

Regional cerebral hypoperfusion after acute sleep deprivation

A STROBE-compliant study of arterial spin labeling fMRI

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Abstract

Previous neuroimaging studies have shown that functional changes occur after acute sleep deprivation, which suggest detrimental effects of a lack of sleep on the intrinsic functional architecture of the brain. We aimed to identify regional resting perfusion changes in subjects with acute sleep deprivation.

Thirty-three healthy subjects with habitual good sleep participated in 36 hours (2 days and 1 night) of sleep deprivation and then underwent the attention network test and pseudo-continuous arterial spin labeling scanning. Regional cerebral blood flow was used to compare cerebral perfusion before and after sleep deprivation. Correlation analyses of regional perfusion changes and scores on the attention network test were performed.

Compared with the baseline ($n=20$) scans, the scans of subjects after sleep deprivation ($n=26$) revealed a slower response time (549.99 milliseconds vs 603.36 milliseconds; $t=-2.301$; $P=.028$) and a significantly higher lapse rate (0.88% vs 22.85%; $t=-2.977$; $P=.006$). The sleep deprivation subjects showed lower cerebral blood flow (CBF) in the left parahippocampal gyrus/fusiform cortex (pHipp/Fus), right pHipp/Fus, and right prefrontal cortex (PFC) relative to the baseline subjects (Gaussian random field correction, voxel level $P<.01$, and cluster level $P<.05$). Although no significant relationships were observed between the altered regional CBF (rCBF) values and the attention network test scores, the receiver-operating characteristic and leave-one-out cross-validation analyses revealed that significant decreases in rCBF in the bilateral pHipp/Fus and right PFC could discriminate between sleep deprivation and good sleep status.

We observed that rCBF was reduced after 36 hours (2 days and 1 night) of sleep deprivation. Our preliminary findings suggest an acute vulnerability to hypoperfusion due to lack of sleep.

Abbreviations: ANT = attention network test, AUCs = areas under the curves, BOLD = blood oxygenation level dependent, CBF = cerebral blood flow, fMRI = functional magnetic resonance imaging, Fus = fusiform cortex, GRF = Gaussian random field, LOOCV = leave-one-out cross-validation, MNI = Montreal Neurological Institute, pCASL = pseudo-continuous arterial spin labeling, PFC = prefrontal cortex, pHipp = parahippocampal gyrus, ROC = receiver-operating characteristic, RW = rested wakeful, SD = sleep deprivation.

Keywords: arterial spin labeling, regional cerebral blood flow, sleep deprivation

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1. Introduction

Sleep deprivation (SD) is a common negative event due to working, insomnia, and other causes (including sleep apnea and mental illness). In humans, acute SD (usually understood as wakefulness ≥ 16 hours) can produce changes in mood, attention, memory, and cognitive performance.^[1] SD can adversely affect the brain, as has been confirmed by functional magnetic resonance imaging (fMRI) for both task activated^[2,3] and resting states.^[4–7] SD can cause alterations in regional activity, namely, reduced activity in the anterior brain but increased activity in the posterior brain^[4,5]; it can also cause decreased default network^[8] and thalamocortical^[7] connectivity but increased interhemispheric connectivity.^[6] Blood oxygenation level-dependent (BOLD)-fMRI studies have proven to be an essential and noninvasive method for studying neural processes underlying sleep disorders in humans.^[1,2,9]

Far less is known about the effect of SD on brain perfusion during wakefulness. A few single photon-emission computed tomography studies have reported decreased regional cerebral blood flow (rCBF) in the inferior temporal gyrus in sleepwalkers after a night of total SD^[10] and decreased rCBF in the frontoparietal attentional network^[11] and ventral visual cor-

Table 1
Participant information.

