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Connectivity within the default mode network mediates the association between chronotype and sleep quality

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Abstract

A late chronotype is associated with poor sleep quality, but the fundamental neural mechanism underlying this association remains unclear. Eyes-open resting-state functional MRI scans were obtained from 87 participants after extended wakefulness, and four subregions of the default mode network were extracted and analysed. Partial correlation analysis revealed that the functional connectivity between the precuneus and the medial prefrontal cortex (mPFC) was significantly correlated both with sleep quality and circadian preference of the participants. Mediation analysis found that the precuneus–mPFC link fully mediated the correlation between chronotype and sleep quality. We concluded that increased neural communication in the midline cores of the default mode network (DMN) may be responsible for the poor sleep quality of late chronotypes. As late chronotypes exhibit vulnerability to many mental disorders, our results can be used to refine pathophysiological models and provide therapy for such psychological disorders.

KEYWORDS

chronotype, default mode network, rs-fMRI, sleep quality

1 | INTRODUCTION

Individuals whose physiological activity reaches a peak in the afternoon or evening (i.e., the late chronotypes, rather than early chronotypes) have been observed to be more likely to face poor sleep quality and many other adverse health consequences, including mood disorders, alcohol and substance abuse, and negative cognitive and physical responses (Hasler, Sitnick, Shaw, & Forbes, 2013; Kivela, Papadopoulos, & Antypa, 2018; Taylor & Hasler, 2018).

The default mode network (DMN), known as the task-negative network, is suppressed when the brain needs to handle externally directed attention tasks (Raichle, 2015). The DMN mainly includes the precuneus, the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC) and the bilateral inferior parietal lobule (Raichle, 2015). The precuneus and mPFC combined, known as the midline cores of the DMN, play the most critical roles in this task-negative network (Andrews-Hanna, 2012). The DMN is considered to be closely associated with multiple cognitive functions, including spontaneous cognition, mood regulation, self-referencing and basic arousal levels (Davey, Pujol, & Harrison, 2016; Raichle, 2015).

In neuroimaging studies related to sleep quality or circadian preferences, the DMN is a primary brain region of interest. Facer-Childs, Campos, Middleton, Skene, and Bagshaw (2019) have compared the connectivity between different chronotypes and found that the functional connectivity of the DMN could predict an individual's attention performance and sleepiness level. Poor sleep quality is accompanied by more frequent thought wandering and daydreaming (Carciofo, Du, Song, & Zhang, 2014), which are the main functions of the DMN (Raichle, 2015). In the awake state, the functional connectivity within the DMN is related to sleep pressure, and increased sleep pressure corresponds to a reduced functional coupling within the DMN (Samann et al., 2010). A questionnaire widely used to measure sleep quality is the Pittsburgh Sleep Quality Index (PSQI), which plays a key role in psychiatric clinical practice and sleep research activities (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). For instance, in normal adults, poor sleep quality was found to be

associated with decreased connectivity between the mPFC and bilateral orbitofrontal cortex, and increased mPFC connectivity with the bilateral supplementary motor area, the left superior frontal cortex and the bilateral precuneus (Song, Scullin, & Park, 2016). Khalsa et al. (2016) have also reported that shorter sleep durations are associated with reduced functional connectivity within the DMN. In patients with persistent insomnia, Suh, Kim, Dang-Vu, Joo, and Shin (2016) have found reduced structural covariance within the DMN, and this change was correlated with higher PSQI scores, representing worse sleep quality.

The circadian rhythm genes are considered to have a coincident function in mediating neurotransmission, and connectivities within the DMN are associated with plenty of genes for neurotransmission (Wang et al., 2015), which reminds us that there might be an inextricable link between chronotype and the DMN. Chronotype is usually tested with the self-assessment Morningness-Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976). Based on the MEQ and some other similar tools, it has been found that the chronotype is related to multiple cognitive components, such as self-discipline, prosocial behaviour, rumination and extraversion, which are closely related to the functions of the DMN (Antypa et al., 2017; Lei, Zhao, & Chen, 2013; Lipnevich et al., 2017). Therefore, it can be inferred that the DMN is an indispensable brain network in chronotypes.

Although in the study of neural mechanisms related to sleep quality, or separately to circadian preferences, the DMN always plays a critical role, the multilateral relationship among sleep quality, circadian preference and the DMN remains unclear. Based on the above evidence, we hypothesized that the impact of circadian preference on sleep quality is mediated by the communication among the DMN subregions. We used resting-state fMRI (functional magnetic resonance imaging) data from 87 healthy participants and implemented the independent component analysis (ICA) method to dissociate the main components of the DMN. The main reason for adopting ICA is that this approach is a multivariate method and requires no *a priori* specification of activation waveforms. Another important virtue of ICA is the ability to implicitly remove artifacts and noise. In addition, ICA can better characterize individual differences compared to a seed-based approach (Calhoun, Adali, Hansen, Larsen, & Pekar, 2003), which makes the method more suitable for the purpose of the study. To enhance the reproducibility of the study, an region of interest (ROI)-based analysis was also added for validation of our main results. Considering the influence of the circadian rhythms, the scanning time of all participants was fixed to around midnight to maximize sleep pressure. Multiple demographic variables were used as covariates when the partial correlations were calculated among the three variables. We further conducted a mediation analysis to test whether the precuneus–mPFC link mediated the correlation between the MEQ and PSQI. As people of late chronotype and of poor sleep quality exhibit vulnerability to depression, anxiety and other emotional disorders, our study may deepen the understanding of the neuromechanism of these mental diseases.

Highlights

- A significant negative correlation between chronotype and sleep quality was found.
- Chronotype was negatively correlated with the DMN functional connectivity (FC).
- Sleep quality was positively correlated with the DMN FC.
- The precuneus–mPFC FC mediates the correlation between chronotype and sleep quality.

