Nature and Science of Sleep

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ORIGINAL RESEARCH

Altered Functional Connectivity of the Thalamus Subregions Associated with Impaired Attention After Sleep Deprivation

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Objective: The thalamus plays a critical role in attentional maintenance. Previous studies have revealed the dysfunction of the thalamus in attention decline after acute sleep deprivation (SD). However, the functional connectivity (FC) between the thalamus subregions and cortical regions underlying attentional impairment after acute SD remains unclear. Here, we aimed to probe the relationship between attentional function and the altered thalamocortical FC after acute SD.

Methods: In this study, 25 healthy participants with regular sleep conducted an attentional network test and received a resting-state fMRI scan before and after 24 hours of SD. Then, we analyzed the FC between the thalamus and cerebrum and relationships with attentional function in the enrolled subjects.

Results: Our results showed that the participants showed a significantly lower alerting effect, a higher executive effect, and lower accuracy after acute SD. Compared to the rested wakefulness state, we observed decreased FCs between the "somatosensory" thalamic seed and left frontal pole, right frontal pole, left middle temporal gyrus (posterior division), and right middle temporal gyrus (posterior division). Furthermore, the reduced FC between the right middle temporal gyrus and "somatosensory" thalamic seed was negatively associated with the change in orienting effect of the participants.

Conclusion: Our findings reveal that the disrupted FC between thalamus subregions and cortical regions may contribute to impaired attention after SD.

Keywords: sleep deprivation, fMRI, attention, thalamus, functional connectivity

Introduction

Sleep deprivation (SD) is very common in society, which is sleep duration of less than 4 hours in a typical 24-hour day.[1,2] SD is harmful to physical and mental health, including the increasing risk of cardiovascular disease, cancer, mood disorders, and cognitive impairments.[3,4] Besides, SD interferes with multi-dimensional cognitive functions, including executive function, sustained attention, and long-term memory, which affects working efficiency.[5] Notably, attention is an essential part of cognitive processing and acts as a "bind" and "guide".[6] The attention system can be divided into three subsystems: alerting, orienting, and executive control, while different subsystems involve different brain regions.[7,8] Increasing evidence has indicated that SD diminishes not only attentional focus but also the duration of sustained attention.[4,9–12] It is necessary to further explore the brain activities underlying attentional decline after SD.

Resting-state functional magnetic resonance imaging (fMRI) is widely used to explore the potential mechanisms of attention impairment after acute SD.[13,14] Functional connectivity (FC) can assess connections between different brain

Received: 14 May 2024
Accepted: 22 July 2024
Published: 29 July 2024

regions and reflect differences in the network at resting state.[15] Altered FC between brain regions contributes to the generation of impaired attention after SD.[16,17] Previous fMRI studies have demonstrated that individuals with SD have several altered brain networks, primarily within the limbic system, such as the amygdala and thalamus.[18] Significantly, attention impairments after acute SD are correlated with decreased frontal-thalamus connectivity, increased frontal-visual connectivity, and increased thalamus-parietal connectivity.[12,19] Prior studies have investigated that significant changes in the thalamus were affected after acute SD.[20–22] Thalamus is regarded as a pathway for transforming sensory information into the cortex, involving cognitive functions such as attention and memory.[23–26] Moreover, the thalamus is divided into several sub-nuclei, which have strong interconnection with the corresponding cerebral cortex, and play different roles.[27] According to the connectivity information between the thalamus and the cortex, thalamic subregions are functionally defined as "motor" thalamic subregions, "somatosensory" thalamic subregions, "prefrontal" thalamic subregions, "parietal" thalamic subregions, "temporal" thalamic subregions, and "occipital" thalamic subregions.[28] Among these parceled thalamic subregions, "occipital" thalamic subregions are located in the region around the medial and posterior thalamic nuclei. And the posterior thalamic nuclei, which have a robust connectivity with the visual cortex, play a critical role in the contacts between different brain regions of the cerebral cortex.[29] However, the relationship between the divided thalamus subregions and the cortical regions that underlie attentional impairment following acute SD is still unclear.

To fill in this gap, we hypothesized that the changed FC between certain thalamus subregions and corresponding cortical regions might be linked to a loss of attention after SD. We enrolled thirty healthy subjects with regular sleep to scan fMRI before and after 24-hour SD to verify the hypothesis. We used the attention network task to evaluate the abnormal attention function following SD. Then, we investigated the relationship between the altered FC between the thalamus subregions and cortical regions, as well as reduced attention after acute SD.

