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The Complex Relationship Between Sleep and Memory

New research has implications for shift workers and those recovering from damage to brain, spinal cord

WASHINGTON, DC — Research released today reveals exciting new insights into the intricate relationship between sleep and memory, advancing understanding about how to protect the brain from problems associated with chronic sleep deprivation and traumatic brain injury, as well as suggesting potential methods for helping people to better learn how to use neuroprosthetic devices. The findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Today's new findings show that:

- Increasing the production of a naturally occurring protein in mice enables the animals to retain spatial memory skills after being deprived of sleep, confirming that the brain pathway activated by that protein is a factor in memory problems associated with sleep loss (Jennifer Choi Tudor, PhD, abstract 291.07, see attached summary).
- Eating during what would normally be the "sleep" phase of the day causes memory problems in mice, even if the animals get enough sleep at another time of the day, a finding that may have implications for shift workers and others who experienced disrupted sleep patterns (Christopher Colwell, PhD, abstract 454.30, see attached summary).
- Two drugs restored function and reduced excessive sleepiness in brain-injured mice, perhaps by protecting the brain from inflammation, a dangerous after-effect of TBI (Rachel Rowe, PhD, abstract 608.04, see attached summary).

Other recent findings discussed show that:

- Triggering activity in the brain's place cells during sleep can create "positive" artificial memories in mice that make the animals prefer a particular place in their environment, a finding that suggests complex forms of memory can be created during sleep (Karim Benchenane, PhD, presentation 559.04, see attached speaker summary).
- Neural processing that occurs during sleep enhances the ability of mice to control neuroprosthetics (computer-controlled devices designed to help restore lost motor function), a finding that may help people learn how to use such devices more effectively (Tanuj Gulati, PhD, presentation 177.03, see attached speaker summary).

"Sleep is essential to memory and brain function, but we are only beginning to understand the complex neurological mechanisms that are involved," said press conference moderator Ravi Allada, MD, of Northwestern University, an expert on the neurobiology of sleep. "These latest discoveries are helping us to identify those mechanisms and to create new approaches to preserving and enhancing memory."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find more information about sleep and memory at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Special Lecture: What Drives Sleep-Wake Cycles: Identification of Molecules and Circuits in Drosophila
Sunday, Nov. 16, 8:30–9:40 a.m., Hall D, WCC

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Abstract 291.07 Summary

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Boosting Production of Specific Brain Protein Reduces Memory Loss From Sleep Deprivation

Animal study identifies key brain pathway affected by sleep loss

Memory problems caused by lack of sleep were reduced in animals that produced more of a protein that is important in the synthesis of other proteins, according to new research presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

These results have implications for those who suffer from chronic lack of sleep, a number estimated to be as high as 45 percent of people worldwide, according to the World Association of Sleep Medicine. Insufficient sleep is linked with heart and kidney disease, type 2 diabetes, obesity, and degenerative brain disorders, and affects thinking and other cognitive skills, especially memory.

"The exact mechanism by which loss of sleep affects memory has been unclear," said lead author Jennifer Choi Tudor, PhD, of the University of Pennsylvania in Philadelphia. "In previous research, our lab has demonstrated that sleep deprivation causes a particular molecular pathway in the brain to become less active. In this new research, we've shown that keeping that pathway active after sleep deprivation helps to retain memory."

In the study, Tudor and her colleagues injected mice with a virus that triggers the production of a specific protein in the hippocampus, an area of the brain involved in memory formation. Levels of this protein, called phosphorylated eukaryotic translation initiation factor 4E binding protein 2 (4EBP2), are known to fall in mice when the animals are kept from sleeping. Other mice were given placebo injections. Three weeks later, all the mice were taught a task involving spatial memory. The animals were then deprived of sleep. When placed back in the environment where the spatial memory task had been learned, the sleep-deprived mice that had been injected with 4EBP2 — but not the ones that had received the placebo injections — performed the task as well as mice that were fully rested. These results suggest that reduced levels of 4EBP2 are a key component underlying memory problems associated with sleep deprivation.

Research was supported with funds from the National Institute of General Medical Sciences and National Institute of Mental Health.

Scientific Presentation: Monday, Nov. 17, 8–10:45 a.m., Room 206

291.07, Restoration of phosphorylated eukaryotic translation initiation factor 4E binding protein 2 (4EBP2) in the hippocampus rescues memory impairment due to sleep deprivation
J. C. TUDOR, E. J. DAVIS, R. HAVEKES, T. ABEL; Univ. of Pennsylvania, Philadelphia, Pa.

