

Sleep deprivation disturbed regional brain activity in healthy subjects: evidence from a functional magnetic resonance-imaging study

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Objective: The aim of this study was to use amplitude of low-frequency fluctuation (ALFF) to explore regional brain activities in healthy subjects after sleep deprivation (SD).

Materials and methods: A total of 16 healthy subjects (eight females, eight males) underwent the session twice: once was after normal sleep (NS), and the other was after SD. ALFF was used to assess local brain features. The mean ALFF-signal values of the different brain areas were evaluated to investigate relationships with clinical features and were analyzed with a receiver-operating characteristic curve.

Results: Compared with NS subjects, SD subjects showed a lower response-accuracy rate, longer response time, and higher lapse rate. Compared with NS subjects, SD subjects showed higher ALFF area in the right cuneus and lower ALFF area in the right lentiform nucleus, right caudatum, left dorsolateral prefrontal cortex, and left inferior parietal cortex. ALFF differences in regional brain areas showed high sensitivity and specificity. In the SD group, mean ALFF of the right caudatum showed a significant positive correlation with accuracy rate ($r=0.687$, $P=0.013$) and a negative correlation with lapse rate ($r=-0.706$, $P=0.01$). Mean ALFF of the dorsolateral prefrontal cortex showed a significant positive correlation with response time ($r=0.675$, $P=0.016$).

Conclusion: SD disturbed the regional brain activity of the default-mode network, its anticorrelated “task-positive” network, and the advanced cognitive function brain areas.

Keywords: sleep deprivation, amplitude of low-frequency fluctuation, default-mode network, functional magnetic resonance imaging

Introduction

Sleep is very important for humans to live a normal life. Sleep deprivation (SD), widespread in today's society, is a sleep-loss status generally caused by personal or environmental reasons.¹ SD can lead to a series of changes in emotional balance, and has a detrimental effect on cognitive function, attention, learning, and working memory.²⁻⁵ Long-term SD duration is associated with exaggerated neural reactivity, multisystemic and multiorganic dysfunction, and negative metabolic, psychological, physiological, or even behavioral reactivity.^{1,6-8}

Many studies have been carried out in short-term SD (24 hours), and found that SD adversely affects brain function and cognitive domains.^{9,10} A previous study employing resting-state functional magnetic resonance imaging (rs-fMRI) to explore brain-activation patterns by acupuncture stimuli during SD status found that sanyinjiao (SP6) elicits greater and anatomically different activations in the salience network than those of sham stimuli.¹¹ rs-fMRI studies have found altered functional connectivity in the

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sleep-deprived brain.^{12–15} Furthermore, multiple observations of altered connectivity within and between various resting-state networks have been reported for SD.^{12–18} These findings suggest that SD disturbs resting-state brain-activity patterns for internal processing of information.¹⁹ However, the neurologic mechanisms remain unclear.

The amplitude of low-frequency fluctuation (ALFF) can locate which brain region has abnormal regional spontaneous neuronal activity in blood oxygen level-dependent signals, and has been shown to have good-to-moderate test–retest reliability ranging from minimal to robust.^{20–22} Therefore, the simple calculation and reliable characterization of the ALFF measurement make it a potentially useful tool for rs-fMRI data analysis to investigate various functional brain changes.¹⁵ Recently, the use of ALFF measurement has been successfully applied to SD,^{15,23} wakefulness and light sleep,²⁴ obstructive sleep apnea,²⁵ primary insomnia,²⁶ and primary angle-closure glaucoma.²⁷ In this study, we hypothesized that SD would result in aberrant regional brain activity. To test the hypothesis, we utilized ALFF as an index to investigate the potential neurologic mechanisms of SD.

Materials and methods

Subjects

Sixteen healthy university students (mean age 24.51 ± 2.75 years, mean education duration 16.8 ± 1.8 years) responding to a web-based questionnaire were recruited. All subjects met the following criteria, as in previous studies:^{1,15,28} 1) no symptoms associated with sleep disorders and no history of any psychiatric or neurologic disorders; 2) right-handed; 3) good sleeping habits; 4) good sleep onset and/or maintenance, and no history of swing shift, shift work, sleep complaints, or other sleep disorders; 5) regular dietary habits, and had not consumed any stimulants, alcohol, tea, cigarettes, medications, or caffeine for at least 3 months prior to the study; 6) no foreign implants in the body, and no inborn or other acquired diseases; 7) moderate body shape and weight; and 8) Pittsburgh Sleep Quality Index score < 5 .

