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Altered frontal connectivity after sleep deprivation predicts sustained attentional impairment: A resting-state functional magnetic resonance imaging study

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Summary

A series of studies have shown that sleep loss impairs one's capability for sustained attention. However, the underlying neurobiological mechanism linking sleep loss with sustained attention has not been elucidated. The present study aimed to investigate the effect of sleep deprivation on the resting-state brain and explored whether the magnitude of vigilance impairment after acute sleep deprivation can be predicted by measures of spontaneous fluctuations and functional connectivity. We implemented resting-state functional magnetic resonance imaging with 42 participants under both normal sleep and 24-hr sleep-deprivation conditions. The amplitude of low-frequency fluctuations (ALFF) and functional connectivity was used to investigate the neurobiological change caused by sleep deprivation, and the psychomotor vigilance task (PVT) was used to measure sustained attention in each state. Correlation analysis was used to investigate the relationship between the change in ALFF/functional connectivity and vigilance performance. Sleep deprivation induced significant reductions in ALFF in default mode network nodes and frontal-parietal network nodes, while inducing significant increments of ALFF in the bilateral thalamus, motor cortex, and visual cortex. The increased ALFF in the visual cortex was correlated with increased PVT lapses. Critically, decreased frontal-thalamus connectivity was correlated with increased PVT lapses, while increased frontal-visual connectivity was correlated with increased PVT lapses. The findings indicated that acute sleep deprivation induced a robust alteration in the resting brain, and sustained attentional impairment after sleep deprivation could be predicted by altered frontal connectivity with crucial neural nodes of stimulus input, such as the thalamus and visual cortex.

KEYWORDS

amplitude of low-frequency fluctuations, frontal cortex, functional connectivity, resting-state, sleep deprivation, thalamus

1 | INTRODUCTION

Sleep is crucial for survival, but sleep loss commonly occurs in modern society. Individuals experience acute or chronic sleep deprivation due to work pressure, shift work or sleep disorders (Killgore, 2010), and insufficient sleep leads to various dysfunctions of health and cognitive performance (Lim & Dinges, 2010). Acute sleep deprivation can strongly impair various human cognitive functions, including attention, working memory, executive function, and decision making (Chee et al., 2010; Lim & Dinges, 2008; Xu et al., 2016). Within these cognitive domains, attention is a fundamental component that is very sensitive to sleep deprivation (Killgore, 2010; Lim & Dinges, 2008), which involves

four different but interrelated subsystems: selective, divided, orienting (switching), and sustained attention (Petersen & Posner, 2012). Among these attentional subsystems, sustained attention is robustly affected by sleep deprivation, reflecting slower reaction times (RTs) and increased errors or omissions in vigilance tasks (Lim & Dinges, 2010).

According to published reviews (Peterson & Posner, 2012; Sarter et al., 2001), sustained attention is a fundamental component of attention that characterised by the individual's readiness to detect rarely and unpredictably occurring signals over prolonged periods of time, which corresponded to the activation of frontal and parietal cortical areas. The thalamus and basal forebrain are regions that mediate sustained attention performance (Sarter et al., 2001). In sleep deprivation domain, task-related functional magnetic resonance imaging (fMRI) studies indicated altered activation in several critical brain networks or regions that contribute to vigilance decline. Reduced activities appeared in the frontal-parietal attention network (FPN), including the prefrontal cortex and intraparietal sulcus, when performing selective attentional tasks after sleep deprivation (Chee & Tan, 2010; Chee et al., 2010). In addition, the default mode network (DMN), including the medial prefrontal cortex and posterior cingulate cortex, showed reduced activation when performing attentional tasks after sleep deprivation (Drummond et al., 2005). In 2015, a meta-analysis reviewed neuroimaging studies on attention after sleep deprivation and revealed that the function of the FPN and salience network (including the anterior cingulate cortex and anterior insula) were affected following sleep deprivation (Ma et al., 2015). According to the meta-analysis, the thalamus is another vital region susceptible to the effect of sleep deprivation, and increased activation was observed in the attentional task. Researchers have suggested that this might reflect an interaction between sleep loss and task performance based on the arousal level and thalamic activity (Ma et al., 2015).

Resting-state fMRI has been applied to investigate intrinsic spontaneous brain fluctuation without task intervention in recent years. Similar to task-related fMRI, research has revealed that the thalamus and critical nodes of the DMN and FPN show altered resting-state brain fluctuation after sleep deprivation, and brain fluctuation in the sleep-deprived state in some of these regions (i.e. the dorsolateral prefrontal cortex and thalamus) can predict subsequent attentional task performance (Gao et al., 2015; Wang et al., 2015). Studies concerning functional connectivity in sleep loss have mainly focussed on the connectivity within the DMN or the anti-correlation between the DMN and the FPN (De Havas et al., 2012). Although there is an opinion that the instability of the DMN and the reduced functional segregation between the DMN and FPN in the resting state might contribute to the vigilance decline seen after sleep deprivation, altered functional connectivity failed to predict subsequent vigilance task performance (De Havas et al., 2012). In addition, thalamo-cortical connectivity also changed after sleep deprivation. Researchers found decreased functional connectivity between the thalamus and parahippocampal gyrus, middle temporal gyrus, and superior frontal gyrus after 1 night of sleep deprivation (Shao et al., 2013). However, the relationship between altered functional connectivity and vigilance decline has not been verified.