Clinical information	Baseline (RW, n=20)	Sleep deprivation (SD, n=26)	t-test (P-values)
Age, yr	21.06 ± 1.18	21.11 ± 1.13	-.122 (.903)
Gender (male/female)	13/7	16/10	.017 (.897)*
Education, yr	14.06 ± 1.18	14.17 ± 1.20	-2.555 (.801)
Response accuracy rate	98.56% ± 1.57%	97.55% ± 2.38%	1.444 (.158)
Total response time, ms	549.99 ± 56.5	603.36 ± 78.07	-2.301 (.028)
Lapse rate	0.88% ± 0.35%	22.85% ± 2.93%	-2.977 (.006)
Response time of spatial orientation	50.01 ± 26.14	69.39 ± 30.88	-1.981 (.056)
Response time of executive control	78.30 ± 21.74	78.94 ± 35.90	-.063 (.950)

RW = rested wakeful, SD = sleep deprivation.
* Chi-square test.

tex^[12] after acute sleep loss (<24 hours). However, whereas acute sleep restriction increase the tendency to fall asleep, a long total duration of SD (>24 hours) is sufficient to impair neuro-behavioral functioning. To quantify rCBF changes due to mandatory sleep loss, we used a noninvasive pseudo-continuous arterial spin labeling (pCASL) pulse sequence and then investigated differences in brain perfusion during wakefulness between before and after 36 hours of SD. pCASL is a promising imaging technique for the quantitative measurement of cerebral blood flow with low intersubject variability and without the need for administration of contrast material and radiation.^[13] It has applications in vascular diseases such as stroke^[14] and “functional” diseases, including Alzheimer disease^[15] and schizophrenia.^[16] In this study, we hypothesized that acute SD would cause local hypoperfusion during wakefulness, consistent with its effects on behavioral performance.

2. Materials and methods

2.1. Participant selection

Thirty-three healthy subjects with habitual good sleep were recruited from medical schools through advertisements for this study. The subjects were recruited based on the following criteria: being right-handed and having good sleeping habits without a history of swing shifts, shift work, or sleep complaints; having no sleep disorders; having regular dietary habits and no consumption of any stimulants, for example, alcohol and caffeine; and

having no history of any psychiatric or neurological disorders. Some of the participants were reported in a previous study,^[17] and a detailed description of the inclusion criteria can be found in a previous study.^[17] All subjects underwent evaluations of the quality and quantity of sleep prior to SD by means of actigraphy, sleep diaries, and/or questionnaires.

The demographic and behavioral data of the subjects are shown in Table 1. This case control study was approved by the Medical Research Ethics Committee and the Institutional Review Board of The First Affiliated Hospital of Nanchang University. In all cases, written informed consent for the research was obtained from each participant. The present study was conducted according to approved guidelines and was in compliance with the principles of the Declaration of Helsinki.

2.2. Sleep deprivation and attention tests

The experiment was conducted in a closed room, which had an area of approximately 8 m² and was equipped with monitors and ventilation. The administrator did not directly interact with the SD subjects but provided food and other necessities. After normal sleep (day 1), all the subjects were subjected to 36 hours of SD, from 8:00 AM on the 2nd day to 8:00 PM on the 3rd day. During the 36 hours of total SD, the participants were required to continually remain awake. An outline of the SD is depicted in Figure 1. Each subject underwent MRI scanning within the period from 9:00 PM to 10:00 PM on 2 occasions: once before normal sleep on day 1 (called the rested wakeful night, RW), and

