Embargoed until November 18, 11:30 a.m. ET
Press Room, November 15–19, (202) 249-4125

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WHY DO WE SLEEP? STUDIES REPORT NEW EVIDENCE THAT SLEEP INFLUENCES BRAIN'S ABILITY TO LEARN AND REMEMBER

Sleep creates brain chemical environment conducive to memory; sustained sleep disturbances may impair brain functions weeks after sleep habits return to normal

Washington, DC — New studies released today shed important new light on the role sleep plays to promote learning and memory. The findings report that learning and memory problems caused by sleep disturbances may take weeks to overcome due to a drop in new brain cell birth; identify chemical conditions during sleep that promote memory; and support the benefits of a quick daytime nap to improve creative thought. The studies were released today at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health. At the meeting, researchers discussed new investigations into sleep, learning, and memory, and report they are getting closer to providing one answer for the fundamental question, why do we sleep?

New findings released today report that:

- Sustained sleep disturbances impaired learning in an animal study, even weeks after sleep habits returned to normal. Researchers speculate it may be due to a recently reported drop in new brain cell development caused by lack of sleep (Noemie Sportiche, abstract 784.9, see attached summary).
- The chemical environment in the brain during sleep may help strengthen memories. In a rat study, the lack of serotonin in the hippocampus during REM sleep established conditions that promote memory (Jorge Lopez, abstract 539.13, see attached summary).
- A nap boosts the brain's ability to create associations ("relational memory") and deduce general concepts from independent details (Hiuyan Lau, abstract 587.1, see attached summary).

In addition, researchers in two other sessions discuss emerging results indicating that:

- "Local sleep" — sleep induced in one part of the brain — can boost learning performance. Such evidence is helping build support for a new concept: that the strength of cortical circuits, and the synapses that make them up, grows while we are awake and scales down during sleep, ultimately allowing us to have plastic, flexible brains (see attached speaker's summary).
- A recent study showed how sleep affects developmental learning in young animals. When a young songbird wakes, its ability to imitate a tune decreases. However, birds with the worst performance upon awakening end up learning the song the best, indicating the importance of sleep processes to learning what becomes songbird "language" (see attached speaker's summary).

"We are learning that not only do we need to remember to sleep, we need to sleep to remember," said press conference moderator Robert Stickgold, PhD, of Harvard Medical School. "Proper nervous system function involves coordinated action of neurons in many brain regions, and sleep's ability to increase, alter, or slow that action is a key area for study. This is especially true for the ability to learn and remember, key skills for today's increasingly complex society."

– more –

In the last 12 months, Stickgold has received research support and/or speaker/consultant fees from Merck & Co., Actelion Pharmaceuticals, Sepracor, and Epix Pharmaceuticals.

Related Presentations:

Symposium: **Sleep, Neuroenergetics, and Neural Plasticity**
Tuesday, November 18, 1:30–4 p.m., Washington Convention Center, Ballroom B

Minisymposium: **Neuronal Development in the Context of Behavior: The Power of Birdsong**
Sunday, November 16, 8:30–11 a.m., Washington Convention Center, Room 202B

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Abstract 784.9 Summary

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Sleep Fragmentation Impairs Learning Weeks After Sleep Habits Normalize

Animal study shows cognitive effect of common human sleep disturbance

Sustained sleep disturbances can impair learning for weeks, even after sleep habits return to normal, according to new animal research reported at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings suggest that sleep quality has long-lasting effects on cognition and that it is difficult to make up for periods of poor sleep.

Sleep fragmentation, or frequent arousal from sleep, is a widespread form of sleep disturbance in humans. Previous studies have shown that sleep loss and fragmentation affect the storage of information that has already been learned. Dennis McGinty, PhD, and his colleagues at the University of California, Los Angeles, asked whether sleep fragmentation also affected the learning of new information. They induced sleep fragmentation in rats by briefly activating a treadmill every time the rats fell asleep and tested the rats in a spatial learning task.

The researchers found that rats that had experienced 12 days of sleep fragmentation showed learning deficits 14 days after returning to a normal sleep schedule. These rats had difficulty locating an escape hole using spatial cues. They also showed difficulty adjusting to the changing demands of the task, taking longer to find a new route when the location of the escape hole changed.

