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# Thalamic Influences Affecting NREM Sleep Dependent Electrical Activity

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## ABSTRACT

*The SHY proposal, which posits that sensorial input asymptotically leads to a limiting level of synaptic potentiation thus constraining neuroplastic learning, reflects a corollary thesis expressed by the free energy principle. This latter hypothesis claims that ongoing sensorial flow leads to a saturable rise in the information related, state variable, entropy, paralleling the claim advanced by the SHY proposal. Sleep, accordingly, is regarded as a homeostatic system essential for overcoming intrinsic thermodynamic constraints to optimize learning. Consistent with the circumvention of neuroplastic potentiation during sleep, subcortical nuclei have evolved mechanisms for extensive cortical influences that a) regulate sensorial input, b) globally synchronize neuroplastic recovery, c) initiate synaptic renormalization, and d) optimize learned and learning capacity. Among key nuclei involved in modulating NREM cortical activity are the thalamic reticular nucleus (TRN) and the centromedian nuclei. Cell intrinsic and cell microcircuit neural activity within these nuclei modulate the slow oscillation, a synchronized wave pervasive throughout the neocortex during NREM sleep, thereby promoting UP state initiation via gated non-sensory input and enhancing brain wide, slow wave synchrony, respectively. Slow wave nested, action potential bursting, driven by $Ca^{2+}$ spiking, results in the opening of low-voltage-gated T-type $Ca^{2+}$ channels (T-VGCCs) that appear to drive synaptic rescaling, while nested bursting in delta oscillatory activity may preserve neuroplastic learning. The possibility of bimodal synaptic modulation supports a dual behavioral role that is apparently grounded in an underlying drive to maximize learning efficiency.*

## Keywords

NREM slow oscillation, SHY proposal, Thalamic reticular nucleus, T-type $Ca^{2+}$ channels.

## Introduction

Each time sleep occurs the ability to appraise the events around us is inevitably lost. For this reason, sleep has often seemed at odds with daily needs, where attention and responsivity are critical to survival. The interruption of sensorial content nonetheless represents a definitional and unique feature of sleep, one that distinguishes it from other behavioral states, all of which otherwise retain the ability to promptly respond to stimuli. The fact that humans and all other animal species require sleep, therefore, strongly indicates the existence of some fundamental physical and neural reason for it to occur; that is, sleep reveals the presence of some undetermined physical feature, which no other neural mechanism can respond to. Indeed, the notion that sleep is vital is supported by the existence of various cognitive impairments associated with sleep deprivation [1-3]. For example, in the extreme case of fatal familial insomnia [4], sleep is impossible eventually leading to death.

One widely acknowledged proposal, the SHY hypothesis, links this essential function to neuronal properties evoked by centrally directed communication, which involve changes in the strength of interneuronal exchange at the level of the synapse. This hypothesis, termed the synaptic homeostasis hypothesis (SHY), privileges the unique ability of the brain to learn from external events of the world that become inscribed through neuroplastic changes in synaptic connections [5]. The SHY hypothesis proposes that these neuroplastic changes entail increases in synaptic potentiation, which can be visualized electro physiologically in alterations of size and frequency of miniature end plate potentials. Because the extent of potentiation necessarily possesses an upper limit, there is a need to regularly reduce the level of potentiation so that the

brain can continue to learn. This readjustment is proposed to occur during sleep [6].

According to the SHY model, sleep is vital not merely for the restoration of depleted resources but for preservation of the capacity for learning; hence, implicit in the model is a role for learning in order to successfully interact with events occurring in the external world. Sleep therefore represents a homeostatic system that is essential for overcoming intrinsic physical limitations to optimally use sensorial information for behavior. Mechanisms governing the events of sleep can thus be expected to regulate sensorial flow and recalibrate changes introduced by sensorial input that would lessen optimal responsivity during wakeful states. These mechanisms would also be expected to selectively retain previously learned, neuroplastic change that facilitates interactive success.