Research design and procedures

To evaluate sleep status, all subjects were monitored for 1 week by wearing a Fitbit Flex tracker (<http://help.fitbit.com>).²⁸ Each of the subjects underwent the session twice randomly. Once was after normal sleep (NS), and the other was after a total of 24 hours' SD. Each subject underwent an MRI scan at each session, before which all subjects underwent an attention network test.^{15,29,30} A simple questionnaire was administered immediately after the scans to ascertain whether

the subjects were awake during the scans. SD was conducted in a specialized room, and started from 7 pm and ended at 7 pm the following day.

All volunteers were informed of the purposes, methods, and potential risks. This study was approved by the human-research ethics committee of Sir Run Run Shaw Hospital of Zhejiang University. All volunteers participated voluntarily, and all signed an informed consent form.

MRI parameters

MRI scans were performed on a 3 T MR scanner (Trio; Siemens, Munich, Germany). High-resolution T_1 -weighted images were acquired with a three-dimensional spoiled gradient-recalled sequence in a sagittal orientation: 176 images (repetition time 1,900 ms, echo time 2.26 ms, thickness 1 mm, gap 0.5 mm, acquisition matrix 256×256 , field of view 250×250 mm, flip angle 9°) were obtained. Finally, rs-fMRI scan was obtained with eyes opened. A total of 240 functional images (repetition time 3,000 ms, echo time 30 ms, thickness 4 mm, gap 1.2 mm, acquisition matrix 64×64 , flip angle 90° , field of view 220×220 mm; 36 axial slices with gradient-recalled echo-planar imaging pulse sequence) covering the whole brain were obtained.

fMRI data analysis

Based on the MatLab 2012a (MathWorks, Natick, MA, USA), data preprocessing was performed by Data Processing Assistant for Resting-State fMRI (<http://rfmri.org/DPARSE>) software, including Digital Imaging and Communication in Medicine form transformation, slice timing, head-motion correction, spatial normalization, and smooth. The first ten time points of the functional images were discarded, due to the possible instability of the initial MRI signal and the participants' adaptation to the scanning environment. Participants who had more than 1.5 mm maximum translation in x , y , or z and 1.5° motion rotation were rejected. Friston six head-motion parameters were used to regress out the head-motion effects based on recent work showing that the higher-order models were more effective in removing head-motion effects.^{31,32} After head-motion correction, the fMRI images were spatially normalized to Montreal Neurological Institute space and resampled at a resolution of $3 \times 3 \times 3$ mm. Smoothing was performed with a Gaussian kernel of $6 \times 6 \times 6$ mm³ full width at half maximum. After preprocessing, the time series for each voxel was temporally band-pass filtered (0.01–0.08 Hz) and linearly detrended to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise. The details of the ALFF calculation have

been reported in previous studies.^{15,27,33} To reduce the global effects of variability across the participants, the mean ALFF value of each voxel was divided by the global mean ALFF value for each participant.

Receiver-operating characteristic curve

Discrimination results are considered excellent for areas under the curve between 0.9 and 1, good between 0.8 and 0.9, fair between 0.7 and 0.8, poor between 0.6 and 0.7, and failed between 0.5 and 0.6.³⁴ Since different ALFF areas might be utilized as markers to separate the SD group from the NS group, the mean signal values of the different areas were extracted and used for receiver-operating characteristic (ROC)-curve analysis to investigate whether these specific ALFF differences had the sensitivity and specificity to distinguish the SD group from the NS group.

Brain–behavior correlation analysis

Based on the ALFF findings, the mean ALFF-signal values of the different brain areas were extracted and their correlations calculated with the behavioral performances using the IBM Statistical Package for the Social Sciences (SPSS, version 21.0) software, with the statistical threshold set at $P < 0.05$.

Statistical analysis

A two-paired *t*-test was used to assess the differences in brain activity between the two groups. A corrected significance level of individual voxels of $P < 0.001$ and contiguous cluster volume ≥ 351 mm³, using an AlphaSim corrected threshold of cluster $P < 0.05$, were used to determine statistical significance.

Results

Behavioral results

Compared with the NS subjects, the SD subjects showed a lower response-accuracy rate (SD: 92% \pm 1.95%, NS: 97.25% \pm 2.42%, $t = -5.852$; $P < 0.001$), a longer response time (SD: 631.61 \pm 86.67 ms, NS: 527.49 \pm 39.06 ms, $t = 3.794$; $P = 0.002$), and a higher lapse rate (SD: 7.11% \pm 9.59%, NS: 0.09% \pm 0.25%, $t = 2.534$; $P = 0.028$).

