Neurosci Bull Febuary 1, 2008, 24(1):45-48. http://www.neurosci.cn
DOI: 10.1007/S 12264-008-0910-z

·Minireview·

Effects of sleep deprivation on cognitive functions

Na ZHANG, Hong-Tao LIU

Institute of Health and Environmental Medicine, Academy of Military medical sciences, Tianjin 300050, China

Abstract: Sleep deprivation (SD) is a common condition that afflicts many people in modern life. Deficits in daytime performance due to SD are experienced universally. Recent evidence indicates that SD causes impairments in cognitive functions. However, the mechanisms that SD impairs cognitive functions are not clear. This review will focus on the behavioral and neural effects of SD with the aim to elucidate the possible mechanisms of SD-induced deterioration in cognitive functions and to identify directions for future research.

Keywords: sleep deprivation; cognitive function; mechanism

1 Introduction

Sleep deprivation (SD) is a common condition that afflicts many people in modern life. It can interfere with cognitive abilities, motor performance, and emotional mood[1,2]. There is still significant controversy regarding the function of sleep and many theories have been set forth. The idea that sleep is involved in learning and memory processes is gaining widespread acceptance. Deficits in daytime performance due to SD are experienced universally, which associated with a significant social, financial, and human cost. Military personnel of many professions, including health care workers, routinely participate in rotating shift work and serial night shifts, which often challenged their cognitive performances.

There are two types of SD, i.e. partial and total. Partial SD is defined as "a night of reduced or interrupted sleep". Total sleep deprivation (TSD) occurs when an individual gets no sleep during the normal sleep/wake cycle. For example, one or more nights of sleep are skipped. In the present article, we will review some experimental literatures on TSD, especially focus on the behavioral and neural effects of SD to elucidate the neurophysiological underpinnings of SD-induced deterioration in cognitive functions and to identify directions for future research.

Corresponding author: Na ZHANG
Tel: 86-22-84655302
Fax: 86-22-84655017
E-mail: zhangnatj@sina.com
Article ID:1673-7067(2008)01-0045-04
CLC number: Q428
Document code: A
Received date: 2007-09-10

2 Effects of TSD on cognitive functions

Applied and fundamental researches have identified the detrimental effects of SD on mood and cognitive performance. The cognitive functions that especially associate with right anterior hemisphere or subcortical areas, such as motor, rhythm, receptive and expressive speech, memory and complex verbal arithmetic function were decreased after TSD for 24 h[3]. And motor procedural, implicit memory and working memory were sensitive to one night of TSD[4]. Bocca ML *et al.* selected ten healthy young male subjects to assess the effect of one night SD on visuo-spatial attention. The results showed that the disengagement of attention was impaired but alertness was not altered by SD[5]. Adam M *et al.* found that vigilant attention was more impaired after one night without sleep in young men, which has important implications for the prevention of accidents associated with the loss of sleep[6]. Decision making which is one of cognitive tasks was vulnerable to sleep loss following 49.5 h of TSD[7]. And integrative executive function was significantly impaired after one night's SD[8].

Chronic SD is becoming common and affects millions of people, especially in certain professions, such as medicine. The negative effects of SD on the quality of patient care have been well studied. For example, in the randomized study of the SD effects in residency training, interns working in the "traditional schedule" made 36% more serious medical errors than interns did under the "intervention schedule" that included

more sleep[9]. Another study demonstrated that traditional-schedule interns had more than twice the rate of attentional failures compared with the intervention-schedule interns[10]. Tsai LL *et al.* found that one night of TSD impaired both the error detection and error remedial actions, and highlighted the inability to avoid making errors again after erroneous responses[11]. A vicious cycle occurred between performance deterioration and impairment of error-remedial mechanisms, which inevitably led to making more successive errors.

Studies have been done on the occurrence of SD among military personnel. The performance decrements among sleep-deprived military personnel are significant. One night of SD tends to decrease cognitive performance by 30% to 40%, whereas two nights of SD can result in 60% to 70% declines in performance[12].