Among the defining mechanisms of NREM sleep is the slow oscillation, a synchronized wave pervasive throughout the neocortex during NREM sleep, which has been hypothesized to mediate sleep related neuroplastic recovery. Since its discovery, the slow oscillation has generally been considered a predominantly cortical phenomenon. the sufficiency of the cortex for the generation of the slow oscillation, notably, was inferred from its survival following thalamic lesions [7]. For instance, while expressed at a lower frequency, the slow oscillation could also be recorded from cortical slabs *in vivo* [8] and cortical slices maintained *in vitro* [9]. The role of the thalamus in regulating the properties of the slow oscillation, however, has been increasingly evidenced since the original work of Steriade and colleagues that characterized the slow oscillation.

This paper will first briefly review some extant models describing physical principles that govern sensorium induced neuroplastic change and then explore how sleep associated cortical and subcortical activity both accommodates the constraints imposed by these principles yet has also evolved to overcome their limitations. In particular, the paper will focus on mechanisms associated with thalamic activity that regulate sensorial flow between subcortex and cortex and that modulate neuroplastic status to shape both learned responses and restoration of neuroplastic capacity.

## Sleep, Neuroplastic Competence, and Entropic Saturation

The SHY proposal, that afferent input asymptotically leads to a limiting level of synaptic potentiation, lays claim to the presence of a fundamental physical principle governing sensorium induced, neuroplastic change. There is considerable evidence that this physical principle is thermodynamic in nature. Ilya Prigogine, for example, first proposed that organisms required ongoing free energy input to sustain their far from equilibrium, highly ordered, entropic states [10]. This he based on his observation that living organisms were highly ordered structures juxtaposed against a low order surround. Extending Prigogine's analysis, Friston hypothesized that cognition was itself subject to free energy constraints, determining the level of informational entropic order within the brain, which he termed the free energy principle [8,9]. According to this principle, ongoing informational flow from the sensorium led to a rise in the information related, state variable, entropy [10]. Like potentiation, entropy thus represented a saturable, albeit abstract, quantity driven by sensorial input toward some saturable level that was dictated by thermodynamic constraints.

Unlike the potentiation hypothesis, however, the free energy principle did not posit a specific period devoted to recovery from synaptic change. Instead, the brain was proposed to counter information accumulation by optimizing behavioral patterns that then minimized the need for future change. Inputs that occurred together more frequently than might be expected by chance, for instance, were 'registered' because they suggested regularities in the environment that were predictable. Once these 'coincidences' were detected, a neuron would communicate them to its target neuron, leading to synaptic strengthening, or potentiation between the two. The effect of registering these 'coincidences' thus enabled the brain to structure its behavior in such a way as to minimize unexpected occurrences and guide the selection of behavioral responses on the basis of their likelihood. By such 'active inferencing' [11,12] the brain would come to reflect the regularities observed in the external world, an organizational arrangement that served to maximize free energy efficiency.

The free energy principle governing cognition thus resembled aspects of the SHY hypothesis in providing an explanation for changes in synaptic events that were due to sensorial input and that built on the brain's ability to enable the organism to better confront a continually changing, environmental landscape. Moreover, by staging causal optimization in terms of an entropic cost function the model accounted for some physical constraints that placed an upper bound on synaptic change.

Nonetheless, while the free energy principle accounted for increases in a synapse related, saturable physical quantity – albeit an abstract one - it did not specifically address the attainment of saturability that is the ultimate result of ongoing sensorial novelty and that is inherent in the relentless circumstances encountered in the external world [13]. This relentlessness means that the persistence of novel input continues to generate synaptic reorganization and increase entropic order, despite causal inferencing that may act to diminish the rate of attainment of an overall entropic level. Faced with ongoing novelty, the organizational resources of brain synapses can be expected to approach saturation, operating within physical ranges that regularly encounter upper limits under the assumptions posited by both the SHY and free energy principle proposals. Indeed, the observation that all known animal species need to 'regularly disconnect' constitutes a strong argument that sensorial novelty is persistent and that its input repeatedly saturates a physical condition that must subsequently be replenished; that is, the brain is 'awash' in new experiences for which physical compensation is required. Hence, sleep is the mechanism that has evolved to account for the cost of the physical events of neuroplasticity, which enable the organism to adapt and survive [14]. When this cost is not accounted for cognitive function is poor. Acute and

chronic sleep loss, for example, have pervasive negative effects on performance and many brain functions, including the ability to learn, remember, speak clearly, judge risk, and understand complex information needed for decision making [2]. Physically, therefore, sleep assists in maintaining an overall balance of synaptic strength across brain circuits, which may be conceived as a synaptic renormalization. Both hypotheses thus predict that overall synaptic strength in the brain should not be balanced at all times, but instead be biased toward a net potentiation during the major wake period and toward a net depression during sleep [6].

