Sleep suppresses brain rebalancing

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Credit: Brandeis University

Why humans and other animals sleep is one of the remaining deep mysteries of physiology. One prominent theory in neuroscience is that sleep is when the brain replays memories "offline" to better encode them ("memory consolidation").

A prominent and competing theory is that sleep is important for re-balancing activity in brain networks that have been perturbed during learning while awake. Such "rebalancing" of brain activity involves homeostatic plasticity mechanisms that were first discovered at Brandeis University, and have been thoroughly studied by a number of Brandeis labs including the lab of Brandeis professor of biology Gina Turrigiano.

Now, a study from the lab just published in the journal *Cell* shows that these homeostatic mechanisms are indeed gated by sleep and wake, but in the opposite direction from that theorized previously: homeostatic brain rebalancing occurs exclusively when animals are awake, and is suppressed by sleep.

These findings raise the intriguing possibility that different forms of brain plasticity - for example those involved in memory consolidation and those involved in homeostatic rebalancing - must be temporally segregated from each other to prevent interference.

The requirement that neurons carefully maintain an average firing rate, much like the thermostat in a house senses and maintains temperature, has long been suggested by computational work. Without homeostatic ("thermostat-like") control of firing rates, models of neural networks cannot learn and drift into states of epilepsy-like saturation or complete quiescence.

Much of the work in discovering and describing candidate mechanisms continues to be conducted at Brandeis. In 2013, the Turrigiano lab provided the first in vivo evidence for firing rate homeostasis in the

mammalian brain. Lab members recorded the activity of individual neurons in the visual cortex of freely behaving rat pups for 8 hours per day across a nine-day period during which vision through one eye was occluded.

The activity of neurons initially dropped, but over the next four days, firing rates came back to basal levels despite the visual occlusion. In essence, these experiments confirmed what had long been suspected - the activity of neurons in intact brains is indeed homeostatically governed.

Due to the unique opportunity to study a fundamental mechanism of brain plasticity in an unrestrained animal, the lab has been probing the possibility of an intersection between an animal's behavior and homeostatic plasticity. In order to truly evaluate possible circadian and behavioral influences on neuronal homeostasis, it was necessary to capture the entire 9-day experiment, rather than evaluate snapshots of each day.

For this work, the Turrigiano Lab had to find creative computational solutions to recording many terabytes of data necessary to follow the activity of single neurons without interruption for more than 200 hours.

Ultimately, these data revealed that the homeostatic regulation of neuronal activity in the cortex is gated by sleep and wake states. In a surprising and unpredicted twist, the homeostatic recovery of activity occurred almost exclusively during periods of activity and was inhibited during sleep. Prior predictions either assumed no role for behavioral state, or that sleeping would account for homeostasis.

Finally, the lab established evidence for a causal role for active waking by artificially enhancing natural waking periods during the homeostatic rebound. When animals were kept awake, homeostatic plasticity was

further enhanced.

This finding opens doors onto a new field of understanding the behavioral, environmental, and circadian influences on homeostatic plasticity mechanisms in the brain. Some of the key questions that immediately beg to be answered include:

- What it is about sleep that precludes the expression of homeostatic plasticity?
- How is it possible that mechanisms requiring complex patterns of transcription, translation, trafficking, and modification can be modulated on the short timescales of behavioral state-transitions in rodents?
- And finally, how generalizable is this finding? As homeostasis is bidirectional, does a shift in the opposite direction similarly require wake or does the change in sign allow for new rules in expression?

More information: Keith B. Hengen et al. Neuronal Firing Rate Homeostasis Is Inhibited by Sleep and Promoted by Wake, *Cell* (2016). DOI: 10.1016/j.cell.2016.01.046

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