TECHNICAL ABSTRACT: Sleep loss produces deficits in hippocampal synaptic plasticity and hippocampus-dependent memory storage. However, the molecular and cellular mechanisms that underlie these effects of sleep deprivation remain unclear. Previous work from our laboratory demonstrated that a prominent effect of even brief periods of sleep deprivation is attenuation of mammalian target of rapamycin (mTOR) signaling in the hippocampus. Specifically, five hours of total sleep deprivation reduces phosphorylated eukaryotic translation initiation factor 4E binding protein 2 (4EBP2) that subsequently leads to impaired protein synthesis. However, it is yet to be determined whether restoring downstream mTOR signaling in the hippocampus is sufficient to prevent the cognitive deficits associated with sleep deprivation. To address this important question, we developed an adeno-associated virus (AAV) with a CamKII alpha promoter fragment to induce expression of 4EBP2 selectively in excitatory neurons of the hippocampus. Mice were bilaterally injected with 4EBP2 AAV, and mice injected with enhanced green fluorescent protein (eGFP) AAV served as controls. Three weeks after hippocampal AAV infection, mice were trained in the hippocampus-dependent object place recognition task. Afterwards, mice were sleep deprived for five hours or left undisturbed in their home cage. We found that hippocampal overexpression of 4EBP2 resulted in increased phosphorylated 4EBP2, which was sufficient to prevent the memory deficits associated with sleep deprivation in the object place recognition task. These findings indicate that attenuated phosphorylated 4EBP2 levels in the hippocampus and subsequent impaired protein synthesis is the critical component underlying the memory deficits associated with sleep deprivation in hippocampus-dependent learning tasks. Furthermore, this study defines the molecular mechanism by which loss of sleep impairs cognitive processes and highlights a vital role for translation and mTOR activation on long-term memory formation.

Abstract 454.30 Summary

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Eating During Sleep Periods May Impair Memory

Animal study suggests eating at inappropriate time of day can disrupt learning, memory

A study in mice suggests eating during the sleep phase of a daily sleep-wake cycle — even if the animals get adequate sleep at another time of the day — may be harmful to memory. The research was released today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"With so many members of our society experiencing chronic disruptions in their sleep-wake cycle due to shift work and illness, these findings could have broad implications for human health and wellness," said study co-author Christopher Colwell, PhD, of the University of California, Los Angeles.

For the study, Colwell and his colleagues synchronized mice to a normal daily sleep-wake cycle. Some of the mice were allowed to eat only during the active (awake) phase of the cycle, while the others were fed only during the sleep phase. These feeding schedules altered when the animals slept, but not how long they slept, so the mice still slept for the same total length of time. The schedules did not change the total amount of food either group of animals ate, nor their weight. When the mice's memory was tested, however, a significant difference was observed between the two groups. The mice fed during the sleep phase of the daily cycle scored worse on the memory tests than those fed during the active phase.

Further investigation revealed that the timing of the feedings altered the molecular clock of the hippocampus, one of the key brain regions involved in learning and memory, in the animals fed during the sleep phase. Together, these results suggest that eating at an inappropriate time of the day may disrupt learning and memory.

Scientific Presentation: Monday, Nov. 17, 2–3 p.m., Halls A-C

454.30, Pronounced impact of out-of-phase food intake on learning and memory
D.H.-W. LOH[1], R.E. FLORES[1], D. TRUONG[1], S.A. JAMI[2], C.A. GHIANI[1], T.J. O'DELL[2], **C.S. COLWELL[1]**; [1]Psychiatry and Biobehavioral Sci., [2]Physiol., Univ. of California, Los Angeles, Los Angeles, Ca.

TECHNICAL ABSTRACT: The circadian system is a finely tuned network of central and peripheral oscillators headed by a master pacemaker, the suprachiasmatic nucleus (SCN). This network of oscillators governs daily rhythms in behavior and physiology, including cognition. Disruption of the circadian system by genetic mutations or environmental manipulations has severe consequences on cognition. In this study, we sought to determine the effects of chronic but stable misalignment of the circadian network by scheduling access to food at an inappropriate phase of the daily cycle. This manipulation alters the phase of many peripheral circadian oscillators without affecting the SCN. Mice were allotted a six-hour window in which food was made available either during their active phase (aligned) or during their inactive phase (misaligned). We determined that misaligned feeding also altered the temporal pattern of gene expression of the hippocampus. Chronic misalignment of food access resulted in reduced performance on the novel object recognition test and had a severe impact on the recall of contextual fear conditioning, indicating deficits in hippocampal-dependent learning and memory. Critically, although the temporal pattern of sleep was altered, there was no difference in the amount of sleep between the aligned and misaligned groups, thus ruling out effects of sleep deprivation on memory. At the physiological level, misaligned feeding led to deficits in hippocampal long-term potentiation, suggesting a role for the circadian oscillator in regulation of hippocampal function. Our findings suggest that circadian misalignment of the hippocampal oscillator has far-reaching effects not only on hippocampal physiology, but also on long-term memory, and highlight the importance of circadian regulation on cognition.

