



Sleep and Neuroimaging

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Abstract

We spend about one-third of our lives either sleeping or attempting to sleep. Therefore, the socioeconomic implications of sleep disorders may be higher than expected. However, the fundamental mechanisms and functions of sleep are not yet fully understood. Neuroimaging has been utilized to reveal the connectivity between sleep and the brain, which is associated with the physiology of sleep. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging studies have become increasingly common in sleep research. Recently, significant progress has been made in understanding the physiology of sleep through neuroimaging and the use of various radiopharmaceuticals, as the sleep–wake cycle is regulated by multiple neurotransmitters, including dopamine, adenosine, glutamate, and others. In addition, the characteristics of rapid eye and non-rapid eye movement sleep have been investigated by measuring cerebral glucose metabolism. The physiology of sleep has been investigated using PET to study glymphatic function as a means to clear the amyloid burden. However, the basic mechanisms and functions of sleep are not yet fully understood. Further studies are needed to investigate the effects and consequences of chronic sleep deprivation, and the relevance of sleep to other diseases.

Keywords Sleep · Brain · Positron emission tomography · Single-photon emission computed tomography

Introduction

Each day, we sleep and then wake up. However, we do not know why we sleep everyday. In addition, sleep duration varies from individual to individual, and we spend around one-third of our life either sleeping or attempting to sleep [1]. Sleep disorders are associated with hypertension [2] and obesity [3], and sleep–wake disturbance is frequent in neurodegenerative disorders such as Alzheimer’s disease [4] and Parkinson’s disease [5]. The socioeconomic implications of sleep disorders may also be greater than expected [6].

However, the basic mechanisms and functions of sleep are not fully understood. Traditionally, sleep has been considered a restorative process [7].

Neuroimaging has been utilized to reveal the connectivity between sleep and the brain, which is associated with the physiology of sleep [8]. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging studies have become increasingly common in sleep research [8]. Information can be gathered at the molecular level using PET, and specific molecules can be labeled to detect their targets [9]. In addition, PET scanning can be

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performed repeatedly over time with minimal invasiveness and strong reproducibility [9]. However, it is limited by low spatial/temporal resolution and nonspecific binding of radiopharmaceuticals [10]. Other disadvantages include restricted availability, exposure to radiation, and high cost [11].

Recently, significant progress has been made in understanding the physiology of sleep through neuroimaging and the use of various radiopharmaceuticals, as the sleep–wake cycle is regulated by multiple neurotransmitters. Therefore, this review provides an overview of brain imaging under conditions of sleep and sleep deprivation.

Sleep, Wakefulness, and Neuroimaging

Sleep is not the opposite of wakefulness, rather it is a more active, metabolically distinct state than previously expected [12]. The hypothalamus and the brain stem control the balance between sleep and wakefulness [13]. Several neurotransmitters such as histamine, acetylcholine, norepinephrine, serotonin, orexin, adenosine, glutamate, gamma aminobutyric acid (GABA), and dopamine are involved in regulating sleep and wakefulness [13].

Sleep consists of two fundamentally distinct cycles: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep [12]. NREM sleep consists of three stages that progressively deepen from stage 1 to stage 3 [12]. Stage 1 of NREM sleep usually occurs at the beginning of sleep with slow eye movement and is the lightest stage of NREM sleep [12]. During stage 2, body temperature begins to decrease, and the heart rate slows. In stage 3, delta waves are common in electroencephalograms [12]. REM sleep is characterized by rapid eye movements, muscle atonia, and increased heart rate, blood pressure, sympathetic nerve activity, and respiration [12]. Throughout the night, there are four to six cyclical switches between NREM and REM sleep every 1–1.5 h [12, 14].

PET neuroimaging was first used to study sleep in 1985 by Heiss et al. [15], who used ^{18}F -fluorodeoxyglucose (FDG) to compare cerebral glucose metabolism between wakefulness,

