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FINDINGS REVEAL BRAIN MECHANISMS AT WORK DURING SLEEP

Insights into how sleep deprivation impacts dementia, different types of memory, and learning

NEW ORLEANS — New findings presented today report the important role sleep plays, and the brain mechanisms at work as sleep shapes memory, learning, and behavior. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

One in five American adults show signs of chronic sleep deprivation, making the condition a widespread public health problem. Sleeplessness is related to health issues such as obesity, cardiovascular problems, and memory problems.

Today's findings show that:

- Sleepiness disrupts the coordinated activity of an important network of brain regions; the impaired function of this network is also implicated in Alzheimer's disease (Andrew Ward, abstract 909.05, see attached summary).
- Sleeplessness plays havoc with communication between the hippocampus, which is vital for memory, and the brain's "default mode network;" the changes may weaken event recollection (Hengyi Rao, PhD, abstract 626.08, see attached summary).
- In a mouse model, fearful memories can be intentionally weakened during sleep, indicating new possibilities for treatment of post-traumatic stress disorder (Asya Rolls, abstract 807.06, see attached summary).
- Loss of less than half a night's sleep can impair memory and alter the normal behavior of brain cells (Ted Abel, PhD, abstract 807.13, see attached summary).

Other recent findings discussed show:

- How sleep enables the remodeling of memories — including the weakening of irrelevant memories — and the coherent integration of old and new information (Gina Poe, PhD, see attached speaker's summary).
- The common logic behind seemingly contradictory theories of how sleep remodels synapses, aiding cognition and memory consolidation (Giulio Tononi, MD, PhD, see attached speaker's summary).

"As these research findings show, we cannot underestimate the importance of a good night's sleep," said press conference moderator Clifford Saper, PhD, MD, from the Harvard Medical School, an expert on sleep and its deprivation. "Brain imaging and behavioral studies are illuminating the brain pathways that are blocked or contorted by sleep deprivation, and the risks this poses to learning, memory, and mental health."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations.

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Abstract 909.05 Summary

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Sleepiness Linked to Brain Changes in the Elderly

Similar changes have been associated with Alzheimer's disease

Elderly adults and people with Alzheimer's disease frequently report problems with sleep. Now, new research points to a possible brain malfunction that may link sleepiness and Alzheimer's disease. It finds that sleepiness is related to disrupted activity in the default mode network (DMN), a group of brain regions that are active when the brain is at rest, and which may be important in introspection. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Animal studies have linked sleep problems to an increased likelihood of developing Alzheimer's. Human studies have shown that disruption of DMN activity is associated with Alzheimer's disease-type brain plaques that form before the onset of memory symptoms. But no previous work has examined the effects of disrupted sleep in the DMN of the cognitively healthy elderly. The new research, presented by lead author Andrew Ward of Massachusetts General Hospital provides this missing link — a human study showing that daytime sleepiness is associated with disrupted DMN function in elderly adults who do not have memory problems.

"The level of coordination within this network appears to be a sensitive measure of problems within the brain, and a possible indicator of Alzheimer's or other related memory problems," Ward said. "Ultimately, simple changes in sleep patterns may be beneficial for memory problems."

To explore the impact of chronic sleepiness on the brain in the absence of dementia, the researchers used a simple questionnaire to estimate the amount of daytime sleepiness experienced by 84 elderly people. Functional magnetic resonance imaging of the DMN (including the posterior cingulate cortex, the medial prefrontal cortex, and the lateral parietal cortices) revealed that those who reported more daytime sleepiness also showed less coordinated activity in these brain regions.

Research was supported with funds from the National Institute on Aging; the Fidelity Medical Foundation, the Harvard NeuroDiscovery Center; and the American Health Assistance Foundation.

