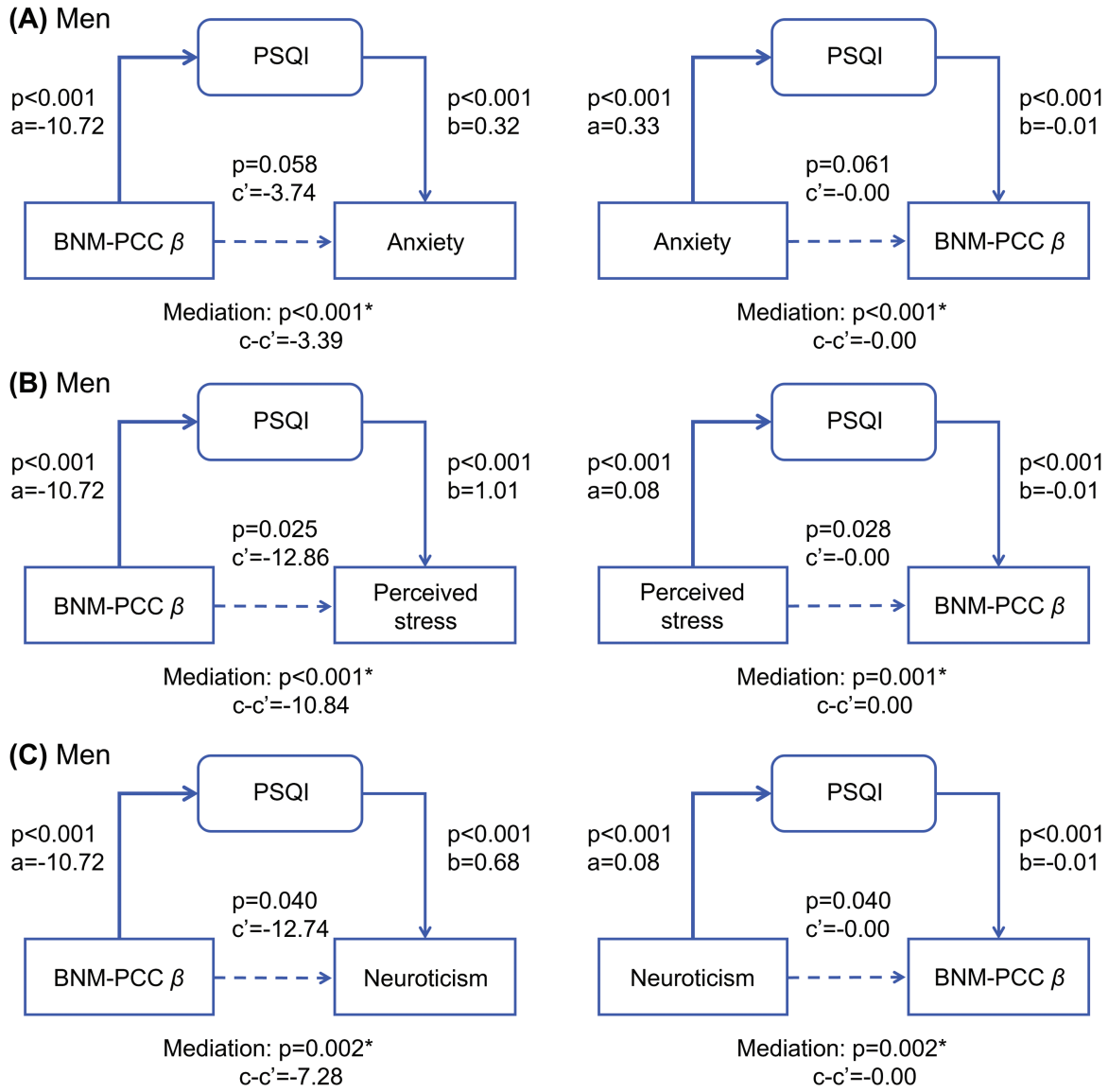

Figure 3. **Mediation analyses: PSQI score mediated the correlation between BNM-PCC β for (A) anxiety, (B) perceived stress, and (C) neuroticism score in men.**

but not in women, raising an important question regarding sex differences in the neural processes underlying sleep and emotional dysfunction.

Sex Differences in BNM Connectivity and Sleep Dysfunction

Sex differences are widely reported in the sleep and emotion literature. Women report insufficient sleep, stress, anxiety (Suh et al., 2018), and other emotional states associated with hyperarousal (Bangasser et al., 2019) more frequently than men. Here, consistent with an earlier work of a similarly large sample (Al-Rashed et al., 2021), we did not observe significant differences in PSQI scores between men and women. Another study of 7626 college students aged 18–29 years showed that women's overall PSQI scores (7.05 ±3.35) were higher than those of men (6.44 ±3.10), though the group difference in overall sleep quality was small in effect size (Becker et al., 2018). Other studies reported more nuanced sex differences in sleep regulation. Women and men did not differ in subjective reports of nighttime sleepiness, but women experienced significantly less sleepiness during the day than men, likely because of sex differences in neuroendocrine, including sex hormonal, signaling (Santhi et al., 2016). Women also showed an earlier timing of the circadian rhythm, as reflected in endogenous body temperature and melatonin levels (Cain et al., 2010), and a significantly shorter circadian period (Duffy et al., 2011). As a result, women may be more likely to be out of synchrony with the circadian rhythm. Although women relative to men were more susceptible to stress-induced hyperarousal, they were more resilient to stress-induced attention deficits (Bangasser et al., 2019). Because women are more likely to report physical symptoms and seek medical help, the extent of sex differences in sleep deficit and its impact on emotion and cognition may require more research with objective measures (Suh et al., 2018).

