ORIGINAL RESEARCH

Abnormal functional connectivity density in sleep-deprived subjects

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Abstract

Sleep deprivation (SD) can alter the intrinsic brain functional organization. However, its effects on intrinsic low-frequency connectivity in the whole brain have not been well characterized. In this study, we used voxel-based functional connectivity density (FCD) analysis to investigate the effects of SD on the spontaneous functional organization of the brain. Thirty-seven healthy participants underwent this within-subject crossover functional magnetic resonance imaging (fMRI) study during rested wakefulness (RW) and after 36 h of total sleep deprivation (TSD). Decreased long-/short-range FCDs were observed in the posterior cingulate cortex, precuneus, inferior parietal lobule, dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and ventromedial prefrontal cortex. Increased long-/short-range FCDs were found in the sensory integration and arousal regulating areas, including the postcentral gyrus, thalamus, superior temporal gyrus, and occipital-temporal cortex. Moreover, a significant negative correlation was found between the short-range FCD of the PCC and the reaction time of Psychomotor Vigilance Task. In the present study, spontaneous functional organization with significant group-wise differences between RW and TSD sessions was identified. Our findings extend our understanding of the neural mechanism of how brain activity is altered in sleep-deprived individuals.

Keywords fMRI · Functional connectivity density · Resting state · Sleep deprivation

Introduction

Sleep deprivation (SD), commonly defined as staying awake for more than 24 h, could lead to a variety of cognitive deficits such as poor attention, executive function, and decision-making(Chee et al. 2010; Lei et al. 2016; Mu et al. 2005a; Namni Goel et al. 2009). A number of neuroimaging studies have examined the neurobiological correlates between sleep deprivation and impaired cognitive functions(Chee et al. 2010; Kong et al. 2014; Lei et al. 2016; Menz et al. 2012; Simon et al. 2015). However, the neural mechanism underlying the effects of sleep deprivation on cognitive functions still has yet to be elucidated.

Resting-state functional connectivity (rsFC) analysis is a powerful way to assess the spontaneous functional organization via functional connectivity, which measures the temporal correlation between the time series of the blood oxygen level–dependent (BOLD) signals of two brain regions. This technique offers a compelling paradigm for investigating cognitive dysfunction after sleep deprivation, suggesting that cognitive deficits induced by SD are characterized by multiple brain areas involving several distinct brain systems. Drummond and colleagues showed that a cortical network which was important for sustained attention was altered during sleep deprivation (Drummond et al. 2005). Large-scale brain network analysis revealed that SD was linked to reduced functional connectivity of main default mode network (DMN) and anti-correlation network (ACN) nodes

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during rest (De Havas et al. 2012; Lei et al. 2015; Sämann et al. 2010). Graph-based analysis demonstrated that the brain's small-worldness was significantly enhanced after sleep deprivation which could be regarded as a compensatory effect (Liu et al. 2014) and the modularity was impaired by sleep deprivation (Ben Simon et al. 2017). In addition, the rsFC was used to study the vulnerability of different people to sleep deprivation (Wang et al. 2015; Yeo et al. 2015). However, these studies have investigated the functional coupling within one or a limited few networks (e.g., the DMN, ECN), or a limited structural distance, and thereby the alterations in the whole brain network were overlooked.

In the present study, we used a functional connectivity density (FCD) (Tomasi and Volkow 2010) approach to measure the strength of intrinsic connectivity between one voxel and others within the whole brain. In contrast to other analysis method, FCD method is a voxel-wise and model-free approach to the measurement of rsFC. Greater FCD values for particular voxels indicate that those voxels are functionally connected to a greater number of other brain voxels and suggest that those voxels play more important roles during information processing. Based on neighboring relationships between brain voxels, the global FCD can be further divided into long- and short-range FCDs. The FCD analysis has been successfully used to examine the abnormal functional integration in neuropsychiatric patients, and demonstrated to reveal extra information which cannot be provided by rsFC analysis (Qin et al. 2015; Tomasi and Volkow 2012a, b).

In this study, we recruited 37 participants, and conducted a within-subject crossover study. The purpose of this work was to assess the effects of 36 h of total sleep deprivation (TSD) on spontaneous functional organization using whole brain FCD analysis.