The intrinsic spontaneous fluctuation in the resting state has been shown to be correlated with extrinsic behavioural performance (Fox & Raichle, 2007). The amplitude of whole-brain low-frequency fluctuations (ALFF) is an index reflecting the intensity of regional spontaneous fluctuations in blood-oxygen-level-dependent (BOLD) signals (Zang et al., 2007). It has been shown that ALFF can predict the subsequent attentional performance in sleep-deprivation states (Gao et al., 2015; Wang et al., 2015). In addition, functional connectivity is another important index of functional integration of resting brain function and reflects the temporal correlation of low-frequency fluctuations between different brain regions (Biswal et al., 1997), which has also been found to be sensitive to the individual resistant after sleep deprivation (Yeo et al., 2015; Zhang et al. 2019). The combination of these two methods has been widely used to provide additional understanding of the functional organisation in several brain disorders or substance addiction (Chen et al., 2017; Tadayonnejad et al., 2015), and the pre-test ALFF/functional connectivity can predict the subsequent behavioural performance (Tian et al., 2012; Zou et al., 2013). Thus, we considered that by combining these two methods and correlating with the subsequent behavioural performance may provide more information about the altered brain activity corresponding to attention impairment following sleep deprivation.

In the present study, the whole-brain ALFF was used to investigate the changes in spontaneous neural fluctuations following sleep deprivation and to locate the seed regions for the functional connectivity analysis. We hypothesised that altered ALFF might be shown in the FPN, the DMN, and the subcortical region of the thalamus based on a previous neuroimaging meta-analysis (Krause et al., 2017; Ma et al., 2015). Furthermore, we used regions demonstrating significant state differences in ALFF to define regions of interest (ROIs) as seed regions to further evaluate the functional connectivity affected by sleep deprivation. Finally, to identify the altered ALFF and functional connectivity that can predict subsequent attentional impairment induced by sleep deprivation, we further calculated the correlation between altered ALFF, functional connectivity and behavioural changes in the psychomotor vigilance task (PVT) to uncover the relationship between changes in the resting-state function and behavioural impairment following sleep deprivation.

2 | METHODS

2.1 | Participants

A total of 42 participants were included in this study (23 females, mean [*SD*] age 21.57 [2.25] years). All participants met the following inclusion criteria: (1) normal or corrected-to-normal vision; (2) no history of major disease and were free from neurological, psychiatric, and sleep disorders; (3) no habitual smoking, drinking, or other substance addiction; (4) no trans-meridian travel, shift work or irregular sleep–wake routines in the 60 days prior to the in-laboratory experiment; (5) no caffeine or medicine intake 48 hr before each session; (6) normal sleep patterns and were not extreme morning or evening types based on the

Horne–Ostberg Morningness–Eveningness Questionnaire. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of South China Normal University. Each participant provided written informed consent; they were paid a certain amount of money after finishing the study.

2.2 | Experimental protocol

The present study was conducted by using a within-subject design. All participants went over two sessions corresponding to rested wakefulness (RW) after normal sleep and acute sleep deprivation, which were counterbalanced by participants and separated by at least 1 week. Prior to the study, participants were asked to attend a semi-structured interview as a screening session to ensure that they met all inclusion criteria. Eligible participants habitually had 6.5–8 hr of sleep and habitually awakened between 06:00 and 09:00 hours, as assessed by sleep diary and actiography (Actiwatch Spectrum, Philips) within 2 weeks before the in-laboratory experiment. Participants made an additional visit to sleep to the laboratory with polysomnography (PSG) recording 1 night before RW to adapt to the laboratory environment and to ensure that they did not have any sleep disorders. In the RW session, participants had a mean (*SD*) of 7.9 (0.3) hr of sleep according to the PSG recordings. Resting-state fMRI scanning was performed at 09:30 hours (± 1 hr) the next morning. Participants were instructed to lie down and stay awake with their eyes opened. After the scanning session, all participants had to report whether they have fallen asleep in the scanner. One of the participants reported a sleep experience in the scanner and was excluded from data analysis. After the scanning session, participants completed a 10-min PVT. In the sleep-deprivation session, most of the protocol was the same as that in the RW session, and participants went through a 24-hr total sleep-deprivation period during the night, in which participants were monitored by well-trained experimenters (Figure 1).

2.3 | Psychomotor vigilance task (PVT) and subjective sleepiness rating

The PVT is widely used to measure sustained attention in sleep research because of its high reliability and high sensitivity to sleep loss (Chua et al., 2019; Lim & Dinges, 2008). In the present study, we used a 10-min visual PVT. Participants were asked to focus their attention on a red, rectangular box subtending 2 × 1.3 degrees of visual angle in the middle of a black screen and monitor that space for the appearance of a millisecond counter, which appeared at random intervals ranging from 2 to 10 s. They were instructed to stop the counter as quickly as possible with a button press, after which they would be able to view their RT. Participants were also instructed to avoid anticipating the stimuli so as not to register "false starts" or responses when no stimulus was present on the screen. Trials with RTs of <100 ms were excluded, and those >500 ms were defined as lapses.

In addition, subjective sleepiness was assessed by the Karolinska Sleepiness Scale (KSS) immediately before the PVT. The KSS is a 9-point, verbally anchored scale ranging from 1 ("extremely alert") to 9 ("extremely sleepy").

2.4 | Behavioural data analysis

Behavioural data were processed with SPSS®, version 21 (SPSS Inc.). We used mean RTs and lapse numbers as indices to evaluate individuals' sustained attention. The change in lapse numbers was calculated as lapse numbers at the sleep-deprivation state − lapse numbers at the RW state. A higher value would represent a more severe sustained attention deficit after sleep deprivation. Two-tailed paired *t* tests were performed to compare lapse numbers between RW and sleep deprivation.