Materials and Methods

Participants

Thirty healthy subjects (16 males and 14 females) from the college, aged between 20 and 30 years (25.20 ± 2.20 years) and 18.10 ± 2.45 years of education duration, were enrolled from November 2020 to August 2021. The enrolled subjects must meet the criteria as follows: (i) Pittsburgh Sleep Quality Index (PSQI) score < 5; (ii) regular sleep without excessive morning or evening types; (iii) right-handed; (iv) no history of neurologic or psychiatric diseases; (v) no trauma stimuli; (vi) no caffeine, smoking, alcohol or drug addictions; (vii) no MRI contraindications. The Ethics Committee of Beijing Anding Hospital, affiliated with Capital Medical University, approved our study procedure (Number of clinical registration: ChiCTR2000039858). Before the study, informed consent was signed by each enrolled individual.

Study Procedure

This study was part of a clinical trial that explored brain function after SD with and without an acupuncture intervention (ChiCTR2000039858), and the methods and results were previously published.[30–32] Each enrolled participant visits our laboratory twice. They had to sign informed consent while receiving a concise overview of the study. At the second visit, the participants had to get up at 7:00 am and returned to the laboratory before 8:00 am for a 24-hour SD. During the study, all recruited subjects should stay awake, not take tea, alcohol or coffee. To make sure each participant was awake, the researchers took turns monitoring. And all of the participants did not engage in excessive physical activity during this study. Our researchers would wake them up if they showed any indication of falling asleep. Each subject had to complete two MRI scans before and after 24 hours of SD, respectively. We conducted the 250 s T1 and 490 s resting-state scans during the first MRI scan and the 490-s resting-state scan at the second MRI scan around 7:00 am the following day. We would remind all subjects to stay during scanning and exclude the subject who falls asleep during the fMRI scan. Overall, 26 of the 30 participants completed the entire trail.

Attentional Network Test

The procedure of the attentional network test (ANT) was used as described previously, and was programmed by E-Prime Software.[33] A total of 336 trails were conducted for this task, including 24 trails in practice and 312 trails for testing.

Figure 1 displayed the details of each trial. The enrolled participants were required to identify the direction of an arrow (ie, target) in the center and press either a key for "left" or another key for "right". The detailed procedure was as follows: After a variable period of fixation (400–1600 ms), a cueing period (100 ms) was presented. There were 4 types of cue presentation, including no cue (25%), center cue (25%), double cue (25%), and spatial cue (25%). And another fixation period was presented for 400 ms, followed by a period of target (1700 ms). The target and the four flankers were presented simultaneously on the screen, including the neutral condition, the congruent condition, and the incongruent condition (shown in Figure 1C). Following the participants' responses, the target disappeared and a fixation period lasted for an unpredictable duration (400–1600 ms). The median reaction times (RT) were calculated for each participant over all the above conditions (4 cue conditions and 3 congruency conditions). The effects of the alerting, orienting, and conflict networks were defined as RT differences. Finally, we analyzed the variables of this task, containing alter effect, orienting effect, control conflict, RT, and accuracy.

MRI Acquisition

The MRI scan was performed using a Siemens 3.0 Tesla Prisma at Beijing Anding Hospital in Beijing, China. During the MRI scan, subjects had to stay still, keep their eyes closed, and resist falling asleep. In addition, the participants needed to freeze their foam head supports to avoid head movement. A single-shot, gradient-recalled echo-planar imaging

