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Cortical Inhibition, Plasticity, and Sleep

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Review of Brécier et al.

Sleep is essential for the formation of long-term memory (Diekelmann and Born, 2010). Two major hypotheses have emerged linking the memory functions of sleep to cortical excitability and plasticity. The synaptic homeostasis hypothesis (Tononi and Cirelli, 2003) states that sleep renormalizes the net increase in synaptic strength that accrues during wakefulness. In this framework, learning during waking experience leads to a cumulative potentiation of synapses. To avoid excessive potentiation and maintain homeostatic equilibrium, sleep resets the excitability of neurons by facilitating a net downscaling of synapses (Tononi and Cirelli, 2003). The two-stage theory postulates that sleep consolidates memory through hippocampo-cortical transmission (Frankland and Bontempi, 2005). According to this theory, waking experience is initially encoded as a labile, short-term representation in the hippocampus. In subsequent sleep, neuronal replay of hippocampal activity that occurred in prior wakefulness drives the strengthening of corticocortical connections, consolidating the labile memory into stable, long-term storage in the cortex.

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An element common to these two hypotheses is the modification of synaptic strengths within cortical networks. In the cortex and elsewhere in the mammalian brain, synapses undergo two major forms of long-lasting plasticity, LTP and LTD, characterized by a persistent increase or decrease in synaptic efficacy, respectively. Both processes are involved in memory (Malenka and Bear, 2004); and importantly, both processes depend on the activation of postsynaptic NMDARs and the resulting Ca^{2+} influx (Collingridge et al., 2010). Whether LTP or LTD occurs can depend on whether the postsynaptic cell spikes (Bi and Poo, 1998), which is determined partly by inhibitory input.

The principal projection neurons of the cortex (i.e., pyramidal cells) receive inhibitory inputs at specific somatodendritic regions from different interneuron subtypes, including parvalbumin (PV)-, somatostatin (SST)-, and vasoactive intestinal polypeptide (VIP)-expressing neurons (Tremblay et al., 2016). PVs inhibit the soma and proximal dendrites of pyramidal cells, whereas SSTs inhibit distal dendrites. VIP interneurons, in contrast, inhibit SST cells, causing disinhibition of pyramidal-cell distal dendrites (Fig. 1). The combinatorial input from different interneuron subtypes can generate distinct spatiotemporal patterns of inhibition over the pyramidal cell, allowing precise control of cortical output.

Much evidence points to inhibition as a key mediator of cortical plasticity (Maffei et al., 2010; Kuhlman et al., 2013). During the highly plastic "critical period" of visual system development, occlusion of one eye causes the representation of the spared eye to expand rapidly in the visual cortex (Wiesel and Hubel, 1963). This sensory-driven remapping depends on the transient suppression of PV interneurons and the consequent disinhibition of pyramidal cell somata (Kuhlman et al., 2013). Disinhibition also underlies enhanced plasticity in adulthood, although this involves primarily dendritic disinhibition through suppression of SST activity or increased VIP activity (Fu et al., 2015). Conversely, increased SST action blocks somatosensory plasticity associated with neuropathic pain (Cichon et al., 2017). Together, these findings indicate that PV, SST, and VIP interneurons control cortical plasticity in addition to controlling pyramidal cell output.

The role of inhibitory interneurons in sleep-dependent plasticity is only beginning to be understood (Aime et al., 2022). A recent study by Brécier et al. (2022) examined how the activity of PV, SST, and VIP interneurons evolves over the sleep/wake cycle. Using transgenic mice injected with a genetically encoded Ca^{2+} indicator, the authors selectively targeted PV, SST, or VIP interneurons and measured Ca^{2+}-driven fluorescence changes over wake, rapid-eye movement (REM) sleep and non-REM (NREM) sleep. The Ca^{2+} signal is commonly used as a measure of neuronal activity; and although it does not resolve fast events such as action potentials, it enables the simultaneous monitoring of multiple cells *in vivo*. Using mice that were trained to sleep

in head-restraints, the experimenters imaged interneurons of the S1 barrel cortex with two-photon microscopy while recording physiological measures of sleep and wakefulness. Physiologically, REM sleep is defined by low/absent muscle tone and high-frequency activity or the emergence of theta (5-8 Hz) oscillations in the EEG. NREM sleep is characterized by low muscle tone and high amplitude, δ (1-4 Hz) and spindle (10-15 Hz) oscillations in the EEG. Using these parameters to distinguish states of vigilance, Brécier et al. (2022) found that PV activity was significantly increased in NREM and REM compared with wake, indicating that pyramidal neurons experience high perisomatic inhibition during sleep. In contrast, SST activity remained unchanged over sleep/wake cycles, but VIP activity increased during REM.