## Implications of Current Sleep Models

### Circumventing thermodynamic constraints

This conclusion, from two leading proposals describing the physical principles governing sleep mechanisms, has several implications. First, observable replenishment mechanisms should entail a sensorial disconnection from the external world so that a process of renormalization can occur; this means that renormalization should take place during unconsciousness. It has been argued, for instance [6], that if the nervous system must acquire information about the environment to survive, such acquisition should be confined to periods of waking, when responsivity is maximal, rather than during sleep, when neural activity is largely disconnected from the external world [7]. Second, such mechanisms should occur globally; in particular, they should minimally be found in all brain domains having sensorial input. Additionally, neuroplastic changes should affect downstream-targeted destinations; that is, rather than modifying only brain regions receiving direct sensorial input, connectivity changes should be distributed across most domains of the brain. Finally, renormalization should subserve behaviorally significant learning functions, specifically maintenance of capacity and behavioral salience. Considerable evidence now exists supporting these implications.

### Overcoming entropic saturation

For excitatory synapses, which account for a majority of the synapses in the mammalian brain, the first prediction has received support from molecular, ultrastructural, and electrophysiological measures of synaptic strength [15-17]. At the molecular level, changes in the strength of excitatory synapses have been shown to involve changes in the surface expression and subunit composition of the glutamatergic AMPA receptors, as well as phosphorylation and other post-translational changes that alter the open probability of these receptors and their ability to remain anchored to the membrane. Surface insertion of GluA1-containing receptors, and the phosphorylation of GluA1 at Ser831 and Ser845 by CaMKII and PKA, particularly, have been correlated with synaptic potentiation. RNA-sequence analysis in the adult mouse frontal cortex, moreover, has revealed significant overlap of transcripts differentially expressed between stages of acute sleep deprivation and sleep, and transcripts affected by the loss of the transcription factor myocyte enhancer factor 2C (MEF2C) [18,19]. In addition, there is a relative dephosphorylation of MEF2C after 6 h of sleep deprivation as compared to sleep, consistent with a wake-related increase in MEF2C transcriptional activity. Together, these findings point to a key role for MEF2C in mediating the response to sleep deprivation and the sleep-dependent decline in excitatory synaptic strength. Consistent with this, MEF2 transcriptional activity is activated in response to glutamate release and membrane depolarization, and the main effect of MEF2 activity in post-mitotic neurons is to constrain the density of dendritic spines and excitatory synapses. Many targets of MEF2, additionally, have been shown to be involved in synaptic weakening, including the genes Arc and Homer1a.Electrophysiologically, experimental evidence shows the occurrence of distinct physical changes during wake or sleep periods that are reflected in spontaneous miniature excitatory postsynaptic currents (mEPSCs) in the rodent cortex. By the end of the wakeful period, the amplitude and frequency of mEPSCs increase in the superficial layers of the rat and mouse frontal cortices whereas following recovery from sleep they decrease. Ultra structurally, the increase in the former has been correlated with the synaptic insertion of calcium permeable AMPA receptors [20]. During sleep, this GluA1 synaptic expression decreases with a corresponding shrinkage of the axon-spine interface.

### Global renormalization of synaptic potentiation

A second implication of these proposals is that renormalization should occur globally; that is, if sleep is a consequence of enhanced synaptic strengthening, renormalization should occur in all brain regions where sensorial input causes neuroplastic change. Current evidence indicates that this is crucially dependent on neuronal activity, especially during NREM sleep, which comprises roughly four fifths of all sleep time. New studies show that down selection is, surprisingly, a consequence of spiking activity involving several distinct electrophysiological signatures, including hippocampal sharp waves, ripples, and slow wave oscillations [21].

