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Long-term total sleep deprivation reduces thalamic gray matter volume in healthy men

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Sleep loss can alter extrinsic, task-related functional MRI signals involved in attention, memory, and executive function. However, the effects of sleep loss on brain structure have not been well characterized. Recent studies with patients with sleep disorders and animal models have demonstrated reduction of regional brain structure in the hippocampus and thalamus. In this study, using T1-weighted MRI, we examined the change of regional gray matter volume in healthy adults after long-term total sleep deprivation (~72 h). Regional volume changes were explored using voxel-based morphometry with a paired two-sample *t*-test. The results revealed significant loss of gray matter volume in the thalamus but not in the hippocampus. No overall decrease in whole brain gray matter volume was noted after sleep deprivation. As expected, sleep deprivation significantly reduced visual vigilance as assessed by the continuous performance test, and this decrease was correlated significantly with reduced regional gray matter volume in thalamic regions. This study provides the first evidence for sleep loss-related changes in gray matter in the healthy adult brain. *NeuroReport* **25:320–323 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Previous studies have demonstrated the effect of sleep deprivation (SD) on psychological measures and neural systems [1–6]. It has been demonstrated that sleep loss can reduce performance on a broad variety of tasks and affects brain functional activity [7,8]. Nevertheless, no previous study has examined the effects of sleep loss on gray matter (GM) structures in healthy adults. Considering sleep loss decreases a wide range of cognitive functions, the association of reduced performance and GM structure changes is a matter of interest. To date, no human studies have provided direct evidence that sleep loss affects the structure of the brain. Case–control studies with patients with sleep problems (e.g. insomnia, obstructive sleep apnea, depression, and sleepiness during the day) have attempted to test the hypothesis that chronically disturbed sleep is associated with changes in hippocampal and thalamus brain structure [9–11]. These related studies, have provided some hints about the effects of SD on human brain structure, but these models are not representative of sleep loss in healthy human adults.

In this study, we investigated this issue using voxel-based morphometry (VBM) and long-duration (~72 h) SD. Before and after the intervention, each individual participated in MRI experiments. We hypothesized that there are changes induced by SD in the regional GM structures of healthy young adults, such as volume reductions in the hippocampus and thalamus.

Methods

Participants

Twelve healthy college students (aged between 20 and 32 years, mean = 24.83, SD = 2.88; right-handed; all males) were recruited from Beijing Normal University (BNU) (Beijing, China). All participants received a psychiatric interview, physical examination, and routine laboratory screening, they were free of physical and mental disorders, and were all right-handed. The experimental protocol was approved by the Institutional Review Board of BNU. In accordance with the Declaration of Helsinki (1991), written informed consent was obtained from each participant before the investigation.

Sleep deprivation

The SD experiment was conducted in the SD laboratory at the Astronaut Center of China. Participants were studied with MRI twice, at the same time of day (8:00–12:00 a.m.): once after a normal night of sleep (mean duration of sleep, 7 ± 1 h) and once after total sleep deprivation (72 ± 0.8 h). Before the SD, all participants experienced a normal night of sleep in bed, which was recorded by polysomnography. During the 72-h SD period, participants were required to stay awake at all times. Three research assistants remained with them throughout the day and night to ensure that they did not fall asleep for the SD. If there were any signs of a

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participant falling asleep, they were awakened by an alarm clock immediately. All participants experienced roughly the same amount of sleep loss.

On the day before SD, a T1-weighted image was acquired from each participant, after which the SD was initiated. After the SD, all participants, except one, participated in the post-test of structural MRI scanning. During the break in the scanning, the participants did the continuous performance test, a visual vigilance task [12], which they had practiced previously. This involves a button press response to stimuli occurring at 2-s intervals, ensuring that subjects remain awake during MRI scanning.

MRI data acquisition

MRI were acquired on a 3-T Siemens Trio MRI scanner (Siemens, Erlangen, Germany) at the Beijing Normal University Imaging Center for Brain Research (Beijing, China). A 3D magnetization-prepared rapid gradient-echo (MP-RAGE) MRI sequence (TR/TE/TI = 2530/3.39/1100 ms, flip angle = 7°, voxel size = 1 × 1 × 1.33 mm, 128 slices) was used to obtain the T1-weighted image of the entire brain, and data were acquired twice before and after the SD period for each participant.

MRI data preprocessing

First, the quality of the T1-weighted MRI was assessed by visual examination. Second, these images were segmented for GM using the segmentation tools in VBM8 from Statistical Parametric Mapping 8 (SPM8, *http://www.fil.ion.ucl.ac.uk/spm*). The GM images for each participant were then normalized to a study-specific template in MNI152 space using diffeomorphic anatomical registration through exponential lie algebra [13]. To ensure that the total amount of GM was conserved after spatial transformation, we modulated the transformed images by the Jacobian determinants of the deformation field. The modulated GM images were then smoothed with a Gaussian kernel (full width at half maximum = 8 mm) before being used for further analyses.