Materials and methods

Participants

This study was approved by the Research Ethics Committee of the Military General Hospital of Beijing, and all experiments were performed in accordance with relevant guidelines and regulations. Thirty-seven participants were recruited through a web-based questionnaire who (1) were male; (2) were right-handed; (3) were between 18 and 28 years of age; (4) had habitually good sleeping habits (i.e., sleep no less than 6.5 h each night in the month before the study); and (5) had no diseases of the central and peripheral nervous systems, head trauma, cardiovascular diseases and/or hypertension, cataracts and/or glaucoma, pulmonary problems, and alcohol or drug abuse. Written informed consent according to the Declaration of Helsinki was obtained

from each of the participants after a complete description of the study. The participants (mean age of 23.1 ± 1.9 years, all males) were required to keep a regular sleep schedule and refrain from alcohol, caffeine, chocolate, and napping for 1 week before the study. Sleep diaries were required for all the participants 1 week before the study and during the 2-week duration of the study, in order to ensure that the volunteers went to sleep no later than 0:00 A.M., and woke no later than 9:00 A.M. Eleven of the study participants were excluded from the following neuroimaging analysis for extreme head movement (larger than 0.5 voxel) and behavioral data missing, leaving a final dataset of twenty-six participants.

Study procedure

Participants made three visits to the laboratory throughout the entire study. The first was a briefing session, during which the procedure and requirements of the study were explained to them. The subsequent two sessions (rested wakefulness [RW] and total sleep deprivation [TSD]) were counterbalanced across all the participants and separated by a minimum interval of 2 weeks to minimize the residual effects of TSD on cognition.

For the TSD session, participants arrived at the lab at 7:00 A.M after sleeping normally at home prior to the study and were monitored throughout the TSD session. The MRI scanning took place at 7:00 P.M. the next day, accumulating approximately 36–40 h of TSD before scanning. For the RW session, participants slept normally at home prior to scanning and were required to arrive at the laboratory at least 1 h before scanning, which took place at 7:00 P.M. The participants were then required to complete the behavioral tasks before entering the scanning room. In the TSD session, participants were tested two at a time, and were monitored 24 h a day by nursing staff to keep them awake throughout the TSD session. Three meals a day were provided by our nutritionist. Participants completed a 5-min Psychomotor Vigilance Task (PVT) and a Likert-type rating scale (0–10) of sleepiness every 4 h to measure their alertness. For the remaining time, the participants were allowed to engage in some nonstrenuous activities such as reading and talking with others in the laboratory illuminated with standard office lighting (~ 500 lx).

MRI acquisition

MRI acquisition was conducted at the Military General Hospital of Beijing in China on a GE 3.0T Discovery 750 scanner (General Electric Medical System, Milwaukee, WI) using an eight-channel head coil. The whole MRI scanning included an anatomical scan, a resting-state fMRI scan, a balloon analogue risk task (BART) scan, and

a diffusion tensor imaging scan. The neural correlates of altered risk-taking propensity in sleep-deprived individuals based on the BART data has been previously reported in another study (Lei et al. 2016). In the resting-state scan session, a gradient echo-planar imaging sequence was used to collect 240 functional volumes with the following parameters: repetition time (TR), 2000 ms; echo time (TE), 30 ms; field of view (FOV), 240×240 mm; slice thickness, 3 mm; slice gap, 1 mm; flip angle (FA), 90°; matrix size, 64×64; 35 oblique slices parallel to the AC-PC line were acquired with interleaved acquisition. High-resolution T1-weighted anatomical images were acquired using a sagittal FSPGR-BRAVO sequence with the following parameters: TR, 8.208 s; inversion time (TI), 450 ms; TE, 3.22 ms; FA, 12°; FOV, 240×240 mm; voxel size, 0.5 mm $\times 0.5$ mm $\times 1$ mm.

Participants were required to relax and remain still in the scanner with their heads comfortably restrained to reduce head movement. They were instructed to keep their eyes open and focus on a fixation cross during the scan. In addition, an MRI-compatible camera system was used during the scanning to make sure the participants did not fall asleep.

Image preprocessing

Functional images were preprocessed using Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh. nih.gov/afni/). For each participant, the first five volumes were discarded to allow for the equilibration of the magnetic resonance imaging signal and subjects' adaptation to the scanning environment. Then, the data were corrected for slice acquisition time differences, realigned to the first volume of each participant for head movement, and normalized to the standard Montreal Neurological Institute (MNI) space with a resampled resolution of $3 \times 3 \times 3$ mm^3. A set of regressors, including the signal averaged over the white matter mask, cerebrospinal fluid mask, and six motion vectors (3 translations and 3 rotations) and their first derivatives, were regressed out of the BOLD time series. Finally, a band-pass filter was applied to maintain only low frequency fluctuations between 0.015 and 0.1 Hz.

