

Review (Narrative)

Sleep and Memory Consolidation

Fuzhou Wang, M.D., Ph.D.

SUMMARY

Sleep occupies about one third of a person's life. It is a critical physiological process. It is essential for the formation and consolidation of memory. Deficiency, lack of sleep will obviously affect the body's cognitive function. With the development of society and changes in lifestyle, more and more of people suffer from lack of sleep. We herein review the research history of the relationship between sleep and memory and discuss the most relevant fields and corresponding research progress, introduce various mechanisms of sleep to consolidate memory, and clarify the effects of sleep problems on memory. So as to help people better weigh the pros and cons of sleep, improve the quality of life, and respond to growing competition struggling for pressure and aging. ■

KEYWORDS

Sleep; Memory Consolidation; Dementia; Stress; Insomnia

Sci Insig. 2019; 31(3):107-115. doi:10.15354/si.19.re127.

Author Affiliations: Author affiliations are listed at the end of this article.

Correspondence to: Dr. Fuzhou Wang, M.D., Ph.D., Group of Neuropharmacology and Neurophysiology, Division of Neuroscience, The BASE, Chapel Hill, NC 27510, USA.
Email: fred.wang@basehq.org

Copyright © 2019 The BASE. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

WHEN awakening, the body can effectively perceive the external environment, ensuring the performance of various functions such as learning and memory, decision-making, and exercise; while sleeping, the body's perception and response reversibility to the surrounding environment is weakened. Sleep is divided into non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep by detection of brain/electromyography. During NREM sleep, EEG showed synchronized low-frequency delta oscillations and weakened EMG; while REM sleep showed characteristic theta high-frequency oscillations of EEG and further weakened EMG (1). With the increasing pressure of social competition, nearly 30% of people around the world have various sleep problems. Awakening sleep disorders have become an important factor affecting people's health. For this reason, research on awakening sleep has important theoretical and practical significance. There are two important issues in basic research on awakening sleep that need to be clarified: (i) the neural mechanism of awakening sleep; (ii) the function of sleep.

BASIC SLEEP PATTERNS

Sleep is vital to your health. Sleep abnormalities are closely related to the occurrence of neurodegenerative diseases, cardiovascular diseases and cancer. It has been revealed that sleep can promote development, energy recovery, elimination of metabolites, and boost immunity. For the brain, sleep is even more important. Sleep can restore synaptic homeostasis. The input of sensory information during awakening will lead to enhanced synaptic transmission and increase in number. To ensure that synapses are not oversaturated as a result, the synapses need to be weakened during sleep to counteract synaptic strengthening during wakefulness. Another important function of sleep is memory consolidation. After learning, the body will form the initial memory traces in the brain after learning, and then sleep will gradually transform the initial and unstable memory traces into a stable state for storage (2). In the past year, there has been new understanding of how sleep can achieve synaptic homeostasis and memory consolidation.

Sleep is a kind of external stabbing with loss of consciousness and reduced irritant response and relatively inactive natural reversible state. Sleep deprivation and sleep disruption can lead to severe cognitive and

emotional problems; animals show body temperature after weeks of sleep deprivation and weight disorders, eventually dying from infections and tissue lesions. Mammalian sleep composed of both slow wave sleep (SWS) and Rapid-eye-movement (REM) sleep. Sleep and alternate in a circular fashion (**Figure 1**). In humans, during night sleep, SWS dominates early stages, but its intensity and duration gradually decrease throughout sleep, while REM sleep becomes stronger before sleep ends strong and extensive. SWS shows slow high frequencies in EEG rhythmic oscillation-slow wave activity (slow wave activity, SWA), while REM sleep has similar brain activity characteristics in the awakening state such as fast low-frequency rhythmic oscillations. In addition, the characteristics of REM sleep the points are staged REM and hypotonia. Almost 50% Adults sleep with a mild non-REM sleep (stage "N2"), which is unique in EEG Special (undulating) sleep spindle waves (**Figure 1**) and K complex, and SWA will ease.