Region of interest analysis

We obtained masks for the bilateral hippocampus and thalamus from a widely used human brain probability template, the Harvard-Oxford subcortical structural atlas. We chose to use the common 25% threshold subtemplate. To rule out the possibility that any potential effects observed with the 25% atlas were driven by peripheric region inclusion, analyses were also conducted with the 50% atlas. The results of this additional analysis were highly convergent with those for the 25% atlas (data not shown). In each analysis, a paired two-sample *t*-test was performed on the mean GM volume of each region of interest (ROI) to determine whether they displayed a SD-caused reduction. The mean GM volume within these regions was calculated with an in-house Python-coded tool.

Whole-brain analyses

For the areas outside the ROIs, we conducted a paired *t*-test on each voxel across the whole brain before and after the SD. However, we did not find regions that displayed significant reduction because of sleep loss with appropriate corrections for false-positive error at a threshold of P less than 0.05. To search for other possible candidate regions for future studies, we also performed an analysis with a slightly more lenient criterion ($P < 0.001$, uncorrected, cluster size > 40 mm^3).

Results

Task performance

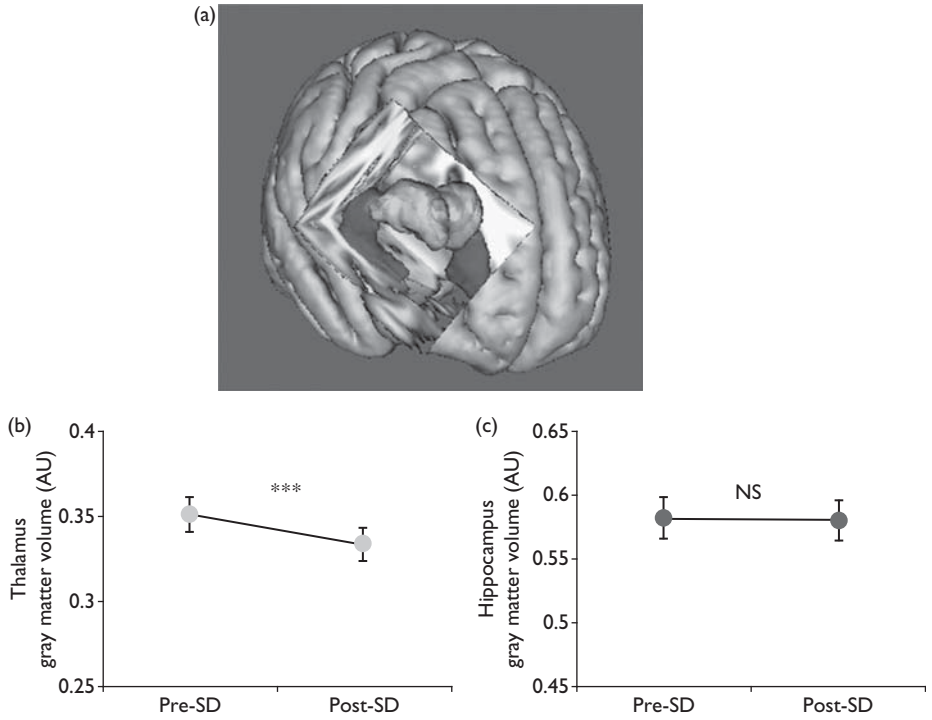
As expected, vigilance performance significantly declined after SD ($d' = 1.82 \pm 1.01$) compared with normal sleep [$d' = 2.56 \pm 0.95$, $t(10) = 2.87$, $P < 0.01$] (d' represents that portion of the signal–noise distribution attributable to veridical perception of the signal according to the signal detection theory, and thus d' provides a means for assessing an individual's discriminative power).

Gray matter volume

To test the hypothesis that SD reduces the regional GM volume in the thalamus and hippocampus, we recorded structural MRI scans from 11 healthy young adults (male) before and after a long-duration SD. We then used VBM analysis to investigate the change of regional GM volume in these regions after the SD period. Among the four candidate regions, we found that the regional bilateral thalamus GM volume was significantly reduced (survived Bonferroni correction for multiple testing) after SD [left: $t(10) = 3.832$, $P = 0.006$; right: $t(10) = 3.924$, $P = 0.006$]. However, we did not observe any significant hippocampal changes [left: $t(10) < 1$; right: $t(10) < 1$]. The two bilateral brain subcortical regions and changes of regional GM volume averaged across the bilateral ROIs are shown in Fig. 1.