Scientific Presentation: Wednesday, Oct. 17, 1–2 p.m., Hall F-J

909.05, Daytime sleepiness is associated with a loss of default mode network connectivity in cognitively intact elderly
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TECHNICAL ABSTRACT: *Background*: A set of cortical brain regions, collectively known as the default mode network (DMN) exhibit coherent activity during rest. DMN coherence can be quantified using functional connectivity magnetic resonance imaging (fcMRI) and has been suggested as a candidate biomarker for detecting early changes related to Alzheimer's disease (AD). Specifically, decreases in DMN connectivity have been associated with mnemonic deficits and amyloid-β plaque pathology, but also "normal aging". The sleep-wake cycle is disrupted in AD, and these relationships may be detectable before the onset of symptoms. However, the relationship between chronic sleepiness and DMN connectivity in non-demented elderly individuals remains unclear.
Methods: Eighty-four elderly subjects (age 73.2±5.7 years, 44 male) were administered the Epworth Sleepiness Scale (ESS) questionnaire, a subjective rating of sleepiness, and underwent a resting-state fcMRI scan. A subset of subjects (n=75, age 72.6±5.6 years, 39 male) was assessed with a battery of neuropsychological (NP) examinations. A confirmatory factor analysis was applied to this NP data and factor loadings for 6 factors (Speed, Executive Function, Memory, Fluency, Switching, and Working Memory) were derived.
For the fcMRI analyses, we extracted time series data from a set of previously published seed regions (8mm diameter spherical) in the posterior cingulate cortex (MNI [0 -53 26]), medial prefrontal cortex ([0 52 -6]), and lateral parietal cortices (averaged between [-48 -62 36] and [46 -62 32]). The seed time courses were correlated, normalized using Fisher's z, and averaged to produce a global measure of DMN integrity.
Results: We found that increasing daytime sleepiness was associated with decreased global DMN coherence. The correlations between nodes were also significantly related to ESS scores. We found no relationship with ESS and correlations between bilateral seeds in motor cortex, or between the DMN and three

other cortical networks. We did not find a relationship with ESS and neuropsychological scores, except a trend-level relationship between increasing ESS scores and decreasing factor scores for the Speed factor, consistent with previous work. All analyses controlled for age.
Conclusion: A self-reported measure of chronic daytime sleepiness in cognitively intact elderly subjects is related to decreased DMN coherence during resting-state. Additionally, there is a trend-level relationship between NP speed of processing and sleepiness. These findings may have important implications for elucidating age-related and AD-related alterations in sleep and network dysfunction.

Abstract 626.08 Summary

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Researchers Study the Impact of One Sleepless Night

Sleeplessness appears to tamper with brain function, impair memory

Researchers know that sleep deprivation impairs the human brain's "episodic memory" — its ability to form memories of scenes, events, and experiences — but just how this happens has been a mystery. New findings report that one sleepless night is associated with changes in how the brain's hippocampus communicates with a network of brain regions known as the default mode network (DMN), which may be related to self-perception. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Previous neuroimaging studies have shown that sleep deprivation impairs hippocampal activity during memory formation. The new research, reported by Hengyi Rao, PhD, of the University of Pennsylvania, shows the effects of such deprivation on hippocampal-DMN connectivity while the brain is at rest. The DMN is more active when the awake brain is resting and is neither task-oriented nor focused on the outside world. (For example, the DMN is thought to be active during daydreaming.)

"Sleep deprivation not only impairs active memory formation in the hippocampus, it also alters hippocampal connections to the DMN during times when the brain turns to introspection and musing," Rao said. "Moreover, these altered connections appear to correlate with later diminished episodic memory."

The researchers examined the effects of one night without sleep and two nights of recovery sleep on episodic memory and on the functional connectivity between the hippocampus and the DMN. Brain scans of 22 healthy adults were conducted three times: at baseline after nine hours of sleep; after 24 sleepless hours; and after two nights of recovery sleep. The participants also completed a scene encoding and recognition task each day. The results showed reduced functional connectivity between the DMN and hippocampus after sleep deprivation, compared to both base line and recovery sleep. Results after recovery sleep were the same as those at baseline.

The research was supported with funds from the National Institutes of Health and National Natural Science Foundation of China.