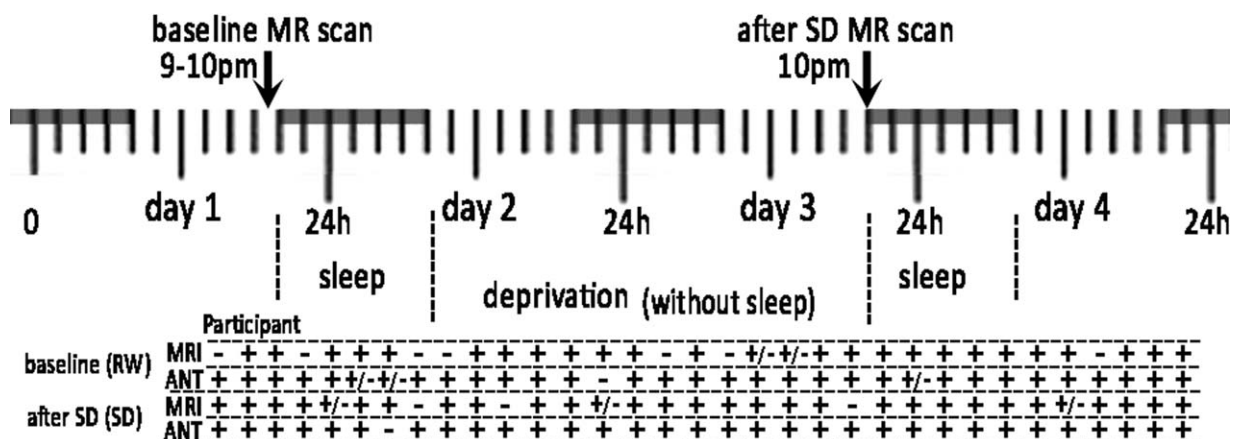


Figure 1. Sleep deprivation (SD) study timeline. +, magnetic resonance imaging (MRI) scans or attention network test; +/-, poor data quality or attention network test (ANT) performance; -, missing MRI or ANT data.

once after the SD period on day 3. A video monitor was installed and monitored to ensure that the participants were awake with their eyes open during the MRI scans. A simple questionnaire was administered immediately after each scan inquiring whether the subjects were awake during the scan.

Before the scans, all subjects were administered the attention network test (ANT). During assessment, participants were seated in a comfortable chair at approximately 60 cm distance from a 14-inch computer monitor. In this study, the ANT consisted of 2 runs of 96 trials preceded by 1 practice run with 20 trials. For a detailed description of the ANT, please see the Westlye study.^[18] None of the participants had been administered the ANT task before the study.

2.3. MRI data acquisition

Experiments were performed on a 3-T MR system (Trio; Siemens, Erlangen, Germany). Each subject underwent a task-free pCASL scan with high-resolution 3-dimensional (3D) T1-weighted imaging. 3D T1-weighted images were acquired in the sagittal plane with the following parameters: repetition time/echo time, 2530 milliseconds/3.39 milliseconds; flip angle, 7°; thickness, 1.33 mm; gap, 0 mm; matrix, 256 × 256; and field of view, 240 mm × 240 mm. The imaging yielded 176 contiguous slices through the brain. The pCASL protocol followed Aslan and Lu^[19] and Jann et al^[20]: repetition time, 4000 milliseconds; echo time, 12 milliseconds; time interval between consecutive slice acquisitions, 32.0 milliseconds; RF duration, 0.5 milliseconds; labeling (duration 1650 milliseconds) block positioned 9 cm below the plane of the isocenter of the readout slices; post-spin-labeling delay, 1520 milliseconds; labeling pulse flip angle, 18°; bandwidth, 3.3 kHz/pixel; field of view, 240 × 240; matrix, 64 × 64; and 20 slices acquired in ascending order with a 7-mm slice thickness and a 1-mm gap. In addition, we acquired conventional axial T2-weighted turbo spin echo images (repetition time/echo time, 4507/80 milliseconds; voxel size = 3.75 × 3.75 × 3.75 mm) to exclude significant central nervous system lesions.

2.4. ASL data processing

The ASL and high-resolution T₁WI data were processed using the ASLtbx toolbox (<https://www.cfm.upenn.edu/ASLtbx.php>) in Matlab (Math Works, Natick, MA). The main processing steps were as follows: preprocessing: median filter (a nonlinear digital filtering technique) applied to reduce spike noise; head motion correction performed on tag and control images separately following Wang et al^[21] (following rejection of participants with greater than 2° angular rotation along any axis and greater than 2 mm of translation along any axis on the whole functional MR scan). Segmentation, coregistration, and spatial normalization: high-resolution individual T1-anatomical images registered to the mean ASL data, with the resultant aligned T1-weighted images segmented and transformed into the standard Montreal Neurological Institute space using diffeomorphic anatomical registration through the exponentiated lie algebra (DARTEL) toolbox^[22]; CBF calculation with a single compartment model. Smoothing: 6-mm full-width smoothing at half maximum Gaussian kernel performed to decrease spatial noise and compensate for the inexactitude of normalization.