sleep, and dreaming. During sleep, there was a significant decrease in the cerebral metabolic rate of glucose (CMRglu) compared to wakefulness, which could be interpreted as less CMRglu being needed while asleep than during wakefulness. NREM sleep in particular tends to show a significantly lower CMRglu than REM sleep and wakefulness [16]. The decrease in CMRglu during NREM sleep is greater in the frontal and temporal lobes than in other parts of the brain [16] (Fig. 1). In addition, the number of eye movements during REM sleep correlates with CMRglu in areas that correspond to the neural system that involves oculomotor control and visual spatial attention, i.e., the frontal eye fields, dorsolateral prefrontal cortex, superior/inferior parietal lobules, and occipital cortex [10]. However, ^{18}F -FDG has a half-life of 109.7 min, which may limit repeated measurements within the same night, resulting in inaccuracy in investigating each sleep phase [17]. Studies that have used ^{15}O - H_2 PET to measure cerebral blood flow (CBF) [18, 19] have reported similar results to those that have used CMRglu. CBF in the cerebellum, thalamus, basal ganglia, prefrontal cortex, anterior cingulate cortex, precuneus, and mesial temporal lobes is significantly decreased during slow wave sleep, which is referred to as deep sleep of NREM, compared to wakefulness and REM sleep [18, 19].

Although the connection between sleep and the amyloid β ($\text{A}\beta$) burden is not clear, sleep disorders are one of the most common comorbidities associated with Alzheimer's disease [20]. In addition, diurnal physiological fluctuations in $\text{A}\beta$ levels in the cerebrospinal fluid have been reported to increase during wakefulness and decrease during sleep, particularly during NREM sleep [21]. In a study that used ^{11}C -Pittsburgh compound B PET in healthy older adults, self-reported shorter sleep duration and poor sleep quality were associated with a greater $\text{A}\beta$ burden [22]. Similarly, in another self-report study that used ^{18}F -FDG PET, longer sleep latency and poor sleep quality were associated with a greater $\text{A}\beta$ burden but not with glucose metabolism [23]. In another study, sleep duration did not show any significant association with $\text{A}\beta$ burden [24]. Amyloid is released during synaptic activity [25], which is



Fig. 1 PET scans at the mid-ventricular level show an overall decrease in the metabolic rate during NREM sleep (a) and right basal ganglia elevation in REM sleep (b) compared with wakefulness (c). Scale bar is in metabolic rate in micromoles glucose/100 g/min. Reprinted from

Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography, *Life Sci.* 1989;45(15):1349–56. Buchsbaum et al., with permission from Elsevier

decreased during sleep [26]. Therefore, subjects with poor sleep quality can show higher A β levels due to having elevated neuronal activity [24], in addition to reduced clearance of waste products such as A β aggregations [27].

Dopamine agonists cause wakefulness via the dopamine receptor (DR) [28], and poor sleep maintenance is the most frequent sleep disorder in Parkinson's disease, a neurodegenerative disorder of the dopaminergic neurons [29]. However, there are no significant differences between good sleepers and poor sleepers in terms of dopamine transporter (DAT) availability [30] and DR availability [31]. In good sleepers, sleep duration is negatively correlated with striatal DR availability; however, this is not the case in poor sleepers [31].

Sleep Deprivation and Neuroimaging

Studies on sleep deprivation have been conducted to understand the functions and physiology of sleep. Sleep deprivation can induce behavioral, hormonal, and neurochemical changes [32]. In acute sleep deprivation studies, subjects are kept

awake continuously for 24–72 h while being closely monitored [33].

The first ^{18}F -FDG PET study that investigated the effects of sleep deprivation was carried out in 1991 and included eight normal controls over approximately 32 h of sleep deprivation [34]. After sleep deprivation, CMRglu of the thalamus, basal ganglia, cerebellum, and frontal/temporal lobes decreased, while that of the occipital lobe increased. As sleep deprivation has an antidepressant effect [35], a study investigated the effects of sleep deprivation by means of CMRglu. Subjects who showed a >40% decrease in their Hamilton depression scores following sleep deprivation were considered responders to sleep deprivation, and the baseline CMRglu of the cingulate cortex and amygdala of responders was higher than in those of non-responders or normal controls [36]. In addition, after sleep deprivation, CMRglu of the cingulate cortex and amygdala of the responders decreased significantly, while that of non-responders or normal controls showed minimal change [36]. Interestingly, overactivation of CMRglu in the limbic system has been reported in patients with depression, and in these cases, sleep deprivation might reduce depression by reducing overactivity in the limbic system [36].