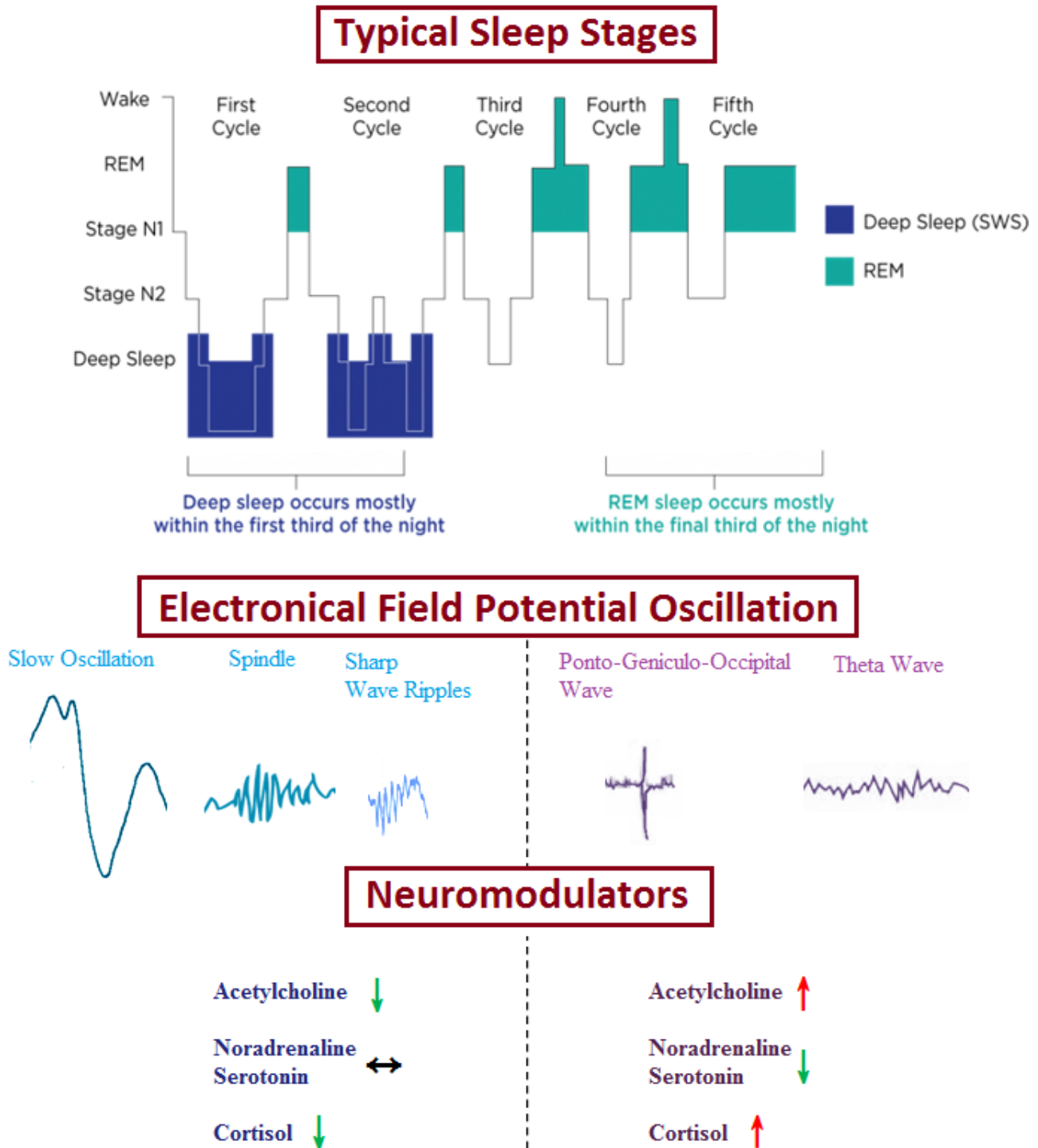
THE PROCESS OF MEMORY

Forming and retrieving memories is one of the basic abilities of living things, it can help individuals respond to thousands of problems by adjusting their actions. The changing external environment can also enable individuals to make choices and improve performance. The memory function mainly includes three processes: encoding, consolidation and extraction. During the encoding process, the perception of stimuli can form a new memory trace, and this trace is easily disturbed or subsided at first. During the consolidation stage, the unstable memory traces can be gradually stabilized. The whole process may be related to multiple brain areas in the process of memory consolidation, and eventually strengthening and integrating memory into pre-existing memory networks (preexisting knowledge network). During extraction, the stored memories can be accessed and retrieved.

Memory System

In neuropsychology, declarative and non-declarative notes can form the memory system depend on whether it depends on the medial temporal the hippocampus) distinguishes it from the key role in memory acquisition. Declarative memory includes: events embedded in the context of time and space. Episodic memory (including

Figure 1. Human Sleep Pattern, EEG Formats, and Neuromodulators.



SWS: slow-wave sleep. REM: rapid-eye-movement. (Modified from *Physiol Rev* 2013; 93: 681-766.)

autobiographical memory) is the context-independent knowledge of facts and semantic memory. Declarative memory can be intentional or inadvertently coded, but can usually be made clear by active recall (i.e., consciously) extracted. Acquisition of episodic memory would be very quickly, but forgetting also would be very quickly as well. Semantic memory can repetitive coding or activated knots of overlapping episodic memory. The integrity of the hippocampus is to retain a section in memory prerequisites for scenario, space and time information over 15 minutes. In contrast to declarative memory, non-declarative memory can be obtained without involving the medial temporal lobe structure. Non-declarative memory involves completely different memories that