Sleep to Upscale, Sleep to Downscale: Balancing Homeostasis and Plasticity

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The synaptic homeostasis hypothesis of sleep proposes that slow wave sleep (SWS) causes downscaling of synaptic networks potentiated during information uptake in prior wakefulness. Two studies in *Neuron* challenge this mechanism. Chauvette et al. (2012) show that SWS mediates an up- rather than downregulation of excitatory postsynaptic potential responses. Grosmark et al. (2012) find that downscaling in hippocampal networks might be mediated through REM sleep theta rather than SWS.

Sleep is a phylogenetically highly preserved process that appears to be particularly well developed in the human brain. Much of sleep research focuses on identifying the main function of sleep, which over the centuries has been accounted for in quite different ways. The currently most widely accepted of these theories, the synaptic homeostasis theory proposed by Tononi and Cirelli (2003, 2006) (Figure 1), links the evident homeostatic regulation of sleep to mechanisms of plasticity and learning capabilities within the brain. The synaptic homeostasis theory assumes that uptake of information and encoding activity during wakefulness are associated with widespread synaptic potentiation, i.e., an upscaling of net synaptic strength, whereas sleep is associated with the global downscaling of synaptic strength. Synaptic downscaling during sleep is necessary to counter waking activity synaptic potentiation and associated growth, which would otherwise exceed available resources of energy and space. Of importance, the theory proposes that downscaling is achieved during slow wave sleep (SWS) rather than rapid eye movement (REM) sleep, because SWS is subject to the same direct homeostatic regulation as the sleep process as a whole. In this model, EEG slow waves (0.5–4 Hz) that include the <1 Hz slow oscillations and hallmark SWS reflect the increased overall strength of connections in the synaptic network, because their amplitude is particularly high at the beginning of the sleep period. Simultaneously, slow waves represent a mechanism for downscaling, because the repeated sequence of widespread membrane depolarization and hyperpolarization at a frequency of ~1 Hz favors processes of synaptic depotentiation and depression in the network (Tononi and Cirelli, 2006). As a consequence of ongoing downscaling, slow wave activity gradually decreases across the sleep period.

This hypothesis efficiently integrates a huge body of experimental findings in the field. Most importantly, it has stimulated a unique upsurge of research targeting sleep's role for the brain's plasticity. The current issue of *Neuron* presents two such studies that are remarkable inasmuch as their findings fundamentally question the concept of downscaling as proposed by the synaptic homeostasis theory.

In the first study, Chauvette et al. (2012) probed somatosensory cortical-evoked local field potential (LFP) responses to electrical stimulation (1 Hz) of the medial lemniscal fibers in cats before and after a period of SWS. Responses during waking following the first period of SWS, after a transient peak in amplitude, remained at a significantly higher level in comparison to the response amplitude during waking before this first SWS epoch (Figure 1). Neither subsequent periods of SWS nor the additional occurrence of REM sleep appeared to substantially alter this enhancement; i.e., once saturated after the first (or second) SWS period, responses remained at a distinctly higher level during all later wake phases. Longer SWS periods appeared to be associated with higher increases in the LFP response. Altogether, the data provide a coherent picture of particularly the first epoch of SWS during the rest phase upscaling rather than downscaling cortical networks. Importantly, this SWS-induced upscaling appears to be a global process that is not specifically linked to certain memories encoded during waking, because the slow 1 Hz stimulation rate used by Chauvette et al. (2012) is unlikely to induce plasticity itself, given the high spontaneous (~5 Hz) and evoked (up to 125 Hz) firing rates the stimulated medial lemniscal fibers typically show. Thus, the stimulations presumably probed responsiveness of the cortical network without producing themselves substantial synaptic changes.

Additional in vitro studies in slice preparations suggested that the SWS-induced potentiation of cortical responses is mediated by a calcium-dependent postsynaptic mechanism that requires coactivation of AMPA and NMDA receptors, further corroborating the view of synaptic potentiation rather than downscaling induced by SWS. While the synaptic homeostasis hypothesis allocates such long-term potentiation (LTP)-mediated synaptic upscaling to the waking brain, neither in vivo nor in vitro recordings by Chauvette et al. revealed any hints that cortical responsiveness globally increases across the wake period. Interestingly, the upscaling of excitatory postsynaptic potential responses observed after SWS-like stimulation patterns in vitro occurred only when the stimulation pattern included an intracellular hyperpolarizing current pulse mimicking the down phase of the slow waves. While the hyperpolarizing down phase of a slow wave has been considered a time framing

signal resetting activity in extended cortical networks (e.g., Mölle and Born, 2011), this result is the first to indicate a functional significance specifically for the slow-wave down state for LTP.