Since functional connectivity is particularly sensitive to head motion, the frame-wise displacement (FD), which represents the scalar quantity of instantaneous head motion of each volume relative to its earlier neighboring volume, was also calculated based on the head motion parameters (Power et al. 2012). Then, a "scrubbing" method was used to remove image time points that could be severely contaminated with motion (Power et al. 2012). For this purpose, the root mean square variance across voxels (DVARS) of the difference in %BOLD intensity was also computed. Then, images with

$FD_i > 0.5$ mm and $DVARS_i > 0.5\%$ were considered potentially contaminated with motion artifacts and excluded from the time series (Power et al. 2012).

FCD calculation

The long-/short-range FCD was calculated for each voxel using an in-house script written on Linux platform based on the method described by Tomasi and Volkow (2010). The global FCD was first computed based on Pearson correlation of two voxels. According to previous work (Tomasi and Volkow 2011a, b), threshold of correlation (TC) < 0.4 leads to increased false positive rate and increased CPU time to compute the maps and that TC > 0.7 leads to short-FCD maps with lower sensitivity due to reduced dynamic range. Therefore, two voxels were considered functionally connected if their Pearson correlation coefficient was greater than 0.6. The global FCD of a given voxel was defined as the number of functional connections between this voxel and all other voxels in the brain.

The short-range FCD of voxel x_0 was generated by the following algorithm: (1) calculated functional connectivity between x_0 and all of its directly neighbors, and each of the neighbors (x_i) was counted as a neighboring voxel if the functional connectivity between x_0 and x_i was greater than 0.6; (2) calculated the functional connectivity between x_0 and each voxel (x_j) that directly neighboring with x_i but not with x_0; (3) for each x_j, if the functional connectivity was greater than 0.6, it was counted as a neighboring voxel with x_0; (4) repeated this search algorithm until no further voxels could be added. Long-range FCD was calculated as the global FCD minus the short-range FCD and thus reflected the number of non-neighboring voxels of x_0 that were functionally connected to x_0.

For standardization purposes to increase the normality, the long-/short-range FCDs of each voxel was divided by the global mean of the whole brain FCDs of each participant. Finally, the normalized FCDs were spatially smoothed using a Gaussian kernel of full-width at half-maximum (FWHM) of 6 mm.

Statistical analysis

A voxel-wise paired two-sample t-test was performed on the normalized FCD data to test the group differences between RW and TSD sessions. All statistical images were thresholded with a significance level of $p < 0.005$, and corrected for multiple comparison using the 3dClust-Sim method in AFNI (cluster size > 303 voxels). Intrinsic smoothness of the data was estimated by the 3dFWHMx tool in AFNI. To investigate the relationship between alertness and the FCDs, voxel-wise correlation of the

whole brain (Pearson correlation coefficient) was computed between the SD-induced changes of long-/short-range FCDs and the changed RT of PVT after SD.

Results

Behavioral results

The sleepiness score indicated that participants were significantly sleepier after 36 h of TSD (Sleep $Score_{RW} = 2.2 \pm 0.9$, Sleep $Score_{TSD} = 4.27 \pm 1.54$; paired two sample t-test, $p < 0.001$). TSD also increased the response time (RT) of the PVT, indicating that sleep deprivation could reduce the vigilance of participants ($RT_{RW} = 330.0 \pm 30.6$ ms, $RT_{TSD} = 373.6 \pm 73.2$ ms, paired two sample t-test, $p = 0.004$). No significant differences were found in head movement between the RW and the TSD conditions (paired two-sample t-test, $p > 0.05$) (Table 1).

Spatial distribution of the FCDs in RW and TSD sessions

The FCD patterns in both RW and TSD sessions were bilateral. For participants in RW session, the long-/short-range FCDs were greatest in the posterior cingulate cortex (PCC), precuneus, medial occipital cortex, and inferior parietal lobe (IPL). Relatively greater FCDs were also observed in the medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), and postcentral gyrus (PostCG). In contrast, the FCDs were weaker in the ventral temporal cortex, insula and dorsal anterior cingulate cortex (dACC) (Fig. 1).

In TSD session, the long-/short-range FCDs were greatest in the PostCG, superior temporal cortex (STG), and thalamus. Relatively greater FCDs were observed in the PCC, precuneus, and DLPFC. In contrast, the FCDs were weaker in ventral temporal cortex, insula, and dACC (Fig. 1).