Scientific Presentation: Tuesday, Oct.16, 1–3 p.m., Room 268

626.08, Scientific Abstract: Reduced pcc-hippocampus connectivity predicts memory deficits after sleep deprivation
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TECHNICAL ABSTRACT: Introduction Sleep plays an important role in learning and memory processing. Growing evidence suggests that sleep deprivation (SD) degrades behavioral and neural capacity to encode new memories, particularly in the hippocampal complex. Recent neuroimaging studies have demonstrated the attenuation effects of SD on hippocampal activity during memory encoding tasks, while the effects of SD on hippocampal function during resting states remain largely unknown. In this study, we examined the effects of one night of acute total SD as well as two nights of recovery sleep on resting state functional connectivity (FC) and its relationship to episodic memory. Methods We scanned 22 healthy adults (12 male, age 22-48 yrs) three times between 7-9 AM on a Siemens 3T Trio scanner at rest using a standard EPI sequence. All subjects underwent the three scans in a fixed order: a first scan at baseline (BS) after normal 9hours sleep, the second scan after 24hours without sleep, and a third scan after two nights of recovery sleep (RS, 20 hours total sleep time). The subjects also completed a behavioral hippocampus-dependent scene encoding and memory task each afternoon. The hippocampus as well as the core node of the default mode network (DMN), and the posterior cingulate cortex (PCC), were selected as the seed regions for FC analyses, respectively. Data were analyzed with SPM8 and REST toolbox. Results Using PCC and hippocampus as the seed regions, both analyses showed significantly reduced functional connectivity between the DMN and hippocampus for SD compared with BS and RS (Fig.1, $p < 0.001$). However, no connectivity differences were found between BS and RS. Moreover, decreases in connectivity between PCC and hippocampus correlated with memory performance changes following SD ($r = 0.72$, $p < 0.001$). Conclusions: This study demonstrated significantly reduced PCC-hippocampal connectivity following SD. The observed correlation between PCC-hippocampal connectivity decreases and memory performance changes suggests that resting connectivity changes may be one mechanism by which SD impairs episodic memory.

Abstract 807.06 Summary

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Sleep to Forget: Unlearning Fear During Sleep

Proof of concept could lead to new treatments for PTSD

According to new work in a mouse model, fearful memories can be reactivated and potentially alleviated during sleep, a finding that could lead the way to more effective treatments for post-traumatic stress disorder (PTSD). The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The research, presented by Asya Rolls of Stanford University, found that if a fearful memory is linked to an odor, that stimulus could be used to reactivate the memory during sleep without disturbing slumber. Heller and colleagues found that if the reactivation were simply repeated, the fearful memory was exacerbated. But if the reactivation was carried out in the presence of a treatment that blocked the production of protein in the mouse's basolateral amygdala — a brain region involved in fear — the fearful memory was reduced.

PTSD is characterized by strong, highly emotional memories that can be triggered by specific environmental or social stimuli. In a treatment called extinction therapy, a patient repeatedly recalls the memory in a non-threatening environment, such as a therapist's office. But the treatment can become so closely associated with the office that it is not effective when the patient re-experiences the traumatic trigger in a different environment, such as on a street.

"Sleep is not linked to any particular place, and therefore the changes made to traumatic memories during sleep may weaken the fear response generally, regardless of where it is subsequently evoked," Heller said. "This could address a major limitation of current PTSD treatment."

In their experiments, the researchers paired an odor with a footshock experience in awake mice. That odor or a control odor was then introduced into the mouse's cage during sleep, and the mice's responses to the odors were tested the next day. Experiencing the conditioned odor during sleep caused an increase in the subsequent fear response. However, if a protein synthesis inhibitor was injected into the basolateral amygdala prior to sleep, the introduction of the conditioned odor during sleep resulted in a reduced fear response during subsequent tests when the animals were awake.

Research was supported with funds from the Down Syndrome Research and Treatment Foundation, the National Institute of Mental Health, and the Klerman Family Foundation.

Scientific Presentation: Wednesday, Oct. 17, 9–10 a.m., Hall F-J

807.06, Sleep to forget: Context independent interference with fear during sleep
*A. ROLLS, M. MAKAM, D. KROUGER, D. COLAS, L. DE LECEA, **C. H. HELLER**; Psychiatry, Stanford Univ., PALO ALTO, CA; Stanford, Stanford, CA

TECHNICAL ABSTRACT: Extinction therapy, in which a cue associated with a trauma is introduced in a safe environment, is one of the most effective treatments for post-traumatic stress disorder (PTSD). Evidence suggests that extinction is mediated by the formation of a new "safe" memory limiting the therapeutic effect to the environment in which it was generated. Therefore fear responses to previously extinct cues reemerge in novel environments. Sleep, rather, is a context-free environment during which therapy can be given. We hypothesized that the manipulation of memories during sleep will result in a generalized response to the cue, not limited to any specific environment. We tested this in mice using Pavolvian fear conditioning in which we paired an odor (Amyl acetate) to a footshock. After 24 hours (required for memory consolidation), we reactivated fear memories by applying the conditioned odor during NREM sleep (20 applications within 2 hours). To interrupt fear memories, we injected the protein synthesis inhibitor (Anisomycin) in the basolateral amygdala (BLA), a brain region necessary for memory storage, prior to applying odors. Two control groups were included. Both were injected with the protein synthesis inhibitor, however, one group received a novel odor during sleep that was not associated with a footshock and another control group received odor applications during the wake episodes in the following two hours to determine the specificity of this effect on sleep. Twenty-four hours later (for all groups), alert mice were placed in a novel environment and exposed to the conditioned odor, and their freezing response to that cue was measured. We found that while the mice that were injected with the protein synthesis inhibitor and exposed to the control odor during sleep or with the conditioned odor during wake showed similar freezing responses, the mice that received the conditioned odor during sleep showed an attenuated freezing response. These findings demonstrate the concept that sleep is a unique environment that enables the manipulation of specific memories in a context-independent manner.

