Editorial

Imaging homeostatic sleep pressure and circadian rhythm in the human brain

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It is well-known that our sleep-wake patterns and alertness level during wakefulness are mainly modulated by two interactive processes, a homeostatic sleep debt process (S) refers to the drive for sleep that increases as a saturating exponential when we stay awake and decreases exponentially when we sleep, and a circadian processes (C) refers to the internal oscillatory rhythm that runs about 24 hours and can be reset by the environmental light (1-3). Although the detrimental effects of prolonged wakefulness with accumulative sleep debt after sleep deprivation on cognitive performances have been well documented in numerous studies (4-8), sleep duration continues decreasing in the modern societies and hundreds of millions of people does not have sufficient sleep due to life styles, family demands, and/or medical situations (9,10). A meta-analysis on 70 behavioral experiments and 147 cognitive tests has revealed that vigilance or sustained attention, which can be precisely measured by the psychomotor vigilance test (PVT), is the most significantly impaired cognitive function domain affected by sleep deprivation (6). Behavioral studies have further shown that circadian dynamics interact with sleep debt and modulate cognitive performance after sleep loss (11-14). Specifically, previous studies have demonstrated that sleep deprivation impaired vigilant attention most prominently during circadian night, the accumulative neurobehavioral deficits reached largest on the morning, and became progressively smaller across the hours of the day, particularly on the late afternoon and early evening, which may reflect a period of relatively protected alertness from circadian rhythm during prolonged wakefulness.

The negative effects of homeostatic sleep debt on brain function have also been well demonstrated by numerous sleep deprivation studies using various experimental paradigms and different neuroimaging techniques, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These studies have demonstrated that sleep loss not only impairs brain activations during various cognitive tasks (5,14-16), but also alters functional connectivity at resting state without task demands (17-20). A recent meta-analysis study on 11 sleep deprivation studies across different attention tasks revealed significantly decreased activation in the frontoparietal attention network and salience network, and increased activation in the thalamus after acute total sleep loss (21).

Due to the high-demanding workloads, transdisciplinary expertise, and expensive research costs associated with brain imaging studies of sleep deprivation, most previous studies only measured brain activation or connectivity changes at one time point of the circadian cycle after sleep loss as compared to those at a similar time point following normal sleep, therefore wiped off the potential influence of circadian rhythm on brain function. Currently, a small number of neuroimaging studies have examined the effects of time-of-day on brain activation patterns in response

to different cognitive tasks, including autobiographic memory (22), visual processing (23), conflict processing (24), executive attention (25,26), and working memory (27). However, these studies usually measured brain function at two time points of circadian phase and did not combine with sleep deprivation, therefore were still unable to demonstrate the time course of brain function changes across a full cycle of circadian rhythm.

In a very interesting paper published in a recent issue of SCIENCE (28), Muto and colleagues employed a repeated fMRI design and studied brain function changes in a cohort of 33 healthy volunteers who stayed awake for a 42-hour period under constant environmental and behavioral conditions. This in order to address this important yet largely neglected question about how brain function varies with the dynamic phase of circadian rhythm and the buildup of homeostatic sleep pressure. In this study, brain activation and behavioral responses to the PVT were repeatedly assessed in 12 fMRI sessions during 42 hours of wakefulness including a full cycle of circadian rhythm, and were realigned to the dim-light melatonin secretion onset (DLMO) to determine the corresponding circadian phase. An additional fMRI session was also acquired after a night of 12-hour recovery sleep. Two sophisticated analysis were conducted. The first one did not use the actual time courses of circadian rhythm but assumed that regional brain activation fluctuated as a sine wave. Not surprisingly, this analysis revealed significant circadian modulation in a large set of cortical regions. However, the phase of regional brain responses relative to DLMO varied across cortical and subcortical areas, with earliest phase observed in the amygdala and latest phase found in the inferior prefrontal cortex. The second analysis modeled homeostatic sleep pressure as monotonically decreasing with elapsed time awake and increasing after recovery sleep, and examined whether PVT brain responses were modulated by sleep pressure and how sleep pressure and circadian rhythm interact in the brain. This analysis found a significant negative effect of sleep debt in a large set of high-order association cortical areas in the frontal, parietal, visual, sensorimotor, insular, and cingulate cortices, while the main effect of circadian rhythm were found in much fewer cortical areas and a number of subcortical areas. In addition, significant interactions between homeostatic sleep pressure and circadian rhythm were observed in the occipital poles and thalamic areas. Finally, as expected, brain responses and cognitive performance returned to baseline after the recovery sleep.