depend on different parts of the brain memory system. It includes motor skills (motor zones, striatum and cerebellum) and sensory skills (sensory cortex), some forms procedural memory for regulation and implicit learning (startup), etc. non-Declarative memory can be obtained implicitly (i.e., unconsciously) and recall, and the learning process is slow, usually multiple times training attempts.

Two-Level Memory System

The hypothesis that sleep strengthens memories is conceptually derived from standards two-level memory system, which is currently the most acceptable human memory model and has been developed by simple associative memory. The network model produces solutions to several key problems. This mechanism assumes that memory is initially encoded into fast learning storage area (Hippocampus) and then gradually transferred to slow learning. The storage area is to be stored for a long time (new cerebral cortex). The learning memory guarantees that the memory can be encoded quickly and efficiently. However these performances are unstable and susceptible to newly encoded information. Over time, this information is expelled step-by-step integration into slow learning long-term storage without disrupting the original earlier memories. New notes in this system recalling the transformation and consolidation process also includes refining constant prototypes and development. For declarative memory, two-level models have been well supported by dysfunction studies. Persistence-Hippocampus damage could impair acquisition of new declarative memory, but also cause temporary gradual progress of the old complete memory retrograde

oblivion. The time interval of the status can be from one day to several months or years, etc., it depends on the information obtained and the long-term memory in advanced existing patterns. The standard two-level memory model has also been successfully explained for non-declarative memory types, such as procedural memory, this demonstrated that recently remembered offline reactivation as well as from quick coding redistribution of permanent memory from slow learning to slow learning may be the characteristics of periodical memory formation.