Abstract 807.13 Summary

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How Much Sleeplessness Is Enough To Impair Memory?

Mouse study suggests memory impaired with loss of less than half a night's sleep

New studies in mice show that it takes a very small amount of sleep loss, equivalent to less than half a night's sleep, to produce significant impairments to memory and brain plasticity — the brain's ability to physically adapt and change on a cellular level. The findings were presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Ted Abel, PhD, of the University of Pennsylvania, reported that a brief three- to four-hour period of sleep loss is sufficient to disrupt memory formation and hippocampal long-term potentiation (LTP), a long-lasting strengthening of communication between nerve cells in the brain. LTP is considered a correlate of learning.

"Sleep disturbances have high co-morbidity rates with several neuro-psychiatric diseases, including bi-polar disease, as well as with aging," Abel said. "Understanding the minimal amount of sleep loss necessary to impair learning should ultimately provide new insights into treatments for these conditions."

To determine both the shortest period of sleep loss and the time of onset necessary to impair memory, mice were sleep-deprived for varying time increments. The onset of sleep deprivation began at varying hours following training in a special memory task.

If the mice were sleep-deprived for four or more hours immediately after the training, they had memory impairment. Three hours of sleep deprivation was sufficient to impair memory when the deprivation began an hour or more after learning.

The researchers also studied effects of sleep deprivation on LTP, and determined that sleep deprivation for four or more hours significantly hindered this molecular process in the brain.

Research was supported with funds from the National Institutes of Health.

Scientific Presentation: Wednesday, Oct.17, 8– 9 a.m., Hall F-J

807.13, Identifying the time course of sleep deprivation in modulating memory and hippocampal synaptic plasticity
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TECHNICAL ABSTRACT: Despite the fact that sleep exposes the organism to great risk with time spent unaware of its surroundings, it is an evolutionarily conserved phenomenon that is critical for survival. Chronic sleep loss leads to severe deficits in the ability of the organism to fight infection, regulate metabolism, and have proper cognitive function. Our lab has previously demonstrated that even a brief bout of sleep deprivation for six hours impairs hippocampal function, which is required for episodic memory formation. The purpose of this project is to examine the temporal dynamics of sleep deprivation, both in terms of period length and onset time post-learning, to determine the critical time frame when sleep deprivation impairs hippocampus-dependent memory consolidation in mice. To determine both the minimal amount and onset time of sleep deprivation sufficient to impair memory, mice were sleep deprived for decreasing time increments with onset occurring at varying hours post training in a spatial memory task, spatial object recognition (SOR). Long-term memory was assessed 24 hours later. Spatial memory in this task was impaired with 6 hours and 4 hours of sleep deprivation occurring immediately post-training. Memory was also impaired to a lesser extent when the animal was subjected to 3 hours of sleep deprivation post-task training, with onset occurring 1 hour following training. The temporal dynamics of sleep deprivation sufficient to impair hippocampal synaptic plasticity, the neural correlate of hippocampus-dependent memory consolidation, was also examined. Mice were sleep deprived for decreasing time increments and long-term potentiation (LTP) maintenance was examined. LTP maintenance was impaired by 5 hours and 4 hours of sleep deprivation. These findings suggest that a minimum of 3 hours of sleep deprivation is sufficient to impair hippocampal function. By identifying the temporal dynamics of sleep deprivation in terms of its effects on memory consolidation and synaptic plasticity we can effectively design molecular experiments with matching sleep deprivation time periods to elucidate the time frame for disruptions in the signaling pathways required for memory consolidation. This body of work will add to the field by enabling researchers to understand what occurs molecularly during the time span of sleep deprivation.

Speaker's Summary

Speaker: Giulio Tononi, MD, PhD (608) 263-6063
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Sleep Function and Synaptic Homeostasis: Implications for Learning and Memory

Symposium: Sleep Plasticity Pathways: Synapses, Circuits and Memory Consolidation (820.04)
Wednesday, Oct. 17, 1:30–4 p.m., New Orleans, La Nouvelle C

The function of sleep remains an unsolved biological puzzle.