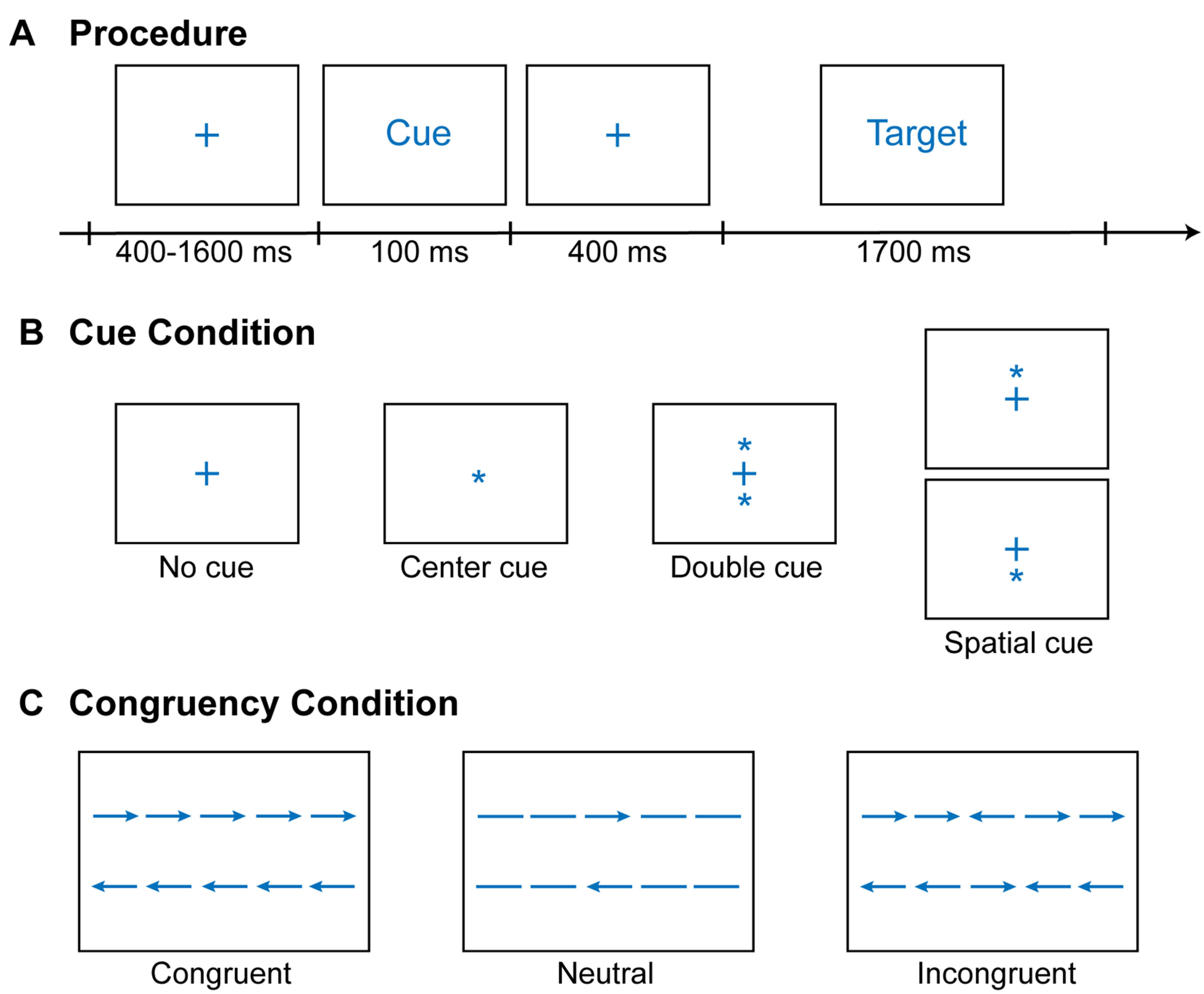

Figure 1 A visual presentation of the attentional network test.

sequence was used for the resting-state fMRI data. A rapid gradient-echo sequence with T1-weighted multi-echo magnetization preparation was used to acquire high-resolution structural images.[34] The parameters were set as follows: echo time = 3.39 ms, repetition time = 2530 ms, slice thickness = 1.3 mm, voxel size = $1.3 \times 1 \times 1$ mm^3, field of view (FOV) = 256×256 mm^2, and 128 volume. The resting-state fMRI data were collected with the following parameters: echo time = 30 ms, repetition time = 2000 ms, flip angle = 90°, matrix = 64× 64, gap = 1 mm, field of view = 225 mm × 225 mm, slice thickness = 3.5 mm, 32 interleaved axial slices, and 180 volumes.