Abstract 608.04 Summary

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Scientists Identify Drugs That May Restore Function After Traumatic Brain Injury

Findings from animal study show reducing 'post-traumatic sleep' may improve recovery

Scientists have identified two new anti-inflammatory drugs that curb excessive sleepiness in mice after traumatic brain injury (TBI). Researchers also showed that these drugs help restore sensory, motor, and cognitive function in mice after TBI, perhaps by reducing post-TBI sleepiness — an indicator of brain inflammation. The animal research was presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Previously, these researchers confirmed that increased sleep is a primary consequence of TBI — even in the mildest cases — and that inflammation in the brain contributes to brain injury-induced sleep. They termed this phenomenon "post-traumatic sleep." Now the researchers have applied that knowledge to evaluate whether new drugs may reduce the inflammation that causes sleepiness and secondary injuries after TBI.

"Excessive sleepiness right after a brain injury is a marker of the brain's inflammatory response to an injury," said co-author Rachel K. Rowe, PhD, of the Barrow Neurological Institute at Phoenix Children's Hospital in Arizona. "Our initial findings indicated that two drugs could be used to reduce post-traumatic sleep, and presumably inflammation in the brain, to minimize the damaging effects of the inflammation and ultimately restore function, like motor skills and dexterity, shortly after the TBI."

A small protein called tumor necrosis factor alpha (TNF-α) plays a major role in the brain's inflammatory response to an injury and the post-traumatic sleep that follows an injury. While the body's inflammatory response is used to clean up and repair damaged tissue, it can also damage brain cells when too much inflammation occurs. In the new study, the researchers found that two drugs designed to inhibit receptors for TNF-α reduced post-traumatic sleep in brain-injured mice. These preliminarily effective drugs were then demonstrated to restore neurological and motor function in mice a week after injury.

Research was supported by Phoenix Children's Hospital and the Science Foundation Arizona.

Scientific Presentation: Tuesday, Nov. 18, 2014, 4–5 p.m., Halls A-C

608.04, Novel allosteric inhibitors of TNF-R1 modulate post-traumatic sleep resulting from experimental diffuseTBI in the mouse
J. LIFSHITZ[1,2], **R.K. ROWE**[3], *J.L. HARRISON[2,3], H. ZHANG[4], D.P. HESSON[4], *M. GREENE[4]; [1]Dept Neurosurg., Univ. Pennsylvania, Philadelphia; [2]Neurosci., Arizona State Univ., Tempe, Ariz.; [3]Barrow Neurolog. Inst., Phoenix Children's Hosp., Phoenix; [4]Pathology and Lab. Med., Univ. of Pennsylvania Perelman Sch. of Med.

TECHNICAL ABSTRACT: Clinical studies indicate that as many as 70% of traumatic brain injury (TBI) survivors suffer from sleep-wake disturbances. We have previously shown diffuse TBI acutely (1-6 hours post-injury) increases sleep in the mouse, a phenomenon we termed post-traumatic sleep. During this acute window of post-traumatic sleep, cortical levels of inflammatory cytokine tumor necrosis factor-α (TNF-α) were significantly increased, suggesting a relationship between inflammation, sleep regulatory cytokines, and sleep. In the preliminary study, we administer three novel allosteric inhibitors of TNF receptor 1 (TNF-R1) to test their effect on post-traumatic sleep in the mouse following diffuse TBI. We hypothesize that the administration of TNF-R1 inhibitors immediately following TBI will modulate post-traumatic sleep in the mouse through suppression of neuroinflammatory signaling. Adult male C57Bl/6 mice were subjected to moderate midline fluid percussion injury (n=26; 1.3 atm; 6-10 min righting reflex) or sham injury (n=7). Cohorts were divided into groups receiving either high (20 mg/kg) or low (2 mg/kg) doses of novel TNF-R1 inhibitors (Compound 7, SGT11, F002) or vehicle (10% DMSO in PBS). Immediately following TBI or sham injury, mice were given intraperitoneal injections of a TNF-R1 inhibitor or vehicle. Post-traumatic sleep was recorded via non-invasive piezoelectric sleep cages. In the first 6 hours immediately following injury, brain-injured vehicle-treated mice slept significantly more than uninjured sham mice ($F(1,11)=6.8$, $p=0.02$). Brain-injured mice treated with high dose Compound 7 ($F(1,8)=5.4$,$p=0.04$) or SGT11 ($F(1,7)=7.7$,$p=0.03$) slept significantly less than vehicle-treated mice. These data suggest a therapeutic potential of Compound 7 and SGT11 following TBI through the inhibition of post-traumatic sleep. As an extension to the preliminary sleep findings, these compounds were tested for efficacy in improving functional recovery following TBI on an additional cohort of mice (n=38). SGT11 restored sensorimotor function measured by the rotarod ($F(3,34)=6.6$, $p=0.001$) and neurological function measured by a modified neurological severity score ($F(3,34)=4.1$, $p=0.01$). Both SGT11 and Compound 7 restored cognitive function assessed by the novel object recognition task. These preliminary studies will guide future investigation of these novel compounds on pathological outcome after diffuse TBI in the mouse, potentially identifying a therapeutic intervention for sleep-wake disturbances following TBI.