Outside these ROIs reflecting our prior hypotheses, we also conducted a whole-brain analysis to reveal any additional brain structures that displayed reduction because of sleep loss. However, no regions displayed a reduction that survived correction for multiple comparisons across the whole brain ($P_{FDR} > 0.05$). With a more lenient statistical criterion ($P < 0.001$ uncorrected and cluster size >40 mm^3), we found clusters in which GM volume was significantly reduced (Table 1) after SD in the left middle temporal gyrus ($Z = 3.91$, $P < 0.0005$), right inferior temporal gyrus ($Z = 4.49$, $P < 0.0005$), left postcentral gyrus ($Z = 3.81$, $P < 0.0005$), right lateral occipital cortex ($Z = 3.91$, $P < 0.0005$), and bilateral cerebellum (right: $Z = 3.9$, $P < 0.0005$; left: $Z = 4.01$, $P < 0.0005$; $Z = 3.68$, $P < 0.0005$). No regions displayed an increase after SD, as we had expected. In addition, the reduction in total GM volume after SD was not significant [$t(10) = 1.61$, $P = 0.15$]. Thus, our data

Fig. 1



Reduction of regional gray matter (GM) volume after sleep deprivation (SD). (a) Two subcortical brain structures are shown in different colors. Green indicates the bilateral thalamus and purple indicates the bilateral hippocampus. (b) The region of interest (ROI) in the thalamus (left) displayed significant reduction of GM volume after SD. The changes (right) in regional GM volume averaged across the bilateral ROIs are shown. (c) The region of interest (ROI) in the hippocampus (left) displayed significant reduction of GM volume after SD. The changes (right) in regional GM volume averaged across the bilateral ROIs are shown. ***$P<0.001$; NS, $P>0.05$. Error bars represent the SEM.

Table 1 Brain structures that displayed reduction after sleep deprivation in the whole-brain analysis

Brain region	L/R	Maxima of cluster (mm)			*Z*	*P*	Cluster size (voxels)
Thalamus	R	16	−30	12	3.94	0.000041	110
Cerebellum	R	36	−60	−56	3.9	0.000048	106
	L	−16	−64	−50	4.01	0.00003	50
	L	−30	−90	−36	3.68	0.00012	41
Postcentral gyrus	L	−54	−4	36	3.81	0.00007	55
Inferior temporal gyrus	R	54	−50	−16	4.49	0.0000035	49
Middle temporal gyrus	L	−58	−56	4	3.91	0.000045	43
Lateral occipital cortex	R	52	−62	16	3.91	0.000045	41

L, left; R, right.

indicated regional bilateral thalamus specificity for the loss of GM after SD.

Regional gray matter volume correlation with task

In this study, the greater the decrease in attention scores from rest to SD, the greater the reduction in GM volume (data combined for right and left side). These correlations were positive in the thalamus ($r = 0.83$, $P < 0.01$). No lateral cortical lobe correlations reached significance.

Discussion

The present study revealed the effect of long-term total SD on GM volume. Consistent with our hypothesis, sleep loss actually reduced regional GM volume in the human brain. In particular, we observed reduced regional GM volume in the bilateral thalamus.

Some studies reveal that experiencing sleep loss can cause a reduction of regional GM volume, for example, in human patients with primary insomnia [9]. With healthy younger adults and within-subject design, we first observed a significant reduction in regional GM in the bilateral thalamus, which is considered to be connected to consciousness as it functions as the gatekeeper for all sensory information in the human brain [14,15]. As the thalamus connects different areas of the brain to each other, it is involved in the relaying of sensory signals to

the cerebral cortex; reception of auditory, physical, and visual signals; motor control; and regulation of cognitive and emotional processing [16]. Thus, if the human thalamus is damaged physically or neurologically (e.g. from stroke, accident, medication, or genetics), such damage can lead to problems with sleeping, pain perception, memory issues, and sensory impairment, among other areas. For example, previous studies observed increased thalamic responses during SD for working memory [17,18] and attention tasks [19,20], which might reflect a 'compensatory' response caused by regional GM reduction in the thalamus. Thus, the observed structural reduction in the thalamus caused by SD may underlie the observed decreased cognitive and emotional performance and reflect the nonspecific mechanisms that support cortical function and maintain steady performance of the thalamus. In addition, the reduction of regional brain structure volume may provide us with new insight into the clinical implications of sleep loss.

In contrast to previous studies, we did not observe reduced regional GM in the hippocampus. Although several studies in rats and insomnia patients have reported reduced hippocampal volumes, the mechanism underlying this reduction is not clear. For example, in studies with insomnia patients, findings may be clouded by other comorbidities. Unlike those studies using patients or nonhuman mammals as participants, we recruited healthy younger adults and conducted SD for an entire 72 h. In fact, reduced regional GM in the hippocampus apparently does not occur in young adults after acute 72-h SD, which contrasts with the reduction in hippocampal volume seen in patients with insomnia. Additional research on the changes in the hippocampus after SD is needed.

Conclusion

We found that long-term SD reduces thalamic regional GM volume in the human brain. To the best of our knowledge, this is the first report on the effects of total SD on regional brain structure during wakefulness in humans, using VBM. Although these results should be regarded as preliminary and require replication and extension in future studies, they do suggest that the changes in brain structure during and after SD can inform our understanding of the effects of SD on cognitive and emotional performance from the perspective of brain structure.

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Conflicts of interest

There are no conflicts of interest.

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