2 | METHODS

2.1 | Participants

Healthy university students (n = 105, ages 18–25 years, mean age = 21.1 ± 1.8 years, 53 males) were recruited using online advertising. The vision of all participants was normal or corrected-to-normal. None of the participants had a problematic psychiatric or neurological history. All participants signed consent forms and the Southwest University Ethics Committee approved the study. All participants were required to sleep on a regular schedule and fill in a sleep diary every day for 1 week before scanning. The collection of the sleep diary was performed twice a day (morning and evening). At the corresponding time of each day, the sleep diary was sent to the participants to fill out. Participants needed to answer a series of questions, including but not limited to the sleep onset time, wake-up time and subjective feeling of sleep quality, to ensure that they maintained a regular schedule. On the day of the scan, they were instructed to get up according to their weekend habits and not to nap in order to make them experience the same waking hours, to avoid confusion caused by inconsistent sleep homeostatic pressure and match their rhythm preferences. The participants arrived at the laboratory between 21:00 and 21:30 hours and they answered a set of questionnaires, which included the health information scale, MEQ, PSQI, Self-rating Depression Scale (SDS) and Self-rating Anxiety Scale (SAS). Taking into account the effect of daily rhythmicity on resting-state brain networks (Blautzik et al., 2013), the scanning time of all participants was fixed at around 00:00–03:00 hours. For each participant, his/her scanning time was determined by his/her mid-sleep time (i.e., we fixed the scanning time to be 2 hr before his/her maximum sleep pressure). The mid-sleep time is the midpoint between sleep onset and wake-up time on free days (Wittmann, Dinich, Merrow, & Roenneberg, 2006). In this study, the mid-sleep time is determined by the time of sleep onset and wake-up at weekends, collected by sleep diary. The statistical information for this variable is provided in Appendix S1.

These data are the first part of an ongoing sleep project. First, participants were instructed to remain awake to complete a resting-state session, then they were required to sleep in the fMRI scanner for the following sessions. Participants were required to focus on a fixed white cross in the centre of the display panel and to not think of anything deliberately during the 5-min resting-state scan. After the scan was over, the operator would immediately confirm with the participant whether

he/she was asleep in the scanner. Because the resting-state scan was scheduled at the beginning and the scan duration was relatively short (5 min), no participants were asleep in the scanner. Other psychological tests and MRI scans, such as the sleeping-state scans, were beyond the scope of the current study. After the experiment, they were given a monetary reward of 120–150 RMB. Of the 105 participants who completed the experiment, 11 participants were excluded due to incomplete or problematic data, one due to left-handedness, three due to obesity (BMI > 28) and three due to excessive head movement (>2 mm or 2°) in the scanner. Exclusion criteria for SDS and SAS scores were set at 63 and 60. Individuals who scored above these cutoffs were generally considered to have a moderate tendency to depression or anxiety. No participants were excluded by the criteria. Finally, 87 right-handed participants (42 males) were included in the following analyses.

2.2 | Psychological measures assessed by questionnaire

The Chinese translation version of the MEQ (Horne & Ostberg, 1976) was used to evaluate each subject's circadian chronotype. This questionnaire consists of 19 items, integrated into a total score, where lower scores indicate more preference for a late chronotype. The PSQI (Buysse et al., 1989) questionnaire evaluates subjective sleep quality for the previous month. It contains seven clinically derived components, each with an equal weighting from 0 to 3. Then each component's score is accumulated to get a single score from 0 to 21, where higher scores reflect worse sleep quality. The Self-rating Depression Scale (SDS) (Zung, 1965) and Self-rating Anxiety Scale (SAS) (Zung, 1971) scores were also collected to control for the potential impact of pathological behaviours. Demographic information and health status were collected using a self-reported 7-point Likert scale. Health status score was used to assess whether the participant had recently experienced physical discomfort, such as a cough, a cold, abdominal pain, etc. A higher score means that the individual felt more physical discomfort over the previous month. All remaining 87 participants scored <3, which indicated they were physically healthy.

2.3 | Acquisition of MRI data

All whole-brain resting-state blood oxygen level dependent images were attained with a 3 tesla Siemens Trio scanner. A T2*-weighted gradient echo-planar imaging (EPI) sequence (repetition time (TR)/time of echo (TE) = 1500/29 ms, field of view (FOV) = 192 × 192 mm^2, flip angle = 90°, acquisition matrix = 64 × 64, thickness/gap = 5/0.5 mm, in-plane resolution = 3.0 × 3.0 mm^2, axial slices = 25) was used to attain 200 functional volumes of 5 min for each participant. Last, a high-resolution T1-weighted structural image was acquired over 5 min with the three-dimensional spoiled gradient-recalled sequence (TR/TE = 8.5/3.4 ms, FOV = 240 × 240 mm^2, flip angle = 12°, acquisition matrix = 512 × 512, thickness/gap = 1/0 mm, slices = 176) and was used in subsequent resting-state fMRI preprocessing. Participants were told to relax and remain stationary in the scanner, and a cushioned head support device was used to control head motion.

2.4 | fMRI pre-processing

SPM12 was used to preprocess the fMRI data and this toolbox was developed by the Wellcome Department of Cognitive Neurology, London, UK (Friston et al., 1994). The steps and details of the preprocessing were as follows. First, slice timing was implemented to correct the problem that slices were not acquired at the same time. The middle slice was selected as the reference slice to minimize the interpolation error. Second, to correct for head motion, a six-parameter rigid-body transformation was applied to align all volumes to the first volume. If translational or rotational plane movement exceeded 2 mm or 2°, respectively, the participant's data were omitted. Third, the resting-state fMRI images were co-registered to the subject-specific T1 structural images and then spatially normalized to the template for the International Consortium for Brain Mapping. Finally, all functional images were spatially smoothed using a Gaussian kernel with a 6-mm full width at half maximum to reduce the bias of high-frequency noise and improve the signal-to-noise ratio.

2.5 | Functional connectivity within the DMN

Group ICA Of fMRI Toolbox (GIFT) software (Calhoun, Adali, Pearlson, & Pekar, 2001) was adopted for conducting a spatial group independent component analysis (ICA) on the preprocessed data. First, principal component analysis (PCA), which is a popular data dimension reduction method, was applied to reduce the subject-specific functional image with 200 time-points into 150 dimensions. Then all 87 participants' reduced data were concatenated across time and a group-level PCA was applied to get 100 dimensions with maximal variance explained. ICA used the infomax algorithm to get 100 independent components from the group-level PCA data. To ensure the stability of the final components, the ICA flow was repeated 20 times by ICASSO (Himberg, Hyvärinen, & Esposito, 2004). Spatial maps and time courses for each subject were obtained by the spatiotemporal regression back reconstruction method within GIFT. By visual inspection, possible artifacts related to non-neural noise, which may result from motion, vein, ventricular or cerebrospinal fluid, respirations and pulse, were excluded.