This study by Muto and colleagues offers an example using non-invasive neuroimaging technique for simultaneous assessment of homeostatic sleep pressure and circadian rhythm modulation in the human brain. As commented by Czeisler (29), this study may open new doors for research on a broad range of basic questions in the sleep and circadian field, such as the role of melatonin in mediating the effects of circadian rhythm on brain responses, and the mechanisms underlying longitudinal changes in sleep/wake pattern and circadian rhythm during brain development. The study paradigm and imaging techniques in this research can also be applied for clinical research on many psychiatric and neurologic disorders in which disrupted sleep and circadian rhythm are common co-morbidities, such as alcoholism, depression, schizophrenia, and neurodegenerative diseases. However, it is noteworthy to point out a couple of important limitations in this study which have implications for future research.

The first limitation is the relatively small number of sample size. There were 33 subjects involved in this study, which is not a large sample that can be used to characterize individual differences in the magnitude of sleepiness and cognitive performance deficits after sleep loss and cross the circadian cycle. Health individuals differ in their preferred sleep-wake times and dynamics of homeostatic sleep pressure, which can be classified as different chronotypes (i.e., early/morning-type or late/evening-type) (30). Moreover, while most individuals show substantial cognitive deficits and drowsiness without sufficient sleep, some adults can maintain alertness and display little cognitive changes during sleep deprivation (31). Previous studies have indicated that differential vulnerability to sleep deprivation and chronotype both significantly modulate cognitive performance and brain activation patterns (16,26,27,32). It will be of great interest to demonstrate how time courses of brain responses during circadian rhythm varied in individuals with different chronotype and sleep deprivation vulnerability.

Another limitation is the conventional blood oxygen level dependent (BOLD) fMRI used to measure brain responses to the PVT and n-back tasks in this study. As an index reflecting a complex interaction among a number of physiological variables including cerebral blood flow (CBF), cerebral blood volume, and cerebral oxygenation metabolic rate, task-related BOLD fMRI only measures relative signal changes between different events (e.g., fastest *vs.* slow reaction times) or task conditions (e.g., 3-bask *vs.* 0-back), therefore is not able to provide absolute quantification of brain activity. In addition, due to low frequency noise in the BOLD signal, task-related BOLD fMRI has poor sensitivity

to track slow neural activity changes over a time scale longer than a few minutes (33). These unfavorable characteristics of BOLD signal make it very difficult or sometimes misleading when drawing conclusions for the observed brain activation changes, particularly for sleep deprivation and circadian studies which involve slow neural activity changes over hours and days. For example, the meta-analysis on sleep deprivation and attention fMRI studies revealed significantly increased activation in the thalamus (21), which was also observed in the Muto *et al.* study. However, it is impossible for these studies to dissociate the effects of sleep deprivation or circadian rhythm on brain function per se from the effects of sleep deprivation or circadian rhythm on task performance that contaminates the observed brain activation differences. Consequently, it is hard for these studies to conclude if increased thalamic activation following sleep deprivation reflects increased activity during task performance, or decreased activity during resting baseline or control condition, or some combination of both. In fact, increased thalamic activation contradicts with reduced alertness level and vigilance performance after sleep loss in behavioral observations (4-6) and is opposite to decreased thalamic metabolism reported in PET studies (34-36). It is likely that increased thalamic activation may reflect a complex interaction between the de-arousing effects of sleep loss and the arousing effects of task performance (21). Future studies using more quantitative imaging techniques, such as arterial spin labeling fMRI (37-40), which offers absolute quantification of regional cerebral blood flow (CBF, in units of mL/min/100 g tissue) that is tightly coupled with brain metabolism, are necessary to verify the finding from this study and further dissociate the potential differential effects of sleep deprivation and circadian rhythm on brain activity during task performance and at resting baseline. Nevertheless, findings from the Muto *et al.* study provide new insights into an understanding of brain mechanisms underlying homeostatic sleep pressure, circadian rhythm, and the interactions between these two essential processes in our life.

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Footnote

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References

1. Borbély AA. A two-process model of sleep regulation. Hum Neurobiol 1982;1:195-204.
2. Daan S, Beersma DG, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 1984;246:R161-83.
3. Achermann P, Borbély AA. Simulation of daytime vigilance by the additive interaction of a homeostatic and a circadian process. Biol Cybern 1994;71:115-21.
4. Lim J, Dinges DF. Sleep deprivation and vigilant attention. Ann N Y Acad Sci 2008;1129:305-22.
5. Goel N, Rao H, Durmer JS, et al. Neurocognitive consequences of sleep deprivation. Semin Neurol 2009;29:320-39.
6. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. Psychol Bull 2010;136:375-89.
7. Kerkhof GA, Van Dongen HP. Effects of sleep deprivation on cognition. Human sleep and cognition: basic research 2010;185:105.
8. Basner M, Rao H, Goel N, et al. Sleep Deprivation and Neurobehavioral Dynamics. Current Opinion in Neurobiology 2013;23:854-63.
9. Basner M, Spaeth AM, Dinges DF. Sociodemographic characteristics and waking activities and their role in the timing and duration of sleep. Sleep 2014;37:1889-906.
10. Ford ES, Cunningham TJ, Croft JB, et al. Trends in self-reported sleep duration among US adults from 1985 to 2012. Sleep 2015;38:829-32.
11. Mollicone DJ, Van Dongen HPA, Rogers NL et al. Response surface mapping of neurobehavioral performance: testing the feasibility of split sleep schedules for space operations. Acta Astronaut 2008;63:833-40.
12. Cohen DA, Wang W, Wyatt JK, et al. Uncovering residual effects of chronic sleep loss on human performance. Sci Transl Med 2010;2:14ra3.
13. Zhou X, Ferguson SA, Matthews RW, et al. Sleep, wake and phase dependent changes in neurobehavioral function under forced desynchrony. Sleep 2011;34:931-41.
14. Goel N, Basner M, Rao H, et al. Circadian rhythms, sleep deprivation, and human performance. Prog Mol Biol