ALFF differences

Compared with the NS subjects, the SD subjects showed higher ALFF area in the right cuneus (Brodmann's area [BA] 17, BA 18), and lower ALFF area in the right lentiform nucleus, right claustrum, left middle frontal gyrus (BA 46), and left inferior parietal cortex (IPC; BA 39). Details are presented in Figure 1 and Table 1.

ALFF analysis shows high sensitivity and specificity

Figure 2 shows the mean ALFF-signal values of the altered regional brain areas. These different values were used for ROC-curve analysis to investigate whether these specific ALFF differences had the sensitivity and specificity to distinguish the SD group from the NS group. ROC-curve analysis showed that the area under the curve of the five different brain areas (from cluster 1 to cluster 5) was 0.861 with a cutoff point of 0.996 (mean ALFF-signal value), 0.757 with a cutoff point of -0.538 , 0.944 with a cutoff point of -0.93 , 0.826 with a cutoff point of 0.084, and 0.736 with a cutoff point of 0.471. Further diagnostic analysis showed that the different brain areas alone discriminated SD status from NS status with high sensitivity and specificity: corresponding values from clusters 1–5 were 0.667 and 0.917, 0.667 and 0.833, 0.833 and 0.917, 0.833 and 0.833, and 0.583 and 0.833, respectively. Details are presented in Figure 3.

Brain–behavior correlation results

In the SD group, the mean ALFF value of the right claustrum showed a significant positive correlation with accuracy rate ($r = 0.687$, $P = 0.013$) and a negative correlation with lapse rate ($r = -0.706$, $P = 0.01$). The mean ALFF value of the middle frontal gyrus showed a significant positive correlation with response time ($r = 0.675$, $P = 0.016$).

Discussion

In this study, our results confirmed functional alterations in resting-state networks after SD. Compared with the NS subjects, the SD subjects showed higher ALFF areas in the right visual network and lower ALFF areas in the right lentiform nucleus, right claustrum, left dorsolateral prefrontal cortex (DLPFC), and left IPC. ALFF differences in regional brain areas showed high sensitivity and specificity. The reliability of the ALFF differences revealed that the different ALFF areas could serve as markers to distinguish the SD condition from the NS condition. Our findings may suggest that SD is associated with the model of excitation–inhibition imbalance in the central nervous system.

Previous studies have demonstrated that hyperarousal reactivation in the occipital gyrus was found in SD subjects and patients with insomnia.^{1,28} These findings supported our results that the SD group showed higher ALFF area in the right cuneus compared with the NS group. The vision-related regions were not only activated by real vision but also by visual mental imagery,^{35,36} since the visual cortex is relevant to emotional activities and emotional changes can lead to

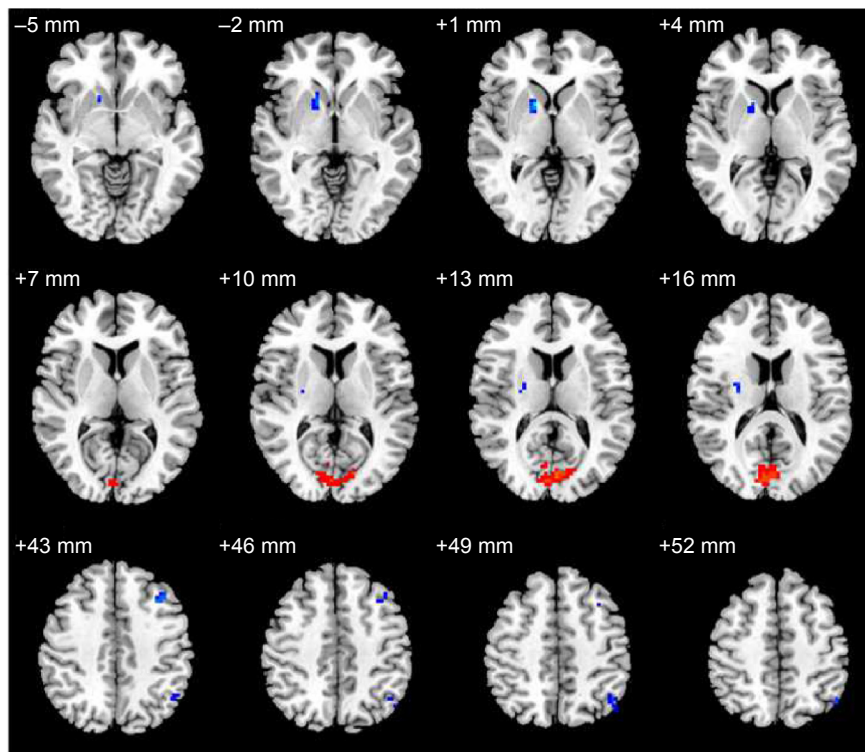


Figure 1 ALFF differences between the SD and NS groups.