The subregion maps of the DMN from a template with 90 functional ROIs were used as spatial templates for component selection, which is widely used and proven to be superior to anatomical templates in functional connectivity analyses (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012). This template is available at http://findlab.stanford.edu/functional_ROIs.html. The spatial maps included in the subsequent analysis corresponded to the components with the highest spatial correlations with the DMN subregion maps, and the correlation values with DMN subregion templates must be >0.4. Spatial correlation is the voxel by voxel correlation between components and

the DMN subregion template as a measure of spatial correspondence (GIFT toolbox; Esposito et al., 2005). All selected independent components (ICs) were visually validated by two experienced experts (XC and XL) to ensure that the IC matching algorithm worked correctly. From the 100 independent components generated (Figure 1), four ICs finally remained through the above processes. Time courses of these clusters were used in the following functional connectivity calculations. The corresponding Montreal Neurological Institute (MNI) coordinates and the anatomical locations of these clusters are summarized in Table 1.

The subject-specific time courses corresponding to the components were low-pass filtered with canonical cut-off 0.15 Hz and then were despiked by algorithms within GIFT. The despiking procedure can reduce the interference of outliers on subsequent functional connectivity calculation. The Pearson correlation coefficients were transformed to Z scores by Fisher's Z transformation before further statistical analyses.

2.6 | Statistical analyses

The demographic variables age, gender, body mass index (BMI) and health status were included as confound variables when the partial correlation between pairs of the three variables, the MEQ, PSQI and functional connectivity (FC), was calculated. BMI was included as a confound variable because it has been found to affect resting-state FC (Kullmann et al., 2012). These confound variables were also implemented on the following mediation effect analysis. Specifically, the residuals after regressing out covariates were used in the subsequent statistical analysis. Mean head motions were also regressed out when residuals' FC was calculated.

Mediation analysis was performed by R Version 3.5.1 (R Core Team, 2013) and R package mediation Version 4.4.6 (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014). Statistical significance tests were implemented by the non-parametric method Bootstrap for 10,000 times. In order to verify the correctness of our model hypothesis, we repeated the same analysis steps for reverse validation. In the analysis of reverse validation, the positions of independent variables and dependent variables were exchanged; that is, the direction of this model was reversed. All other analytical procedures remained the same. This method was used by some studies to test whether the model in the opposite direction is statistically significant (Cheng, Rolls, Ruan, & Feng, 2018).

Considering that relying on the ICA method might put the research at a disadvantage regarding reproducibility, we added an ROI-based analysis to validate our finding. Detailed information about the processes of the ROI-based analysis is provided in Appendix S1.

3 | RESULTS

3.1 | Demographic variables and questionnaire scores

The sample used in the subsequent analyses included 87 participants (42 males). The mean and standard deviation of age and BMI were

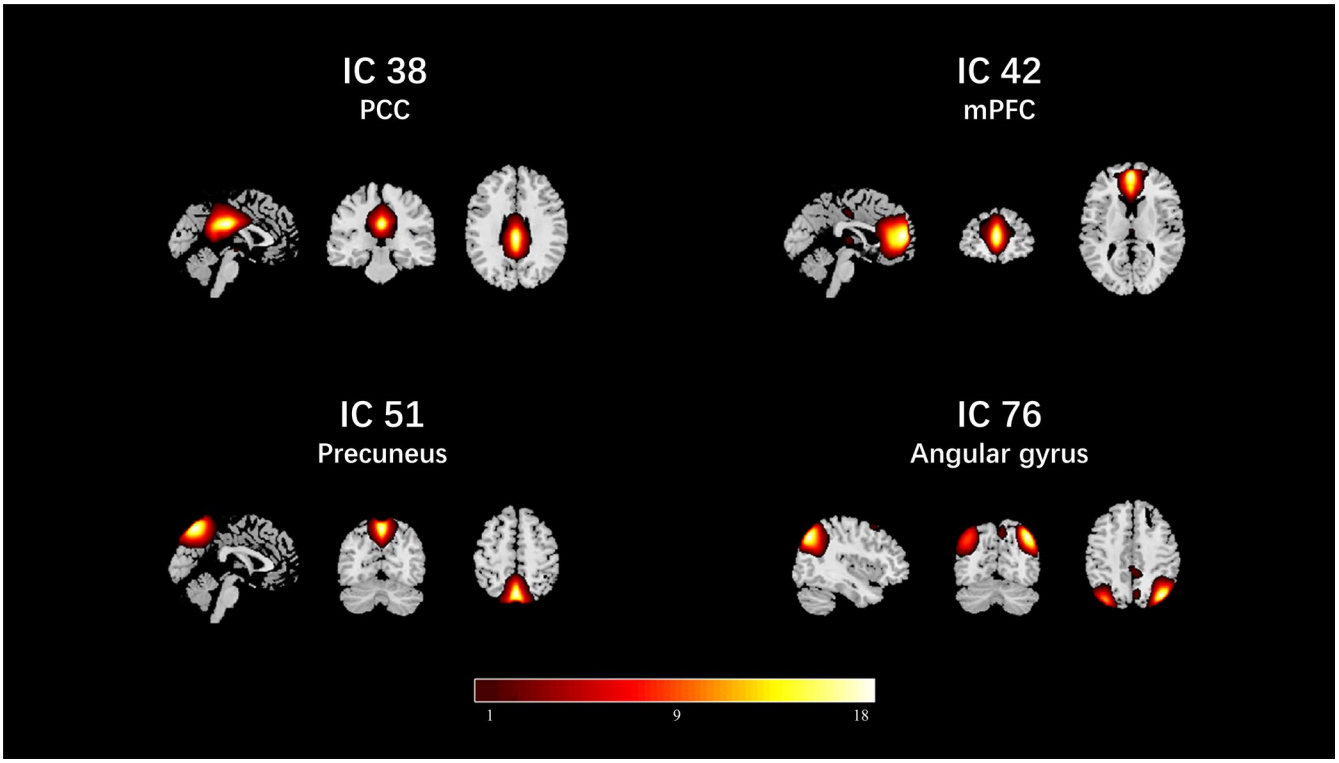

FIGURE 1 Representative sagittal, coronal and axial images of each statistical map are displayed in neurological convention. Four components of the DMN are illustrated, including the posterior cingulate cortex (PCC), the medial prefrontal cortex (mPFC), the precuneus and the angular gyrus. The color bar on the bottom stands for Z-score.