The organization of sharp waves and ripples appears to be structured by the slow wave oscillation, which features prominently during NREM sleep. During non-REM (NREM) sleep, for instance, neural activity observed in the EEG inludes a succession of K-complexes, sleep spindles, and slow waves. This slowly oscillating wave originates from the thalamus and cortex and oscillates roughly every second between an UP period of depolarization with spiking and a DOWN/OFF period of hyperpolarization with neuronal silence [22]. As a defining feature of NREM sleep this slow oscillatory activity occurs roughly in synchrony across all neurons, allowing their pooled activity to be detected at the cortical surface as slow waves. This means that the slow oscillation is a global, synchronized network phenomenon, involving neurons throughout the cortex and, to a lesser degree, neurons in subcortical areas, including the thalamus, striatum, and cerebellum. Within the local cortical network (within a few tens of millimeters), cortical neurons synchronously depolarize and hyperpolarize during the slow oscillations.

Studies monitoring the distribution of selected slow oscillation phases reveal that the timing of the negative peak exhibits a continuous shift that can be traced spatially throughout the cortex [23]. On average, the maximum delay across the cortex, calculated by determining the difference between the negative peaks of the initial slow wave trace to the negative peak of the terminal trace is

about 120 msec. It has also been shown that oscillations originate more frequently in anterior regions and propagate posteriorly. Streamline maps that condense the spatio-temporal dynamics of the slow oscillation display an origin density that coincides with the positioning of anterior electrodes, while the average delay map assumes a predominant fronto-occipital direction of propagation. Importantly, the pattern of origin and propagation of slow oscillations is reproducible across time and across subjects. Taken together, these studies show that post-learning sleep occurs throughout the cortex leading to a slight increase in firing in a small set of neurons whose activity is causally linked to neuroplasticity learning, with an activity synchronized and much greater decrease in firing of a larger set of neurons not involved in learning, consistent with the renormalization hypothesis.

## Mechanisms Regulating Neuroplastic Capacity

### The Slow Oscillation

A key postulate of current sleep models is the restorative effect of sleep on learning in brain areas that have experienced heavy neuroplastic changes during wakeful periods. The link between neural activity mentioned above and the retrieval of neuroplastic capacity has been specifically tested in the context of the slow wave. This linkage was studied in experiments that focally perturbed deep sleep in the motor cortex and investigated the consequences on behavioural and neurophysiological markers of neuroplasticity related to motor practice. The restoration in the ability to learn was markedly attenuated in these experiments when slow waves were selectively perturbed in the motor cortex [24,25].

In humans similar evidence has been suggestive but not confirmatory due to the inability to sleep deprive one target area while keeping the overall natural sleep pattern intact. In a novel experimental approach Fattinger et al. used transcranial magnetic stimulation (TMS) to focally perturb slow waves, which were simultaneously monitored by EEG recordings [26]. Using this approach they showed that large amplitude slow waves occurred less frequently, an effect that was only observed for electrodes close to the target area. Additionally, perturbing the slow oscillation in the M1 brain region during sleep resulted in a general increase in motor variability the next morning, a variability that was significantly elevated when compared to performance after unperturbed sleep. These and other studies suggest that the slow oscillation is a key mechanism evoked for renormalization during slow wave sleep. In addition to organizing and synchronizing the several brain activity patterns mentioned, the slow wave is characterized by unique up and down activity states that help to reprime cortical neurons. Of the two states, activity associated with UP states alone appears to contribute to renormalization. Optogenetically introduced, experimental inhibition that reduces firing of the SWS, for example, prevents post-sleep improvement in neuroprosthetic learning [24]. When such optogenetic manipulation occurs during the DOWN/OFF periods alone no such effect is observed. According to the widely accepted spike timing dependent plasticity (STDP) rules, presynaptic activation can lead to either no change in synaptic strength, synaptic depression (a diminished synaptic response), or synaptic potentiation depending on the absence, presence, or relative coincidence of timing of postsynaptic spiking. During the UP states of the slow oscillation, a strong bias toward synaptic depression is observed. Specifically, following stimulation of layer 4 to layer 2/3 connections, synaptic strength never significantly increases and remains unchanged when presynaptic activation is quickly followed by postsynaptic activity. When postsynaptic activity either precedes presynaptic activation or follows it after long intervals, it decreases [27]. The presence of synaptic depression during the slow oscillation could explain how sleep can result in diffuse but synapse-specific synaptic renormalization: synapses strengthened during wake, as well as those that are most coherently reactivated during sleep, would be more likely to show coincident firing during the UP states and thus be protected from synaptic depression [24]. Whereas a much larger group of neurons activated asynchronously would experience depression and become renormalized. Similar to the events of slow wave induced depression (and contrary to expectation) recent studies have shown that SWRs also promote synaptic weakening [28]. Consistent with these results closed-loop optogenetic inhibition of SWRs prevents the decline in the slope of hippocampal fEPSPs that normally occurs in sleeping mice. In like manner, a recent study showed that SWRs also promote synaptic weakening [29]. The authors first replicated a previous finding that SWRs become more frequent after spatial learning. Then they showed *in vivo* in adult mice that closed-loop optogenetic inhibition of SWRs prevents the decline in the slope of hippocampal fEPSPs that normally occurs in sleeping mice. The authors also took advantage of an *in vitro* model of SWRs, obliquely cut hippocampal slices, which spontaneously emit SWRs. As occurred *in vivo* in adult mice, the occurrence of SWRs in slices taken from adolescent mice led to a progressive decline in the fEPSPs slope, which could be blocked by optogenetic inhibition of SWRs. By contrast, the fEPSPs did not decline in horizontal slices that lacked SWRs. Two-photon imaging also showed that the head size of most CA1 spines decreases with time in spontaneously emitting SWRs slices [6].