2.5 | Imaging data acquisition

All neuroimaging data were collected under both RW and sleep deprivation conditions with a 3-T Magnetom Trio MRI scanner system (Siemens Medical Systems) using a 12-channel head coil. Functional resting-state data were collected with T2*-weighted echo-planar imaging (EPI) (repetition time [TR] = 2,000 ms, echo time [TE] = 24 ms, slices = 30, slice thickness = 4 mm, matrix size = 64 × 64 mm^2, flip angle = 90°, field of view [FOV] = 220 × 220 mm^2, 3.4 × 3.4 × 4 mm^3). High-resolution T1-weighted structural imaging was acquired using the magnetisation prepared rapid gradient-echo (MPRAGE) sequence (176 slices, TR = 2,300 ms, TE = 3.24 ms, slice thickness = 1 mm, flip angle = 9°,

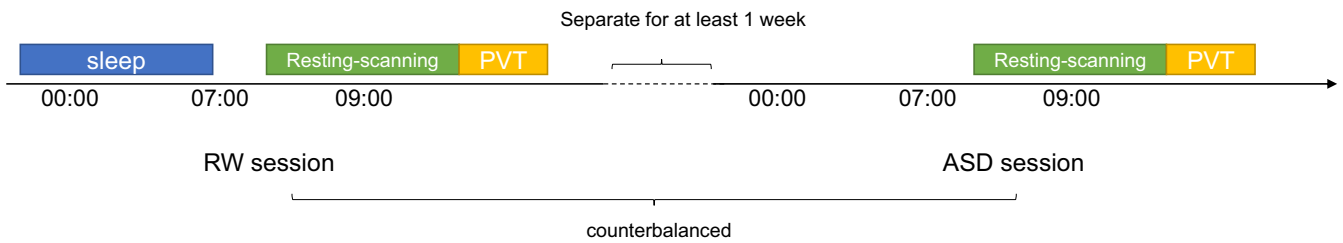


FIGURE 1 Experimental protocol. ASD, acute sleep deprivation; PVT, psychomotor vigilance task; RW, rested wakefulness after normal sleep. RW and ASD were counterbalanced by participants and separated for at least 1 week

FOV = 256 × 256 mm^2, 1 × 1 × 1 mm^3 voxels). Functional images were scanned in the axial direction, while T1 structural images were scanned in the sagittal direction.

2.6 | Image pre-processing and statistical analysis

Resting fMRI data pre-processing was performed using the Data Processing Assistant for Resting-State fMRI Advanced Edition (DPASFA) version 4.5, based on the toolbox for Data Processing and Analysis of Brain Imaging (DPABI, http://rfmri.org/DPABI; Yan et al., 2016) version 4.21 using the following steps: (1) Slice timing and realignment was performed after removing the first 10 time points. (2) Head motion was corrected based on framewise displacement (FD). Volumes with a FD of >0.2 were excluded, which resulted in the exclusion of six high-motion participants. (3) Nuisance covariate regression was performed to remove the white matter signal, cerebrospinal fluid examination signal, head motion (based on Friston-24) and global signal. (4) T1-weighted images were co-registered to the mean functional image. Spatial normalisation to the standard Montreal Neurological Institute (MNI) brain space using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) was performed for each participant. (5) Smoothing was performed with an 8-mm full-width-at half-maximum (FWHM) Gaussian kernel. Finally, (6) filtering was performed using a 0.01–0.08 Hz band-pass.

Individual participant analyses included ALFF and functional connectivity calculations using the pre-processed data. For the ALFF calculations, the time series of each given voxel were first converted to the frequency domain using a fast Fourier transform. Next, the square root of the power spectrum was computed and then averaged across 0.01–0.08 Hz. This averaged square root was taken as the ALFF at the given voxel (Zang et al., 2007). To detect the neural networks affected by sleep deprivation, we performed functional connectivity analysis. Voxel-wise functional connectivity was performed to calculate correlation coefficients between the seed region and all other voxels in the brain. The seed regions were defined as ROIs based on the ALFF results. Connectivity maps were produced by extracting the mean time series from the three seed regions separately and then calculating its correlation coefficients with the remaining voxels of the brain. ALFF and functional connectivity values were all converted to *z* scores using Fisher's *r*-to-*z* transformation. The DPABI toolbox, based on the automated anatomical labelling (AAL) atlas, and Brodmann atlas were used for anatomical identification.

The group-level analysis was conducted between RW and sleep-deprivation states. To evaluate ALFF, we compared ALFF *z*-score maps between RW and sleep-deprivation states by a paired *t* test. Multiple comparison correction was performed through Gaussian random field theory (GRF) by the toolbox in DPABI (Yan et al., 2016) at a threshold of $p < .001$ at the voxel level (uncorrected) with $p < .05$ at the cluster level (corrected). Peak voxels of survival clusters were used to define ROIs, as spheres with a 4-mm radius, for the following whole-brain functional connectivity calculation. For functional connectivity analysis, we compared the functional connectivity *z*-score maps between RW and sleep deprivation by paired *t* test (sleep deprivation > RW) for each participant and each ROI sphere separately. Multiple comparison correction was performed with a threshold of $p < .001$ at the voxel level (uncorrected) and $p < .05$ at the cluster level (GRF corrected).

2.7 | Correlation analysis between ALFF/functional connectivity changes and behavioural changes

2.7.1 | ALFF-behaviour correlation analysis

To investigate the relationship between the altered ALFF regions and lapse numbers change, we computed the ALFF change by subtracting ALFF maps of the RW state from ALFF maps of the sleep-deprivation state in each participant. Lapse numbers change was calculated by subtracting lapse numbers in the RW state from that in the sleep-deprivation state. Then, we computed the Pearson's correlation analysis between ALFF change maps and lapse numbers change.