The researchers previously showed that sleep fragmentation in adult rats suppressed neurogenesis, the production and maturation of new brain cells called neurons. New neurons take approximately four weeks from production to maturity. According to McGinty, sleep fragmentation may have delayed or prolonged effects on learning by inhibiting neurogenesis.

"Our study suggests that sustained sleep supports neurogenesis," said McGinty. "Because the proliferation of new neurons yields its benefits only after a few weeks, cognitive deficits resulting from its interruption — by sustained sleep disturbance — may be manifested even weeks after sleep has normalized," McGinty said.

The research was supported by the U.S. National Institute of Mental Health and the Research Service of the Veterans Administration.

Scientific Presentation: Wednesday, November 19, 8–9 a.m., Washington Convention Center, Hall A-C

784.9, Prolonged sleep fragmentation induces delayed hippocampal-dependant learning deficits
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TECHNICAL ABSTRACT: Introduction. Sleep fragmentation is prevalent in human sleep-related disorders. In rats, sustained sleep fragmentation has a potent suppressive effect on adult hippocampal dentate gyrus (DG) neurogenesis. Normally, newly-generated DG neurons progressively mature over at least 4 weeks, and are hypothesized to participate in hippocampal-dependent learning. However, a prediction that suppression of neurogenesis would impair hippocampal-dependent learning at the time when neurons are expected to reach maturity has not been tested.
Methods. Sprague-Dawley rats were surgically-prepared with EEG and EMG electrodes for sleep state detection. We used a computer controlled treadmill system to induce sleep-dependent sleep fragmentation for 12 days, and used both yoked controls (YC), on the same treadmill, and cage controls (CC). Rats were injected with 5-bromo-2-deoxyuridine (BrdU, 200 mg/Kg) to label proliferating cells on days 4 and 11 of the procedures. Rats were then permitted to rest in their home cages for 14 days prior to cognitive testing. Cognitive performance was then tested

between 2 and 4 pm in a Barnes maze for 7 days, 5 trials a day, with 5 days at a constant escape tunnel position followed by 2 days with a rotated position (135° to the right). All groups were perfused the day after completion of the Barnes maze and DG sections were immunolabeled for both BrdU and NeuN to identify mature cells.
Results. Average time to reach the escape tunel and use of random search strategies were elevated in sleep fragmented compared to both YC and CC groups. Preliminary results suggest that sleep fragmented animals had lower double-labeled (BrdU and NeuN) cell counts than CC animals.
Conclusions. Sustained sleep fragmentation induced spatial learning deficits when tested 2 weeks after terminating the procedure. The poorer performance of the sleep fragmented rats could be due to the suppression of hippocampal DG neurogenesis.

Abstract 539.13 Summary

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Chemical State of Brain During Sleep Conducive to Strengthening Memories

Findings support growing evidence that sleep is important for learning and memory

The chemical environment in the brain during sleep may help strengthen memories, according to new findings reported at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The study shows that the addition of a chemical that is normally absent in the brain during a stage of sleep reduces long-term potentiation (LTP), a cellular "building block" for learning, in a brain circuit important for memory. The findings add to a growing body of evidence suggesting that sleep is important for memory.

During rapid eye movement (REM) sleep, brain activity increases. Previous research has suggested that this stage of sleep is important in information processing and storage. "Our lab has been investigating the hypothesis that the chemical milieu present in the hippocampus during REM sleep — that is, the absence of the chemicals norepinephrine and serotonin — serves a unique function for memory, giving REM sleep a singular role for learning that is not replaceable by more waking practice," said Gina Poe, PhD, at the University of Michigan, a co-author of the study.

Poe and colleagues found that a brain circuit connecting the cortex and the hippocampus showed more robust LTP in the absence of serotonin (as during REM sleep) than in its presence (characteristic of all other states). "This initial finding suggests that REM sleep provides a unique environment allowing memory consolidation," a process important in converting new memories to long-term ones, Poe said.

This work was supported by the U.S. National Institutes of Health and the University of Michigan Department of Anesthesiology.