Significantly, sleep-dependent renormalization seems to spare those neurons and/or synapses that are most active during sleep. It is well established, for example, that neurons activated during exploration and learning are preferentially reactivated with a similar sequential pattern of firing during SWRs, whereas disruption of SWRs impairs memory, suggesting an important role in memory consolidation [30].

## Thalamic Mechanisms Involved in Neuroplastic Recovery

### Thalamic sensory gating

To optimize rescaling, sensory input must be subject to termination throughout the renormalization phase. While the mechanisms for such gating remain to be confirmed, numerous studies suggest that a major factor in sensory suppression is activity originating from thalamic nuclei [31-33]. For example, recordings from various thalamic nuclei indicate that thalamocortical neurons may contribute to slow wave processes in ways other than the initiation of the UP state of each oscillation cycle. Contributions from sensory thalamic nuclei via the relay cells, including the ventral posterior

medial nucleus and the lateral geniculate nucleus, notably, are strongly inhibited by thalamic activity, thus preventing spiking at nearly all times. By contrast, excitation is dominant in neurons within non-sensory thalamic nuclei, including the posterior nucleus and the intralaminar nuclei. Their continuous activity permits their neurons to exert ongoing influence on cortical neurons throughout the duration of the UP state [34].

The resulting cortical firing patterns thus appear to be due to inhibition of sensory thalamic nuclei originating from the thalamic reticular nucleus (TRN) as well as a corresponding lack of inhibition of non-sensory thalamic nuclei that have their origin in the zona incerta [35]. TRN neurons that project to sensory thalamic nuclei display particularly high activity during the slow oscillation, while those with projections to limbic thalamic nuclei have relatively low activity. Accordingly, excitation from non-sensory thalamic nuclei is likely to have the greatest influence on the UP state, including both its initiation and its persistence. Indeed, the prolonged excitation of thalamocortical neurons by non-sensory thalamic nuclei during Up states suggests that these neurons are likely to suppress most afferent influence into the cortex besides the facilitation of synchronization of the slow oscillation throughout this region.

## Slow wave modulation

Besides gating afferent input, thalamic nuclei are also likely to modulate such slow wave features as UP state initation, duration and frequency. It is known, for instance, that direct thalamic stimulation enhances cortical activity under various circumstances, including the evoking of UP states. In anesthetized animals, for example, either prolonged sensory stimuli, using drifting gratings [36] or whisker deflections in rodents [37], effectively initiate UP states in the respective sensory cortices. (Due to the high spiking level in the TRN, thalamocortical neurons, after their initial spike burst, are quickly silenced by the massive synaptic inhibition from the TRN.) Additionally, electrical or optogenetic stimulation of the thalamus in slice preparations containing axons of thalamocortical neurons can cause UP states [38-40]. Burst firing of thalamocortical neurons, moreover, has been shown to occur prior to the discharge of cortical neurons during the UP state of the slow oscillation. Together, these data show an active contribution of thalamic input to the initiation of UP states. In addition to their initiation, thalamic input also modulates the duration of UP states. For instance, recent *in vivo* studies have demonstrated an important contribution of thalamic activity to the pacing of the slow oscillation. Acute pharmacological blockade of action potentials in thalamic neurons in anesthetized and naturally sleeping rats decreases the frequency of the slow oscillation [41], an effect that has been linked to T-type $Ca^{2+}$ channels, discussed below, which have been shown to significantly reduce slow oscillation frequency. Using the anesthetized cat, *in vivo* preparation, for example, thalamic inactivation reduces both slow oscillation frequency and the synchronization of Up states in parallel with activity in cortical neurons [42]. Interestingly, these continuous recordings reveal that while the frequency of the slow oscillation changes immediately following the lesion, remaining significantly lower up to 12 h, they reassume a frequency comparable to the sensory input state after 30 h. These results suggest that the regaining of the 'normal' slow oscillation frequency entails changes in excitatory synaptic connections, and therefore in internal circuitry adjustments that result from the thalamic influence. In sum, extant evidence indicates that the thalamus modulates not only the initiation of the UP state, but also the events occurring throughout the duration of the slow wave, an influence that apparently involves cortical, microcircuit alterations.