WAKEFULNESS SLEEP MECHANISM

Early wake-up sleep was considered a passive process. In the 1950s, through electrical stimulation and damage experiments, it was found that the head of the brainstem reticular structure contains neurons necessary for maintaining wakefulness; the caudal side of the brainstem contains specific regions that can induce sleep, suggesting that specific brain regions are active. Regulates awake sleep. To date, a number of arousal sleep regulatory nuclei have been identified (1, 3). Awakening regulation includes the acetylcholine system in the brainstem inner pontine / lateral dorsal tegmental area, the blue norepinephrine system, the dorsal raphe serotonin system, the ventral tegmental dopamine system, and the hypothalamic nodule papillary body histamine System, lateral hypothalamus orexin and gamma-aminobutyric acid (GABA) can neuron system and basal forebrain acetylcholine system. The occurrence of NREM sleep depends on GABA neurons in the ventrolateral preoptic area of the hypothalamus, the reticular nucleus of the thalamus and the parafacial area of the brainstem. REM sleep is mainly closely related to the subcleral nucleus in the brainstem, the cholinergic system of the pontine/lateral lateral dorsal tectum, the ventral medulla GABAergic neurons, the central gray matter of the midbrain aqueduct, and the lateral hypothalamus melanin-concentrating hormone neurons Related. In the past year, new nucleus and neural circuits involved in wakeful sleep have been identified using cell-specific tracing and intervention techniques. These findings have further promoted our understanding of the mechanism of wakeful sleep.

New “Switch” to Control Wakefulness-Thalamus and Nucleus Accumbens

For a long time, the thalamus has been considered to be involved in the regulation of arousal, but because these thalamus have complex anatomical structures (containing more than 30 nuclei), the specific thalamic nuclei and their neural circuits involved in the regulation of arousal have not been elucidated (4, 5). Hu Zhi'an's group at Army Military Medical University found that pharmacogenetics specifically inhibited paraventricular thalamus (PVT) glutamate neurons can reduce arousal time, and optogenetic activation of PVT promoted the transition from sleep to arousal. The arousal maintenance function of PVT depends on the PVT-nucleus accumbens (NAc) loop, and is controlled by the regulation of lateral hypothalamus orexin neurons (6). Acsády and Li found that calcineurin-positive neurons in PVT mediate maintenance of wakefulness, and these neurons mediate starvation-induced wakefulness (7, 8).

Antoine R. Adamantidis found that the use of optogenetic tonic activation of neurons in the central medial nucleus of the thalamus induces the transition from NREM sleep to wakefulness, and burst activation can simulate the active state of the EEG during sleep (Up state), and Enhanced cortical slow wave activity synchronization, the above-mentioned effect is replaced by the anterior dorsal thalamus (9). The Chiara Cirelli team at the University of Wisconsin found that the frequency of neuronal firing in the ventromedial nucleus of the thalamus was higher during wakefulness and REM sleep, and lower during NREM sleep. Optogenetics activates the ventromedial nucleus of the thalamus to quickly induce arousal, and can also induce desynchronization of EEG under anesthesia. Chemical genetics inhibits the ventromedial nucleus of the thalamus and shortens the length of arousal fragments, suggesting that the ventromedial nucleus of the thalamus participates in the regulation of arousal (10).

NAc is considered to be a key structure that mediates reward, addiction, and feeding activities. These brain activities operate based on arousal. NAc adenosine A2A receptor-positive neurons have been shown to be involved in slow-wave sleep (11), but does NAc participate in the regulation of wakefulness? Huang found that NAc dopamine D1-receptor-positive neurons showed high levels of activity during wakefulness. Optogenetic activation of these neurons can induce a transition from NREM sleep to wakefulness. Inhibiting these neuronal activities can induce nesting behavior and reduce wakefulness. Dopamine D1-receptor-positive neurons exert

an arousal effect mainly through the ventral dorsal region of the midbrain and lateral hypothalamus (12). In addition, two other studies have proven that both PVT and glutamate neurons in the ventral tegmental region regulate NAc to control wakefulness (6, 13).

Biological Clock Neurons Regulate Upstream and Downstream Pathways of Wakefulness and Sleep

Sleep behavior is regulated by circadian signals, but how do these signals output to the sleep center and participate in sleep development? Michael Rosbash found that optogenetic activation of dorsal circadian clock neurons in *Drosophila* can significantly increase sleep time and make sleep oscillating patterns in the central ellipsoid of sleep homeostasis. It has been discovered through neurobeam tracer technology that circadian neurons can indirectly project to the homeostasis regulation center of sleep through nodular bulb neurons and participate in the regulation of sleep behavior (14).

