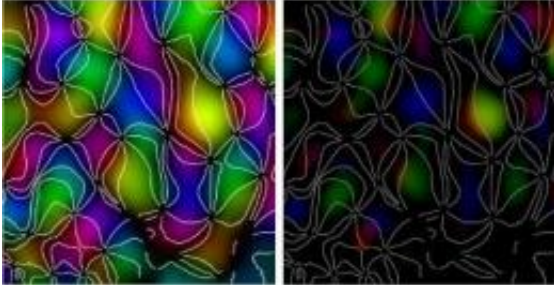


Why Sleep is Needed to Form Memories

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The world as the brain sees it. Optical "polar" maps of the visual cortex are generated by measuring micro-changes in blood oxygenation as the left eye (left panel) or right eye is stimulated by bars of light of different orientations (0-180 degrees). The cortical response to each stimulus is pseudo-colored to represent the orientation that best activates visual cortical neurons. If vision is blocked in an eye (the right eye in this example) during a critical period of development, neurons no longer respond to input from the deprived eye pathway (indicated by a loss of color in the right panel) and begin to respond preferentially to the non-deprived eye pathway. These changes are accompanied by alterations in synaptic connections in single neurons. This process, known as ocular dominance plasticity, is enhanced by sleep via activation of NMDA receptors and intracellular kinase activity. Through these mechanisms, sleep strengthens synaptic connections in the non-deprived eye pathway. Credit: Marcos Frank, PhD, University of Pennsylvania School of Medicine

If you ever argued with your mother when she told you to get some sleep after studying for an exam instead of pulling an all-nighter, you owe her an apology, because it turns out she's right. And now, scientists are beginning to understand why.

In research published this week in *Neuron*, Marcos Frank, PhD, Assistant Professor of Neuroscience, at the University of Pennsylvania School of Medicine, postdoctoral researcher Sara Aton, PhD, and colleagues describe for the first time how cellular changes in the sleeping brain promote the formation of memories.

"This is the first real direct insight into how the brain, on a cellular level, changes the strength of its connections during sleep," Frank says.

The findings, says Frank, reveal that the brain during sleep is fundamentally different from the brain during wakefulness.

"We find that the biochemical changes are simply not happening in the neurons of animals that are awake," Frank says. "And when the animal goes to sleep it's like you've thrown a switch, and all of a sudden, everything is turned on that's necessary for making synaptic changes that form the basis of memory formation. It's very striking."

The team used an experimental model of cortical plasticity - the rearrangement of neural connections in response to life experiences.

"That's fundamentally what we think the machinery of memory is, the actual making and breaking of connections between neurons," Frank explains

In this case, the experience Frank and his team used was visual stimulation. Animals that were young enough to still be establishing neural networks in response to visual cues were deprived of stimulation through one eye by covering that eye with a patch. The team then compared the electrophysiological and molecular changes that resulted with control animals whose eyes were not covered. Some animals were studied immediately following the visual block, while others were allowed to sleep first.

From earlier work, Frank's team already knew that sleep induced a stronger reorganization of the visual cortex in animals that had an eye patch versus those that were not allowed to sleep. Now they know why.

A molecular explanation is emerging. The key cellular player in this process is a molecule called N-methyl D-aspartate receptor (NMDAR), which acts like a combination listening post and gate-keeper. It both receives extracellular signals in the form of glutamate and regulates the flow of calcium ions into cells.

Essentially, once the brain is triggered to reorganize its neural networks in wakefulness (by visual deprivation, for instance), intra- and intercellular communication pathways engage, setting a series of enzymes into action within the reorganizing neurons during sleep.

To start the process, NMDAR is primed to open its ion channel after the neuron has been excited. The ion channel then opens when glutamate binds to the receptor, allowing calcium into the cell. In turn, calcium, an intracellular signaling molecule, turns other downstream enzymes on and off.

Some neural connections are strengthened as a result of this process, and the result is a reorganized visual cortex. And, this only happens during sleep.

"To our amazement, we found that these enzymes never really turned on until the animal had a chance to sleep," Frank explains, "As soon as the animal had a chance to sleep, we saw all the machinery of memory start to engage." Equally important was the demonstration that inhibition of these enzymes in the sleeping brain completely prevented the normal reorganization of the cortex.

Frank stresses that this study did not examine recalling memories. For

example, these animals were not being asked to remember the location of their food bowl. "It's a mechanism that we think underlies the formation of memory." And not only memory; the same mechanism could play a role in all neurological plasticity processes.

As a result, this study could pave the way to understanding, on a molecular level, why humans need sleep, and why they are so affected by the lack of it. It could also conceivably lead to novel therapeutics that could compensate for the lack of sleep, by mimicking the molecular events that occur during sleep.

Finally, the study could lead to a deeper understanding of human memory. Though how and even where humans store long-lasting memories remains a mystery, Frank says, "we do know that changes in cortical connections is at the heart of the mystery. By understanding that in animal models, it will bring us close to understanding how it works in humans."

Provided by University of Pennsylvania School of Medicine

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