2.5. Statistical analysis

We first evaluated the attention deficits (correct reaction times of ANT) using 2-sample *t*-tests (or paired *t*-tests) with the Statistical

Package for the Social Sciences version 13.0 (SPSS 13.0; SPSS Inc, Chicago, IL; statistical threshold $P < .05$).

Next, 2-sample *t*-tests (or paired *t*-tests) to assess the between-condition difference in rCBF were performed using Statistical Parametric Mapping 12 (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/>), with age, gender, and years of education as nuisance covariates of no interest (voxel level of $P < .01$ and Gaussian random field [GRF] theory correction at a cluster level of $P < .05$). Correlation analyses of rCBF values and the behavioral measure (correct reaction time of ANT) were assessed using age, gender, and years of education as nuisance covariates.

2.6. Discriminant analysis

In the 2nd step of the ASL data analysis, receiver-operating characteristic (ROC) curves were used to estimate the sensitivity and specificity of the regions with significant between-group differences of rCBF to distinguish SD subjects from good sleep subjects. The area under the ROC curve was used to estimate the accuracy of the classification. Leave-one-out cross-validation (LOOCV) was used to assess the validity of the results.

3. Results

Ultimately, we obtained complete pCASL and behavioral data for 20 subjects at baseline (RW) and 26 subjects after SD for group comparisons (see Fig. 1). The baseline (RW) data of 9 participants were excluded due to missing MRI data or poor data quality, and those of 4 subjects were excluded due to poor ANT performance. The post-SD data of 6 participants were excluded due to missing MRI data or poor data quality, and those of 1 participant were excluded due to poor ANT performance. The main behavioral and imaging results are given in the following section.

3.1. Behavioral results

Compared with the baseline (RW) subjects, the SD subjects showed a slower response (549.99 milliseconds vs 603.36 milliseconds; $t = -2.301$; $P = .028$) and a significantly higher lapse rate (0.88% vs 22.85%; $t = -2.977$; $P = .006$) on the ANT (Table 1). These participants comprised the 16 participants with complete data for both before and after SD.

3.2. Spatial patterns of rCBF before and after sleep deprivation

The spatial patterns of rCBF across the whole brain are shown in Figure 2 for the baseline (RW, $n = 20$) scan and the post-SD (SD, $n = 26$) scan. Both scans revealed high rCBF in the precuneus/posterior cingulate cortex, anterior cingulate cortex/medial prefrontal cortex (PFC), precentral gyrus, postcentral gyrus, superior temporal cortex, and middle occipital gyrus. On visual inspection, the SD group appeared to have slightly decreased rCBF relative to the RW group, especially in the PFC and parahippocampal gyrus (pHipp).

3.3. rCBF difference between before and after sleep deprivation

Compared with the subjects at baseline ($n = 20$), the SD subjects ($n = 26$) showed lower rCBF in the left pHipp/fusiform cortex (pHipp/Fus), right pHipp/Fus, and right PFC (2-sample *t*-tests, voxel level $P < .01$ and GRF correction at cluster level $P < .05$;