Shafer used calcium imaging technology to monitor the excitability of *Drosophila* circadian neurons, and found that these neurons can sense ambient temperature: low temperature can activate this group of neurons, and high temperature can inhibit these neurons. Inhibition of tetanus toxin release of these neuronal transmitters can affect *Drosophila*'s sleep cycle in response to temperature changes, suggesting that in addition to sensing changes in ambient light, the circadian clock can also sense rhythmic changes in environmental temperature signals and participate in the regulation of sleep behaviors (15). These studies provide a more comprehensive link between the circadian clock and sleep regulation, and provide a new perspective for understanding the neural mechanisms of highly conservative sleep and circadian rhythm integration. At present, these studies are carried out in *Drosophila*. Whether there is a similar mechanism in the mammalian brain needs further research. In addition, research on the mechanism of awakening sleep has promoted understanding of the pathological mechanisms of sleep disorders. Paroxysmal narcolepsy is a chronic arousal disorder caused by loss of orexin neurons in the lateral hypothalamus. Federica Sallusto has discovered autoreactive CD4+ T cells that specifically recognize orexin neurons. Specific autoreactive CD8+ T cells were also detected in the blood and cerebrospinal fluid of patients with narcolep-

sy. CD4+ T cells can secrete cytokines and enhance the inflammatory response to damage peptide neurons, while autoreactive CD8+ T cells can directly kill peptide neurons (16). This finding further reveals the molecular pathology of narcolepsy.

Network Oscillations and Proteome Phosphorylation Mechanisms for Restoring Synaptic Homeostasis in Sleep

In the slow-wave sleep state, the hippocampus will spontaneously release instant high-frequency oscillations. This special brain wave is called sharp wave ripple (SWR). Yuji Ikegaya found that the frequency of sea SWR increased after spatial learning. The researchers tested synaptic function in the brains of mice. In normal mice, after experiencing SWR, the strength of synaptic connections in the hippocampal CA1 region decreased, and synaptic homeostasis recovered. After closed loop combined with optogenetic silencing of SWR during sleep, hippocampal CA1 synaptic connection intensity did not decrease significantly. At the same time, the ability of mice to learn and memory was impaired after being silenced by SWR, suggesting that SWR is the key to the restoration of synaptic homeostasis during sleep. Losing it will affect the formation of new memory (17).

Liu used the selected Sleepy sleepy mutant (the mutant gene is a protein kinase named SIK3), and based on this, he used the advanced tandem mass tag (TMT) labeling technology to systematically compare the “sleepy mouse” and “sleep-deprived mice”, and found that sleep needs and brain proteome phosphorylation level: 6 hr sleep deprivation can cause a significant increase in proteome phosphorylation. In further research, 80 hyper-phosphorylated proteins were found, of which 69 were classified as synaptic proteins. Some of them are structural proteins of synapses, and some are related to neurotransmitter release. Protein phosphorylation is a major way to regulate intracellular signal transduction and enzyme activity. This study proposed a new theory of synaptic homeostasis molecular regulation from the perspective of “phosphorylation/dephosphorylation cycle regulation” (18).

Network Oscillation Mechanism of Sleep Promoting Information Consolidation

During sleep, neurons associated with a task in the hippocampus are rapidly activated in a precise sequence, which strengthens memory of such tasks. Zugaro from the French National Institute of Health and Medical Research found that a theta sequence exists in rats during space exploration. The theta sequence parallel to the slow sequence can quickly and repeatedly activate the same location cells. For this reason, these theta sequences are called nested sequences. The awakening period enables rats to passively move for space exploration, which can specifically suppress nested sequences without affecting slow sequences. After suppression of nested sequences, the positional cells in the rat’s hippocampus did not reactivate in the same order during sleep as they did when they awoke. This result indicates that nested sequences are essential for memory consolidation during sleep (19).