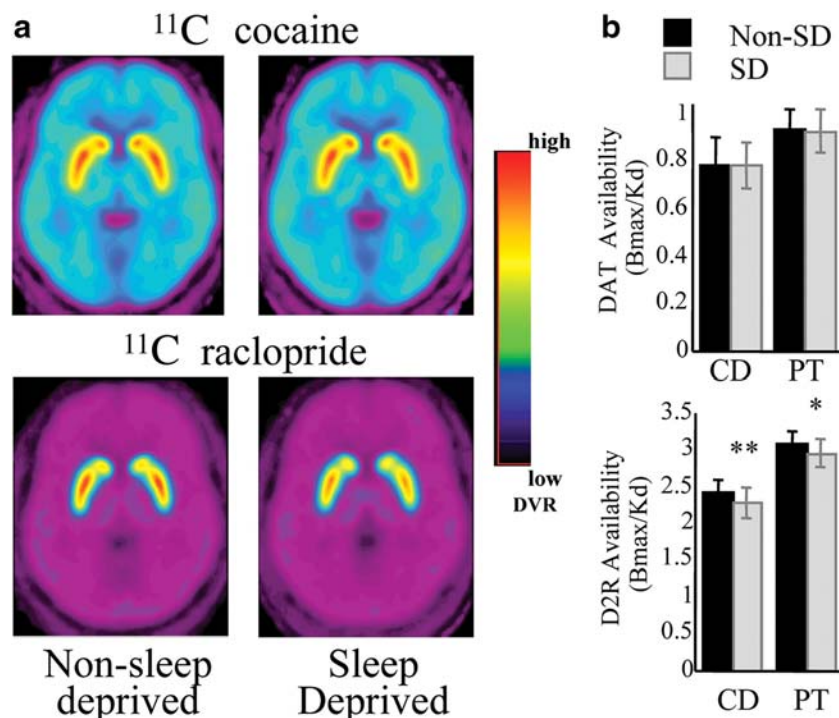


Fig. 2 Effects of one-night sleep deprivation (SD) on A β . **a** Voxel-wise paired *t* test between rested-wakefulness (RW) and SD conditions highlighting the hippocampus and other subcortical structures ($P_{\text{FWE}} < 0.05$, cluster-size corrected). **b** Subject-level changes in florbetaben (FBB) standardized uptake value ratio (SUVr) (in the red cluster identified in **a**) from RW to SD. There was no significant effect of gender or gender \times sleep interaction ($p > 0.15$). **c** Association between changes in mood from RW to SD and changes in the FBB SUVr for the cluster identified in **a**. Mood change was quantified using the principal component of the changes in self-reported measures from RW to SD, which

accounted for 35.5% of the variance. Self-reported measures of alert, friendly, happy, social, and energetic significantly decreased, and measures of tiredness and difficulty staying awake significantly increased from RW to SD ($p < 0.001$, two-tailed). **d** Average FBB SUVr in the a priori hippocampus region of interest across all subjects. Error bars show the standard deviation. Reprinted from β -amyloid accumulation in the human brain after one night of sleep deprivation, Proc Natl Acad Sci USA. 2018;115(17):4483–4488. Shokri-Kojori et al., with permission from PNAS