Scientific Presentation: Tuesday, November 18, 8–9 a.m., Washington Convention Center, Hall A-C

539.13, Serotonin prevents LTP induction in the temporo-ammonic pathway of the anesthetized rat

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TECHNICAL ABSTRACT: Many findings linking Rapid Eye Movement Sleep (REMS) to information processing and storage come from studies of the influence of REMS on synaptic plasticity mechanisms. Synaptic plasticity changes are thought to be the basis for storage of information in the CNS. Our lab has been investigating the hypothesis that the neurochemical milieu generated in the hippocampus (i.e. low catecholamine levels) during REMS leads to the resetting of familiar information stored in the Schaffer collateral (SC) pathway. Increased activity in the temporo-ammonic (TA) pathway after long-term potentiation (LTP) may contribute to the resetting of the SC pathway. In the present study, we tested the effect of local injections of serotonin on LTP at the TA pathway in the anesthetized rat. We predicted that the presence of serotonin would reduce LTP induction in the TA pathway, which would suggest that REMS plays an important role for the consolidation of memories in the hippocampus.

Sprague-Dawley rats (270-450g) were anesthetized with urethane (1.5 g/Kg, i.p.) and mounted in a stereotaxic apparatus (Neurolab, St. Louis, MO). A cannulatrode was positioned in the CA1 stratum radiatum region (L:-3.1, AP:-4.0 from bregma) of the left hippocampus to record field EPSPs (fEPSPs) in response to stimulation of the TA pathway (L:-1.9, AP:-4.2 from bregma). Recordings were made every 30 sec utilizing a stimulus intensity that evoked 50-60% of the maximum fEPSP amplitude. An initial 15 min baseline was followed by a local injection (3 µl at a rate of 0.5 µl/min) of saline or serotonin (20 mM). A second 15 min baseline was established before attempting to induce LTP with theta burst stimulation (TBS: 10 bursts at 5 Hz and each burst with 4 pulses at 100 Hz) and recordings continued for 60 min post-TBS. Waveforms were acquired using the program WINWCP, stored on a PC, and analyzed off-line for the amplitude of the fEPSP.

Saline injection reduced the fEPSP amplitude by 14%, whereas serotonin infusion caused a 34% decrease, suggesting that serotonin has a negative effect on synaptic transmission. TBS induced LTP in 3 out of 4 rats in the saline group (mean 49% above 2nd baseline) and in 1 out of 4 animals in the serotonin treated group (10% above 2nd baseline). These *in vivo* findings are in agreement with previous *in vitro* studies investigating the effect of serotonin on LTP at the TA pathway. Here, we show that serotonin reduced basic synaptic transmission and the likelihood of LTP in the TA pathway. Accordingly, during REM sleep (when serotonin levels are low) LTP occurrence should be more likely than during waking, allowing for a unique consolidation function for this state.

Abstract 587.1 Summary

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Brief Naps Improve Relational Memory

Findings suggest that a daytime nap supports memory and creative thought

Napping improves some types of learning and memory, according to new research. The study shows that a brief daytime nap improves relational memory — the ability to make associations, extract rules, and generalize concepts. The findings were reported at Neuroscience 2008, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Chinese characters with the same graphical elements, or radicals, have related meanings. William Fishbein, PhD, and his doctoral student Hiuyan Lau at the City University of New York taught study volunteers the English meanings of Chinese characters. After some of the volunteers took a brief daytime nap, the researchers tested them on the meanings of familiar Chinese characters and unfamiliar ones that shared radicals with the ones they had learned.

Study participants defined familiar Chinese characters equally well, regardless of whether they had napped or not. However, volunteers that had napped did a better job of identifying the meanings of unfamiliar characters, based on their radicals. Furthermore, they were better able to define the common concepts depicted by the radicals. The results, taken together with a prior study, suggest that a brief nap helps people connect separate and discrete pieces of information and extract general concepts.

"The role of sleep in memory formation is not passive; rather, it is a period that actively fosters deeper processing of what we learned during wakefulness," said Fishbein. "Many people consider napping to be counterproductive. However, the results of our study clearly indicate that a brief period of sleep serves a rather important role in memory processes," he said.

This research was supported by The City University of New York.