Marion Inostroza uses novel object recognition (NOR) was to detect non-hippocampal-dependent memory, and found that hippocampus is crucial for forming long-term memory that is not hippocampal-dependent during sleep. After the NOR task, the hippocampus was inactivated during sleep, and a memory test was performed 3 weeks later to reveal that NOR memory was impaired. Interestingly, in the awakening period of NOR memory acquisition or memory retrieval, inactivated hippocampus does not affect NOR memory, suggesting that the hippocampus is crucial for the formation of persistent NOR memory during sleep. Further mechanistic studies have found that NOR memory during sleep is positively correlated with slow cortical oscillations and spindle wave activity, suggesting that slow oscillations and spindle wave activity participate in the consolidation of non-hippocampal dependent memory (20).

SLEEP PROTECTS MEMORY FROM POST-INTERFERENCE

As early as 1885, Ebbinghaus published a series of “Forgetting Curve” studies on the experimental psychological research on memory. He experimented on himself, unintentionally the oblivious rules of the word pairs, and draw the famous oblivion line indicates that forgetting is fast within an hour of learning, and appeared and reached a plateau after a few days. He noticed, if sleep occurs during the retention interval of memory, forget-

ting will decrease. This phenomenon was also observed in subsequent studies on forgetting curves.

Memory research in the first half of the 20th century focused on forgetfulness. For this reason, researchers have proposed two concepts: one is “fading change” account for the concept-assuming memory traces decay over time, which causes time-dependent forgetting; the other is “interfering” with the concept that supposes forgetting is the result of learning new information, and new knowledge interferes with and overwrites traces of old memories. In a canonical study, Jenkins and Dallenbach concluded: “Forgetting is not a question of the decline of old impressions and associations, but rather an old message that is disturbed, suppressed or newly received information makes the problem of obscuration. Because sleep represents a reduced period of inner-external information coding in time, so by sleeping to reduce information interference seems to be crucial. Many studies later have also confirmed the positive effects of sleep on memory, and observed the longer memory retention intervals from 24 hours to 6 days. Furthermore, interesting study found that the effect of sleep on memory formation is time-dependent, and the effect of sleep shortly after learning had a stronger effect than much later sleep. However, it is assumed that sleep can generally reduce external events.

PERSPECTIVE

In 2018, several new nodes in the brain that regulate arousal sleep were identified; how arousal sleep regulatory nodes are regulated by biological rhythm signals is also further elucidated. At the same time, important breakthroughs have been made in the mechanisms by which sleep promotes synaptic homeostasis and memory consolidation. With the application of advanced nerve beam tracing technology, light / drug genetic technology, two-photon imaging technology and multi-channel recording technology, in the foreseeable future, the key nodes in the brain that regulate wakeful sleep and the connections between nodes are about to be fully resolved. At that time, we will have a panoramic understanding of the mechanism of wakeful sleep. In uncovering the mystery of awakening sleep, we also need to clarify the following aspects.

Previous studies have often used certain types of neurons in the brain area as homogeneous units to evaluate their role in the regulation of arousal sleep. Using

advanced single-cell RNA sequencing, there is growing evidence that within these important wakefulness-regulated brain regions, even morphological and functional heterogeneity exists in neurons of the same type (21-23). For this reason, awakening sleep still needs to analyze the fine loop mechanism of its occurrence on the basis of new cell typing.

At present, a large number of studies have analyzed the cellular and neural circuit mechanisms of awakening sleep. On the other hand, we should explore the nature of awakening sleep. The essence of awakening is to make the brain have conscious and thinking activities, and sleep is the down-regulation of conscious activities. Only by clarifying the core brain regions of consciousness and thinking activity, can we clearly understand how the different wakefulness sleep regulation loops work in harmony from the “whole” point of view to realize the consciousness and thinking activity of the brain.