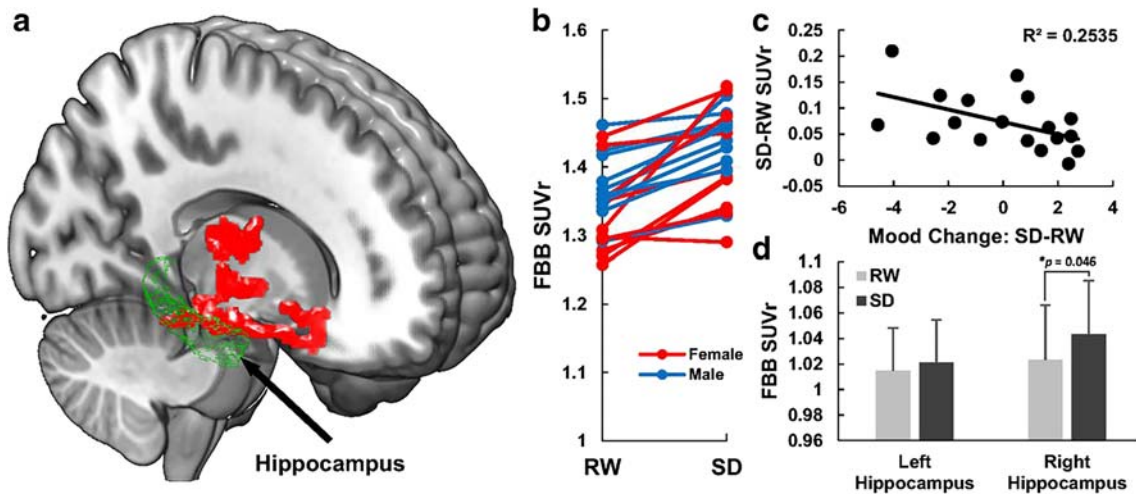


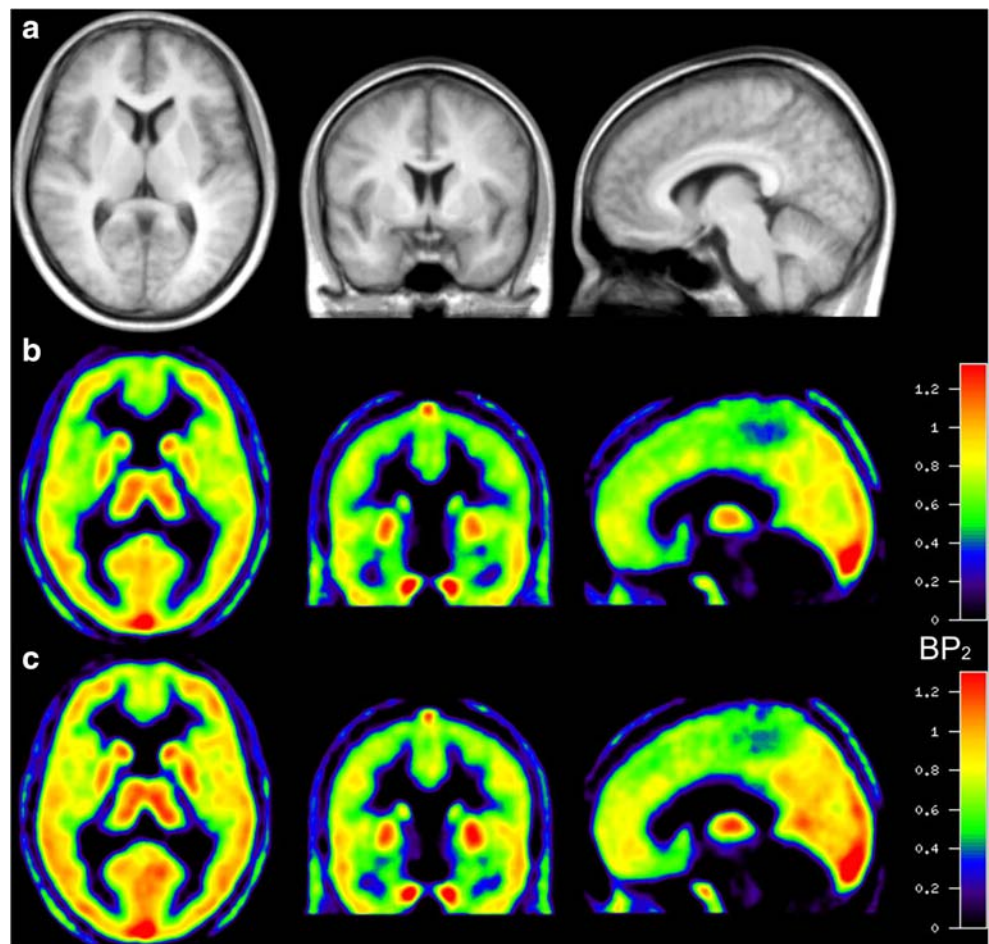
Fig. 3 **a** Averaged brain images of the distribution volume ratio for ¹¹C-cocaine and ¹¹C-raclopride at the level of the striatum for non-SD and SD conditions. **b** Bmax/Kd in the caudate (CD) and putamen (PT) for ¹¹C-cocaine (measure of DAT availability) and for ¹¹C-raclopride (measure of D2 receptor availability) for non-SD and SD. Values represent mean ±

standard deviation. Comparisons correspond to paired *t* tests: **p* < 0.05; ***p* < 0.01. Reprinted from sleep deprivation decreases binding of [¹¹C]raclopride to dopamine D2/D3 receptors in the human brain, *J Neurosci.* 2008;28(34):8454–61. Volkow et al., with permission from *J Neurosci*