Data Preprocessing

Image processing was performed using DPABISurf, developed by Yan et al.[35] A surface-based image preprocessing pipeline was used, as previously described,[36] which included anatomical data preprocessing, the custom methodology of fMRIPrep, bregister, slice-time correction, resampling into standard space, and component-based noise correction. Firstly, a customized methodology of fMRIPrep[37] was performed to generate the reference volume and its skull-stripped version. The Bbregister tool, which utilizes boundary-based registration, was used to co-register the fMRI reference and T1 reference. Furthermore, slice-time was corrected using 3dTshift from AFNI, and spatiotemporal filtering was carried out by Mcflirt. The blood oxygen level dependent (BOLD) time-series were resampled into standard space (MNI 152 NLin2009c Asym space) and produced a preprocessed BOLD run. Simultaneously, the preprocessed BOLD run was used to generate framewise displacement (FD), DVARS and three region-wise global signals. Besides, a series of physiological regressors were extracted to support component-based noise correction. The quality control of images was screened using participants' head motion within 0.5 mm framewise displacement or 1.5 standardized DVARS.[38] Gridded (volumetric) resampling was conducted by using Ants Apply Transforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels.

Parcellation of the Thalamus and FC Analysis

Similar to the procedure in previous studies,[28] the cerebral cortex comprised six bilateral cortical subregions, including the motor, somatosensory, prefrontal, parietal, temporal, and occipital cortex. These cortical subregions were defined by the Harvard-Oxford probabilistic cortical atlas. The following seed-based resting-state FC analysis used the six thalamic subregions as seeds (regions of interest) using the DPABISurf toolbox. Firstly, the BOLD time series of the thalamic seed and the whole cortical cortex were extracted. Then, we calculated the Pearson's correlation coefficients between the time series of each thalamic seed and the whole cortical cortex. To improve normality, correlation coefficients were transformed into Fisher's z-scores. Seed-to-voxel second-level analyses were performed using the paired-sample *t* test, with age and gender as covariates. The false discovery rate (FDR) was used to account for multiple comparisons (corrected to $p < 0.05$).

Statistical Analysis

The clinical characteristics and ANT results were compared using a paired *t*-test. $p < 0.05$ was considered the threshold for statistical significance. For the FC between the parceled thalamic subregions and cortical cortex, we used the FDR for multiple comparisons. We carried out a Pearson correlation analysis to evaluate the relationship between the ANT results and the changed FC between the parceled thalamic subregions and the cortical cortex.

Results

Attention Assessments

The final analysis included 25 participants who completed the entire trail, as shown in Table 1. Compared to the rested wakefulness (RW) state, a significantly lower alerting effect (t = 2.357, $p = 0.023$) and a higher executive effect (t = −2.174, $p = 0.035$) were found in the SD state. And we found that subjects showed lower accuracy (t = 2.091, $p = 0.042$) after SD. There were no significant differences in the orienting effect and reaction time between the RW and SD states.

Table 1 Results of Attentional Network Test (RW Vs SD)

	RW	SD	t value	*p* value
Alert effect	51.75±21.5	36.54±23.1	2.357	0.023
Orienting effect	52.63±22.2	46.00±22.1	1.038	0.305
Control conflict	99.17±25.9	115.38±25.7	−2.174	0.035
Reaction time (ms)	585.83±66.0	601.79±80.9	−0.749	0.458
Accuracy	97.63±1.5	93.92±8.6	2.091	0.042

Abbreviations: RW, rested wakefulness; SD, sleep deprivation.

Altered FC Results After SD

Compared to the RW state, we found decreased FCs between the "somatosensory" thalamic seed and the left frontal pole, right frontal pole, left middle temporal gyrus (posterior division), and right middle temporal gyrus (posterior division). The decreased FCs between the "motor" thalamic seed and the left supramarginal gyrus (anterior division), right supramarginal gyrus (anterior division) were also found after SD. In addition, we found a decreased FC between the left precuneus and "occipital" thalamic seed after SD. The details were illustrated in Table 2 and Figure 2.

Correlation Analysis

We performed a correlation analysis between changes in the ANT task and altered FC. We found that the change in orienting effect of the ANT task was negatively correlated with the altered FC between the right middle temporal gyrus (posterior division) and "somatosensory" thalamic seed ($r = -0.406$, $p = 0.049$, Figure 3).

Discussion

In the current study, we observed the altered FC between thalamus subregions and cortical regions, which was associated with impaired attention after SD. The findings further indicated the critical role of the thalamus in sleep regulation and the underlying mechanisms of impaired attention after SD.