As for the function of sleep, on the one hand, sleep can reactivate the neural circuit that stores information, enhance synaptic functional connections, and achieve information consolidation or transfer (2). However, the brain receives a variety of modal information when awakening, how the sleep period triggers the reactivation of different information, and the characteristics, information transfer pathways and mechanisms of different types of information reactivation are not completely clear. At the same time, it is unclear what different roles NREM sleep and REM sleep play in information processing. On the other hand, sleep promotes the restoration of synaptic homeostasis and down-regulates synaptic functional connections. How to distinguish between “informative synapses” and “non-informative synapses” during sleep? The issue is still unclear. In addition, whether there are other new functions of sleep needs further research.

Finally, the study of awakening sleep urgently needs to apply the innovative results of basic research to clinical transformation and application. Solving the mystery of sleep will greatly promote the development of sleep medicine, and promote the fine typing and diagnosis of sleep diseases at the molecular and cellular level. At the same time, basic research also provides precise targets for the treatment of sleep disorders. Drug development or non-invasive targeted interventions aimed at specific targets will help achieve precise interventions for sleep disorders. ■

ARTICLE INFORMATION

Author Affiliations: Group of Neuropharmacology and Neurophysiology (Wang), Division of Neuroscience, The BASE, Chapel Hill, NC 27510, USA.

Author Contributions: Dr. Wang has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wang.
Acquisition, analysis, or interpretation of data: Wang.
Drafting of the manuscript: Wang.

Critical revision of the manuscript for important intellectual content: Wang.
Statistical analysis: N/A.
Obtained funding: N/A.
Administrative, technical, or material support: Wang.
Study supervision: Wang.

Conflict of Interest Disclosures: Wang declared no competing interests of this manuscript submitted for publication.

Funding/Support: N/A.

Role of the Funder/Sponsor: N/A.

How to Cite This Paper: Wang F. Sleep and memory consolidation. *Sci Insigt.* 2019; 31(3):107-115.

Digital Object Identifier (DOI):
<http://dx.doi.org/10.15354/si.19.re127>.

Article Submission Information: Received, September 10, 2019; Revised: October 29, 2019; Accepted: November 05, 2019.