2.7.2 | Functional connectivity analysis

To further discover the correlation between the functional connectivity changes and behavioural changes induced by sleep deprivation, we first computed the functional connectivity changes by subtracting functional connectivity *z*-score maps of the RW state from functional connectivity *z*-score maps of the sleep-deprivation state in each participant. Similar to the functional connectivity changes, lapse number changes were computed by subtracting lapse numbers in the RW state from those in the sleep-deprivation state. Then, we calculated the Pearson's correlation coefficients between functional connectivity changes and lapse number changes. The results of correlation analysis would suggest that the altered resting functional connectivity could predict an individual's subsequent PVT performance.

3 | RESULTS

3.1 | PVT performance and subjective sleepiness rating

Compared to performance following RW, participants exhibited significantly slower RTs (mean [*SD*] RW: 339.80 [39.27] ms, sleep deprivation: 531.56 [273.53] ms; $t = 4.69$, $p < .001$), increased lapse numbers (mean [*SD*] RW: 2.12 [2.66], sleep deprivation: 11.83 [8.67]; $t = 7.14$, $p < .001$), and increased subjective sleepiness ratings (mean [*SD*] RW: 05 [1.07], sleep deprivation: 7.22 [1.35]; $t = 9.60$, $p < .001$; see Table 1) after sleep deprivation.

TABLE 1 Statistics of behaviour task (PVT) performance and subjective sleepiness rating in both RW and sleep deprivation

Variable, mean (*SD*)	RW	Sleep deprivation	*t*
Number of lapses	2.12 (2.66)	11.83 (8.67)	7.14***
RT, ms	339.80 (39.27)	531.56 (273.53)	4.69***
Subjective sleepiness score	5.05 (1.07)	7.22 (1.35)	9.60***

Abbreviations: PVT, psychomotor vigilance task; RW, rested wakefulness after normal sleep; Mean RT, mean reaction time; subjective sleepiness, a 9-point scale ranging from 1 ("extremely alert") to 9 ("extremely sleepy").

***$p < .001$.

3.2 | Impact of sleep deprivation on ALFF

Paired *t* tests revealed significantly increased ALFF in the regions of the right paracentral lobule, bilateral thalamus, and inferior occipital gyrus after sleep deprivation, while decreased ALFF was shown in the regions of the left middle frontal gyrus, right precuneus, right inferior parietal lobule, and right superior frontal gyrus (see Table 2 and Figure 2).

3.3 | Impact of sleep deprivation on functional connectivity

We performed paired *t* tests to reveal significant differences in the functional connectivity between the RW and sleep-deprivation states. The selected seed regions were based on the regions that showed significant differences in ALFF, including the inferior occipital region, right paracentral lobule, right thalamus, left middle frontal region, and right inferior parietal lobule. The MNI coordinates and cluster information are provided in Table S1.

3.4 | Correlation between behavioural changes and ALFF/functional connectivity changes

3.4.1 | Correlation between ALFF change and behavioural change

We performed correlation analysis between ALFF change regions and lapse numbers change. Within all the altered ALFF regions, only ALFF change in the left calcarine showed a positive correlation with the lapse numbers change ($r = .62$, $p < .001$; Figure 3).

3.4.2 | Correlation between functional connectivity change and behavioural change

We calculated Pearson's correlation coefficients between the lapse number changes and functional connectivity changes. However, within all the functional connectivity altered by sleep deprivation (Table S1) only parts of the altered functional connectivity were correlated with the lapse number change. Specifically, the functional connectivity change between the right thalamus and bilateral inferior frontal gyrus was inversely correlated with the lapse number change (right inferior frontal gyrus: $r = -.53$, $p < .001$; left inferior frontal gyrus: $r = -.67$, $p < .001$), while the functional connectivity change between the left middle frontal gyrus and left inferior occipital gyrus was significantly correlated with the lapse number change ($r = .68$, $p < .001$, see Figure 4).

4 | DISCUSSION

In the present study, we investigated the effect of sleep deprivation on the resting-state ALFF signal and functional connectivity, and explored the neural basis of vigilance impairment after acute sleep deprivation by connecting changes in PVT performance with altered functional connectivity in resting-state fMRI data. The present results demonstrated a widespread detrimental effect of sleep deprivation on the resting brain, especially in the brain areas in the FPN and DMN. However, regional ALFF changes in the thalamus and visual and motor regions were significantly increased, which may suggest a counteracting effect to keep a person alert when combating sleep loss. Within these regions, ALFF changes in the visual regions were correlated with the lapse numbers change. Critically, correlation analyses revealed that a decrease in the functional connectivity between the right thalamus and bilateral inferior frontal gyrus was significantly correlated with increased lapses during the PVT, while an increase in the functional connectivity between the left middle frontal gyrus and left inferior occipital gyrus was significantly correlated with increased lapses during PVT. These findings indicated that decreased co-activation of the thalamus and bilateral inferior frontal gyrus might predict vigilance impairment after sleep deprivation, as well as increased co-activation between frontal and visual areas.