In showing that the slow waves of SWS can convey LTP-mediated synaptic upscaling, Chauvette et al.'s findings provide a neurophysiological basis for a rapidly growing body of data indicating a particular role for SWS in memory consolidation (Diekelmann and Born, 2010). Cortical representations, corticostriatal representations, and episodic memory representations extending over hippocampo-neocortical networks all appear to be enhanced by SWS (e.g., Frank et al., 2001; Huber et al., 2004; Wilhelm et al., 2011), and a causal contribution of slow oscillations (~0.75 Hz) has also been demonstrated (Marshall et al., 2006). Processes of sleep-dependent memory enhancement in these studies could well incur the net upscaling of cortical networks mediated by postlearning SWS.

However, Chauvette et al.'s findings appear to contradict the body of evidence arguing toward synaptic downscaling across sleep. For example, by measuring miniature excitatory postsynaptic currents, a valid indicator of synaptic scaling, Liu et al. (2010) showed signs of increased synaptic potentiation at the end of the wake period and reduced potentiation after sleep in rodent frontal cortex slices. Also, Vyazovskiy et al. (2008) showed that the slope and amplitude of cortical evoked responses to electrical stimulation were increased after wakefulness and decreased after sleep, with these changes correlating with changes in slow-wave activity. Moreover, amplitude and slope of slow waves, as well as the synchrony of cortical cell firing with slow waves, were found to decrease across periods of SWS (Vyazovskiy et al., 2009). Collectively, these and many other studies provide compelling evidence that there are global processes of synaptic downscaling at work during sleep. However, in contrast to Chauvette et al., who examined changes in cortical responsiveness across isolated periods of SWS, these studies examined effects of sleep as a whole comprising the repeating sequence of SWS and REM sleep. Thus, they basically do not exclude the possibility that REM sleep contributes to the net downscaling effect observed after sleep. Likewise, Chauvette et al. cannot exclude such a possibility, because they did not manipulate REM sleep.