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. A recent hypothesis about the function of sleep, the synaptic homeostasis hypothesis, states that plastic processes during wakefulness (and development) result in a net increase in synaptic strength in many brain circuits; such increased synaptic strength comes at the expense of increased metabolic consumption and higher demand for cellular supplies such as proteins and lipids, and reduces the informativeness of neuronal signals. Stronger synapses are also closer to their level of saturation, which may prevent further learning. According to the hypothesis during sleep synaptic strength is globally renormalized to a baseline level that is energetically sustainable and beneficial for memory and performance. Sleep is thus the price we pay for plasticity, and its core function is the homeostatic regulation of synaptic weight impinging on neurons. I will review recent experiments in flies, rodents and humans that provide molecular and electrophysiological evidence for the hypothesis and discuss limitations and future challenges.

Speaker's Summary

Speaker: Gina Poe, PhD (734) 763-2128
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Elegant Synaptic Remodeling During Sleep: Circuit and State/Trait Specificity as Needed

Symposium: Sleep Plasticity Pathways: Synapses, Circuits and Memory Consolidation (820.03)
Wednesday, Oct. 17, 1:30–4 p.m., New Orleans, La Nouvelle C

The theory that sleep plays an important role in memory formation and storage is supported by 50 years of experimental evidence gathered from animal and human subjects. However, the specific way that sleep alters memories remains unclear. Our research suggests that sleep is involved in memory processing in three ways. First, sleep, serves to strengthen incompletely learned memories. Second, sleep serves to streamline memory connections by weakening extraneous connections. Finally, sleep serves to remodel memories by facilitating the integration of old and new information into a coherent whole.

Conscious wakefulness is when new memories are formed through strengthening connections, called synapses, between neurons that encode various aspects of that memory. Our studies show that after the onset of sleep, these new memory connections are further strengthened while those connections made irrelevant by new experience, such as where you parked your car yesterday, are actively weakened during the same stages of sleep. We propose that weakening of synapses within a memory network is accomplished only when two conditions are fulfilled, (1) connected neurons in a network are activated asynchronously and (2) a neurotransmitter that protects against such synaptic weakening, noradrenaline, is absent. The only times when noradrenaline is normally absent are during REM sleep, the state most commonly associated with dreaming, and during brief 1-2 second intervals preceding sleep spindle brain waves during non-REM sleep.

In rats, we studied the physiological underpinnings of memory strengthening, streamlining and remodeling by monitoring neural memory circuits while animals learned and slept. We recorded over one hundred neurons simultaneously in each rat while they freely explored a new maze, and continued recording during the subsequent sleep period. When we removed a familiar wall in the maze, or switched the familiar places where they found their daily food during wakefulness, neurons involved in encoding only the old context exhibited the asynchronous erasure pattern consistent with streamlining the memory during noradrenaline-free non-REM sleep spindles and REM sleep. Meanwhile, neurons involved in encoding the new information displayed a synchronous activity that strengthens synapses during the same states. We also observed that an intermediate stage of sleep, the brief transition-to-REM sleep period, was involved in binding the new and old information together, remodeling memories into a coherent schema. The hippocampus simultaneously co-activated relevant old and new neuronal circuits during this transition, and did so while cells supplying noradrenaline to these networks fired rapidly, helping to form and strengthen a new, integrated network of synapses.

To test the hypothesis that noradrenaline specifically prevented the streamlining and remodeling functions, we prevented the decrease in noradrenaline during the sleep period after learning. We infused noradrenaline during sleep or gave an antidepressant that maintains noradrenaline at synapses for the duration of the post-learning sleep period. We found that treated rats learned the new information less efficiently. Their hippocampal map correspondingly displayed less place-specific activity. Moreover, their ability to efficiently locate food in an altered environment was diminished in proportion to the reduction in noradrenaline-free sleep.

These experiments suggest that efficient memory incorporation utilizes the different states and traits of sleep and wakefulness for specific and unique functions: memory encoding during wakefulness, memory incorporation/remodeling during the transition to REM sleep, and both streamlining and strengthening, during REM sleep and non-REM sleep spindles.

One important implication from these studies is that some of the primary symptoms of neuropsychiatric disorders could result from disturbed sleep characteristics, such as the reduction in sleep spindles in schizophrenia and the presence of noradrenaline throughout sleep in post-traumatic stress disorder. Such sleep disturbances may act to disrupt memory organization, thereby contributing to the debilitating nature of these mental disorders.