Differences in the FCDs between the RW and TSD sessions

Compared with participants in RW session, the sleep-deprived participants exhibited greater long-/short-range

Table 1 Behavioral data about the participants

	RW(std)	TSD(std)	p value (paired t-test)
Sleep score	2.2(0.9)	4,27(1.54)	< 0.001
RT of PVT (ms)	330(30.6)	373.6(73.2)	0.004
Head motion (mm)	0.79(0.51)	1.0(0.64)	0.1
Censored time points	234(5.1)	231(6.4)	0.076

Fig. 1 Spatial distributions of the averaged long- and short-range FCDs. Threshold used to compute long- and short-range FCD: R > 0.6. The color bar represents the normalized FCD value; that is, the average number of functional connections per voxel (k) divided by the grand mean of the whole brain of each subjects (k_0)
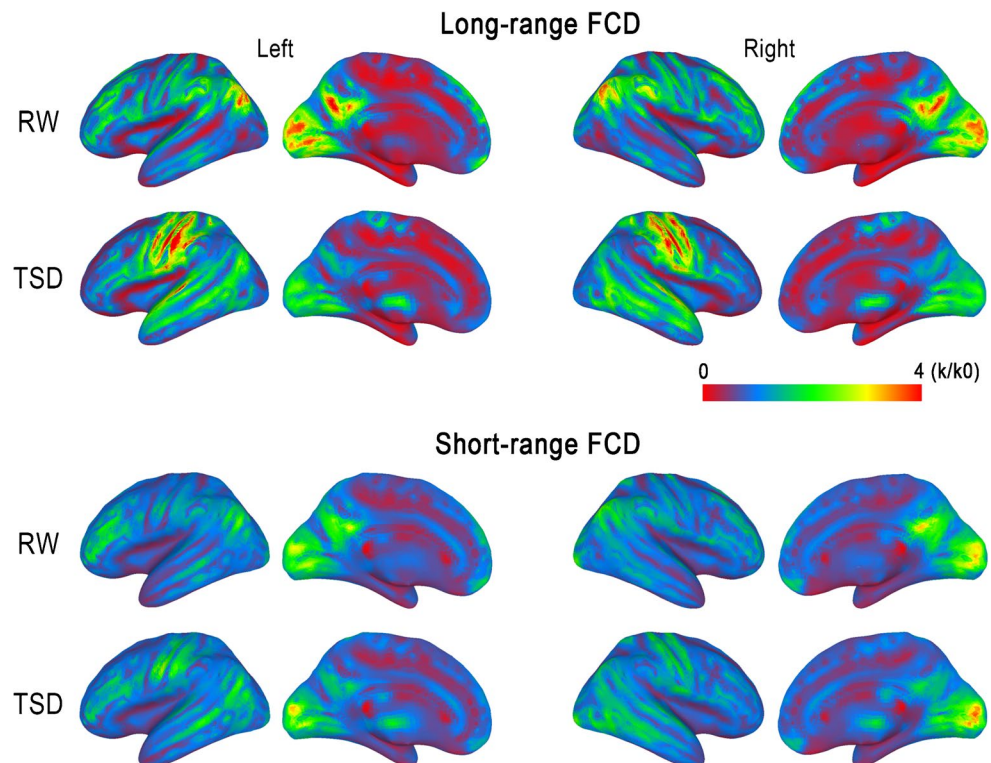
FCDs in the PostCG, thalamus, STG, and occipital-temporal cortex (paired two sample t-test, $p < 0.005$, 3dClustSim corrected). Significantly reduced long-/short-range FCDs were found in the PCC, precuneus, IPL, DLPFC, dorsal medial prefrontal cortex (DMPFC), and ventromedial prefrontal cortex (VMPFC) (paired two sample t-test, $p < 0.005$, 3dClustSim corrected) (Fig. 2).

Correlation results

We conducted a whole brain correlation analysis between the long-/short-range FCDs and the RT of the PVT. No brain regions exhibited a significant correlation between the changes of long-range FCD and the changes of the RT of PVT. A negative correlation was found between the changes of short-range FCD of PCC and the changes of the RT of PVT ($r = -0.55$, $p = 0.0035$) (Fig. 3).

Discussion

The current study investigated the alterations of functional organization induced by 36 h of total sleep deprivation using a recently developed FCD method. We found that long-/short-range FCDs were significantly reduced in a wide range of brain areas after 36 h of sleep deprivation, including the PCC, precuneus, IPL, DLPFC, DMPFC, and VMPFC; besides, greater long-/short-range FCDs were observed in the PostCG, thalamus, STG, and occipital-temporal cortex after TSD. Furthermore, the decreased short-range FCD of the PCC significantly correlated with the increased reaction time of PVT after TSD.