The glymphatic pathway, which clears toxic metabolites including Aβ from the brain, was first identified in 2012 [37]. Glymphatic function increases during sleep, whereas

the accumulation of metabolic byproducts occurs during wakefulness [27]. An accumulation of Aβ in the brain is associated with cognitive impairment [38]. The effects of sleep

Fig. 4 Average images of the sleep deprivation group (*n* = 12) after spatial normalization. **a** Magnetic resonance imaging. **b** Parametric image of binding potential (BP₂) before sleep deprivation. **c** Image after sleep deprivation. Reprinted from Sleep deprivation increases A1 adenosine receptor binding in the human brain: A positron emission tomography study, *J Neurosci.* 2007;27(9):2410–5. Elmenhorst et al., with permission from *J Neurosci*



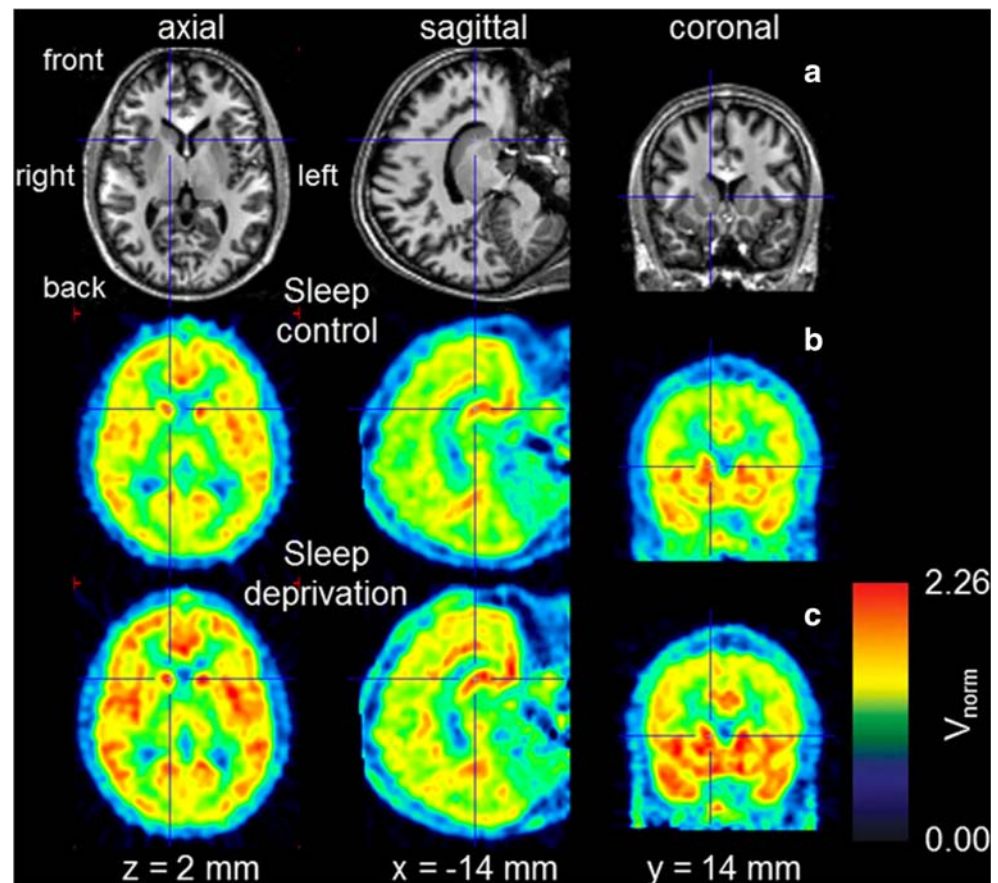
deprivation on A β clearance in the human brain were reported by Shokri-Kojori et al. in 2018 [39]. After 31 h of sleep deprivation in 20 normal controls, a significantly higher A β burden was observed in the hippocampus, parahippocampus, and thalamus, with a mean increase of 5%, although the magnitude of A β changes varied widely regardless of age, sex, and apolipoprotein E status [39] (Fig. 2). Hippocampal A β increases following sleep deprivation may reflect either the reduced glymphatic function in clearing the A β or the increased synthesis of A β following neuronal activity during wakefulness [39]. In addition, the reported sleep hours from the normal controls in that study were negatively correlated with the baseline A β burden, which might imply an effect of chronic sleep deprivation [39].