The regions that exhibited a decreased ALFF signal in the present study, including the superior frontal gyrus and right precuneus, are located at the key nodes of the DMN (Fox & Raichle, 2007). This is consistent with our assumption. Several studies concerning ALFF signals have reported that sleep deprivation reduced the ALFF signal in the middle frontal gyrus and superior frontal gyrus, which are components of the DMN (Gao et al., 2015; Wang et al., 2015). Previous studies have reported that resting DMN connectivity was disrupted in a sleep-deprived state (De Havas et al., 2012; Gujar et al., 2010). These results jointly support our present results that sleep deprivation disrupts resting DMN function, which might be related with reduced responsiveness to the environment. Consistent with our hypothesis, the right inferior parietal lobule and right superior frontal gyrus were found to exhibit decreased ALFF in the present study. According to reviews, these two regions are components of the FPN, which is associated with attention and working memory (Corbetta & Shulman, 2002; Krause et al., 2017). A series of studies consistently indicated that the activity of FPN was reduced when performing attentional tasks

TABLE 2 Regions significantly affected by sleep deprivation determined by ALFF in the resting state (ASD > RW)

Regions	MNI coordinates			*t* value	Cluster size	Brodmann area
	x	*y*	*z*			
Increased ALFF following ASD						
L. Calcarine	0	−87	−3	8.1842***	2,799	N/A
R. Paracentral lobule	9	−27	66	6.8474***	846	4
R. Thalamus	9	−18	6	5.6025***	86	N/A
Decreased ALFF following ASD						
L. Middle frontal gyrus	−27	6	45	−6.4148***	146	6
R. Precuneus	15	−45	39	−6.1102***	116	N/A
R. Inferior parietal lobule	57	−27	27	−4.8552***	78	48
R. Superior frontal gyrus	15	27	42	−4.8368***	68	32

Note: All clusters above survived after multiple comparison correction through Gaussian random field theory ($p < .05$, GRF corrected). Anatomical identification was performed by DPABI toolbox based on the AAL atlas and Brodmann atlas.

Abbreviations: ALFF, amplitude of low-frequency fluctuations (0.01–0.08 Hz bands extracted from the BOLD signal); ASD, acute sleep deprivation; L., left; MNI, Montreal Neurological Institute; R., right; RW, rested wakefulness after normal sleep.

***$p < .001$.

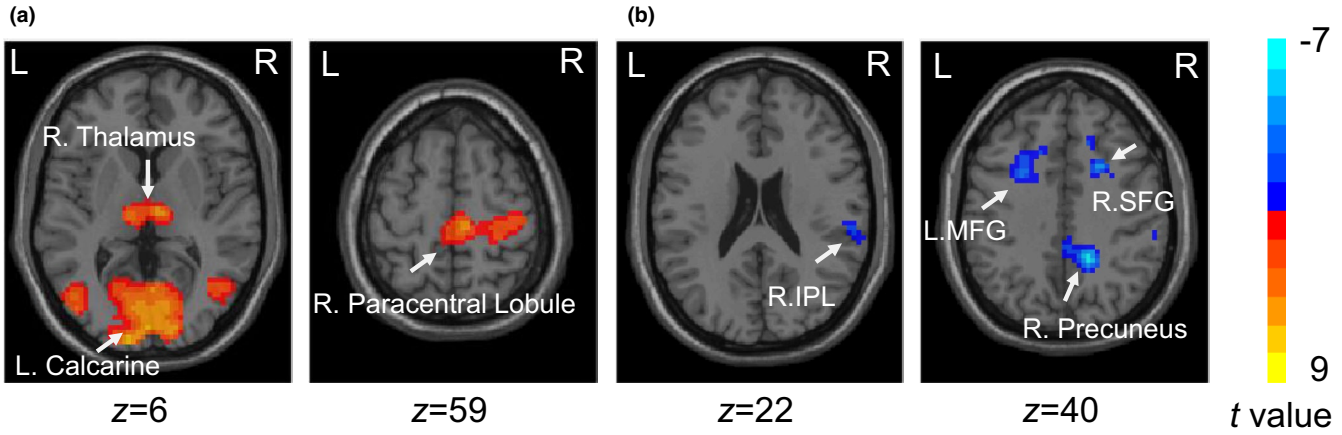


FIGURE 2 Regions significantly affected by sleep deprivation based on amplitude of low-frequency fluctuations (ALFF) in the resting state (ASD > RW). (a) The regions with increased ALFF following sleep deprivation; (b) the regions with decreased ALFF following sleep deprivation. *Z* values represent the horizontal coordinates from the inferior to superior direction based on Montreal Neurological Institute (MNI) space. All clusters above survived after multiple comparison correction through Gaussian random field theory ($p < .05$, GRF corrected). ASD, acute sleep deprivation; L, left; L.MFG, left middle frontal gyrus; R, right; R.IPL, right inferior parietal lobule; R.SFG, right superior frontal gyrus; RW, rested wakefulness after normal sleep

after sleep deprivation (Chee & Tan, 2010). Moreover, resting-state fMRI evidence demonstrated that compared with ALFF in the well-rested state, ALFF in the inferior parietal and dorsolateral prefrontal cortex were reduced during the sleep-deprived state; these regions were also nodes of the FPN (Gao et al., 2015; Wang et al., 2015). This unstable relationship between the DMN and FPN was thought to be crucial for the attention impairment induced by sleep deprivation according to a recent review (Krause et al., 2017). The results in the present study additionally illustrated that the activity in the key nodes of both the DMN and FPN were reduced during the resting state after sleep deprivation, which indicates that sleep deprivation may weaken the anti-correlation between the DMN and FPN during the resting state (Fox et al., 2005). These findings are partially compatible with the results of unresponsive-wakefulness patients during resting-state fMRI (Long et al., 2016). These findings also seem to suggest that the interaction between the DMN and FPN may be a potential biomarker for different attentional states or conscious states.