## Thalamic Mechanisms Regulating NREM Sleep Recovery

Accumulating evidence shows that, rather than being passively entrained by cortical afferents; distinct types of rhythmical electrical activity are produced by the thalamus, which in turn modulate activity patterns in the cortex [43-45]. Rhythms generated in the thalamocortical system are apparently the result of multiple intersecting and distinct oscillatory patterns [46] that affect cortical factors modulating the slow oscillation. For example, selective excitation of thalamocortical neurons strongly entrains EEG slow waves within a narrow frequency band (0.75–1.5 Hz) when thalamic T-type calcium channels are functionally active thus contributing to thalamic fine tuning of the frequency of slow waves during non-REM sleep.

## CentroMedian thalamic nuclei

Among the thalamic nuclei, excitatory drive from the midline thalamus constitutes a dominant hub for control of cortical excitability [47,48] and NREM sleep consolidation [49]. In mammals the midline thalamus consists of five nuclei that receive a broad range of afferent inputs from the brainstem—including that of adrenergic, cholinergic, and serotonergic neurons —and from the hypothalamus, hippocampus, and prefrontal cortex. Unlike dorsal and sensory thalamic neurons, midline thalamic neurons are more susceptible to depolarization by external inputs originating from subcortical areas, since they lack the hyperpolarization-activated current.

Significantly, activity from nuclei of the centro median thalamus (CMT) is phase-advanced with respect to the initiation of the UP state of the cingulate cortex (CING)slow wave during NREM, relative to other neurons of midline nuclei [50], suggesting that CMT neurons contribute to the initiation of cortical UP states in the cingulate cortex. These are synchronized across brain-wide cortical circuits via the thalamic AD relay cells and are apparently directed along a CMT–CING–AD–VIS (i.e., thalamo- cortico-thalamo-cortical) excitatory pathway. The significance of this pathway lies in its maintenance of long-range cortical synchrony of frontally generated slow waves during NREM and in sleep recovery. During the sleep recovery, phase slow-wave power is substantially elevated in the CMT. Burst-like optogenetic activation of CMT neurons both induces cortical slow-wave-like activity and hastens the sleep recovery process. When optogenetic bursting in cingulate neurons is eliminated the sleep recovery process is delayed. These results indicate that the sleep recovery process is modulated by CMT neurons and is dependent on their ability to synchronize electrical activity throughout the CMT–CING– AD–VIS circuit

via the propagation of slow waves.

## The thalamic reticular nucleus: Cell intrinsic and cell circuit mechanisms

As mentioned, *in vitro* studies in the isolated thalamus show that besides the central thalamic nuclei, neurons in the thalamic reticular nucleus (TRN) [51] and thalamic relay nuclei [52] are likely to play a significant role as cellular pacemakers of the slow oscillation. Both the TRN and relay neurons are capable of generating cell-intrinsic rhythms in the 1 Hz range via postsynaptic glutamate receptor (mGluR) activation. Sustained activation of the Group 1 mGluRs by either exogenous agonists or high- frequency corticothalamic activity induces cell intrinsic mechanisms causing increased excitability, due to the closure of a K+ leak conductance. This enables low threshold Ca currents and Ca -activated non-selective cation currents to yield long-lasting plateau potentials that lead to persistent action potential activity [51-54].