Using the FCD method, we identified the posterior cingulate/ventral precuneus, parietal cortices, and occipital cortices as the core regions in the intrinsic functional architecture, consistent with previous studies (Tomasi et al.

Fig. 2 Group differences in long- and short-range FCDs between TSD and RW. The color bar indicates the t values
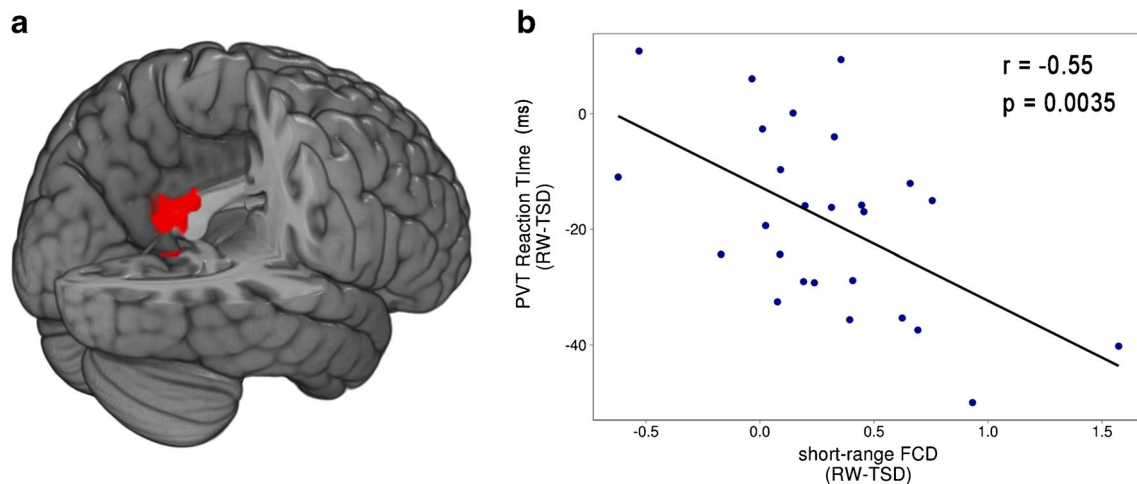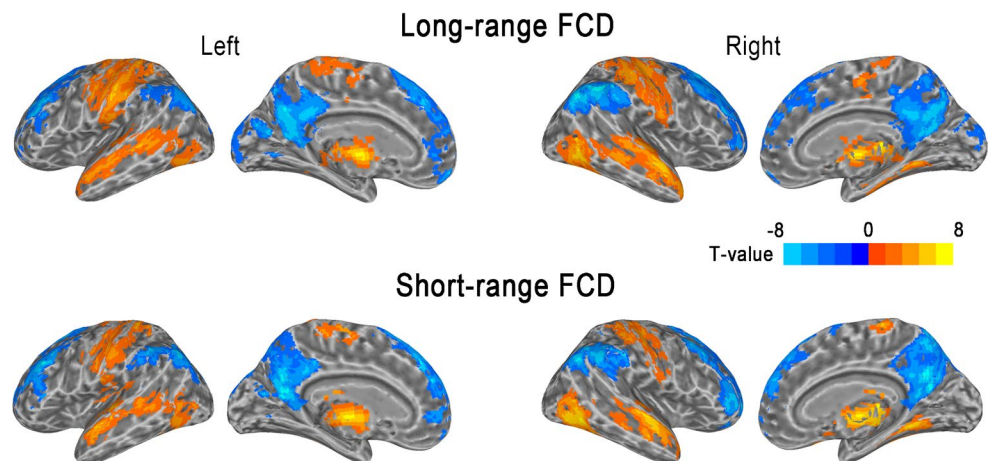
Fig. 3 Correlation between short-range FCD and the reaction time of the PVT. There is a significant negative correlation between the changes of short-range FCD of PCC and the changes of reaction time of PVT

2015; Tomasi and Volkow 2010, 2012c). The similarity of these results suggested that resting-state connectivity analysis could provide a reliable measure for the organization of functional network. Further group comparison showed that the total sleep deprivation exhibited a decreased long-/short-range FCDs in the PCC, precuneus, IPL, DLPFC, DMPFC, and VMPFC. Among these regions, we noted that PCC/precuneus is thought to comprise the functional core of DMN, and additional evidences from PET studies also showed that the metabolic activity in the PCC/precuneus was higher, requiring ~ 35% more glucose than any other regions in the human brain (Fransson and Marrelec 2008; Raichle et al. 2001; Utevsky et al. 2014); besides, the PCC/precuneus showed greater activation during episodic and autobiographical memory tasks (Addis et al. 2004; Lundstrom et al. 2005), suggesting a key role of PCC/precuneus in higher cognitions. As the PCC/precuneus, IPL, and VMPFC all belong to the DMN, which is important for the conscious awareness of the self (Raichle 2015), we demonstrated that sleep deprivation could significantly reduce the interregional and intraregional activity within DMN nodes. In addition, the negative correlation between the changed reaction time of PVT after sleep deprivation and the changes of short-range FCD in PCC indicated that short-range FCD in PCC might be a sensitive biomarker for different vigilance state.