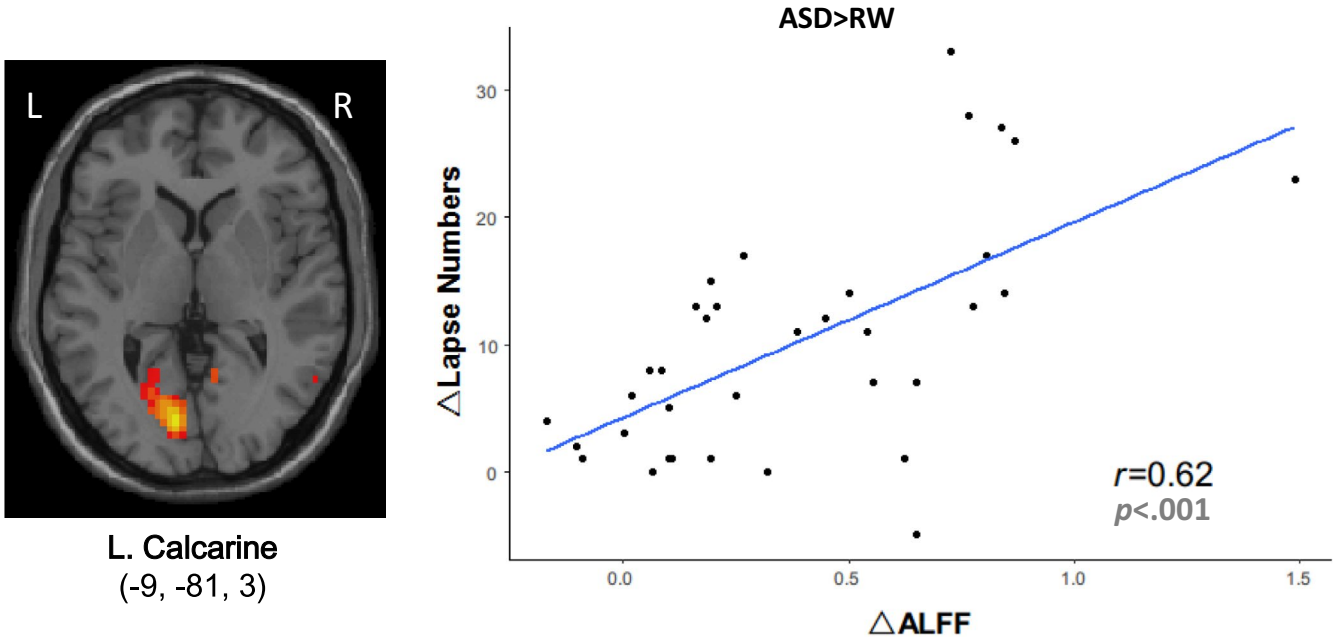


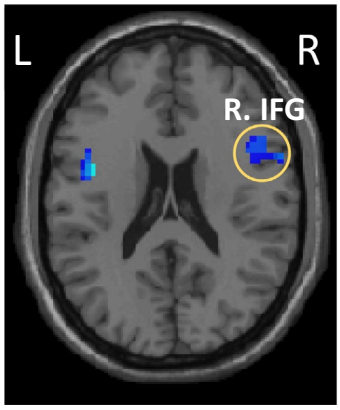
FIGURE 3 Amplitude of low-frequency fluctuations (ALFF) change correlated with lapse numbers change following sleep deprivation. Scatter plots show the relationship between ALFF changes in the region of left calcarine and lapse numbers change following acute sleep deprivation (ASD). Corresponding brain region is illustrated left beside the scatter plot. L, left; R, right; RW, rested wakefulness after normal sleep

Moreover, increased ALFF in the regions of the bilateral thalamus, visual cortex, and paracentral lobule after sleep deprivation was consistent with several recent studies and meta-analysis (Gao et al., 2015; Javaheipour et al., 2019; Wang et al., 2015). As the thalamus is an essential node of the arousal system, increased ALFF in the thalamus after sleep deprivation might represent a compensatory mechanism to maintain relative alertness, as mentioned in a recent meta-analysis (Ma et al., 2015). The increased activity in the visual cortex and motor cortex might correspond to the demand to enhance perceptual function to keep the person alert and aware of his or her environment. Combined with decreased ALFF results in the attention-related regions, sleep deprivation has led to poorer attention function, and thus, increased perceptual load of visual processing, according to a meta-analysis (Javaheipour et al., 2019). This was confirmed by the correlation analysis between ALFF change in the visual cortex and the lapse number change in the present study. Consistent with previous study (Gao et al., 2015), those who performed worse in the PVT after sleep deprivation had higher ALFF value in the visual cortex, which might indicate that the hyperactivity in several brain regions found in the present study might be interpreted as an enhanced neural function to confront the impact caused by sleep deprivation.

Correlation analysis revealed that the functional connectivity between the thalamus and bilateral inferior frontal gyrus is correlated with the vigilance decline induced by sleep deprivation. The disruption of thalamic connectivity with frontal regions might reflect "microsleeps", which indicate instability of the waking state. A microsleep is defined as a short-duration sleep state (5–14 s) intruded into wakefulness, especially when individuals are sleep deprived (Goel et al., 2009). Previous studies have observed transient reduced thalamic activity (Ong et al., 2015; Poudel et al., 2014) and induced frontal activity (Drummond et al., 2005) when microsleeps occurred. The frequently inconsistent altered activity in the frontal cortex and thalamus might parallel decreased synchronisation in the thalamo-cortical connectivity (Poudel et al., 2018; Shao et al., 2013). Consistent with these studies, the present results demonstrated that participants who had reduced thalamo-cortical connectivity had more lapses in the subsequent PVT, which indicated a stronger unstable state and might reflect the neural basis of individual differences of vulnerability to sleep deprivation. In addition, a review demonstrated that as an important node of the arousal system, the thalamus is part of the stimulus-driven control network, anatomically connecting with the temporoparietal junction and inferior frontal cortex (Corbetta & Shulman, 2002). Therefore, the reduced frontal connectivity with the thalamus seen in the present study might be involved in the impairment of the stimulus-driven attentional network, and the increased lapses after sleep deprivation might correspond to the deterioration of the bottom-up control of attention.