We found a significant correlation between PSQI and measures of negative emotions in both men and women. On the other hand, no clusters were identified in whole-brain regression of BNM rsFC with PSQI scores in women. Further, women did not show an inverse association between BNM-PCC rsFC and PSQI score or negative emotions, as observed in men, and these sex differences

were confirmed through slope tests. Thus, although women who are more anxious or stressed do worse in sleep, the neural processes associating anxiety/stress and sleep deficits require more research. Although we are not able to explain these sex differences, we noted sex differences in the structure and function of the BNM from both human and animal studies (Amunts, 2007; Kim et al., 2020). In particular, in rodents, although cholinergic signaling followed a distinct 24-hour rhythm in both sexes, females showed more cholinergic neurons in the BNM, greater release of acetylcholine, and more prominent diurnal differences in spontaneous locomotor activity than males (Takase et al., 2007). These findings suggest sex differences in BNM circuit function that warrants investigation. For instance, females may manifest diurnal changes in BNM circuit connectivities that would not be revealed by a "snapshot" of the brain.

Sleep Deficits and Cognitive Impairment

Sleep deficits are known to be associated with cognitive impairment (Wennberg et al., 2017; Vanek et al., 2020; Maggi et al., 2021). A serious sleep disorder, obstructive sleep apnea can cause intermittent hypoxia and contribute to neuronal damage, particularly in the hippocampus and cortex, leading to cognitive dysfunction. Sleep deficits lead to inflammation, which in turn impairs cognitive function (Liu et al., 2020). However, here, we did not observe a significant association between the accuracy rates or response times identified of the 7 behavioral tasks and the PSQI scores. It is possible that these cognitive tasks were not demanding, and the HCP sample comprised young people 22 to 35 years of age, who may not suffer in performance because of sleep problems. Also notable is that the PSQI score ranged from 0 to 19 in the current sample with a mean of 4.7 (S.D.=2.7), far lower than the average of 8.5 reported of individuals of a clinical sleep disorder, for example, insomnia (Sohn et al., 2012; Fabbri et al., 2021). Studies with more challenging cognitive tasks, in a population with a wide range of PSQI scores, and of a within-subject design (e.g., sleep deprivation) (Lo et al., 2016; Leong and Chee, 2023) are needed to investigate the roles of BNM circuit dysfunction in cognitive deficits in relation to sleep problems.

LIMITATIONS OF THE STUDY

Several additional limitations need to be considered for the study. First, we focused solely on rsFC. Future work combining multi-modal imaging data and/or employing different connectivity metrics may shed more light on BNM circuit dysfunction in link with sleep deficits. Second, although anxiety and stress problems were quantified with Achenbach self-reports, the HCP participants were largely healthy, with those meeting clinical diagnoses and/or requiring treatment excluded from enrollment. Thus, whether or how the current findings may extend to clinical populations remains to be seen. Third, women are known to demonstrate differences in brain functions across menstrual cycle phases (Sacher et al., 2023). HCP provides data on days since last period, and we observed no correlation between days since last period with any of the clinical or neural metrics (data not shown). However, subjective reports are prone to errors, and studies with measurement of sex hormonal levels would be needed to fully appreciate the heterogeneity of findings in women and to what extent this may be reflected in the current results. Fourth, the current findings are largely correlational. Thus, although we conducted mediation analyses to illustrate the inter-relationship between sleep deficits, BNM rsFC correlate, and anxiety/perceived stress, we understand that these results are in no way to imply causality. Longitudinal studies would be needed to provide evidence substantiating the impact of BNM circuit dysfunction on sleep deficits and emotional problems. Finally, the HCP quantified sleep deficits with the PSQI; objective measures (e.g., EEG and/or sleep tracker such as Fitbit) may provide more reliable indices of sleep duration and quality.

CONCLUSIONS

To conclude, resting-state BNM connectivity with PCC is diminished in young men with more severe sleep problems. Sleep deficits inter-link lower BNM-PCC connectivity and perceived stress and anxiety bidirectionally in men. The neural processes inter-relating sleep and emotional deficits in women require further investigations.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Interest Statement

The authors declare that they have no competing interests.

Data Availability

All data needed to evaluate the conclusions in the paper are shown in the paper and the supplement. All raw data supporting the analyses and findings of this study are available from HCP.

Author Contributions

Guangfei Li (Methodology [Equal], Writing—original draft [Equal], Writing—review and editing [Equal]), Dandan Zhong (Writing—original draft [Equal]), Bao Li (Conceptualization [Equal], Data curation [Equal], Funding acquisition [Equal], Project administration [Equal], Supervision [Equal]), Yu Chen (Validation [Equal]), Lin Yang (Investigation [Equal]), and Chiang-shan Li (Conceptualization [Equal], Supervision [Equal], Writing—review and editing [Equal])

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