TABLE 1 Peak foci for the default mode network (DMN) subcomponents defined by group independent component analysis (ICA)

Regions	Anat. label	MNI coordinates			Cluster size	T
		x	*y*	*z*		
PCC (IC 38)						
	R posterior cingulate gyrus	3	−36	24	1878	34.18
	R middle cingulate gyrus	3	−24	27	658	35.28
	L precuneus	−12	−72	36	101	8.98
	L cuneus	−12	−78	42	–	8.50
mPFC (IC 42)						
	L superior medial frontal gyrus	−3	54	3	2,280	39.64
	R posterior orbital gyrus	33	18	−18	87	9.35
	L middle cingulate gyrus	0	−21	42	79	8.49
	L anterior insula	−30	15	−15	71	11.30
	R thalamus proper	3	−18	6	53	8.73
Precuneus (IC 51)						
	L precuneus	0	−60	48	1593	33.99
Angular gyrus (IC 76)						
	R angular gyrus	48	−69	39	1,245	31.99
	L angular gyrus	−36	−78	42	839	28.23
	R middle frontal gyrus	33	21	57	300	13.47
	R superior frontal gyrus	21	36	45	–	7.29
	R posterior cingulate gyrus	6	−39	42	201	10.12
	R middle temporal gyrus	60	−45	−9	131	13.43
	R precuneus	12	−57	21	–	8.42

Note: The significance threshold was set to $p < .05$, family-wise error-corrected, with a cluster size >50 voxels.

Abbreviations: Anat. label, anatomical labels from spm neuromorphometrics; IC, independent component; L, left hemisphere; mPFC, medial prefrontal cortex; PCC, posterior cingulate gyrus; R, right hemisphere.

TABLE 2 Questionnaire data and the cross-correlation between questionnaires

Measure	Mean	*SD*	Range	Correlation with	SAS		SDS		MEQ	
					r	*p*-value	*r*	*p*-value	*r*	*p*-value
SAS	38.9783	7.0164	28–59		–	–	–	–	–	–
SDS	42.1739	7.5340	26–61		.5615***	1.53e−8	–	–	–	–
MEQ	48.2935	7.1936	33–68		−0.1732	.1087	−.0276	.7998	–	–
PSQI	4.9674	2.1094	1–11		.2073	.0541	.1730	.1091	−.2408*	.0247

Note: Partial correlation was implemented and demographic variables (i.e., age, gender, BMI [body mass index] and health status) were included as confound variables. Degree of freedom: 86.

Abbreviations: MEQ, Morningness-Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-rating Depression Scale score; *SD*, standard deviation; SDS, Self-rating Depression Scale (SDS).

***Indicates $p < .001$.

*Indicates $p < .05$.

21.06 ± 1.83 and 20.67 ± 2.24, respectively. For age, the range was from 18 to 25 and for BMI was from 16.16 to 27.22. The mean and standard deviation of the MEQ score were 48.28 ± 7.34. Individuals with scores below 49 are generally classified as late chronotype, which means MEQ scores in the study were slightly biased towards the late chronotype. For PSQI scores, the range was from 1 to 11 and the mean and standard deviation were 4.94 ± 2.09. Details of participants' data and cross-partial correlation results of questionnaire scores are summarized in Table 2. Partial correlation analysis revealed a significant positive correlation between the SAS and SDS scores (r = .5615, p = 1.53e-8). Previous research reported that late chronotype was associated with depression (Kivela et al., 2018), but the result was not replicated in our data (Table 2). The reason for inconsistency may be that participants were healthy college students rather than clinical patients. Besides, a significant negative correlation between MEQ score and PSQI score was found (r = −.2408, p = .0247). Individuals of a late chronotype tended to report worse sleep quality (Figure 2).

3.2 | Correlation among the PSQI, MEQ and functional connectivity

Four components (Figure 1) were identified as DMN subregions across the 100 ICs obtained by the GICA approach. The cluster stability/quality (Iq) indices for these four ICs over 20 ICASSO repetitions were >0.9. The Iq index represents the corresponding stability assessment for each cluster, and the value drops when the cluster grows wider and mixes up with other clusters. The peak foci for the DMN subcomponents are listed in Table 1.

The Fisher's Z-transformed FC values between all pairs of DMN subcomponents are presented in Table S1. Among the six links yielded by the four subregions of the DMN, we found that the functional connectivity between the precuneus and mPFC was positively correlated with PSQI scores (r = .4112, p = .0005). That is to say, individuals with a higher connectivity value between the two regions reported worse sleep quality. A significant negative correlation between the precuneus–mPFC connectivity and MEQ score was found (r = −.2288, p = .0330). It suggested that late chronotypes tended to show increased functional connectivity. Bonferroni-based multiple test correction was implemented for conservative rejection of the null hypothesis. All uncorrected correlation results can be found in Table S2. There was no significant correlation between the other five links and total PSQI score or MEQ score (Table S2). See Figure 2 for details about the correlation between the precuneus–mPFC connectivity and sleep questionnaires.

3.3 | Mediation effect of functional connectivity

Interindividual differences in precuneus–mPFC functional connectivity correlated with their total PSQI score and with their MEQ score. Next, we assessed whether this functional connectivity mediated the correlation between the PSQI and MEQ. A significant mediation effect (β = −0.0242; p = .0064; bootstrap for 10,000 times) revealed that the functional connectivity fully mediated the relation of the MEQ to the PSQI (see Figure 3 for more details). The confidence interval for the mediation effect size was small to medium (k^2 = 0.0877, 95% CI: 0.0199 ~ 0.1805; Preacher & Kelley, 2011). ROI-based validation analysis also revealed a significant mediation effect (β = −0.0209; p = .0056; bootstrap for 10,000 times). The detailed results of this supplementary mediation analysis are provided in Appendix S1. Reverse validation did not reveal any significant mediation effect (β = −0.2286, p = .125; bootstraps for 10,000 times), thus the data did not support the model of the opposite direction from the PSQI to the MEQ.