Several neuroimaging studies have revealed that DLPFC, VMPFC, and DMPFC are involved in multiple higher cognitive functions (Bembich et al. 2014; Charroud et al. 2015; Du Boisgueheneuc et al. 2006; Japee et al. 2015; Schilling et al. 2013). DLPFC significantly contributes to a wide range of executive functions, including working memory, action planning, and abstract reasoning. DMPFC and VMPFC play fundamental roles in reward learning, decision making, value-based evaluation, and self-control. Early PET studies showed significant declines in prefrontal metabolic activity during sleep deprivation (Thomas et al. 2000). Recently, several fMRI studies found reduced activation in prefrontal cortex after sleep deprivation during a large amount of higher cognitive tasks, including working memory (Mu et al. 2005a, b), visual tracking task (Tomasi et al. 2009), go/no-go task (Chuah et al. 2006). Therefore, the reduced long-/short-range FCDs after sleep deprivation were consistent with previous studies, indicating deficits of both interregional and intraregional functional connections in the prefrontal cortex after sleep deprivation. In summary, the decreased long-/short-range FCDs in prefrontal cortex provided additional neuroimaging evidences for the deficits of higher cognitive functions after sleep deprivation.

Another interesting finding of this study was the increased long-/short-range FCDs in a wide range of brain areas including the PostCG, thalamus, STG, and occipital-temporal cortex. Recent studies have demonstrated the multisensory integration function of STG. The thalamus is a vital region in integrating neural activity from widespread neocortical inputs and outputs, and is thought to play an important role in regulating state of sleep and wakefulness. The PostCG is the primary somatosensory cortex. In sum, we demonstrated that sleep deprivation resulted in an increased long-/short-range FCDs in areas critical for sensory processing and regulating arousal. Previous PET studies have revealed that sleep deprivation could change the metabolic rate of glucose (CMRGlu) with increasing metabolic rate in the visual cortex (Wu et al. 1991), somatosensory cortex, occipital cortex, lingual, and fusiform gyrus (Thomas et al. 2003). Specifically, these changes were much higher after 48 and 72 h than that of after 24 h SD (Thomas et al. 2000). As previous studies demonstrated decreased metabolic rate of CMRGlu in thalamus, basal ganglia, and cerebellum (Thomas et al. 2000), we suggested that the increased long-/short-range FCDs implicated the brain's exertion of voluntary control to remain awake and performance. Furthermore, the increase in these regions could be considered as a compensatory effect to sustain alertness and cognitive performance despite a continuing decline of activity in the higher cognition related areas.

When a person remains awake longer, the biological pressure for sleep will become stronger. According to an energy allocation model, during prolonged sleep deprivation, the limited energy resources including cognitive resources will be optimally allocated for survival (Schmidt 2014). Since sensory input is central to survival, the present study provided additional neuroimaging evidences that with the homeostatic pressure for sleep increased, the long-/short-range FCDs in the high-order cognition related areas decreased while the FCDs increased in sensory and arousal related areas to compensate for the effects of sleep loss on alertness and vigilance. In other words, the changed long-/short-range FCDs in a large amount of brain areas after TSD revealed a biased resource allocation in the brain, proving that homeostatic process for survival was the priority during sleep deprivation.

This study had several limitations. First, due to the experimental conditions and the long time needed to complete this experiment, female subjects were excluded from this study. Therefore, generalizing this study to women should be restricted, as gender difference has been found in the brain's FCD map (Tomasi and Volkow 2012b). It would be interesting to further investigate gender differences in SD-induced alterations of long-/short-range FCDs. Second, we interpreted our findings under the assumption that participants under both the RW and TSD states responded similarly to the scanning environment. However, it is possible that the participants experienced higher anxiety levels during the scan after TSD, and this could potentially contribute to the different connectivity patterns that we observed. Third, global signal might be another potential source of variability

in long-/short-range FCDs. In the present study, the global signal was not removed during preprocessing steps considering that it is composed of both neural and non-neural signals (Murphy and Fox 2017). However, global signal regression still has several advantages including improved specificity of positive correlations and removal of motion, cardiac and respiratory signals. Thus, the global signal might decrease the signal-to-noise ratio of the data. Finally, in future studies, the physiological data should be recorded and used as covariates to rule out their effect in brain activity.