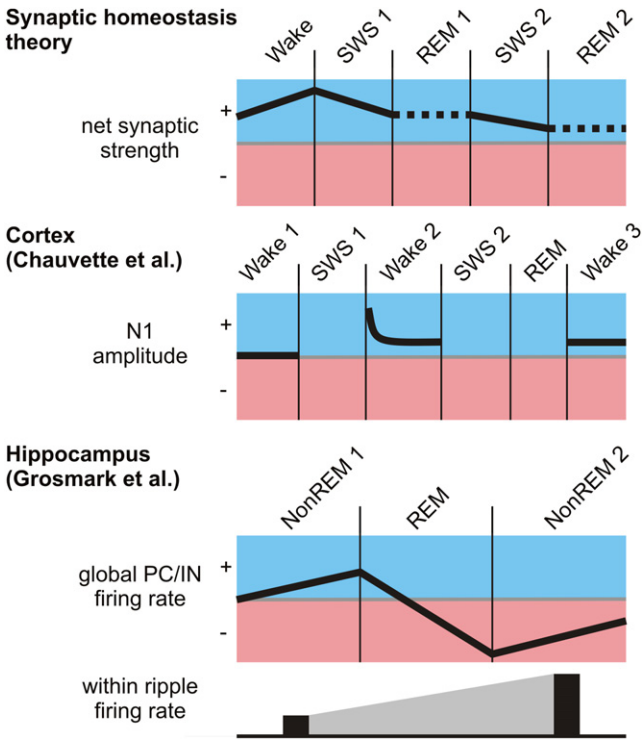

Figure 1. Schematic Overviews

Synaptic homeostasis theory proposes that during sleep, net synaptic strength in the cortex is reduced to afford homeostatic regulation of energy and volume demands, following increases during preceding wakefulness due to encoding of information. The theory appoints SWS the leading role in global synaptic downscaling, without a role for REM sleep. Chauvette et al. (2012) show that in the somatosensory cortex, N1 response amplitude to electrical medial lemniscus stimulation is increased rather than decreased after an initial period of SWS, with this increase remaining essentially unaltered by subsequent SWS or REM sleep periods. Grosmark et al. (2012) show that while global firing rate of pyramidal cells (PC) and interneurons (IN) in the hippocampus increases during SWS, this increase is outweighed by firing decreasing across REM sleep, which leads to a net reduction of firing over the whole sleep period. However, within-ripple firing rate of pyramidal cells, presumably reflecting local replay of newly encoded memories, increases across the complete NonREM-REM-NonREM cycle. Together, these studies challenge the concept that SWS alone is responsible for establishing synaptic homeostasis and tempt speculating on a two-process model of synaptic scaling during sleep, where SWS, through slow waves, supports synaptic upscaling and subsequent REM sleep, through theta activity, supports processes of downscaling, sparing memories tagged by reactivations during prior SWS.

Fortunately, also in this issue of *Neuron*, Grosmark et al. (2012) provide data suggesting such a contribution of REM sleep to processes of downscaling. Across triplets of NonREM-REM-NonREM sleep, they revealed a significant decrease in firing rates of rat hippocampal pyramidal cells and interneurons, consistent with the occurrence of downscaling across sleep (Figure 1). However, analyzing the firing dynamics within each NonREM and REM sleep period in detail revealed a substantial decrease in firing rates only during REM sleep; NonREM sleep periods instead were associated with an increasing firing rate. As the REM-associated decrease in firing rate outreached the firing increase during NonREM sleep, a net decrease in firing resulted across the whole sleep period. Interestingly, the mean decrease in firing rate from one to the next NonREM sleep period was significantly correlated to EEG theta power during the interleaving REM sleep period, suggesting that theta is involved in the downscaling process.

Reductions in firing rates do not necessarily reflect synaptic downscaling. Also, because hippocampal sleep differs from neocortical sleep, it remains unclear whether similar firing relationships occur in cortical neurons. Nevertheless, these data open a new perspective on how sleep could contribute to synaptic homeostasis by suggesting a possible involvement of REM sleep in downscaling. Rather than SWS alone, the sequence of SWS and REM sleep periods might be important (Giuditta et al., 1995).

In combination, the findings by Chauvette et al. (2012) and Grosmark et al. (2012) do not question the concept of global synaptic downscaling during sleep but instead suggest that processes during REM sleep should be taken into consideration. Beyond this, Grosmark et al.'s findings offer an interesting link between global processes of downscaling and the consolidation of specific memories in local networks, because they analyze firing occurring in the presence of hippocampal ripples, which regularly accompany the neuronal replay of newly encoded memory representations from the prior waking period (O'Neill et al., 2010). Ripple-associated replay during SWS has been considered the key mechanism launching the consolidation of newly acquired episodic memories (Diekelmann and Born, 2010). Grosmark et al. report that during ripples, cells fire more synchronously, and this firing paradoxically increases across NonREM-REM-NonREM sleep triplets. Moreover, the increased synchronous within-ripple firing occurred especially in those neuron assemblies that fired with high theta and gamma activity during interleaving REM epochs. The data tempt us to speculate that global processes of downscaling occur in concert with local processes of upscaling and shaping of memory representations across the sleep cycle in an interplay between ripple-associated and theta-associated replay activity. It has been proposed that one function of theta-associated replay might be to select memories for consolidation as, depending on the phase of the theta cycle, replay during theta potentiates or depotentiates the activated synaptic assemblies (Poe et al., 2000). Whatever the case, the findings by Grosmark et al. (2012) suggest that both global synaptic downscaling and local upscaling of specific memory representations originate from sequenced processes across the NonREM-REM sleep cycle. Future research might reveal that these global and local processes are inextricably tied to each other in jointly establishing sleep and memory.

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Neurodegeneration: New Road Leads Back to the Synapse

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Much of Parkinson's research over the last decade has focused on cellular stress as a candidate mechanism. In this issue of *Neuron*, a new study by Matta et al. (2012) addressing the biological functions of the Parkinson's gene LRRK2 now identifies a presynaptic substrate, homing in on the idea that synapse loss might be a central early aspect of neurodegeneration.

Genetic mutations found in familial forms of neurodegeneration have been a popular starting point for mechanistic studies that aim to uncover the early events preceding clinical manifestations. Common late-onset forms of neurodegeneration, such as Parkinson's disease (PD) and Alzheimer's disease (AD), progress slowly, only the pathological endpoints are well