The ANT is applied to evaluate the orienting, alerting and executive components of attention performance. In this study, we found a significant lower alerting effect and a higher executive effect after SD, which indicated declines in alerting and executive functions. It had been confirmed that attention performance was impaired after acute SD.[39] In line with our study, our previous study on shift work disorder, a form of chronic SD, also showed a lower alerting effect and a higher executive effect compared with healthy controls.[40] Several studies on SD revealed the same results as ours.[41,42] Nevertheless, in contrast to our result, one previous study on 47 participants also revealed a decreased orienting effect after SD.[43] The inconsistent result could be attributed to the high inter-subject variability after SD.[44] The relatively small sample size might also be the cause of no significant decrease in the orienting effect after SD in our study. Moreover, our study also showed lower accuracy after SD, which further demonstrated attention declines after SD.

After acute SD, the role of the thalamus in attention decline has been well documented. One recent resting-state fMRI study revealed increased ALFF in the thalamus after 24 hours SD.[12] Another study on acute SD indicated increased

Table 2 Altered FC Between the Cerebellum and Cerebrum After SD

	T value	*p* value
Left frontal pole and "somatosensory" thalamic seed	3.918	0.0005
Right frontal pole and "somatosensory" thalamic seed	3.910	0.0005
Left middle temporal gyrus, posterior division and "somatosensory" thalamic seed	4.415	0.0001
Right middle temporal gyrus, posterior division and "somatosensory" thalamic seed	3.877	0.0006
Left supramarginal gyrus, anterior division and "motor" thalamic seed	4.903	<0.0001
Right supramarginal gyrus, anterior division and "motor" thalamic seed	4.098	0.0003
Left precuneus cortex and "occipital" thalamic seed	4.100	0.0003

Abbreviations: FC, functional connectivity; SD, sleep deprivation.