In conclusion, the sleep-deprived participants showed reduced long-/short-range FCDs in a wide range of brain areas important for self-awareness processing, executive function, and decision making. The increased long-/short-range FCDs in participants after sleep deprivation exhibited in areas which were important for sensory integration and regulating arousal, indicating that it may be regarded as a compensatory effect for maintaining awake and alert against the homeostatic driving for sleep. The present study extends our understanding of the neural mechanism of how brain activity is altered in sleep-deprived individuals.

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Addis, D. R., McIntosh, A. R., Moscovitch, M., Crawley, A. P., & McAndrews, M. P. (2004). Characterizing spatial and temporal features of autobiographical memory retrieval networks: a partial least squares approach. *Neuroimage, 23*(4), 1460–1471.

Bembich, S., Clarici, A., Vecchiet, C., Baldassi, G., Cont, G., & Demarini, S. (2014). Differences in time course activation of dorsolateral prefrontal cortex associated with low or high risk choices in a gambling task. *Frontiers in Human Neuroscience, 8*, 464.

Ben Simon, E., Maron-Katz, A., Lahav, N., Shamir, R., & Hendler, T. (2017). Tired and misconnected: a breakdown of brain modularity following sleep deprivation. *Human Brain Mapping, 38*(6), 3300–3314.

Charroud, C., Steffener, J., Le Bars, E., Deverdun, J., Bonafe, A., Abdennour, M., et al. (2015). Working memory activation of neural networks in the elderly as a function of information processing phase and task complexity. *Neurobiology of Learning and Memory, 125*, 211–223.

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.

Chuah, Y. M. L., Venkatraman, V., Dinges, D. F., & Chee, M. W. L. (2006). The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 26*(27), 7156–7162. https://doi.org/10.1523/JNEUROSCI.0906-06.2006.

De Havas, J. A., Parimal, S., Soon, C. S., & Chee, M. W. L. (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-New York Then Westchester-, 28*(9), 1059.

Du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., et al. (2006). Functions of the left superior frontal gyrus in humans: a lesion study. *Brain, 129*(12), 3315–3328.

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. *Neuroimage, 42*(3), 1178–1184.

Japee, S., Holiday, K., Satyshur, M. D., Mukai, I., & Ungerleider, L. G. (2015). A role of right middle frontal gyrus in reorienting of attention: a case study. *Frontiers in Systems Neuroscience, 9*, 23.

Kong, D., Asplund, C. L., & Chee, M. W. L. (2014). Sleep deprivation reduces the rate of rapid picture processing. *Neuroimage, 91*, 169–176.

Lei, Y., Shao, Y., Wang, L., Zhai, T., Zou, F., Ye, E., et al. (2015). Large-scale brain network coupling predicts total sleep deprivation effects on cognitive capacity. *PLOS ONE, 10*(7), e0133959. https://doi.org/10.1371/journal.pone.0133959.

Lei, Y., Wang, L., Chen, P., Li, Y., Han, W., Ge, M., et al. (2016). Neural correlates of increased risk-taking propensity in sleep-deprived people along with a changing risk level. *Brain Imaging and Behavior*. https://doi.org/10.1007/s11682-016-9658-7.

Liu, H., Li, H., Wang, Y., & Lei, X. (2014). Enhanced brain small-worldness after sleep deprivation: a compensatory effect. *Journal of Sleep Research, 23*(5), 554–563. https://doi.org/10.1111/jsr.12147.

Lundstrom, B. N., Ingvar, M., & Petersson, K. M. (2005). The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *Neuroimage, 27*(4), 824–834.

Menz, M. M., Buchel, C., & Peters, J. (2012). Sleep deprivation is associated with attenuated parametric valuation and control signals in the midbrain during value-based decision making. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3553-11.2012.

Mu, Q., Mishory, A., Johnson, K. A., Nahas, Z., Kozel, F. A., Yamanaka, K., et al. (2005a). Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. *Sleep, 28*(4), 433–446.

Mu, Q., Nahas, Z., Johnson, K. A., Yamanaka, K., Mishory, A., Koola, J., et al. (2005b). Decreased cortical response to verbal working memory following sleep deprivation. *Sleep, 28*, 55–67.

Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *NeuroImage, 154*(2016), 169–173. https://doi.org/10.1016/j.neuroimage.2016.11.052.

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

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage, 59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018.

Qin, W., Xuan, Y., Liu, Y., Jiang, T., & Yu, C. (2015). Functional connectivity density in congenitally and late blind subjects. *Cerebral Cortex, 25*(9), 2507–2516. https://doi.org/10.1093/cercor/bhu051.

Raichle, M. E. (2015). The restless brain: how intrinsic activity organizes brain function. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 370*(1668), 20140172. https://doi.org/10.1098/rstb.2014.0172.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, 98*(2), 676–682.

Sämann, P. G., Tully, C., Spoormaker, V. I., Wetter, T. C., Holsboer, F., Wehrle, R., & Czisch, M. (2010). Increased sleep pressure reduces resting state functional connectivity. *Magma (New York, N.Y.), 23*(5–6), 375–389. https://doi.org/10.1007/s10334-010-0213-z.

Schilling, C., Kühn, S., Paus, T., Romanowski, A., Banaschewski, T., Barbot, A., et al. (2013). Cortical thickness of superior frontal cortex predicts impulsiveness and perceptual reasoning in adolescence. *Molecular Psychiatry, 18*(5), 624–630.

Schmidt, M. H. (2014). The energy allocation function of sleep: a unifying theory of sleep, torpor, and continuous wakefulness. *Neuroscience and Biobehavioral Reviews, 47C*, 122–153. https://doi.org/10.1016/j.neubiorev.2014.08.001.

Simon, E. B., Oren, N., Sharon, H., Kirschner, A., Goldway, N., Okon-Singer, H., et al. (2015). Losing neutrality: the neural basis of impaired emotional control without sleep. *Journal of Neuroscience, 35*(38), 13194–13205. https://doi.org/10.1523/JNEUROSCI.1314-15.2015.

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., et al. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. *Journal of Sleep Research, 9*(4), 335–352.

Thomas, M. L., Sing, H. C., Belenky, G., Holcomb, H. H., Mayberg, H. S., Dannals, R. F., et al. (2003). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research, 9*(4), 335–352.

Tomasi, D., & Volkow, N. D. (2010). Functional connectivity density mapping. *Proceedings of the National Academy of Sciences of the United States of America, 107*(21), 9885–9890. https://doi.org/10.1073/pnas.1001414107.

Tomasi, D., & Volkow, N. D. (2011a). Functional connectivity hubs in the human brain. *NeuroImage, 57*(3), 908–917. https://doi.org/10.1016/j.neuroimage.2011.05.024.

Tomasi, D., & Volkow, N. D. (2011b). Association between functional connectivity hubs and brain networks. *Cerebral Cortex, 21*(9), 2003–2013. https://doi.org/10.1093/cercor/bhq268.

Tomasi, D., & Volkow, N. D. (2012a). Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 71*(5), 443–450. https://doi.org/10.1016/j.biopsych.2011.11.003.

Tomasi, D., & Volkow, N. D. (2012b). Gender differences in brain functional connectivity density. *Human Brain Mapping, 33*(4), 849–860. https://doi.org/10.1002/hbm.21252.

Tomasi, D., & Volkow, N. D. (2012c). Laterality patterns of brain functional connectivity: gender effects. *Cerebral Cortex (New York, N.Y.: 1991), 22*(6), 1455–1462. https://doi.org/10.1093/cercor/bhr230.

Tomasi, D., Wang, R. L., Telang, F., Boronikolas, V., Jayne, M. C., Wang, G.-J., et al. (2009). Impairment of attentional networks after 1 night of sleep deprivation. *Cerebral Cortex (New York, N.Y.: 1991), 19*(1), 233–240. https://doi.org/10.1093/cercor/bhn073.

Tomasi, D., Shokri-Kojori, E., & Volkow, N. D. (2015). High-resolution functional connectivity density: hub locations, sensitivity, specificity,reproducibility, and reliability. *Cerebral Cortex, 200*, bhv171. https://doi.org/10.1093/cercor/bhv171.

Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus is a functional core of the default-mode network. *The Journal of Neuroscience, 34*(3), 932–940.

Wang, Y., 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.

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., & Hershey, T. (1991). The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. *Sleep: Journal of Sleep Research & Sleep Medicine.*

Yeo, B. T. T., Tandi, J., & Chee, M. W. L. (2015). Functional connectivity during rested wakefulness predicts vulnerability to sleep deprivation. *NeuroImage, 111*, 147–158. https://doi.org/10.1016/j.neuroimage.2015.02.018.