To investigate fast neuronal events, Brécier et al. (2022) combined *in vivo* intracellular electrophysiology with genetic targeting of interneuron subtypes. They used three groups of transgenic mice, each of which expressed a fluorophore selectively in PV, SST, or VIP interneurons. Guided by *in vivo* fluorescence microscopy, the authors targeted fluorophore-labeled neurons for patch-clamp electrophysiological recordings in mice cycling through sleep/wake states. These experiments showed that the firing activity of PV interneurons increased during sleep, with the highest firing rates recorded during REM sleep. Similarly, VIP interneurons fired significantly faster in REM than other states. SST firing rates remained stable throughout all states. A similar study (Aime et al., 2022), published at around the same time as Brécier et al. (2022), obtained nearly identical results with respect to PV and VIP activity in REM sleep, but found significantly decreased SST activity, attributed to VIP-mediated inhibition.

Brécier et al. (2022) conclude that, in REM sleep, pyramidal neurons experience a unique pattern of perisomatic inhibition and simultaneous dendritic disinhibition because of increased PV and VIP activity, respectively. Indeed, data from Aime et al. (2022) provide a direct demonstration of this phenomenon. Using Ca^{2+} imaging of the PFC, Aime et al. (2022) found diminished Ca^{2+} signaling in the pyramidal cell soma during REM sleep, despite intense dendritic Ca^{2+} activity, a pattern they termed "somatodendritic decoupling" and one that is achieved through the antagonistic action of PV and VIP interneurons. This activity pattern has striking implications for the propensity of pyramidal neurons to undergo synaptic plasticity and participate in network-level integration during sleep. An essential mediator of plasticity at excitatory synapses is the NMDAR. Although NMDA is activated by the binding of glutamate, at relatively hyperpolarized states, its receptor pore is blocked by an Mg^{2+} molecule that is ejected only under sufficient depolarization (Mayer et al., 1984). Under hyperpolarizing influence, such as during GABAergic inhibition, glutamatergic transmission alone is less likely to drive Ca^{2+} influx through the voltage-dependent NMDA pore (Schulz et al., 2018) and, thus, less likely to trigger intracellular cascades that modulate synaptic efficacy. This implies that, under intense PV-mediated inhibition, as occurs during