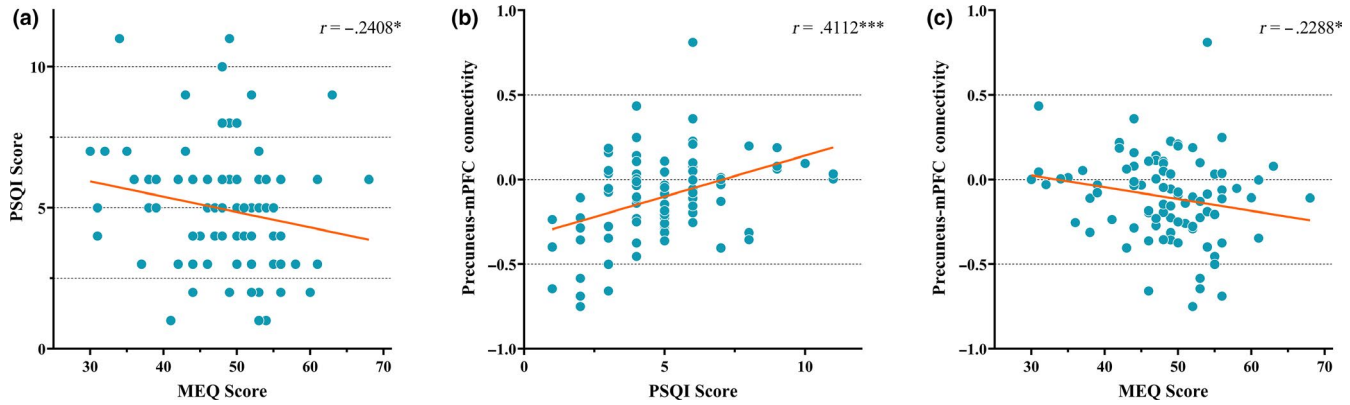

FIGURE 2 Association between MEQ score, total PSQI score, and functional connectivity. Demographic confounds were regressed out during calculation. (a) A significant negative correlation between MEQ and PSQI score (r = −0.2408, p = 0.0247, df = 86) was found. (b) The precuneus–mPFC functional connectivity was significantly positively correlated with PSQI score (r = 0.4112, p = 0.0005, df = 86). (c) A significant negative correlation of the functional connectivity with the MEQ score (r = −0.2288, p = 0.0330, df = 86) was found. Bonferroni-based correction was used. MEQ, Morningness-Eveningness Questionnaire Self-Assessment, a higher score indicates more morningness preference. PSQI, Pittsburgh Sleep Quality Index, a higher score indicates worse sleep quality. *** indicates p < 0.001 and * indicates p < 0.05.

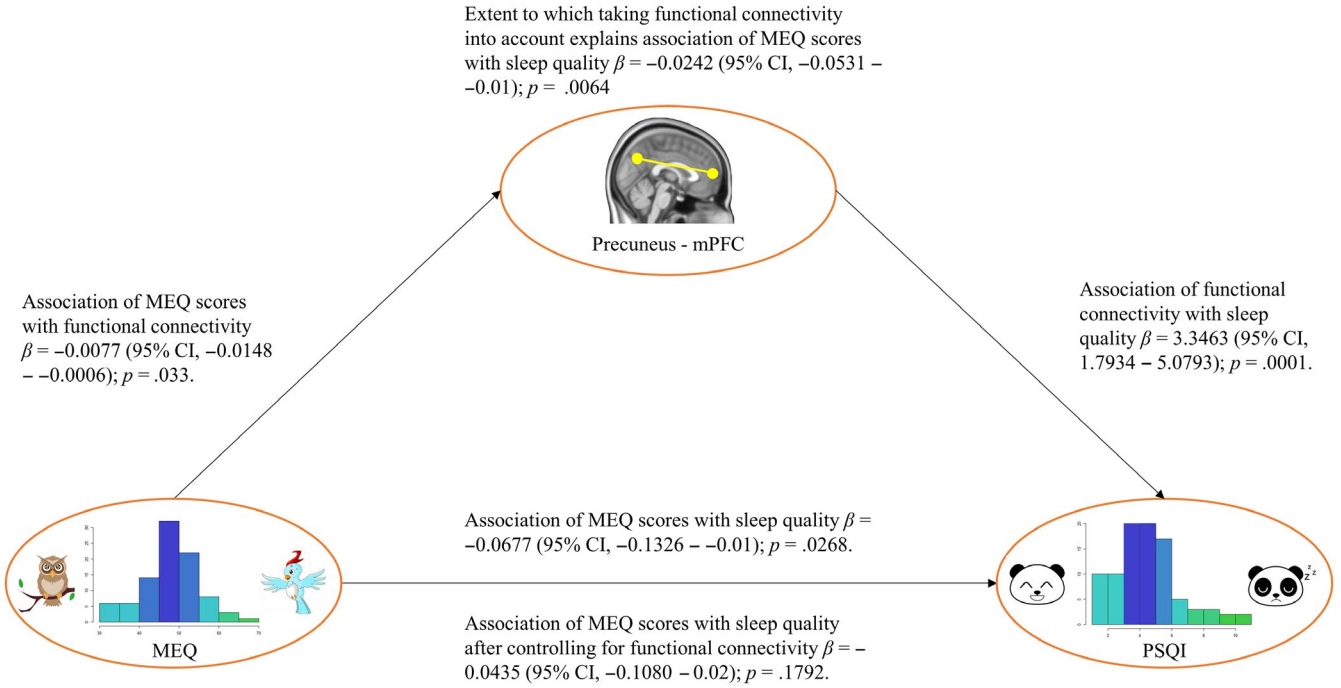

FIGURE 3 The mediation model among Morningness-Eveningness Questionnaire (MEQ) score, total Pittsburgh Sleep Quality Index (PSQI) score and mediator (the precuneus–mPFC functional connectivity). Statistical significance testing was done by the non-parametric Bootstrap method, 10,000 times. Demographic confounds were regressed out during calculation. The frequencies of MEQ and PSQI scores are separately displayed by a histogram within the circle. A higher PSQI score indicated worse sleep quality, while a higher MEQ score indicated that the individual is more inclined to lark (early chronotype) than to owl (late chronotype). The regression coefficient of MEQ to PSQI was significant when the functional connectivity was not considered. The direct effect of MEQ on PSQI, after removing the functional connectivity, shows that the association became insignificant. Mediation effect was significant (β = −0.0242, p = 0.0064). Kappa-squared effect size of the mediation analysis was 0.0877 (95% CI, 0.0199 ~ 0.1805).

4 | DISCUSSION

In this study, resting-state fMRI data of 87 participants were analysed and the midline cores of the default mode network (DMN) were extracted. Partial correlation analysis revealed that the precuneus–mPFC functional connectivity was significantly correlated with both circadian preference and total PSQI score of the participants (r = −.2288, p = .0330 and r = .4112, p = .0005, respectively). Our mediation analysis further revealed the precuneus–mPFC link mediated the correlation between chronotype and sleep quality, suggesting that the link is the key biomarker responsible for poor sleep quality in late chronotypes.

4.1 | Chronotype and sleep quality

The negative correlation between MEQ score and PSQI score (r = −.2408, p = .0247) revealed that late chronotypes were more inclined to poor sleep quality. Compared to early chronotypes, late chronotypes have a slower accumulation of sleep pressure during wakefulness, whereas sleep pressure dissipates more slowly during sleep (Taillard, Philip, Coste, Sagaspe, & Bioulac, 2003). Lower levels of sleep pressure may result in more difficulty in falling asleep during the same waking hours. Another reason may be the restricted sleep duration for late chronotypes. They go to bed very late, but the social clock makes them unable to extend sleep in the morning. More important, because late chronotypes have a higher risk of depression, drug abuse and alcohol addiction (Kivela et al., 2018), we speculated that the poor sleep quality might be the common foundation for these abnormal behaviours.