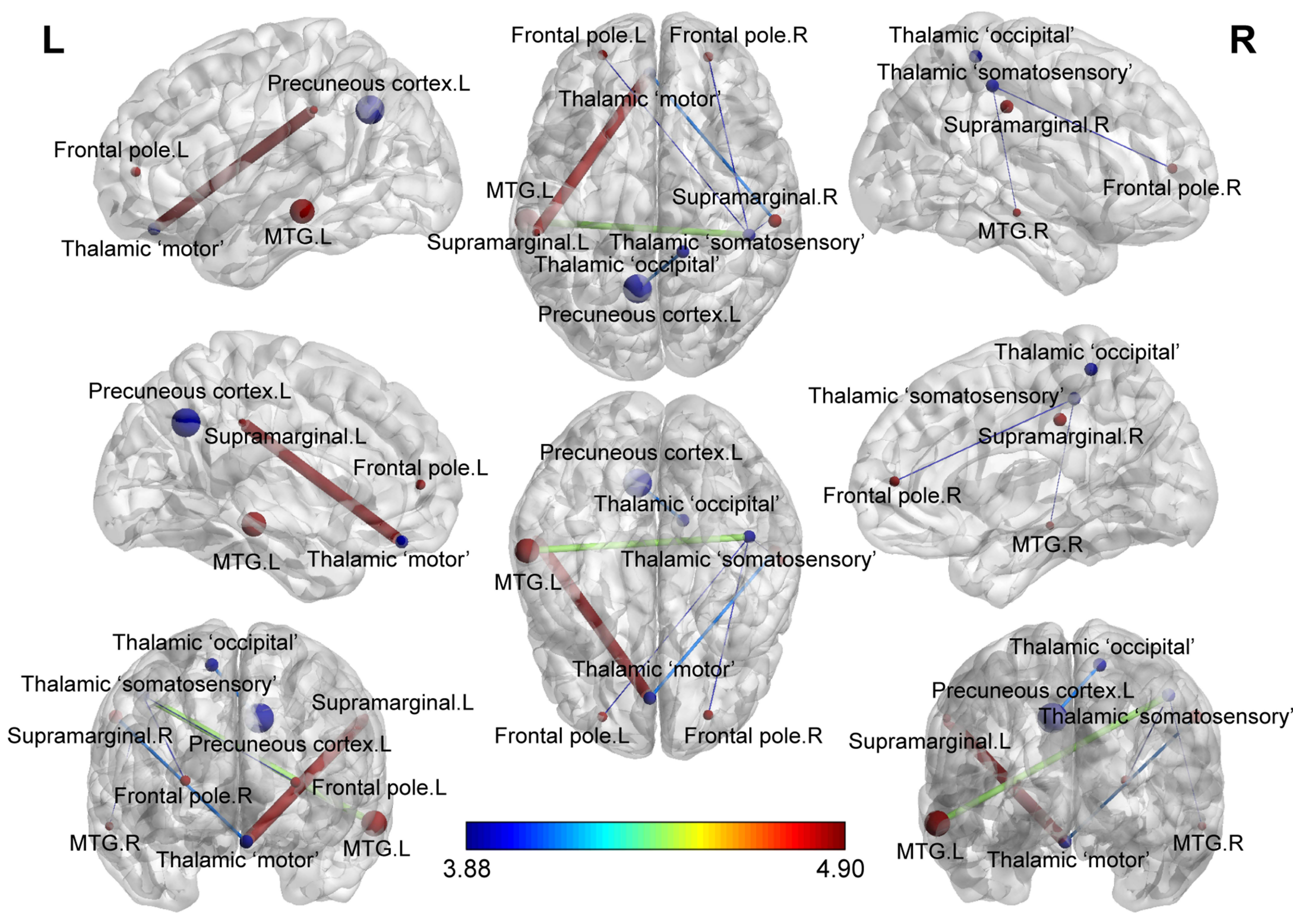

Figure 2 Altered functional connectivity between the thalamic subregions and cortical regions after SD.

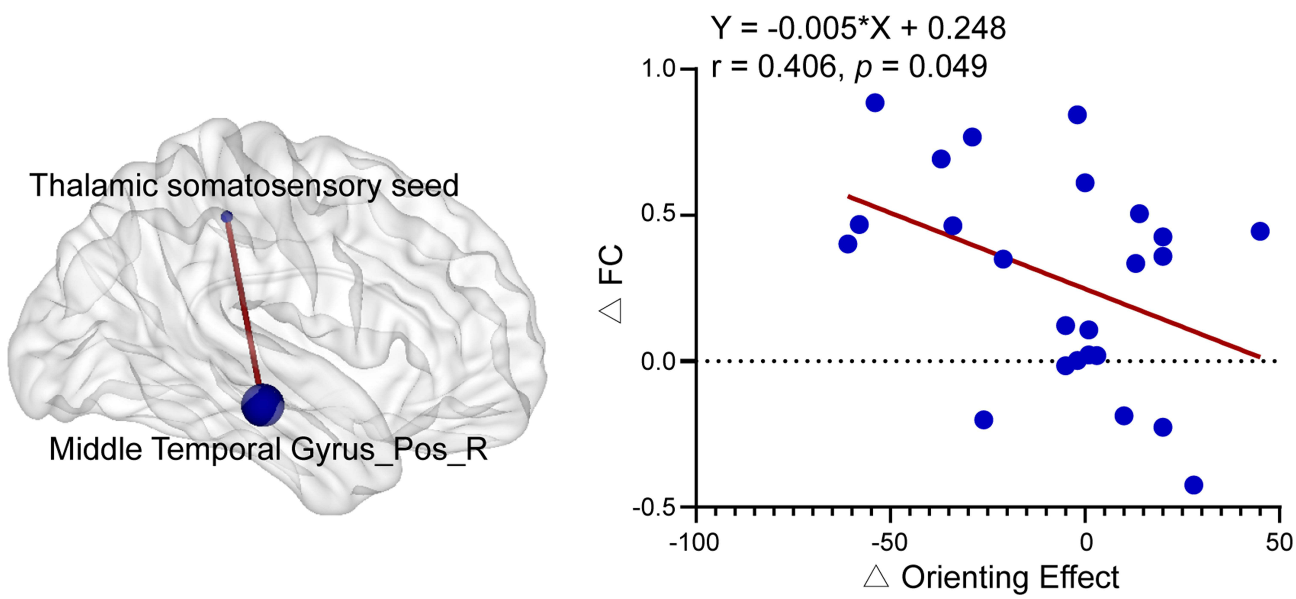

Figure 3 Correlation between the changed orienting effect and the altered functional connectivity between the right middle temporal gyrus (posterior division) and "somatosensory" thalamic seed.