Recently, in order to improve understanding of performance deficits induced by SD, neuropsychophysiologic methods, such as quantitative electroencephalogram analysis and event-related potential (ERPs), have been used to examine brain functions. The latencies of P300 and N200 were significantly prolonged and their amplitudes decreased as a consequence of SD, which may slow down cognitive processing and decrease the efficiency of mental processing[13]. More recently, it has been suggested that two subtypes of P300 should be distinguished, that is "novel P300" and "target P300". The novel P300 is thought to originate from the anterior cingulate cortex or the supplementary motor area and to be related to the detection of unexpected stimuli. The target P300, in contrast, is thought to reflect neural activity at the temporal-parietal junction and to be related to the detection of anticipated stimuli. Gosselin A *et al.* found that both novel and target P300 were reduced in amplitude after 36 h of waking, and that performance on attention-demanding tasks was deteriorated[14]. The authors concluded that SD affects the whole attentional network, consisting of several interconnected cortical regions.

3 Mechanisms of TSD effects on cognitive functions

Recent evidence indicates that SD causes impairments in behavioral performance and hippocampal long-term potentiation (LTP) in animals. However, the mechanisms that SD impairs long-term synaptic plasticity and cognitive function are not clear.

3.1 Changes of synaptic plasticity Synaptic plasticity is believed to underlie memory formation, which may be the mechanism responsible for SD-induced cognitive impairments. LTP is induced by high-frequency stimulation that activates the NMDA receptors (NMDAR). Prolonged depolarization relieves a voltage-dependent Mg^{2+} block from the channel and allows it to conduct. Ca^{2+} influx through these channels is associated with the activation of a number of kinases[15], which ultimately leads to the enhancement of postsynaptic responses through either AMPA receptors increasing at the synapse or the channel conductance enhancing[16].

It has been demonstrated that SD affected LTP of synaptic transmission in the hippocampus, an area crucial for encoding and storing memories[17-19]. However, the mechanisms that SD impairs LTP plasticity are not clear.

Recent studies have attempted to determine the mechanisms responsible for this impairment. McDermott CM *et al.* have found that 72 h of SD, a treatment that reduces LTP at the Schaffer collateral synapse, also reduced the NMDAR current at this synapse[20,21]. This effect was associated with an increase of the NR1 and NR2A subunits in the intracellular pool, which indicated that SD resulted in a lower density of surface NMDAR. Chen C *et al.* have reported that 24 h of SD in mice resulted in impaired hippocampus-dependent contextual memory and LTP, and reduced expression of NMDAR subunit NR1 and NMDAR-mediated excitatory post-synaptic currents at hippocampal dentate granule cell synapses[22]. Guzman-Marin R *et al.* have gained the conclusion that 8 h and 48 h of SD resulted in a reduction in the expression of brain-derived neurotrophic factor (BDNF) and its protein levels, as well as synapsin I and calcium-calmodulin-dependent protein kinase II (CAMK II) in the hippocampus[23]. These genes are critical modulators of hippocampal-dependent learning and LTP. These observations may be responsible for the reduced ability to induce LTP after SD.

Davis CJ *et al.* have found that the lack of sleep severely hampered cortactin protein up-regulation and phosphorylation in the control group, suggesting a functional link between sleep and cytoskeletal reorganization in the hippocampus that is essential for synaptic plasticity[24]. This may be the potential mechanism underlying SD-induced LTP impairment.

3.2 Changes of neural network Sites of deactivation were

found in the posterior cerebellum, right fusiform gyrus and precuneus, and left lingual and inferior temporal gyri; increased activation was found in the bilateral insula, claustrum and right putamen after SD for 48 h[25]. The network whose expression decreased after SD was identified and correlated with memory performance. In particular, several studies have hinted the central role of the prefrontal cortex (PFC) in SD[9,25,26]. PFC is a neocortical region that supports a diverse and flexible repertoire of behavioral functions and develops into the most elaborateness in primates. It consists of a massive network, connecting perceptual, motor, and limbic regions within the brain[27]. Therefore, impaired attention and cognitive performance after SD were due to decreased brain activity and function in the PFC[28]. Similarly, the disrupted memory consolidation after SD indicated involvement of the hippocampus, a crucial structure involved in learning and the consolidation of newly learned materials. Recently, one research has found that sleep restriction in the rats impaired hippocampus dependent learning[29].