Amphetamine promotes wakefulness by enhancing dopamine release and blocking the reuptake of dopamine, which suggests that dopaminergic neurons are relevant to the sleep–wake cycle [40]. A study that used ^{11}C -cocaine PET showed that approximately 30 h of sleep deprivation did not change DAT availability in 15 normal controls [41]. In Martins et al. [42], four nights of REM sleep deprivation and two nights of sleep deprivation did not significantly change DAT availability measured using $^{99\text{m}}\text{Tc}$ -TRODAT-1. However, in another study, sleep deprivation decreased DR availability measured using

^{11}C -raclopride PET in both the caudate nucleus and putamen, which correlated with the “desire to sleep” and “tiredness” [41] (Fig. 3). However, the decrease in DR availability suggests either a decreased number of DRs or a decreased receptor affinity [43]. Volkow et al. [44] tested whether methylphenidate, a DAT blocker, could induce changes in DR availability after sleep deprivation, as ^{11}C -raclopride competes with dopamine for DR binding. They concluded that the downregulation of DR under sleep deprivation might contribute to the associated decreased wakefulness through the action of adenosine, which internalizes the DR [44]. In that same study, microdialysis in rats showed no significant change in dopamine after sleep deprivation, consistent with human studies.

Coffee can make people alert through the action of caffeine, which is a non-selective adenosine antagonist for the adenosine receptor (AR) [45], which is an attractive candidate for the sleep switch [12]. Two previous studies have reported the effects of sleep deprivation on the AR using ^{18}F -CPFPX PET [46, 47]. Twenty-four-hour sleep deprivation led to a significant increase in AR availability, ranging from 10.6% in the cerebellum to 15.3% in the orbitofrontal cortex [46] (Fig. 4). In a follow-up study, 14 h recovery sleep after 52 h sleep deprivation decreased elevated AR availability, which was evident in the striatum, thalamus, orbitofrontal cortex,

Fig. 5 Axial, sagittal, and coronal views of ^{11}C -ABP688 binding in a representative individual. **a** Magnetic resonance image template for anatomical reference. **b** Color-coded normalized volumes of the distribution (V_{norm}) of ^{11}C -ABP688 after 9 h of wakefulness (sleep control condition). **c** Color-coded V_{norm} of ^{11}C -ABP688 after 33 h of wakefulness (sleep deprivation condition). The crosshair was placed in the right caudate nucleus. Reprinted from increased metabotropic glutamate receptor subtype 5 availability in human brain after one night without sleep, *Biol Psychiatry*. 2013;73(2):161–8. Hefti et al., with permission from Elsevier



amygdala, occipital cortex, frontal cortex, anterior cingulate cortex, insula, parietal cortex, and temporal cortex [47]. Fourteen-hour recovery sleep restored AR availability to the levels of the control groups.

Both GABA and glutamate neurons regulate sleep and wakefulness [48]. Previous studies have investigated the action of metabotropic glutamate receptor subtype 5 (mGluR5) during sleep deprivation [49, 50]. In one study, 40 h sleep deprivation in 22 normal controls increased mGluR5 availability by 3.5% [49]. The increase in mGluR5 availability was significant in the anterior cingulate cortex, insula, medial temporal lobe, parahippocampus, striatum, and amygdala, with no regions of decrease (Fig. 5). In addition, sleep deprivation-induced change in subjective sleepiness was correlated with an increase in mGluR5 availability. As subjects with major depression have reduced mGluR5 availability [51], sleep deprivation may have a rapid antidepressant effect [49]. The increase in mGluR5 availability after sleep deprivation is more pronounced in subjects with a lower baseline mGluR5 availability [50]. However, it is uncertain whether increased mGluR5 availability is a compensatory mechanism to induce wakefulness or signals the need for sleep [50].

Conclusions

Sleep involves a more active, metabolically distinct state than previously believed. The basic mechanisms and functions of sleep remain to be fully understood. Neuroimaging could improve our understanding of sleep and help to develop a new treatment for sleep-related disorders. However, further studies are needed to investigate the effects and consequences of chronic sleep deprivation and the relevance of sleep to other diseases.

Compliance with Ethical Standards

Conflict of Interest Kyoungjune Pak, Jiyoung Kim, Keunyoung Kim, Seong Jang Kim, and In Joo Kom declare that they have no conflict of interest. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (2017R1D1A1B03029352, 2017R1D1A1B03032335).

Ethical Statement This article does not contain any studies with human participants performed by any of the authors.

Informed Consent Not applicable.

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