effective connectivity from the thalamus to the nodes in the frontal-parietal attention network, which was significantly correlated with decreased lapses.[19] These findings demonstrate the important role of the thalamus in attentional maintenance after SD. Numerous studies have confirmed that the thalamus plays a vital role in the sleep-wake pathway and is involved in cognitive functions, such as attention, working memory.[4,45] Our findings showed the altered FC in thalamus subregions involving "somatosensory" thalamic seed, "motor" thalamic seed and "occipital" thalamic seed. The "somatosensory" thalamic seed and motor' thalamic seed selectively control the flow of sensory-motor information to the cerebral cortex during different states of the sleep-wake cycle and arousal, which are controlled through the actions of neurotransmitter systems in the cerebral cortex.[46] The "occipital" thalamic seed is located in the medial and posterior groups of thalamic nuclei, which is connected with the visual cortex and critical for attentional processes.[47] Hence, we speculated that the "somatosensory" thalamic seed, "motor" thalamic seed and "occipital" thalamic seed were involved in attention deficits after SD.

Our findings showed the altered FC between the thalamus subregions and the left frontal pole, right frontal pole, left middle temporal gyrus (posterior division), right middle temporal gyrus (posterior division), left supramarginal gyrus (anterior division), right supramarginal gyrus (anterior division), and left precuneus. It had been demonstrated that the alerting component involved the thalamic, frontal and parietal areas, the executive attention component involving the anterior cingulate cortex and the lateral prefrontal cortex, and the orienting component involved the superior parietal lobe, temporo-parietal junctions and superior frontal cortex.[33] Our results revealed the dysfunctional cerebral cortices underlying the three components of attention performance declines after SD. In line with our results, one previous study revealed a decreased FC between the thalamus and right middle temporal gyrus, right superior frontal gyrus, the right medial frontal gyrus, bilateral middle temporal gyri, and left superior frontal gyrus,[48] which suggested that the thalamus had strong reciprocal connections with the cerebral cortex. Moreover, the altered FC between the right middle temporal gyrus and "somatosensory" thalamic seed was negatively correlated with the change in orienting effect, which suggested the association between the thalamocortical FC and attention performance after SD. Overall, our results showed that the changed FC between thalamus subregions and cerebral cortices after SD was linked to impaired attention.

However, there were several limitations to be noted. Firstly, this study only recruited participants aged between 20 and 30 years. Our results could not be extrapolated to individuals in other age groups. Participants from a broader age range should be recruited in the future. Secondly, the sample size was relatively small in our study, which might be the cause of no significant differences in the orienting effect and reaction time after SD. Further studies with a larger sample size are needed in the future. Thirdly, the role of the FC between thalamus subregions and subcortical regions was neglected in this study. Future research is needed to explore the effect of the FC between thalamus subregions and subcortical regions on sleep regulation.

Conclusions

Conclusively, we found decreased FC between thalamus subregions and cerebral cortices after SD. Moreover, the altered FC between the right middle temporal gyrus and "somatosensory" thalamic seed was negatively correlated with the change in orienting effect. These findings suggest disruptive changes in the thalamocortical FC after SD, which may lead to a decline in attention.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author, Yanzhe Ning, on reasonable request.

Ethics Approval and Consent to Participate

The Ethics Committee of Beijing Anding Hospital, affiliated with Capital Medical University, approved this study (Number of clinical registration: ChiCTR2000039858). And our study was performed in accordance with the Declaration of Helsinki. All participants have signed informed consent.

Acknowledgment

This paper has been uploaded to Research Square as a preprint: https://www.researchgate.net/publication/377475866_Altered_functional_connectivity_of_thalamus_subregions_after_sleep_deprivation_associated_with_impaired_attention/fulltext/65a91b2cf323f74ff1c84e5d/Altered-functional-connectivity-of-thalamus-subregions-after-sleep-deprivation-associated-with-impaired-attention.pdf?origin=scientific-contributions.

Consent for Publication

All authors have approved the final version of the manuscript being submitted.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by National Natural Science Foundation (Grant No. 81904120), Scientific Research and Cultivation Fund of Capital Medical University (PYZ23161), Beijing Hospitals Authority Youth Program (Grant No. QML20201901), Beijing Hospitals Authority's Ascent Plan (Grant No. DFL20191901), and Beijing Hospitals Authority Clinical Medicine Development of Special Funding (Grant No. ZYLX202129).

Disclosure

The authors declare no conflicts of interest in this work.

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