Adult neurogenesis, the process of cells proliferating, surviving and differentiating into neurons, has been shown to occur in several species, including birds, rodents, nonhuman primates and humans. Both positive and negative factors affect neurogenesis. One study has been shown that prolonged (72 h) TSD suppressed cell proliferation in the granule cell layer of the hippocampus[30]. Hairston IS *et al.* extended this observation to a much milder sleep restriction paradigm and found that sleep restriction might affect survival and fate determination of newborn cells, which resulted in a net decrease in neurogenesis[29].

3.3 Changes of metabolism SD can reduce regional cerebral metabolism within the PFC. After 24 h of continuous wakefulness, there was significant reduction in glucose metabolism within the PFC[28].

Neurons use not only glucose but also lactate as their energy substrate. The physiological response to elevated neuronal activity is a transient increase in lactate concentrations in the stimulated area. During SD for 40 h, the silent word generation test induced a 40% increase in lactate in the young subjects, but during the prolonged wakefulness period this response disappeared. In the aged subjects, the lactate response could not be detected even in the alert state[31]. The absence of the lactate response may be a sign of malfunction of normal brain energy metabolism. The behavioral effects of prolonged wakefulness and aging may arise from this dysfunction.

Mitochondria plays a significant role in maintaining the physiological functions of the brain. Dou W *et al.* concluded that SD, no matter mild or severe, could have adverse effects on cognitive function and cerebral mitochondrial respiratory function[32].

4 Epilogue

SD studies repeatedly showed a negative impact on cognitive performance. Though several possible mechanisms that SD impairs cognitive functions are explored, it remains to be determined how SD affects cognitive function deeply and whether there are other mechanisms that play important roles in cognitive processing during SD. Also it is unknown whether or not the alteration in proteins related to cognitive function, such as calpacitins, maybe a novel target for intervention studies in future.

References:

[1] Chee MW, Chuah YM. Functional neuroimaging and behavioral correlates of capacity decline in visual short-term memory after sleep deprivation. Proc Natl Acad Sci U S A 2007, 104: 9487-9492.

[2] Kahn-Greene ET, Killgore DB, Kamimori GH, Balkin TJ, Killgore WD. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. Sleep Med 2007, 8: 215-221.

[3] Kim DJ, Lee HP, Kim MS, Park YJ, Go HJ, Kim KS, *et al.* The effect of total sleep deprivation on cognitive functions in normal adult male subjects. Int J Neurosci 2001, 109: 127-137.

[4] Forest G, Godbout R. Effects of sleep deprivation on performance and EEG spectral analysis in young adults. Brain Cogn 2000, 43: 195-200.

[5] Bocca ML, Denise P. Total sleep deprivation effect on disengagement of spatial attention as assessed by saccadic eye movements. Clin Neurophysiol 2006, 117: 894-899.

[6] Adam M, Rétey JV, Khatami R, Landolt HP. Age-related changes in the time course of vigilant attention during 40 hours without sleep in men. Sleep 2006, 29: 55-57.

[7] Killgore WD, Balkin TJ, Wesensten NJ. Impaired decision making following 49 h of sleep deprivation. J Sleep Res 2006, 15: 7-13.

[8] Nilsson JP, Söderström M, Karlsson AU, Lekander M, Akerstedt T, Lindroth NE, *et al*. Less effective executive functioning after one night's sleep deprivation. J Sleep Res 2005, 14: 1-6.

[9] Landrigan CP, Rothschild JM, Cronin JW, kaushal R, Burdick E, Katz JT, *et al*. Effects of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med 2004, 351:

1838-1848.
[10] Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, *et al*. Effect of reducing interns' weekly work hours on sleep and attentional failures. N Engl J Med 2004, 351: 1829-1837.
[11] Tsai LL, Young HY, Hsieh S, Lee CS. Impairment of error monitoring following sleep deprivation. Sleep 2005, 28: 707-713.
[12] Buguet A, Moroz DE, Radomski MW. Modafinil--medical considerations for use in sustained operations. Aviat Space Environ Med 2003, 74: 659-663.
[13] Lee HJ, Kim L, Kim YK, Suh KY, Han J, Park KW, *et al*. Auditory event-related potentials and psychological changes during sleep deprivation. Neuropsychobiology 2004, 50: 1-5.
[14] Gosselin A, De Koninck J, Campbell KB. Total sleep deprivation and novelty processing: implications for frontal lobe functioning. Clin Neurophysiol 2005, 116: 211-222.
[15] Wang JH, Kelly PT. Postsynaptic injection of Ca^{2+}/CaM induces synaptic potentiation requiring CaMK II and PKC activity. Neuron 1995, 15: 443-452.
[16] Poncer JC, Esteban JA, Malinow R. Multiple mechanisms for the potentiation of AMPA receptor-mediated transmission by alpha-Ca^{2+}/calmodulin-dependent protein kinase II. J Neurosci 2002, 22: 4406-4411.
[17] Ruskin DN, Liu C, Dunn KE, Bazan NG LaHoste GJ. Sleep deprivation impairs hippocampal-mediated contextual learning but not amygdala-mediated cued learning in rats. Eur J Neurosci 2004, 19: 3121-3124.
[18] Davis CJ, Harding JW, Wright JW. REM sleep deprivation-induced deficits in the latency-to-peak induction and maintenance of long-term potentiation within the CA1 region of the hippocampus. Brain Res 2003, 973: 293-297.
[19] Campbell IG, Guinan MJ, Horowitz JM. Sleep deprivation impairs long-term potentiation in rat hippocampal slices. J Neurophysiol 2002, 88: 1073-1076.
[20] McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC. Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 2003, 23: 9687-9695.
[21] McDermott CM, Hardy MN, Bazan NG, Magee JC. Sleep deprivation-induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. J Physiol 2006, 570: 553-565.
[22] Chen C, Hardy M, Zhang J, LaHoste GJ, Bazan NG. Altered NMDA receptor trafficking contributes to sleep deprivation-induced hippocampal synaptic and cognitive impairments. Biochem Biophys Res Commun 2006, 340: 435-440.
[23] Guzman-Marin R, Ying Z, Suntsova N, Methippara M, Bashir T, Szymusiak R, *et al*. Suppression of hippocampal plasticity-related gene expression by sleep deprivation in rats. J Physiol 2006, 575: 807-819.
[24] Davis CJ, Meighan PC, Taishi P, Krueger JM, Harding JW, Wright JW. REM sleep deprivation attenuates actin-binding protein cortactin: a link between sleep and hippocampal plasticity. Neurosci Lett 2006, 400: 191-196.
[25] Bell-McGinty S, Habeck C, Hilton HJ, Rakitin B, Scarmeas N, Zarahn E, *et al*. Identification and differential vulnerability of a neural network in sleep deprivation. Cereb Cortex 2004, 14: 496-502.
[26] Muzur A, Pace-Schott EF, Hobson JA. The prefrontal cortex in sleep. Trends Cogn Sci 2002, 6: 475-481.
[27] Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001, 24: 167-202.
[28] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, *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: 335-352.
[29] Hairston IS, Little MT, Scanlon MD, Barakat MT, Palmer TD, Sapolsky RM, *et al*. Sleep restriction suppresses neurogenesis induced by hippocampus-dependent learning. J Neurophysiol 2005, 94: 4224-4233.
[30] Guzmán-Marin R, Suntsova N, Stewart DR, Gong H, Szymusiak R, McGinty D. Sleep deprivation reduces proliferation of cells in the dentate gyrus of the hippocampus in rats. J Physiol 2003, 549: 563-571.
[31] Urrila AS, Hakkarainen A, Heikkinen S, Vuori K, Stenberg D, Häkkinen AM, *et al*. Stimulus-induced brain lactate: effects of aging and prolonged wakefulness. J Sleep Res 2004, 13: 111-119.
[32] Dou W, Zhao ZX, Miao MY, Wang WZ, Huang LQ. The Effect of sleep deprivation on cognitive and cerebral mitochondrial respiratory function in rats. Neurosci bull 2005, 21: 204-209. (Chinese, English abstract)

睡眠剥夺对认知影响的研究进展

张娜，刘洪涛
军事医学科学院卫生学与环境医学研究所，天津 300050

摘要：现代社会，睡眠剥夺(sleep deprivation, SD)是一种常见现象，困扰着很多人，引起人的日间工作能力降低。近年来的研究结果显示，SD 可以使认知功能受损，但是其损害机制尚不清楚。本综述将重点阐述 SD 对行为和中枢系统的影响，进而阐明 SD 引起认知功能受损的可能机制，并且展望未来的研究方向。
关键词：睡眠剥夺；认知功能；机制