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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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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

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

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 >

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").

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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

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

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REFERENCES

Biswal, B. B., Kylen, J. V., & Hyde, J. S. (1997). Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR in Biomedicine*, *10*, 165–170.

Chee, M. W. L., & Tan, J. C. (2010). Lapsing when sleep deprived: Neural activation characteristics of resistant and vulnerable individuals. *NeuroImage*, *51*(2), 835–843. https://doi.org/10.1016/j.neuroimage.2010.02.031

Chee, M. W. L., Tan, J. C., Parimal, S., & Zagorodnov, V. (2010). Sleep deprivation and its effects on object-selective attention. *NeuroImage*, *49*(2), 1903–1910. https://doi.org/10.1016/j.neuroimage.2009.08.067

Chen, V. C. H., Shen, C. Y., Liang, S. H. Y., Li, Z. H., Hsieh, M. H., Tyan, Y. S., Lu, M., Lee, Y., McIntyre, R. S., & Weng, J. C. (2017). Assessment of brain functional connectome alternations and correlation with depression and anxiety in major depressive disorders. *PeerJ*, *5*, e3147. https://doi.org/10.7717/peerj.3147

Chua, E. C. P., Sullivan, J. P., Duffy, J. F., Klerman, E. B., Lockley, S. W., Kristal, B. S., Czeisler, C. A., & Gooley, J. J. (2019). Classifying attentional vulnerability to total sleep deprivation using baseline features of Psychomotor Vigilance Test performance. *Scientific Reports*, *9*(1), 1–14. https://doi.org/10.1038/s41598-019-48280-4

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*, 201–215. https://doi.org/10.1038/nrn755

De Havas, J. A., Parimal, S., Soon, C. S., & Chee, M. W. (2012). Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. *NeuroImage*, *59*(2), 1745–1751. https://doi.org/10.1016/j.neuroimage.2011.08.026

Drummond, S. P. A., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, S. C., & Meloy, M. J. (2005). The neural basis of the psychomotor vigilance task. *Sleep*, *28*(9), 1059–1068. https://doi.org/10.1093/sleep/28.9.1059

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–711. https://doi.org/10.1038/nrn2201

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, *102*(27), 9673–9678. https://doi.org/10.1073/pnas.0504136102

Gao, L., Bai, L. J., Zhang, Y. C., Dai, X. J., Netra, R., Min, Y. J., Zhou, F., Niu, C., Dun, W., Gong, H., & Zhang, M. (2015). Frequency-dependent changes of local resting oscillations in sleep-deprived brain. *PLoS One*, *10*(3), e0120323. https://doi.org/10.1371/journal.pone.0120323

Goel, N., Rao, H., Durmer, J. S., & Dinges, D. F. (2009). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*, *29*(4), 320–339. https://doi.org/10.1055/s-0029-1237117

Gujar, N., Yoo, S.-S., Hu, P., & Walker, M. P. (2010). The unrested resting brain: Sleep deprivation alters activity within the default-mode network. *Journal of Cognitive Neuroscience*, *22*(8), 1637–1648. https://doi.org/10.1162/jocn.2009.21331

Javaheripour, N., Shahdipour, N., Noori, K., Zarei, M., Camilleri, J. A., Laird, A. R., Fox, P. T., Eickhoff, S. B., Eickhoff, C. R., Rosenzweig, I., Khazaie, H., & Tahmasian, M. (2019). Functional brain alterations in acute sleep deprivation: An activation likelihood estimation meta-analysis. *Sleep Medicine Reviews*, *46*, 64–73. https://doi.org/10.1016/j.smrv.2019.03.008

Kaufmann, C., Wehrle, R., Wetter, T. C., Holsboer, F., Auer, D. P., Pollmacher, T., & Czisch, M. (2006). Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: An EEG/fMRI study. *Brain*, *129*, 655–667. https://doi.org/10.1093/brain/awh686

Killgore, W. D. S. (2010). Effects of sleep deprivation on cognition. *Human Sleep and Cognition, Part I: Basic Research*, *185*

intrinsic brain activity alterations in unmedicated depression. *Journal of Affective Disorders*, *172*, 241–250. https://doi.org/10.1016/j.jad.2014.10.017

Tian, L., Ren, J., & Zang, Y. (2012). Regional homogeneity of resting state fMRI signals predicts Stop signal task performance. *NeuroImage*, *60*, 539–544. https://doi.org/10.1016/j.neuroimage.2011.11.098

Wang, Y. L., Liu, H., Hitchman, G., & Lei, X. (2015). Module number of default mode network: Inter-subject variability and effects of sleep deprivation. *Brain Research*, *1596*, 69–78. https://doi.org/10.1016/j.brainres.2014.11.007

Xiang, J., & Chen, J. (2010). *The study on functional connectivity between frontal eye field and other brain cortex in visual processing*. Paper presented at the 2010 International Conference on Computational Aspects of Social Networks, *2010*:333–336. https://doi.org/10.1109/CASoN.2010.81

Xu, J. L., Zhu, Y. Q., Fu, C., Sun, J. B., Li, H. Q., Yang, X. J., Li, W., Qin, W., Shi, D., & Tian, J. (2016). Frontal metabolic activity contributes to individual differences in vulnerability toward total sleep deprivation-induced changes in cognitive function. *Journal of Sleep Research*, *25*(2), 169–180. https://doi.org/10.1111/jsr.12354

Yan, C.-G., Wang, X.-D., Zuo, X.-N., & Zang, Y.-F. (2016). DPABI: Data processing analysis for (resting-state) brain imaging. *Neuroinformatics*, *14*(3), 339–351. https://doi.org/10.1007/s12021-016-9299-4

Yeo, B. T., Tandi, J., & Chee, M. W. (2015). Functional connectivity during rest