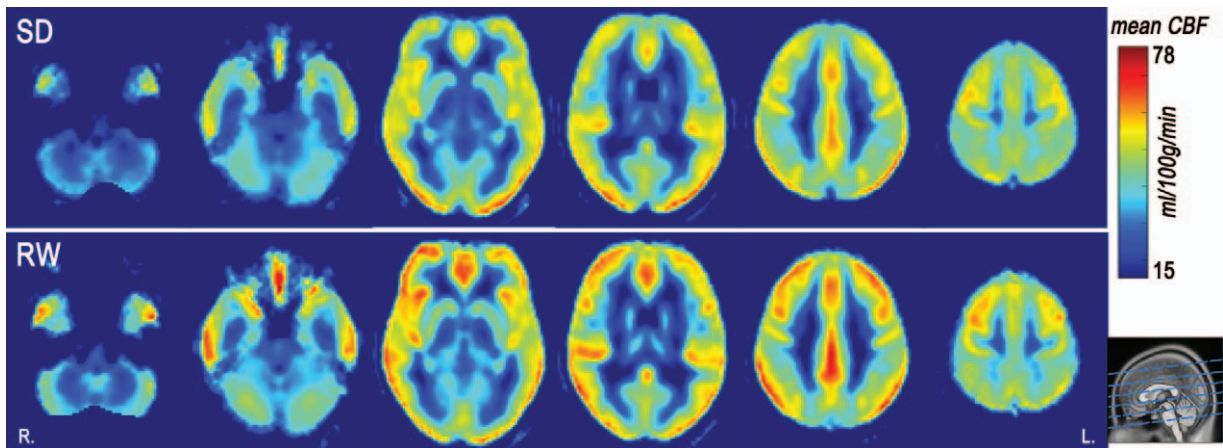


Figure 2. Mean regional cerebral blood flow (rCBF) in the sleep deprivation (SD, n=26) and baseline (RW, n=20) subjects. Reduced rCBF was observed in the frontal cortex after 36 hours of sleep deprivation.

Fig. 3, Table 2). No significant increase in rCBF was observed in the SD subjects relative to the RW subjects. In the alternative, paired-data comparisons (n = 16, paired *t*-tests), more areas with decreased rCBF were detected in the SD scans than in the RW scans (Fig. 4, Table 3).

3.4. Discriminatory performance analysis of rCBF

Among the regions with significant between-group differences in rCBF, the left pHipp/Fus, right pHipp/Fus, and right PFC exhibited lower rCBF in SD subjects. Therefore, these regions could potentially be used to discriminate the periods before and after SD. To investigate this possibility, the mean rCBF values in the 3 regions were extracted. ROC analysis revealed that the areas under the curves (AUCs) were 0.796 for the left pHipp/Fus, 0.798 for the right pHipp/Fus, and 0.819 for the right PFC (Fig. 5, Table S1). The LOOCV showed cross-validated AUCs of 0.796 ± 0.0097 (0.785–0.824) for the left pHipp/Fus, 0.798 ± 0.0098

(0.787–0.832) for the left right pHipp/Fus, and 0.819 ± 0.0056 (0.810–0.838) for the right PFC.

3.5. Correlations of rCBF with behavioral scores in SD subjects

In the SD subjects, no significant relationship was observed between mean rCBF value and any behavioral score, such as the response accuracy rate and response time (Table S2).

4. Discussion

Our study demonstrated reduced rCBF in a few regions of the anterior brain as well as a significantly increased response time and lapse rate on the ANT after 36 hours of SD. Furthermore, significant decreases in rCBF in the left pHipp/Fus, right pHipp/Fus, and right PFC following SD allowed discrimination of the SD effect from that of good sleep (RW status).