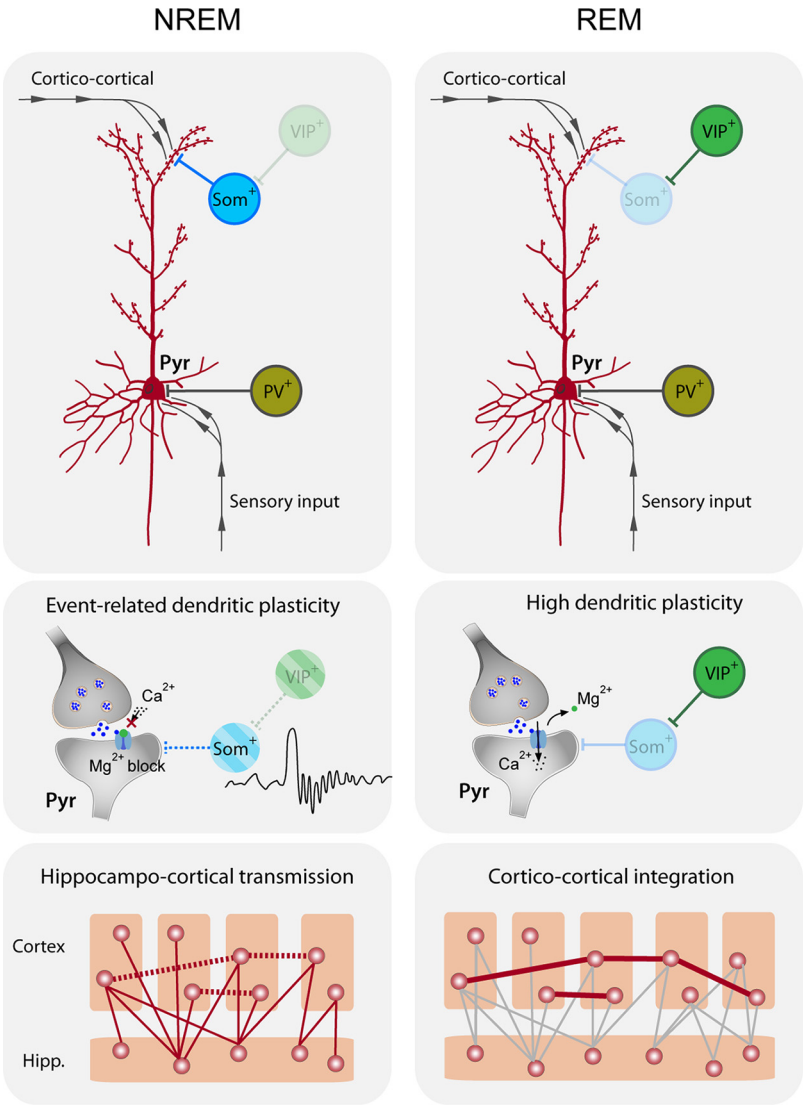

Figure 1. The structure of local inhibitory inputs to pyramidal cells of the cortex and their pattern of activity during NREM and REM sleep. PV-positive interneurons inhibit the pyramidal cell (Pyr) soma, SST-positive interneurons inhibit distal dendrites, and VIP interneurons disinhibit distal dendrites by inhibiting SST (Tremblay et al., 2016). Brécier et al. (2022) report that PV interneuron activity increases during both REM and NREM sleep, indicating broad perisomatic inhibition of the pyramidal cell during sleep. Distal dendrites are disinhibited during REM by the increased action of VIP interneurons. This pattern of interneuron activation imposes a unique mode of pyramidal cell operation characterized by low somatic and intense dendritic Ca^{2+} activity during REM as reported by Aime et al. (2022). The disinhibition of distal dendrites likely facilitates global integration of cortical information by enhancing plasticity at corticocortical synapses through NMDAR-mediated action (Fu et al., 2015; Scheyltjens and Arckens, 2016; Schulz et al., 2018). In NREM sleep, the pyramidal neuron is inhibited at the soma and distal dendrites by PV and SST activity, respectively (Brécier et al., 2022). Network events related to hippocampo-cortical transfer, such as thalamocortical spindles and cortical δ oscillations, modulate PV and VIP activity and transiently decrease SST activity. This pattern of interneuron activation also imposes a REM-like mode of pyramidal cell operation characterized by low somatic and intense dendritic Ca^{2+} activity as reported by Seibt et al. (2017). By transiently disinhibiting the distal dendrites of the pyramidal neuron, spindles likely open brief windows of corticocortical plasticity while simultaneously organizing the hippocampo-cortical transfer of memory through spindle-ripple coupling (Siapas and Wilson, 1998).

REM sleep, the threshold for synaptic plasticity is raised along the entire pyramidal neuron, an assertion that supports the synaptic downscaling claim of the synaptic homeostasis hypothesis. However, dendritic disinhibition and the consequent increase in dendritic Ca^{2+} indicate that vigorous plastic activity can occur at the distal dendrites of the pyramidal neuron in REM. Indeed, suppressing dendritic disinhibition during REM impairs memory consolidation and diminishes synaptic plasticity (Aime et al., 2022). Considering that the distal dendrite is the primary site of corticocortical terminals, REM-mediated disinhibition likely facilitates the global integration of cortical information and the representation of the engram in cortical networks.

In addition to long-term firing rate dynamics related to sleep/wake states, Brécier et al. (2022) examined transient interneuron activity during δ and spindle oscillations, NREM network events that are heavily implicated in neuronal plasticity (Steriade and Timofeev, 2003) and in the hippocampo-cortical dialogue that underlies the two-stage consolidation of memory (Diekelmann and Born, 2010). Neuronal replay in the hippocampus commonly occurs during brief, high-frequency events known as sharp wave ripples, which are often nested within cycles of the spindle oscillation (Siapas and Wilson, 1998). Brécier et al. (2022) show that, during spindles, PV firing increased transiently, whereas SST firing decreased and that the firing of both PV and VIP interneurons was strongly phase-locked to spindle cycles. These results indicate that brief windows of dendritic disinhibition are made available during spindles by the reduced activity of SST neurons and the increased firing of VIP cells. Similar to REM activity patterns, this brief spindle-related somatodendritic decoupling (Seibt et al., 2017) likely facilitates corticocortical integration precisely during the reactivation of memory traces related to hippocampal replay in spindle-sharp wave ripple events.

The findings of Brécier et al. (2022) demonstrate that the pattern of inhibition along cortical pyramidal cells is highly dynamic during sleep/wake states and that it is precisely controlled by the firing activity of interneurons and various oscillations in the brain. Together with data from Aime et al. (2022), these results mark considerable progress in understanding the network-level inhibitory mechanisms in sleep and point to unique patterns of pyramidal cell operation in REM and NREM that likely facilitate the memory function of sleep.

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