4.2 | Chronotype and functional connectivity

A significant negative correlation between the precuneus–mPFC functional connectivity and MEQ score was found (r = −.2288, p = .0330), which indicated that late chronotypes had higher precuneus–mPFC connectivity. The precuneus and mPFC are involved in the theory of mind and self-referencing processing (Davey et al., 2016). Late chronotypes have a higher theory of mind and self-referencing processing ability (Stolarski & Jankowski, 2015), and our result indicates that the higher ability may result from higher connectivity between the precuneus and mPFC. Lifelong development of the DMN is another way to understand its relationship with chronotype. Both young and ageing people have weak DMN connectivity when compared with adults (Mak et al., 2017). Functional connectivity within the DMN has an inverse U-shape over a lifespan and adults have the strongest DMN coupling. This shape is persistent

for circadian preference: young and ageing people are more likely to be early chronotypes, whereas adults are more likely to be late chronotypes (Broms et al., 2014).

Our results were inconsistent with other resting-state fMRI studies (Facer-Childs et al., 2019; Horne & Norbury, 2018). Horne and Norbury (2018) observed decreased precuneus connectivity with other regions of the DMN in late chronotypes. Although we observed a functional connectivity in the opposite direction (i.e., increased connectivity), we suspect that the overall connectivity they observed did not imply there is a decreased precuneus–mPFC connectivity, because this connectivity is only one link within the DMN. Recently, Facer-Childs and her colleagues have compared functional connectivity differences between late and early chronotypes. They did not find a significant difference in precuneus–mPFC connectivity (Facer-Childs et al., 2019), which was inconsistent with our finding. The first reason for this might be that a study with a small sample size (for the Facer-Childs' study it is 38) has a lower probability of detecting a true effect (Button et al., 2013). Second, in the protocol of Facer-Childs's study, the scanning time was fixed at three timepoints (14:00, 20:00 and 08:00 hours [GMT] the following morning), which may result in participants having different durations of wakefulness. Therefore, the resting-state connectivity patterns of the DMN for different participants might be discrepant, making it difficult to detect the real effect (Blautzik et al., 2013). The last reason might be methodological differences. Facer-Childs and colleagues (2019) used a seed-based approach to calculate functional connectivity, whereas Horne and Norbury (2018) and our current study used ICA, which can better characterize individual differences and effectively separate noise components (Calhoun et al., 2003).

4.3 | Sleep quality and functional connectivity

The precuneus–mPFC functional connectivity was significantly positively correlated with PSQI score (r = .4112, p = .0005), which indicated that individuals with higher functional connectivity have worse sleep quality. This is in line with a previous study that revealed that increased connectivities between the mPFC and bilateral precuneus were significantly associated with poor sleep quality (Song et al., 2016). The underlying psychological component may be frequent ruminative thinking, which is a recursive negative-biased self-referential processing. In fact, the dominant functions of the DMN include future imaging (Xu, Yuan, & Lei, 2016), theory of mind and self-referencing (Davey et al., 2016). Some previous studies observed that frequent rumination is associated with abnormal strengthened connectivity within the DMN (Hamilton, Farmer, Fogelman, & Gotlib, 2015; Zhu, Zhu, Shen, Liao, & Yuan, 2017). This leads to two negative effects on sleep quality. First, rumination before sleep may lead to difficulty in falling asleep, or what is worse, complete sleep failure. Second, rumination during wakefulness damages daytime functionality. In previous studies, poor sleep quality was related to more frequent daytime daydreaming, mind wandering and ruminative thinking (Thorsteinsson, Brown, & Owens, 2019; Vogt & Laureys, 2005); all these functions increased the feeling of fatigue during the daytime and led to a negative effect on sleep quality.

An extreme example of poor sleep quality is insomnia disorder. Previous studies on insomnia have found abnormal increased connectivity and hyperactivity within the DMN. Some evidence suggests the lack of deactivation of the DMN in insomnia patients. This phenomenon is presumed to be correlated with self-referential processing and it appears to be altered or imbalanced in insomnia (Marques, Gomes, Caetano, & Castelo-Branco, 2018). Considering the overactivity of the DMN, cognitive-behavioural therapy for insomnia (CBT-I) was proposed to alter the function of this network, improving patients' symptoms and overall quality of sleep (Marques, Gomes, Clemente, Santos, & Castelo-Branco, 2015).

4.4 | DMN mediates the effects of chronotype on sleep quality

Mediation analysis revealed that the precuneus–mPFC connectivity fully mediates the effect of chronotype preference on sleep quality. Individuals with more preference for a late chronotype have stronger synchronized neural activity when they are at rest, whereas stronger connectivity has a negative impact on individual sleep. This contributes to understanding the neurological mechanism behind the correlation between circadian preferences and sleep quality, which has been observed for decades (Kivela et al., 2018).

It has been found that frequent rumination thoughts related to self-referential processing are associated with both late chronotype (Antypa et al., 2017) and poor sleep quality (Thorsteinsson et al., 2019). Our study supports the idea that midline cores of the DMN have the potential to be a biomarker that intervenes to prevent negative-biased self-referential processing and also improve individuals' sleep quality. Two possible trajectories may explain the relationship among circadian preferences, the DMN and sleep quality. First, late chronotypes express hyperarousal in several brain systems, including the DMN. This significantly higher level of DMN arousal may persist at night and possibly during sleep stages. Second, early chronotypes can successfully inhibit the wakefulness system. This is done by deactivation of the DMN and activation of brain structures underlying sleep induction. Accordingly, the sleep of late chronotypes will be affected because their attentional resources are overwhelmed by concerns and rumination.

Our mediation model provides potential therapeutic interventions for the poor sleep quality of late chronotypes. Methods have been discovered that can impact the internal connectivities of the DMN, such as mental imagery-based training, cognitive-behavioural therapy (CBT), meditation and brain stimulations. Meditation and CBT can reverse hyperarousal in the DMN in insomnia (Marques et al., 2015; Sood & Jones, 2013). Non-invasive brain stimulation, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and transcranial magnetic

stimulation (TMS), can achieve changes in synchronous activities in brain networks (Polania, Nitsche, & Ruff, 2018). Based on high-definition tACS, a recent study reconstructed the information flow between frontotemporal regions and this procedure further improved the working-memory performance of older adults (Reinhart & Nguyen, 2019). Elevating specific connectivity to improve performance might be the aim of a number of researchers, but our finding shows that suppressing a specific link, here it is the precuneus–mPFC link, may also make sense. Our study suggests a new direction for future technologies to stimulate the brain, with the aim of improving sleep quality.