Scientific Presentation: Tuesday, November 18, 8–9 a.m., Washington Convention Center, Hall A-C

587.1, Nap and relational memory - a daytime nap facilitates extraction of general concepts
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TECHNICAL ABSTRACT: Introduction: Sleep plays a role in memory consolidation. Despite its universality and long history of study, we still know little of the fundamental role of sleep in relational memory - the ability to make indirect associations based on items learned in separate occasions, to extract rules and to generalize. There is compelling evidence that the hippocampus, a known critical site to memory and to relational memory in particular, is operative during sleep. The present study investigated the effect of a daytime nap on a relational memory task that requires extraction of a general concept.
Method: Participants learned English meanings of Chinese characters, consisting of groups that shared the same left components called the radicals. Each radical represents a certain general concept. Characters sharing the same radical have related meanings. After either a daytime nap or a period of wakefulness, participants were first to match the English meaning to a given character in a multiple-choice task (MC task). However, the task consisted some new characters, which the participants had not seen before but shared the same radicals as the old characters. The choices were selected so that if the participants had extracted the concept of the radical, they would have been able to deduce the correct answer even if they had not been exposed to that given character before. Then, they were asked to state explicitly the meaning of isolated radicals (radical task).
Results: In the MC task, the nap group performed better than the no-nap group with near significance ($p = 0.057$). Importantly, they performed significantly better on the new characters ($t = 2.43$, $p = 0.027$) than the no-nap group. They also performed significantly better on the radical task ($t = 2.46$, $p = 0.026$).
Conclusion: The results suggest a nap facilitates reorganization of memory networks that underlie the extraction of general concepts from discretely learned items.

Speaker's Summary

Speaker: Chiara Cirelli, MD PhD **(608) 263-9236**
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Sleep and Synaptic Plasticity (600.2)
Symposium: Sleep, Neuroenergetics, and Neural Plasticity
Tuesday, November 18, 1:35–2:10 p.m., Washington Convention Center, Ballroom B

The function of sleep is a biological puzzle that is still unsolved. Yet, understanding the function of sleep is obviously important both scientifically and from the perspective of human health. Sleep is a pervasive, universal, and fundamental behavior: It occupies a third of our life, and an even larger proportion in infants; it is present in every animal species where it has been studied, from fruit flies to humans; it is tightly regulated, as indicated by the irresistible mounting of sleep pressure after prolonged wakefulness; and even partial deprivation of sleep has serious consequences on cognition, mood, and health. While all available evidence indicates that sleep is of the brain, by the brain, and for the brain, the function of sleep remains unknown despite decades of intensive research.

In fact, the lack of understanding of why we need to sleep is problematic not only from a scientific viewpoint, but also because of its vast implications for public health. Millions of people complain of sleep problems, from insomnia to excessive daytime sleepiness, from chronic fatigue to irritability associated with unsatisfactory sleep. Sleep problems are an important aspect of several psychiatric disorders, notably mood disorders and anxiety disorders. Finally, sleep deprivation has high social costs, from driving and work-related accidents to chronically poor performance. A large segment of the population is therefore treated routinely with drugs aimed at improving sleep, or at maintaining wakefulness in the face of sleep pressure. However, such treatments are hampered by our ignorance concerning the functions of sleep. Which sleep disturbances should be taken seriously because they reflect a functional impairment and which, if any, do not interfere significantly with the functions carried out by sleep? Which abnormalities of sleep are likely to have neurobiological consequences that can lead to psychiatric disorders such as depression? And finally, what aspect of sleep should be enhanced by pharmacological or behavioral treatments, and what indices should we consider to determine their effectiveness?

I will discuss a new hypothesis about the function of sleep, called the synaptic homeostasis hypothesis, which states that plastic processes during wakefulness result in a net increase in synaptic strength in many brain circuits; such increased synaptic weight comes at the expense of increased metabolic consumption and taxes the limited space in the brain gray matter. The hypothesis then states that, during sleep, synaptic strength is globally downscaled to a baseline level that is energetically sustainable and beneficial for memory and performance. According to the hypothesis, downscaling is mediated by the slow oscillations in membrane potential (around 1 Hz) that occur hundreds of times per night in every cortical neuron. Sleep would therefore be the price we have to pay for plasticity, and its function would be the homeostatic regulation of the total synaptic weight impinging on neurons (Tononi and Cirelli, *Brain Res Bull* 2003, *Sleep Medicine Rev.*, 2006).