Notes: Colors in the map represent differences. Red signifies higher ALFF area in the right cuneus, and blue signifies lower ALFF area in the right lentiform nucleus, right claustrum, left middle frontal gyrus, and left inferior parietal cortices.

Abbreviations: ALFF, amplitude of low-frequency fluctuation; SD, sleep deprivation; NS, normal sleep.

higher blood oxygen level-dependent signal regions in the visual cortex.^{37,38} The higher activity in the visual cortex may represent a compensatory reaction to recover the emotional changes.

Among the spontaneously synchronized neuronal networks, the “task-negative” network and its “task-positive” anticorrelated network (ACN) have received the most attention.¹⁹ The task-negative network was the default-mode network (DMN). The IPC region, one key region of the DMN, is obligatorily or unintentionally engaged in the recall, consolidation, and retrieval of episodic memory information,^{39–41} as well as being implicated in diverse cognitive operations⁴² that include bodily awareness,⁴³ generating a sense of personal

responsibility⁴⁴ and moral decision making.⁴⁵ Chee and Chuah found that SD reduced the IPC deactivation during a visual short-term memory task.⁴⁶ Horovitz et al revealed a decreased functional connectivity between the IPC and the medial PFC during deep sleep and after partial SD.^{47,48} Nie et al found that patients with chronic insomnia demonstrated significantly decreased functional connectivity between the left medial temporal lobe and the left IPC compared with good sleepers.⁴⁹ De Havas et al also found that the IPC node of the DMN was consistently impaired and might represent an early marker for the effects of 24-hour SD, as well as serving as an indicator of hitherto-unexplored behavioral impairments.⁵⁰ Our results were in accordance with these findings. The DLPFC,

Table 1 ALFF differences between SD and NS conditions

Condition	Cluster	Brain region of peak coordinates	R/L	BA	Volume (mm ³)	t-score of peak voxel	MNI coordinates of peak voxel		
SD > NS	1	Cuneus	R	17, 18	4,185	9.6937	9	-87	21
SD < NS	2	Lentiform nucleus (putamen)	R	NA	621	-9.9864	15	9	0
SD < NS	3	Clastrum	R	NA	351	-7.5188	30	-6	18
SD < NS	4	Middle frontal gyrus	L	46	540	-6.9257	-33	21	42
SD < NS	5	Inferior parietal lobule	L	39	837	-6.8085	-48	-57	39

Notes: The statistical threshold was set at voxels with $P < 0.001$, cluster size with $P < 0.05$, and cluster volume ≥ 351 mm³ between SD and NS, corrected by AlphaSim.

Abbreviations: ALFF, amplitude of low-frequency fluctuation; SD, sleep deprivation; NS, normal sleep; NA, not applicable; R/L, right/left; BA, Brodmann's area; MNI, Montreal Neurological Institute.

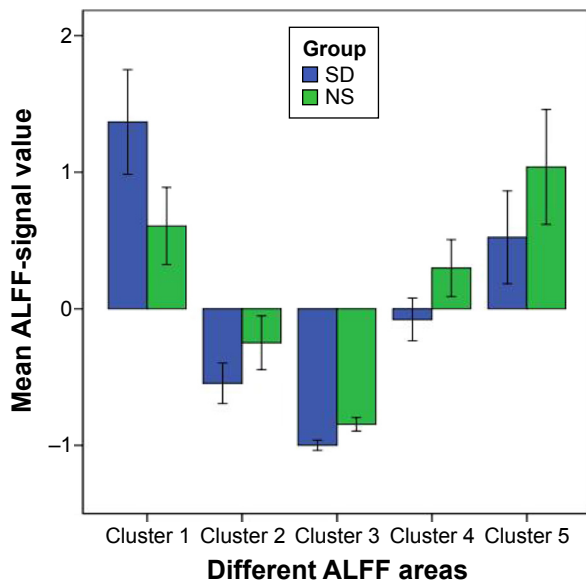


Figure 2 Mean ALFF-signal values of the altered regional brain areas.
Notes: Compared with the NS group, the SD group showed altered ALFF in the right cuneus (1.37±0.6 versus 0.61±0.45) and lower ALFF area in the right lentiform nucleus (-0.55±0.23 versus -0.25±0.31), right claustrum (-1±0.06 versus -0.85±0.08), left middle frontal gyrus (-0.08±0.25 versus 0.3±0.33), and left IPC (0.52±0.54 versus 1.04±0.66).
Abbreviations: ALFF, amplitude of low-frequency fluctuation; NS, normal sleep; SD, sleep deprivation; IPC, inferior parietal cortex.