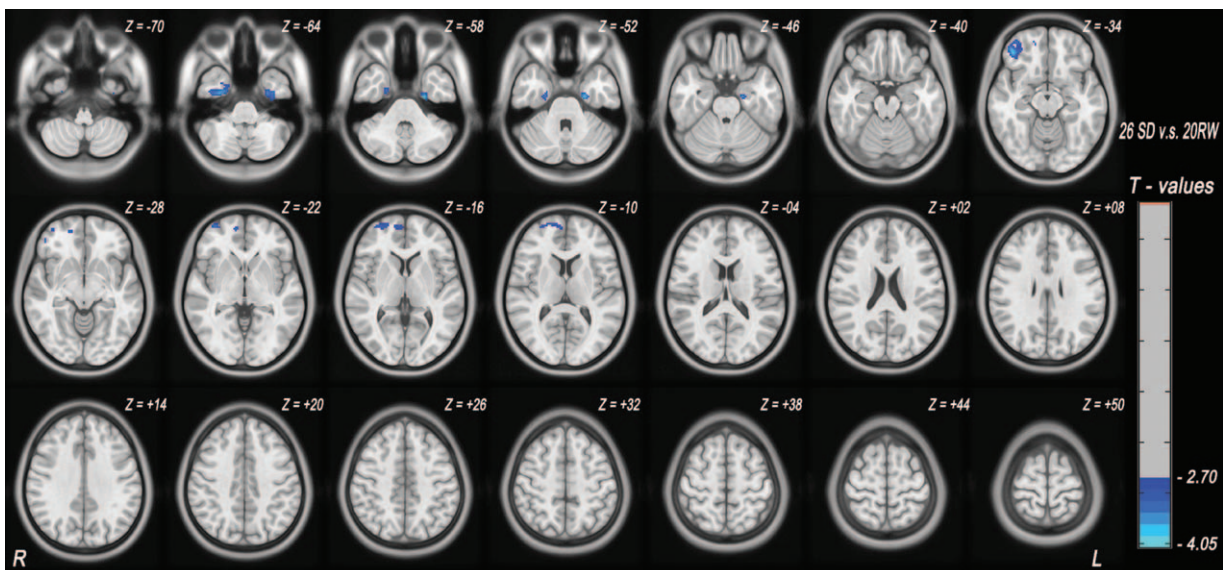


Figure 3. Regional cerebral blood flow (rCBF) differences between before and after sleep deprivation (2-sample *t*-tests, voxel level of *P* < .01 and Gaussian random field (GRF) theory correction at a cluster level of *P* < .05).

Table 2

Regions that showed significant differences in cerebral blood flow before (n=20) and after (n=26) sleep deprivation.

Cluster size	Z-score	MNI coordinates			Brain region
		x	y	z	
217	-4.05	-24	-12	-38	Left parahippocampal gyrus/fusiform cortex
245	-3.618	30	-8	-44	Right parahippocampal gyrus/fusiform cortex
508	-3.713	42	42	-14	Right PFC

MNI=Montreal Neurological Institute, PFC = prefrontal cortex.

In this study, the results from ASL confirmed that cerebral blood flow or perfusion is reduced in the left and right pHipp/Fus after 36 hours of SD (20 vs 26); the reduction was even greater in the paired *t*-test comparison (16 vs 16, Fig. S1), possibly reflecting individual variability in resistance. It is generally believed that sleep is essential to whole-body functioning, and a lack of sleep has been associated with many health problems and cognitive consequences.^[2,9] In previous studies, it was observed that SD caused distributed alterations in the intrinsic functional architecture of the brain^[4-8] and externalized functional achievements (i.e., memory, emotional processing, and executive control).^[2,3,24] Recent imaging data

have illustrated disturbed functional connectivity in the memory and recognition circuit, including the hippocampus,^[2,3] pHipp,^[2,3] and fusiform cortex.^[2,5] Consistent with the notion that a lack of sleep affects patterns of large-scale network connectivity, decreased rCBF in the left and right pHipp/Fus was observed after SD, suggesting perfusion effects due to lack of sleep. This finding of our study suggests that the early improvement of cerebral blood flow might alleviate cognitive-related symptoms after sleep loss.

In a previous study, decreased rCBF was detected in the frontoparietal attentional network after acute sleep restriction.^[11] Not surprisingly, after SD, we found an overall