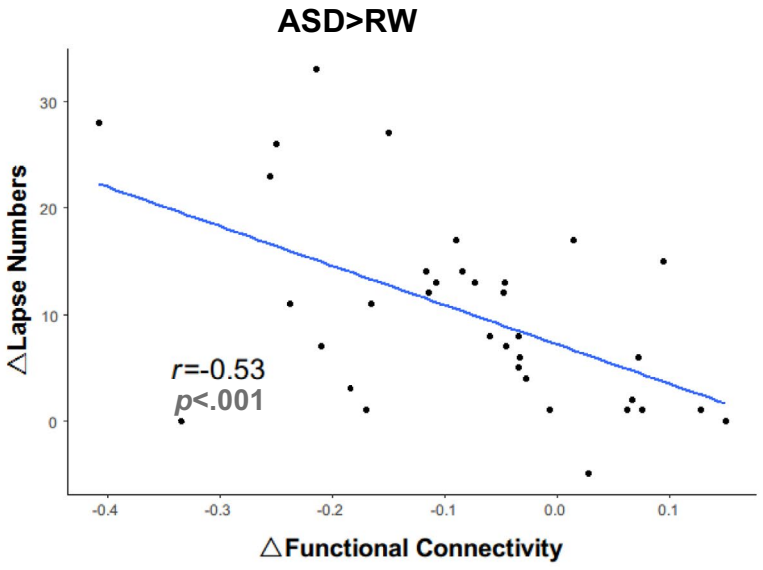
In the present study, the increased functional connectivity between the left middle frontal gyrus and left visual cortex was correlated with increased lapses. The results indicated that individuals with increased functional connectivity performed worse in the PVT. A previous study found that cholinergic potentiation might enhance visual perception efficiently, thus reducing the recruitment of attention regions, thereby reducing the functional connectivity between the visual processing area and the prefrontal cortex; this reduced functional connectivity is accompanied by enhanced attentional performance (Ricciardi et al., 2013). Inversely, the increased functional

(a)



Seed Region: R. Thalamus

(9, -18, 6)



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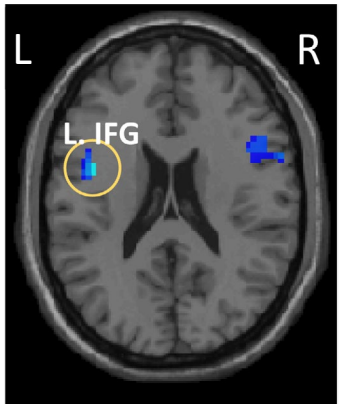
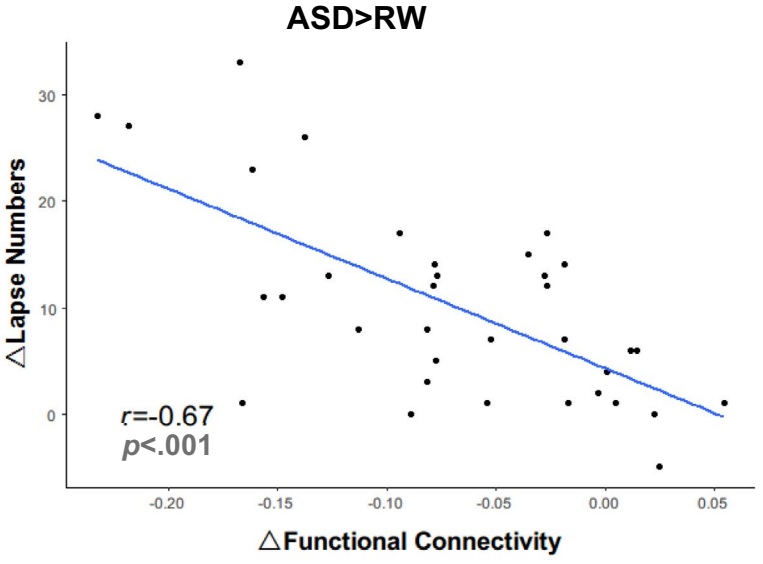
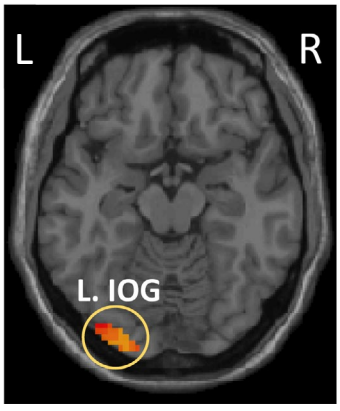


Seed Region: R. Thalamus

(9, -18, 6)



(c)



Seed Region: L. MFG

(-27, 6, 45)