5 | LIMITATIONS

We still have several unsolved problems. First, sleep quality and circadian preferences in this study are in the form of self-reports. These variables require more objective measures in the future, such as sleep monitoring based on polysomnography (PSG) or a wireless activity monitor. Second, during the resting-state scan, the awake state of the subject was not monitored and drowsiness may fluctuate greatly in the awake state. However, in our experiment, the resting-state scanning requires the participants to keep their eyes open and stare at a fixed cross. In order to prevent the subject from falling asleep during the resting-state scan, a relatively short but still common resting-state scanning duration (5 min) was selected. In a study by Shirer et al. (2012), they found even functional connectivities obtained in a 1-min window could reflect naturalistic processing well. Combined with a verbal confirmation, the possibility of participants falling asleep was minimized. Third, the study was mainly focused on normal individuals, which restricts the extension of our results. Groups with conditions such as insomnia, depression or mental illness generally report sleep problems; thus, whether the mediation role of the DMN midline connectivity is destroyed in such groups deserves further attention.

6 | CONCLUSION

In conclusion, our current work has three main contributions. First, we found a significant negative correlation between chronotype and sleep quality. Late chronotypes were more inclined to report poor sleep quality. Second, late chronotypes have enhanced precuneus–mPFC connectivity, which has a negative effect on sleep quality. Finally, the precuneus–mPFC functional connectivity fully mediates the correlation. Because late chronotypes exhibit vulnerability to insomnia, depression, higher consumption of nicotine and alcohol, and other maladaptive behaviours, our finding of this mediation effect may have implications for the treatment of these mental disorders.

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REFERENCES

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *Neuroscientist*, *18*, 251–270. https://doi.org/10.1177/1073858411403316

Antypa, N., Verkuil, B., Molendijk, M., Schoevers, R., Penninx, B., & Van Der Does, W. (2017). Associations between chronotypes and psychological vulnerability factors of depression. *Chronobiology International*, *34*, 1125–1135. https://doi.org/10.1080/07420528.2017.1345932

Blautzik, J., Vetter, C., Peres, I., Gutyrchik, E., Keeser, D., Berman, A., … Meindl, T. (2013). Classifying fMRI-derived resting-state connectivity patterns according to their daily rhythmicity. *NeuroImage*, *71*, 298–306. https://doi.org/10.1016/j.neuroimage.2012.08.010

Broms, U., Pitkaniemi, J., Backmand, H., Heikkila, K., Koskenvuo, M., Peltonen, M., … Partonen, T. (2014). Long-term consistency of diurnal-type preferences among men. *Chronobiology International*, *31*, 182–188. https://doi.org/10.3109/07420528.2013.836534

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*, 365. https://doi.org/10.1038/nrn3475

Buysse, D. J., Reynolds, C. F. 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Calhoun, V. D., Adali, T., Hansen, L. K., Larsen, J., & Pekar, J. J. (2003). ICA of functional MRI data: An overview. In S. I. Amari, A. Cichocki, S. Makino & N. Murata (Eds.), *Proceedings of the International Workshop on Independent Component Analysis and Blind Signal Separation* (pp. 281–288). Nara, Japan: Citeseer.

Calhoun, V. D., Adali, T., Pearlson, G. D., & Pekar, J. J. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping*, *14*, 140–151. https://doi.org/10.1002/hbm.1048

Carciofo, R., Du, F., Song, N., & Zhang, K. (2014). Mind wandering, sleep quality, affect and chronotype: An exploratory study. *PLoS ONE*, *9*, e91285. https://doi.org/10.1371/journal.pone.0091285

Cheng, W., Rolls, E. T., Ruan, H., & Feng, J. (2018). Functional connectivities in the brain that mediate the association between depressive problems and sleep quality. *JAMA Psychiatry*, *75*, 1052–1061. https://doi.org/10.1001/jamapsychiatry.2018.1941

Davey, C. G., Pujol, J., & Harrison, B. J. (2016). Mapping the self in the brain's default mode network. *NeuroImage*, *132*, 390–397. https://doi.org/10.1016/j.neuroimage.2016.02.022

Esposito, F., Scarabino, T., Hyvarinen, A., Himberg, J., Formisano, E., Comani, S., … Di Salle, F. (2005). Independent component analysis of fMRI group studies by self-organizing clustering. *NeuroImage*, *25*, 193–205. https://doi.org/10.1016/j.neuroimage.2004.10.042

Facer-Childs, E. R., Campos, B. M., Middleton, B., Skene, D. J., & Bagshaw, A. P. (2019). Circadian phenotype impacts the brain's resting-state functional connectivity, attentional performance, and sleepiness. *Sleep*, *42*(5), https://doi.org/10.1093/sleep/zsz033

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. P., Frith, C. D., & Frackowiak, R. S. (1994). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*(4), 189–210. https://doi.org/10.1002/hbm.460020402

Hamilton, J. P., Farmer, M., Fogelman, P., & Gotlib, I. H. (2015). Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biological Psychiatry*, *78*, 224–230. https://doi.org/10.1016/j.biopsych.2015.02.020

Hasler, B. P., Sitnick, S. L., Shaw, D. S., & Forbes, E. E. (2013). An altered neural response to reward may contribute to alcohol problems among late adolescents with an evening chronotype. *Psychiatry Research*, *214*, 357–364. https://doi.org/10.1016/j.pscychresns.2013.08.005

Himberg J., Hyvärinen A., & Esposito F. (2004). Validating the independent components of neuroimaging time series via clustering and visualization. *NeuroImage*, *22*(3) 1214–1222.

Horne, C. M., & Norbury, R. (2018). Altered resting-state connectivity within default mode network associated with late chronotype. *Journal of Psychiatric Research*, *102*, 223–229. https://doi.org/10.1016/j.jpsychires.2018.04.013

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, *4*, 97–110.