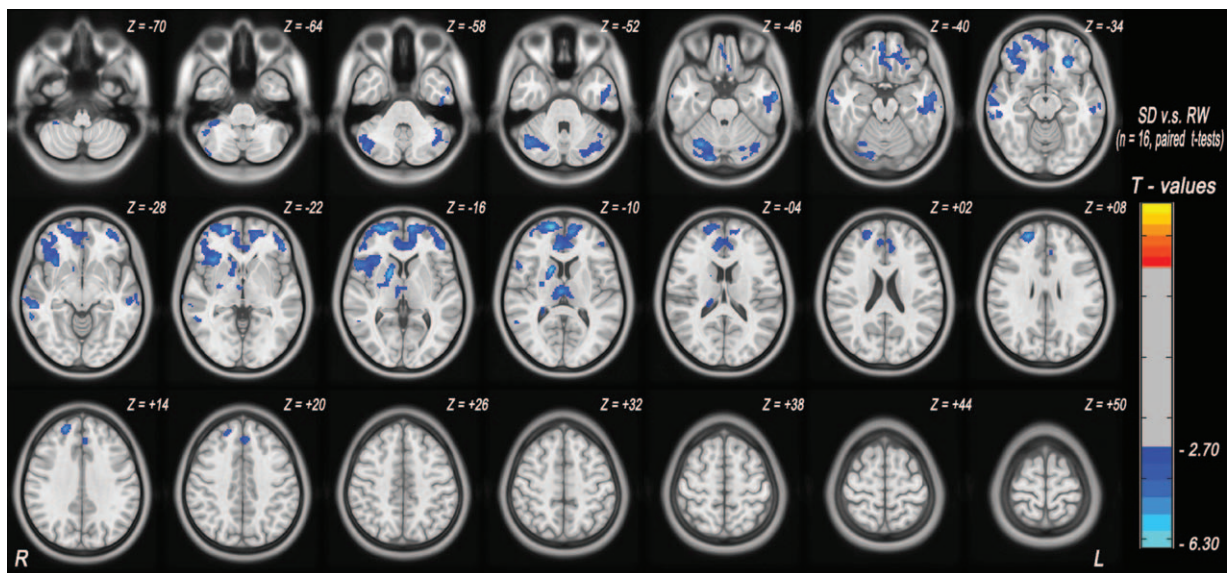


Figure 4. Regional cerebral blood flow (rCBF) differences between before and after sleep deprivation (n = 16, paired *t*-tests, voxel level of *P* < .01 and Gaussian random field theory correction at a cluster level of *P* < .05).

Table 3

Regions that showed significant differences in cerebral blood flow before and after sleep deprivation (n = 16, paired *t*-tests, voxel level of *P* < .01 and Gaussian random field theory correction at cluster level of *P* < .05).

Cluster size	Z-score	MNI coordinates			Brain region
		x	y	z	
1169	-5.032	18	-84	-26	Right cerebellum posterior lobe
754	-5.163	-60	-10	-24	Left inferior temporal gyrus
482	-4.445	-42	-68	-30	Left cerebellum posterior lobe
6054	-6.297	16	62	10	Bilateral PFC
562	-4.750	66	-4	-20	Right middle temporal gyrus
485	-5.895	14	12	10	Right basal ganglia
394	-4.885	2	-14	10	Bilateral thalamus

MNI=Montreal Neurological Institute, PFC = prefrontal cortex.