Transl Sci 2013;119:155-90.
15. Chee MWL, Chuah LYM. Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. Curr Opin Neurol 2008;21:417-23.
16. Chee MWL, Tan JC. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. Neuroimage 2010;51:835-43.
17. Gujar N, Yoo SS, Hu P, et al. The unrested resting brain: sleep deprivation alters activity within the default-mode network. J Cogn Neurosci 2010;22:1637-48.
18. Sämann PG, Tully C, Spoormaker VI, et al. Increased sleep pressure reduces resting state functional connectivity. MAGMA 2010;23:375-89.
19. De Havas JA, Parimal S, Soon CS, et al. Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. Neuroimage 2012;59:1745-51.
20. Bosch OG, Rihm JS, Scheidegger M, et al. Sleep deprivation increases dorsal nexus connectivity to the dorsolateral prefrontal cortex in humans. Proc Natl Acad Sci USA 2013;110:19597-602.
21. Ma N, Dinges DF, Basner M, et al. How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. Sleep 2015;38:233-40.
22. Gorfine T, Zisapel N. Melatonin and the human hippocampus, a time dependent interplay. J Pineal Res 2007;43:80-6.
23. Vimal RL, Pandey-Vimal MU, Vimal LS, et al. Activation of suprachiasmatic nuclei and primary visual cortex depends upon time of day. Eur J Neurosci 2009;29:399-410.
24. Schmidt C, Peigneux P, Leclercq Y, et al. Circadian preference modulates the neural substrate of conflict processing across the day. PLoS One 2012;7:e29658.
25. Marek T, Fafrowicz M, Golonka K, et al. Diurnal patterns of activity of the orienting and executive attention neuronal networks in subjects performing a Stroop-like task: a functional magnetic resonance imaging study. Chronobiol Int 2010;27:945-58.
26. Vandewalle G, Archer SN, Wuillaume C, et al. Functional magnetic resonance imaging- assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. J Neurosci 2009;29:7948-56.
27. Schmidt C,Collette F, Reichert CF, et al. Pushing the Limits: Chronotype and Time of Day Modulate Working Memory- Dependent Cerebral Activity. Front Neurol 2015;6:199.
28. Muto V, Jaspar M, Meyer C et al. Local modulation of human brain responses by circadian rhythmicity. Science 2016;353:687-90.
29. Czeisler CA. SLEEP. Measuring the passage of brain time. Science 2016;353:648-9.
30. Kerkhof, GA, Van Dongen HP. Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. Neurosci Lett 1996;218:153-6.
31. Van Dongen HP, Baynard MD, Maislin G, et al. Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. Sleep 2004;27:423-33.
32. Schmidt C, Collette F, Leclercq Y, et al. Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area. Science 2009;324:516-9.
33. Aguirre GK, Detre JA, Zarahn E, et al. Experimental design and the relative sensitivity of BOLD and perfusion fMRI. NeuroImage 2002;15:488-500.
34. Wu JC, Gillin JC, Buchsbaum MS, et al. The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. Sleep 1991;14:155-62.
35. Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity J Sleep Res 2000;9:335-52.
36. Wu JC, Gillin JC, Buchsbaum MS, et al. Frontal lobe metabolic decreases with sleep deprivation not total reversed by recovery sleep. Neuropsychopharmacology 2006;31:2783-92.
37. Detre JA, Leigh JS, Williams DS, et al. Perfusion imaging. Magn Reson Med 1992;23:37-45.
38. Detre JA, Wang J. Technical aspects and utility of fMRI using BOLD and ASL. Clin Neurophysiol 2002;113:621-34.
39. Detre JA, Wang J, Wang Z, et al. ASL perfusion MRI in basic and clinical neuroscience. Curr Opin Neurol 2009;22:348-55.
40. Rao H. ASL imaging of brain function changes during sleep restriction. Sleep 2012;35:1027-8.

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