Khalsa, S., Mayhew, S. D., Przezdzik, I., Wilson, R., Hale, J., Goldstone, A., … Bagshaw, A. P. (2016). Variability in cumulative habitual sleep duration predicts waking functional connectivity. *Sleep*, *39*, 87–95. https://doi.org/10.5665/sleep.5324

Kivela, L., Papadopoulos, M. R., & Antypa, N. (2018). Chronotype and psychiatric disorders. *Current Sleep Medicine Reports*, *4*, 94–103. https://doi.org/10.1007/s40675-018-0113-8

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H. U., … Preissl, H. (2012). The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. *Human Brain Mapping*, *33*, 1052–1061. https://doi.org/10.1002/hbm.21268

Lei, X., Zhao, Z., & Chen, H. (2013). Extraversion is encoded by scale-free dynamics of default mode network. *NeuroImage*, *74*, 52–57. https://doi.org/10.1016/j.neuroimage.2013.02.020

Lipnevich, A. A., Crede, M., Hahn, E., Spinath, F. M., Roberts, R. D., & Preckel, F. (2017). How distinctive are morningness and eveningness from the Big Five factors of personality? A meta-analytic investigation. *Journal of Personality and Social Psychology*, *112*, 491–509. https://doi.org/10.1037/pspp0000099

Mak, L. E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S. H., & Milev, R. (2017). The default mode network in healthy individuals: a systematic review and meta-analysis. *Brain Connect*, *7*, 25–33. https://doi.org/10.1089/brain.2016.0438

Marques, D. R., Gomes, A. A., Caetano, G., & Castelo-Branco, M. (2018). Insomnia disorder and brain's default-mode network. *Current Neurology and Neuroscience Reports*, *18*, 45. https://doi.org/10.1007/s11910-018-0861-3

Marques, D. R., Gomes, A. A., Clemente, V., dos Santos, J. M., & Castelo-Branco, M. (2015). Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A new perspective. *New Ideas in Psychology*, *36*, 30–37. https://doi.org/10.1016/j.newideapsych.2014.08.001

Polania, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nature Neuroscience*, *21*, 174–187. https://doi.org/10.1038/s41593-017-0054-4

Preacher, K. J., & Kelley, K. (2011). Effect size measures for mediation models: Quantitative strategies for communicating indirect effects. *Psychological Methods*, *16*, 93. https://doi.org/10.1037/a0022658

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience*, *38*, 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience*, *22*, 820–827. https://doi.org/10.1038/s41593-019-0371-x

Samann, P. G., Tully, C., Spoormaker, V. I., Wetter, T. C., Holsboer, F., Wehrle, R., & Czisch, M. (2010). Increased sleep pressure reduces resting state functional connectivity. *Magnetic Resonance Materials in Physics, Biology and Medicine*, *23*, 375–389. https://doi.org/10.1007/s10334-010-0213-z

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, *22*, 158–165. https://doi.org/10.1093/cercor/bhr099

Song, Z., Scullin, M., & Park, D. C. (2016). Sleep quality is associated with functional connectivity of medial prefrontal cortex in healthy middle-aged adults. *Alzheimer's & Dementia*, *12*, 39–40. https://doi.org/10.1016/j.jalz.2016.06.057

Sood, A., & Jones, D. T. (2013). On mind wandering, attention, brain networks, and meditation. *Explore (NY)*, *9*, 136–141. https://doi.org/10.1016/j.explore.2013.02.005

Stolarski, M., & Jankowski, K. S. (2015). Morningness-eveningness and performance-based emotional intelligence. *Biological Rhythm Research*, *46*, 417–423. https://doi.org/10.1080/09291016.2015.1020199

Suh, S., Kim, H., Dang-Vu, T. T., Joo, E., & Shin, C. (2016). Cortical thinning and altered cortico-cortical structural covariance of the default mode network in patients with persistent insomnia symptoms. *Sleep*, *39*, 161–171. https://doi.org/10.5665/sleep.5340

Taillard, J., Philip, P., Coste, O., Sagaspe, P., & Bioulac, B. (2003). The circadian and homeostatic modulation of sleep pressure during wakefulness differs between morning and evening chronotypes. *Journal of Sleep Research*, *12*, 275–282. https://doi.org/10.1046/j.0962-1105.2003.00369.x

Taylor, B. J., & Hasler, B. P. (2018). Chronotype and mental health: Recent advances. *Current Psychiatry Reports*, *20*, 59. https://doi.org/10.1007/s11920-018-0925-8

R Core Team (2013). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org/

Thorsteinsson, E. B., Brown, R. F., & Owens, M. T. (2019). Modeling the effects of stress, anxiety, and depression on rumination, sleep, and fatigue in a nonclinical sample. *The Journal of Nervous and Mental Disease*, *207*, 355–359. https://doi.org/10.1097/NMD.0000000000000973

Tingley, D., Yamamoto, T., Hirose, K., Keele, L., & Imai, K. (2014). mediation: R package for causal mediation analysis. *Journal of Statistical Software*, *59*(5), 1–38.

Vogt, B. A., & Laureys, S. (2005). Posterior cingulate, precuneal and retrosplenial cortices: Cytology and components of the neural network correlates of consciousness. In S. Laureys (Ed.), *The boundaries of consciousness: Neurobiology and neuropathology*. Amsterdam, Netherlands: Elsevier. Retrieved from https://www.sciencedirect.com/science/article/pii/S0079612305500153

Wang, G. Z., Belgard, T. G., Mao, D., Chen, L., Berto, S., Preuss, T. M., … Konopka, G. (2015). Correspondence between resting-state activity and brain gene expression. *Neuron*, *88*, 659–666. https://doi.org/10.1016/j.neuron.2015.10.022

Wittmann, M., Dinich, J., Merrow, M., & Roenneberg, T. (2006). Social jetlag: Misalignment of biological and social time. *Chronobiology International*, *23*, 497–509. https://doi.org/10.1080/07420520500545979

Xu, X., Yuan, H., & Lei, X. (2016). Activation and connectivity within the default mode network contribute independently to future-oriented thought. *Scientific Reports*, *6*, 21001. https://doi.org/10.1038/srep21001

Zhu, X., Zhu, Q., Shen, H., Liao, W., & Yuan, F. (2017). Rumination and default mode network subsystems connectivity in first-episode, drug-naive young patients with major depressive disorder. *Scientific Reports*, *7*, 43105. https://doi.org/10.1038/srep43105

Zung, W. W. (1965). A self-rating depression scale. *Archives of General Psychiatry*, *12*, 63–70. https://doi.org/10.1001/archpsyc.1965.01720310065008

Zung, W. W. (1971). A rating instrument for anxiety disorders. *Psychosomatics*, *12*, 371–379. https://doi.org/10.1016/S0033-3182(71)71479-0

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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