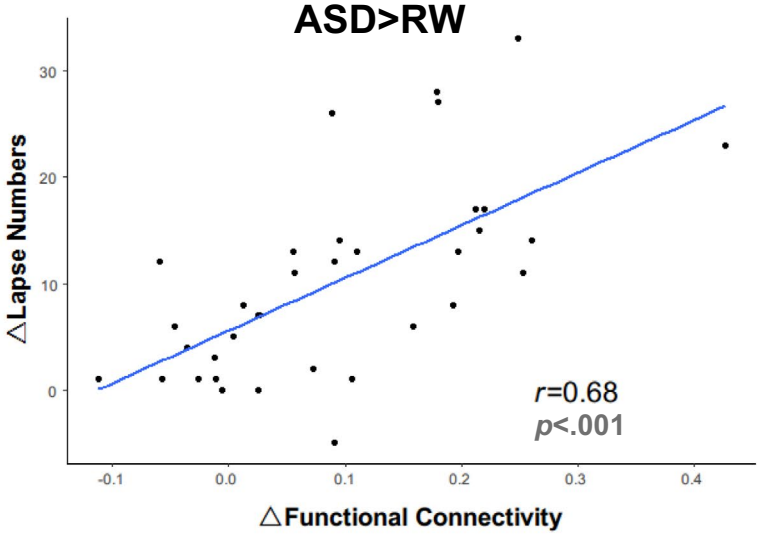


FIGURE 4 Functional connectivity changes correlated with lapse number changes following sleep deprivation. Scatter plots show the relationship between functional connectivity changes and lapse number changes following sleep deprivation. Corresponding functional connectivity is illustrated to the left beside each scatter plot, in which warm colours represent increased functional connectivity and cold colours represent decreased functional connectivity after sleep deprivation. The panels show (a) functional connectivity between the right (R.) Thalamus and R. inferior frontal gyrus (IFG) (18, 8, 24), (b) functional connectivity between the R. Thalamus and left (L.) IFG (−45, −3, 24) and (c) functional connectivity between the L. middle frontal gyrus (MFG) and L. inferior occipital gyrus (IOG) (−36, −90, 15). ASD, acute sleep deprivation; RW, rested wakefulness after normal sleep

connectivity seen in the present study might indicate reduced efficiency of the perceptual processing caused by sleep deprivation, accordingly increasing the effort required to keep the person alert and aware of his or her environment. Similar to sleep deprivation, increased functional connectivity between the prefrontal and visual cortex was found when task load increased (Xiang & Chen, 2010), which also requires more perceptual resources and cognitive effort.

The present study certainly has several limitations that should be mentioned. First, although participants were instructed to stay awake and confirmed by self-report after the scanning, we cannot completely exclude the possibility that they might have fallen asleep in the scanner due to the absence of eyelid monitoring. Besides, several studies have observed decreased thalamic-frontal connectivity in non-rapid eye movement sleep (Kaufmann et al., 2006; Spoormaker et al., 2010), as we found in the sleep-deprived participants in the present study. However, several studies have revealed that sleep onset was companied with thalamus deactivation (Kaufmann et al., 2006; Magnin et al., 2010; Ong et al., 2015), while the hyperactive mean signal in the thalamus was observed in the present study, which is exactly the characteristic of non-lapse period in the sleep-deprived state (Goel et al., 2009). Decreased thalamocortical connectivity and increased thalamic activity suggested that the participants in the present study were under an unstable state or "microsleep", rather than totally falling asleep. Second, although the present study demonstrated the alteration of neural function associated with vigilance affected by sleep deprivation using resting-state fMRI, a task-related fMRI study is warranted to further investigate the dynamic change in neural function during task performance after sleep deprivation. For instance, as the ascending arousal input hub, the thalamus plays a crucial role in modulating the interaction between the DMN and FPN. Sleep deprivation causes the thalamus to be in an unstable state, and an unstable thalamus cannot balance the reciprocal inhibition between FPN and DMN in a sleep-deprived brain, which was suggested by Krause et al. in a recent review (Krause et al., 2017). This helps to explain why performance varied during task performance after sleep deprivation. In resting-state fMRI, hyperactivity in the thalamus is an average signal across the whole scan session. Thus, trial-by-trial analyses of task-related fMRI data are required to verify this hypothesis of thalamic function after sleep loss. Third, the functional connectivity revealed by resting-state fMRI cannot provide information about the direction of interaction between different brain regions or brain networks. For example, in the present study, it is difficult to verify whether the correlation of the increased lapses with the enhanced functional connectivity between the prefrontal and visual cortex after sleep deprivation is due to the alternation of top-down or bottom-up processing. Therefore, future studies may consider causal inferences beyond functional connectivity measures to explore the neural mechanism of sleep deprivation further. Lastly, a control group is needed for conducting RW and sleep deprivation at a time to avoid some expected effect or learning effect.

5 | CONCLUSION

The present study aimed to investigate the effect of sleep deprivation on the resting state and explored the neural basis of vigilance impairment after sleep deprivation. The results revealed reduced spontaneous activity in the key nodes of the FPN and DMN and increased ALFF in the thalamus, visual, and motor regions, which may suggest a counteracting effect to keep a person alert when he or she is combating sleep loss. Critically, the change in frontal connectivity with the crucial neural nodes for stimuli inputting, such as the thalamus and visual cortex, predicted PVT performance deficits during sleep deprivation. These results demonstrate the effects of sleep loss on resting brain function and indicate that resting brain responses to sleep deprivation may be a biomarker of individual differences in the vulnerability of cognitive functions to sleep loss.

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CONFLICT OF INTEREST

All authors have nothing to declare.

AUTHOR CONTRIBUTIONS

YC: Data collection, data analysis, wrote and revised the manuscript; ZM: Data collection and data analysis; ML: Data collection and manuscript preparation. XZ: Review and editing the manuscript; NM: Conceptualization, Funding acquisition, Methodology; Supervision and Review and editing the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

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