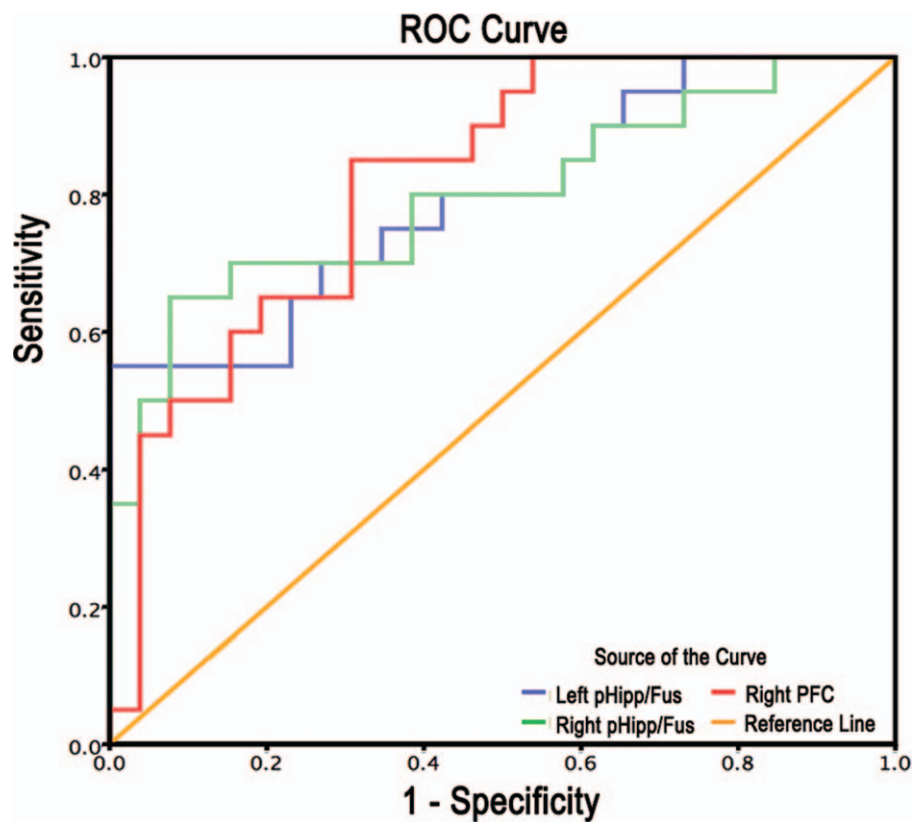


Figure 5. Receiver-operating characteristic (ROC) analysis for differentiating regional cerebral blood flow (rCBF). PFC = prefrontal cortex.

significantly decreased rCBF in the right PFC, which is mostly located in the orbitofrontal cortex. The right PFC is involved in sensory integration, the representation of the affective values of reinforcers, and decision making and expectation.^[26] fMRI studies have demonstrated that SD affects the decision-making function.^[27,28] Our data extend these findings by showing that neural activity in these regions is modulated after sleep loss. Importantly, these functional impairments caused by SD are associated not only with decreased responses to evoking stimuli but also with altered activation or connectivity patterns in large-scale brain networks.^[29,30] Thus, the presence of decreased rCBF on the right side is interpreted as reflecting a dissociated functional state in functional signs.

Growing evidence from neuroimaging studies indicates that sleep is important in synaptic renormalization, which is sustainable and ensures the homeostasis of dynamic blood oxygen changes in the brain. In our study, we observed consistent functional declines in the ability to respond to the ANT following SD, although no relationship between perfusion and behavioral (ANT) test scores was observed in this study. This latter finding conflicts with a recent study showing that individuals vulnerable to the effects of SD to selective attention have attenuated top-down frontoparietal control.^[11,12] The lack of a significant correlation in the present study may be because the changes in resting brain kinetic parameters in the left pHipp/Fus, right pHipp/Fus, and right PFC are independent of the implementation of attention. However, the observed SD-related rCBF differences suggest the potential of rCBF as a neural marker of SD in the left pHipp/Fus, right pHipp/Fus, and right PFC that can be used to distinguish SD from good sleep (RW status) using moderate sensitivity and specificity as cut-off points.

While our results are interesting and encouraging, some limitations of the present study should be noted. First, although we detected altered rCBF in the SD subjects in both 2-sample and paired *t*-tests, this study had a small sample size; a larger sample should be used to confirm our results in future investigations. Second, we did not acquire simultaneous BOLD and CBF data to assess BOLD-CBF coupling, which can be used as a biomarker of brain function changes. Third, although we detected decreased perfusion in the left and right pHipp/Fus and right PFC, which are involved in memory and cognitive function, we did not use specific tasks to investigate the relationships between the ASL findings and the behavioral functioning of the subjects. These relationships should be considered in future studies.

5. Conclusion

In summary, we detected hypoperfusion in the left and right pHipp/Fus and right PFC after 36 hours of SD. Our study suggests an important new avenue of exploration into the nature of functional neural abnormalities caused by SD.

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Author contributions

All authors contributed to the data analysis as well as to the drafting and revision of the paper and agree to be accountable for all aspects of the work.

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