Speaker Summary (559.04)

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Explicit Memory Creation During Sleep: The Causal Role of Place Cells on Navigation
Tuesday, Nov. 18, 11 a.m.–noon, Halls A-C

In this study, researchers used a brain-computer interface while mice slept to create an artificial memory that changed their behavior upon waking. The study also set out to demonstrate the causal role of place cells (hippocampal neurons that fire when animals are in a particular part of the environment) in spatial navigation.

Importantly, this work goes beyond previous observations showing that certain forms of conditioning relying on a reflex response to a stimulus can take place in the sleeping or anesthetized brain. Indeed, in this study, animals used the sleep-created artificial memory trace to navigate toward an explicit goal where reward was expected.

The hippocampus is considered to be the neuronal substrate of the "cognitive map" because of the firing of its principal cells in specific locations when the animal explores a given environment. Interestingly, during sleep, hippocampal neurons replay previous wake experiences during the so-called sharp wave ripples, an oscillatory pattern supporting memory consolidation.

While the animal is awake, however, it is impossible to dissociate its actual position from the associated place-cell firing, and the proposed functional role of place cells in navigation is based entirely on this correlation. We hypothesized that the transient decorrelation of place-cell activity from animal's current location during sleep could provide a way to directly test the functional role of place cells in navigation.

In this study, we used the spontaneous activity of a given place cell during sleep to automatically trigger rewarding stimulations of the medial forebrain bundle (MFB), a neuronal pathway known to induce a positive reinforcement. After waking up from this sleep-pairing protocol, animals displayed a goal-directed behavior toward the place field and a place preference that was sensitive to extinction.

Altogether, the results obtained with our closed-loop system show that a new explicit memory trace was induced during sleep. Moreover, we showed that pairing spikes of a given place cell with rewarding stimulation during sleep, when its firing activity was decorrelated from the animal position, led to a place preference toward the related place field, demonstrating that place-cell activity itself has a functional role in spatial memory and navigation. Finally, our results support the theory of spatial reactivation during sleep by showing that place cells encode the same spatial information during sleep and wakefulness.

We are now investigating whether this closed-loop system can be used to reverse a stressful experience during wake by a positive one during sleep — a potential new therapeutic strategy for post-traumatic stress disorder.

The findings from this study provide a direct proof for the functional role of place cells in spatial navigation and further support the cognitive map theory. They also offer new experimental evidences that complex forms of memory can be created during sleep. Ultimately, this work could lead new therapeutic opportunities by offering the technical possibility of acting on the brain specifically during sleep.

Research was supported with funds from the Foundation for Medical Research, the National Research Agency, the National Center for Scientific Research: Interdisciplinary Research Programs, ATIP-Avenir, and the city of Paris.

Speaker Summary (177.03)

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Reactivation of Emergent Task-Related Ensembles During Slow-Wave Sleep After Neuroprosthetic Learning
Sunday, Nov. 16, 10–11 a.m., Halls A-C

This research shows that neural processing during sleep can improve direct brain control of neuroprosthetic devices.

The field of neuroprosthetics aims to restore motor function by integrating the computational power of artificial electronic systems with the brain. Specifically, the goal is to allow patients with severe disability to exert direct neural control over assistive devices. The main components of such a system include (1) recordings of neural activity from motor areas of the brain, (2) mathematical algorithms to transform the activity into control signals, and (3) an assistive device driven by these control signals.

Past research has shown that learning control of neuroprosthetic systems requires interplay between learning processes in the brain as well as "learning" in the mathematical algorithms, which can modify its own parameters over time. While multiple studies have shown the feasibility of neuroprosthetic control, little was known about neural processes that might allow stable long-term control.

Based on a growing body of literature regarding sleep and improvements in memory, we directly examined whether neural processing during sleep can facilitate neuroprosthetic control. Using a rodent model that requires learning of neuroprosthetic control, we examined the link between sleep-dependent neural processing and improvements in control. We found that successful learning of control was linked to reactivation of neural patterns during sleep. This was not present after poor learning sessions. We also found that time spent in sleep could predict performance improvements upon awakening.

These results suggest that neural processing during sleep can improve neuroprosthetic control upon awakening. The next step is to delve deeper into the neural processes that support this. It is possible that modifying such processes could further improve neuroprosthetic control and more rapidly allow skilled control that resembles natural movements.

Research was supported with funds from the Department of Veterans Affairs and the Burroughs-Wellcome Fund.