one region of the ACN, recruits working-memory tasks, and has been implicated to be responsible for failure in working memory for the sleep-deprived brain.⁵¹⁻⁵⁴ It is well known that sleep plays an important role in the formation and consolidation of memories.⁵⁵ Patients with insomnia show significant reduction in gray-matter concentrations and lower

regional homogeneity in the DLPFC.^{28,56} One recent SD study reported a reduced anticorrelation between the DMN and ACN nodes at both task-related and resting states.⁵⁰ In support of these findings, in the present study we found that the SD subjects showed lower ALFF in the DMN and ACN nodes compared with NS subjects; furthermore, the mean ALFF value of the ACN node showed a significant positive correlation with response time ($r=0.675, P=0.016$). These findings may represent a decline in attention and memory processes by SD.

The lentiform nucleus and claustrum are associated with advanced cognitive function and involved in aberrant regional brain activity in patients with obstructive sleep apnea.⁵⁷ In the SD group, the mean ALFF value of the right claustrum showed a significant positive correlation with accuracy rate ($r=0.687, P=0.013$) and a negative correlation with lapse rate ($r=-0.706, P=0.01$). SD decreased the regional brain activity in several brain areas thus needs to attempt to recruit more specific advanced cognitive function brain areas to sustain alertness and accomplish cognitive performance. In this study, SD showed a continuing decline in the DMN-ACN activity, therefore, the lentiform nucleus and claustrum were recruited to sustain alertness and accomplish cognitive performance.

Conclusion

In this study, our results confirmed that SD demonstrated a compensatory reaction in the visual network and disturbed spontaneous neuronal activity in advanced cognitive function brain areas and the DMN-ACN compared with NS. The mean

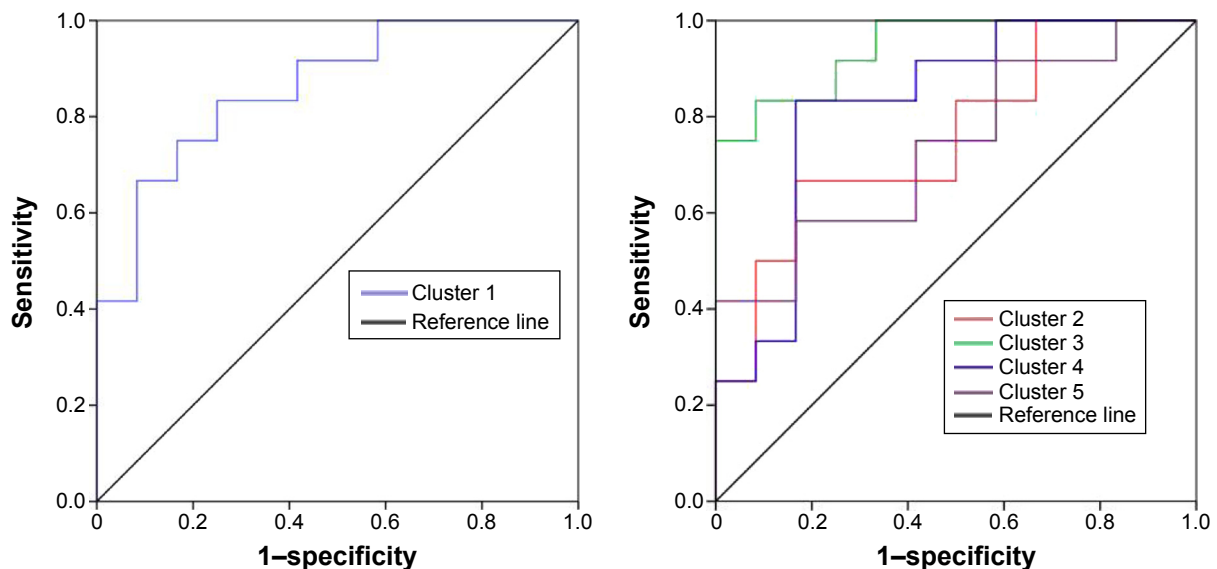


Figure 3 ROC curve of the mean ALFF value of the different brain areas.
Note: The different brain areas showed high sensitivity and specificity.
Abbreviations: ROC, receiver-operating characteristic; ALFF, amplitude of low-frequency fluctuation.

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ALFF-signal values of the different brain areas showed high sensitivity and specificity. Our findings provide insights into the pathophysiological mechanism of SD, and may be helpful for understanding the pathophysiology of SD.

Disclosure

The authors report no conflicts of interest in this work.

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