Synaptic scaling in sleep

Laszlo Acsady and Kenneth D. Harris

We all need a good night's sleep.

Sleep appears to be a universal phenomenon in the animal kingdom (*1*) and lack of sleep leads to severe cognitive disruption(*2*). It seems that, in order to function correctly while awake, the brain must perform some specific processes that cannot be achieved while it is also actively controlling behavior. Yet, the actual biological function of sleep is still unknown. Using an array of cutting edge technologies, two new studies now provide a peek into the night-life of synapses, the basic units of connection in the nervous system. The data show substantial alterations in the structure and molecular machinery of synapses during sleep.

There are two main schools of thought for sleeps's function, which are not incompatible and may both be correct (or neither). "Restorative" theories hold that sleep's function is maintenance, such as repairing wear and tear in its cellular machinery, synthesizing macromolecules, replenishing energy supplies, and removing chemical waste-products (*3*, *4*). "Information-processing" theories instead hold that sleep's function is to allow computational processes that are not possible during behavior, such as consolidation or adjustment of memories. One of the most prominent of these holds that sleep serves primarily to weaken synapses, to counterbalance the enhancement of synaptic strength that occurred during waking (*5*–*7*). Two studies in this week's *Science* provide strong confirmation for synaptic downscaling during sleep, and important clues to its molecular mechanism.

De Vivo et al. used block face scanning electron microscopy to reconstruct large numbers of cortical spines in primary somatosensory and motor cortices after prolonged sleep, wake, or enforced wake states. They found that the area of axon terminals in contact with spines decreases by close to 20% during sleep compared to both wake and enforced wake states. However, this decrease is not uniform: no significant change in size was seen for spines in the upper 20% of the size distribution, with shrinkage observed only in the smaller 80% of the spines. Shrinking spines are also more likely to contain recycling endosomes, organelles whose presence likely reflects increased turnover of synaptic molecules. Since decreasing spine size likely reflects weaker synapses, the data suggest a downscaling of synaptic strength during sleep.

Diering et al. studied the molecular events leading to these changes. Using in vivo imaging they also observed a decrease in spine size, as well as Gria1 glutamate receptor content during sleep. A series of biochemical and proteomic analyses implicated a key receptor complex, involving the type I metabotropic glutamate receptor Grm5 and a scaffold protein, Homer, that links it to downstream signaling molecules such as protein kinase C and IP3 receptors. During sleep, a truncated form of this scaffold, Homer1a, moves from the cytoplasm to the synapse. Because Homer1a cannot fulfil the same scaffold function as the full-length protein, the IP3R signaling complex disassembles and an alternative, agonist-independent pathway finally leads to synaptic downscaling by decreasing Gria1 content of the synapse. Using *in vitro* and *in vivo* approaches, the authors implicate noradrenaline and adenosine – whose concentrations alternate with the sleep cycle – as neuromodulators that can drive these changes in spine dynamics.

These results make an impressive case for the hypothesis of net synaptic weakening during sleep and strengthening during wake. Yet many questions still remain open. First, what computational function might this downscaling during sleep play? If sleep simply downscaled all synapses uniformly, then presumably evolution could have found a way for this to happen during waking, without requiring a long period of behavioral inactivity. One possible answer to this puzzle comes from early studies of artificial neural networks (*8*, *9*). Recurrent neural networks with Hebbian plasticity rules are inherently unstable. If synchronous neural firing leads to synaptic strengthening, and strengthened synapses lead to increased synchrony, then synapses would strengthen without limit. One solution is to balance Hebbian plasticity against an opposing process, where synchronous patterns the network generates when deprived of external input lead to synaptic weakening. Learning rules based on this principle can be shown mathematically to perform a kind of optimal Bayesian inference, and such free-running cortical activity was suggested as the basis of dreams (*8*, *9*). An related but distinct theory holds that "smart forgetting" of synapses not recently used during waking might occur specifically during slow-wave (non-dreaming) sleep (*5*).

Thus a second critical experimental question is which precise synapses change strength during sleep. On this, the two studies suggest different scenarios: while de Vivo et al report no significant size decrease for the largest (presumably strongest) synapses, Diering et al report the largest decreases for spines that had the largest Gria1 content (also presumably strongest). A recent study indicates that actually only a small fraction of synapses are involved in learning a novel situation or motor skill (*10*) - will these show more, or less scaling in sleep? A third question concerns the precise phase of sleep in which these changes occur. Both REM and slow-wave sleep have been proposed as the phase where synaptic downscaling would occur. Finally, although the evidence for synaptic downscaling during sleep is now becoming very strong, the key assumption of the original theories of sleep renormalization (*8*, *9*), that plasticity during sleep is reversed to become anti-Hebbian, remains unproven. Thus, while the experimental evidence for a diurnal change in synaptic strength continues to build, the precise computational function this serves remains as mysterious as ever.

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