The main claims of the synaptic homeostatic hypothesis are consistent with a large body of evidence at the behavioral, molecular, and neurophysiological level, and with results obtained with techniques ranging from computer simulations to human neuroimaging. However, the most stringent tests of any hypothesis have to do with novel, sometimes counterintuitive predictions that we have started to test only recently. For instance, one prediction of the hypothesis is that it should be possible to induce sleep locally, that to do so requires learning, not just use (plasticity, not just activity), and that such local sleep should have a performance-enhancing effect. Indeed, using high-density EEG in humans we found that, after a visuo-motor learning task, the intensity of sleep increases specifically in the cortical regions

involved in learning, and such increase correlates with the post-sleep improvement in performance (Huber et al., *Nature*, 2004). Recent experiments were done to obtain more direct evidence, both molecular and electrophysiological, concerning the occurrence of a progressive increase in the strength of cortical circuits during wakefulness, and concerning its downscaling during sleep. For example, the hypothesis predicts that waking should be associated with the widespread induction of molecular markers of synaptic potentiation, while sleep should be associated with the generalized induction of markers of synaptic depression. We found that indeed this is the case (Vyazovskiy et al., *Nature Neuroscience* 2008). Also, another prediction of the hypothesis is that the amplitude of brain responses to direct cortical stimulation should increase with time awake and decrease after sleep, and this is what we found in rats (Vyazovskiy et al., *Nature Neuroscience* 2008). I will discuss these results, as well as limitations and future challenges in testing this hypothesis.

Speaker's Summary

Speaker: Sebastien Deregnaucourt, PhD **(49) 81-57-932-401**
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Circadian Aspects of Birdsong Production and Learning (108.2)
Minisymposium: Neuronal Development in the Context of Behavior: The Power of Birdsong
Sunday, November 16, 8:35–8:55 a.m., Washington Convention Center: Room 202B

Speech acquisition in humans is a long-term process starting early in life. Human babies transform gradually their babbling into words and sentences by imitating mainly adults. Besides of humans, vocal learning has been described in many groups of animals, including songbirds. One of them is the Zebra Finch (Taeniopygia guttata), a tiny bird originally from Australia that one can find easily in pet stores worldwide. It is easy to breed in captivity and it is therefore extensively used in hundreds of labs in the world as the 'flying mice' of birdsong research. Young zebra finches learn their song during a narrow developmental period that starts around day 25 post hatching, when the birds starts to produce unstructured sounds (called 'subsong', akin of babbling) and ends when the bird is about 120 days of age. The adult song, which consists of the repetition of few syllables in a fixed order, will not change for the rest of the life. If it is still difficult to imagine recording all the sounds that an human infant will produce from birth to puberty, and impossible to control every sound that he/she will be exposed to during this period, such experimental conditions are now available for a songbird like the Zebra Finch. Thanks to recent technologic developments, we can now record all the sounds that this bird produces during the sensitive period and store them on hard disks (about 1GB of sounds is produced during a day). Using analytic tools, we can easily track each syllable from the mature version of the adult song to its emergence in the bird's subsong. We observed in young birds trained to learn a song with daily playbacks that the vocal changes towards the adult song are not monotonic from day to day. Actually, we observed huge song deterioration overnight; deterioration that disappeared progressively as the bird becomes adult. First, we thought that this deterioration was due to the fact that the bird had difficulties following awakening, something similar to what many humans experience when they just get out of the bed. We also thought that it was due to a lack of practice; zebra finches in contrary for example to nightingales do not sing at night. Some experiments consisting to prevent the bird from singing during certain times of the day ruled out these hypotheses, suggesting that this overnight song deterioration could be due to sleep. In humans and other animals, it has been shown that sleep facilitates learning and consolidation of memory, and even a nap is good enough to trigger significant improvements for a given task. So our results could be counterintuitive to what has been described previously. But when we looked at the final result, namely how well the bird succeeded to imitate the song model we were broadcasting during the experiment, we observed that the ones that deteriorated more their song overnight during development were those that imitated better the song model. Learning is a tradeoff between plasticity and consolidation of memory. We found that the birds actually improved daily their imitation during the time following this early period of deterioration. So this morning plasticity permits the bird to reshape its song, in order to achieve a better imitation of the song model. This study was the first one to demonstrate an effect of sleep on developmental learning in juvenile animals. Birdsong might now become a model of choice for investigating the effects of sleep on learning. We know that brain areas activated during song production in the zebra finch are actually reactivated while the bird is sleeping. To some extent, one could believe that the bird dreams of its song during the night, and that this activity is relevant for song learning. Birds share many features of sleep in common with mammals despite differences in the brain organization. For example, sleep in both groups is characterized by two main states: slow-wave sleep (SWS) and rapid-eye movement (REM) sleep. The contribution of these different states to the vocal learning process is now the next challenge in songbirds.