REFERENCES

- Weber F, Dan Y. Circuit-based interrogation of sleep control. *Nature* 2016; 538(7623):51-59.
- Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci* 2010; 11(2):114-126.
- Peever J, Fuller PM. The biology of REM sleep. *Curr Biol* 2017; 27(22):R1237-R1248.
- Gent TC, Bassetti C, Adamantidis AR. Sleep-wake control and the thalamus. *Curr Opin Neurobiol* 2018 52:188-197.
- Hu Z, Ren S. The Role of thalamus in arousal control. *J Third Mil Med Univ* 2018; 40(23):2119-2121.
- Ren S, Wang Y, Yue F, Cheng X, Dang R, Qiao Q, Sun X, Li X, Jiang Q, Yao J, Qin H, Wang G, Liao X, Gao D, Xia J, Zhang J, Hu B, Yan J, Wang Y, Xu M, Han Y, Tang X, Chen X, He C, Hu Z. The paraventricular thalamus is a critical thalamic area for wakefulness. *Science* 2018; 362(6413):429-434.
- Hua R, Wang X, Chen X, Wang X, Huang P, Li P, Mei W, Li H. Calretinin neurons in the midline thalamus modulate starvation-induced arousal. *Curr Biol* 2018; 28(24):3948-3959.
- Mátyás F, Komlósi G, Babiczky Á, Kocsis K, Barthó P, Barsy B, Dávid C, Kanti V, Porrero C, Magyar A, Szűcs I, Clasca F, Acsády L. A highly collateralized thalamic cell type with arousal-predicting activity serves as a key hub for graded state transitions in the forebrain. *Nat Neurosci* 2018; 21(11):1551-1562.
- Gent TC, Bandarabadi M, Herrera CG, Adamantidis AR. Thalamic dual control of sleep and wakefulness. *Nat Neurosci* 2018; 21(7):974-984.
- Honjoh S, Sasai S, Schiereck SS, Nagai H, Tononi G, Cirelli C. Regulation of cortical activity and arousal by the matrix cells of the ventromedial thalamic nucleus. *Nat Commun* 2018; 9(1):2100.
- Oishi Y, Xu Q, Wang L, Zhang BJ, Takahashi K, Takata Y, Luo YJ, Cherasse Y, Schiffmann SN, de Kerchove d'Exaerde A, Urade Y, Qu WM, Huang ZL, Lazarus M. Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice. *Nat Commun* 2017; 8(1):734.
- Luo YJ, Li Yd, Wang L, Yang SR, Yuan XS, Wang J, Cherasse Y, Lazarus M, Chen JF, Qu WM, Huang ZL. Nucleus accumbens controls wakefulness by a subpopulation of neurons expressing dopamine D1 receptors. *Nat Commun* 2018; 9(1):1576.
- Yu X, Li W, Ma Y, Tossell K, Harris JJ, Harding EC, Ba W, Miracca G, Wang D, Li L, Guo J, Chen M, Li Y, Yustos R, Vyssotski AL, Burdakov D, Yang Q, Dong H, Franks NP, Wisden W. GABA and glutamate neurons in the VTA regulate sleep and wakefulness. *Nat Neurosci* 2019; 22(1):106-119.
- Guo F, Holla M, Díaz MM, Rosbash M. A circadian output circuit controls sleep-wake arousal in *Drosophila*. *Neuron* 2018; 100(3):624-635.
- Yadlapalli S, Jiang C, Bahle A, Reddy P, Meyhofer E, Shafer OT. Circadian clock neurons constantly monitor environmental temperature to set sleep timing. *Nature* 2018; 555(7694):98-102.
- Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, Jovic S, Jarrossay D, Mathis J, Zellini F, Becher B, Lanzavecchia A, Khataami R, Manconi M, Tafti M, Bassetti CL, Sallusto F. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature* 2018; 562(7725):63-68.
- Norimoto H, Makino K, Gao M, Shikano Y, Okamoto K, Ishikawa T, Sasaki T, Hioki H, Fujisawa S, Ikegaya Y. Hippocampal ripples down-regulate synapses. *Science* 2018; 359(6383):1524-1527.
- Wang Z, Ma J, Miyoshi C, Li Y, Sato M, Ogawa Y, Lou T, Ma C, Gao X, Lee C, Fujiyama T, Yang X, Zhou S, Hotta-Hirashima N, Klewe-Nebenius D, Ikkyu A, Kakizaki M, Kanno S, Cao L, Takahashi S, Peng J, Yu Y, Funato H, Yanagisawa M, Liu Q. Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. *Nature* 2018; 558(7710):435-439.
- Drieu C, Todorova R, Zugaro M. Nested sequences of hippocampal assemblies during behavior support subsequent sleep replay. *Science* 2018; 362(6415):675-679.
- Sawangjit A, Oyanedel Cn, Niethard N, Salazar C, Born J, Inostroza M. The hippocampus is crucial for forming non-hippocampal long-term memory during sleep. *Nature* 2018; 564(7734):109-113.
- Moffitt JR, Bambah-Mukku D, Eichhorn SW, Vaughn E, Shekhar K, Perez JD, Rubinstein ND, Hao J, Reggev A, Dulac C, Zhuang X. Molecular, spatial, and functional single-cell profiling of the hypothalamic preoptic region. *Science* 2018;

- 362(6416):Eaau5324.
22. Ren J, Friedmann D, Xiong J, Liu CD, Ferguson BR, Weerakkody T, DeLoach KE, Ran C, Pun A, Sun Y, Weissbourd B, Neve RL, Huguenard J, Horowitz MA, Luo L. Anatomically defined and functionally distinct dorsal raphe serotonin sub-systems. *Cell* 2018; 175(2):472-487.
23. Totah Nk, Neves Rm, Panzeri S, Logothetis NK, Eschenko O. The Locus Coeruleus is a complex and differentiated neuromodulatory system. *Neuron* 2018; 99(5):1055-1068.■