Supra cellular mechanisms that include circuit networks of TRN and VB cells also generate robust and long-lasting slow oscillatory activity via bidirectional synaptic connectivity [55]. Underlying burst firing in TRN neurons are large depolarizations and intracellular Ca release from T-type $Ca^{2+}$ channels which activates transient receptor potential melastatin 4 (TRPM4) channels. Ongoing spiking is associated with slow oscillatory activity in these thalamic circuits that involves rapid synaptic transmission without reliance on signaling from mGluR receptors. Importantly, TRPM4 activation within physiological ranges requires large increases in intracellular $Ca^{2+}$ concentration [56]. This is suggested, for example, by dendritic $Ca^{2+}$ signals that experience decay under whole-cell conditions, with a corresponding loss of bursting strength and TRPM4 conductances that rapidly desensitize in excised patches that tend to parallel declines in Ca concentration. Conversely, modulators of Ca concentration like PIP2 restore TRPM4 activity.

It has been shown that pharmacological block of T-type $Ca^{2+}$ channels with the specific antagonist TTA-P2 completely eliminates bursting as does the replacement of $Ca^{2+}$ with $Ba^{2+}$. These findings suggest that the $Ca^{2+}$ increases required for TRPM4 activation are mediated by influx of $Ca^{2+}$ through T-type channels and some release from internal Ca stores. Ca channels mediating IT are known to be expressed primarily in the distal dendrites of TRN neurons with burst firing localized chiefly to dendritic regions [57,58] thus suggesting a dendritic location of TRPM4 activation. Consistent with this, TRPM4 membrane depolarizations from T-type dependent $Ca^{2+}$ spikes at synaptic loci have been shown to propagate effectively into TRN dendrites [59], in contrast to faster Na+ action potentials.

## Thalamic reticular nucleus influences on global slow wave activity

Although thalamo-cortical activities are generated by a wide variety of mechanisms, including cellular, synaptic and network events, intracellular recordings from thalamocortical (TC) and TRN neurons in the above-mentioned studies highlight a common feature that underlies the global distribution of the slow wave: the rhythmic occurrence of action potential bursts driven by voltage-dependent $Ca^{2+}$ spikes [60,61]. During cortical slow waves of NREM sleep these bursts of spiking activity display fast internal frequencies approaching 100-500 Hz in both TC and TRN neurons that are driven after short periods of membrane hyperpolarization by a $Ca^{2+}$ spike due to the opening of low-voltage-gated T-type $Ca^{2+}$ channels (T-VGCCs), also known as the low-threshold spike (LTS). When NREM sleep is light, action potential bursts in TC neurons exhibit a lower frequency (50-70 Hz), which are driven by high-threshold $Ca^{2}$ spikes that appear to involve both T-VGCCs and high voltage-gated, L-type $Ca^{2+}$ channels (L-VGCCs). Paradoxically, both bursting patterns are broadly distributed and highly active during their respective NREM phases [62].

Significantly, cellular mechanisms of thalamic LTS generation involving LTSs and T-VGCCs appear to be linked to the widespread distribution of $Ca^{2+}$ signaling throughout the somatodendritic domain in TC and TRN neurons. This global influence assists in the synchronization of cortical activity and its associated repercussions at the synaptic and neuronal level. Combinations of experimental approaches, including dendritic patch clamp recordings, 2-photon $Ca^{2+}$ imaging from TC and TRN neurons [63,64], and computational modelling, have together shown that whole cells from both classes are broadly depolarized. Somatodendritic depolarization extends throughout the dendritic tree by electrotonic propagation with corresponding transient increases in intracellular $Ca^{2+}$ concentration [65]. The whole cell, LTS $Ca^{2+}$ transient is mediated by T-VGCCs, with contributions from L-VGCCs in TC neurons and voltage-gated R-type $Ca^{2+}$ channels in TRN neurons [66,67]. This means that during NREM sleep, where rhythmic LTSs predominate, burst firing from both TC and TRN neurons is associated with a global intracellular $Ca^{2+}$ signaling, in contrast to wakefulness states, where tonic firing exhibits a more spatially constrained $Ca^{2+}$ signal, a feature having significant behavioral consequences.

## Thalamic Influences on Rescaling and Neuroplastic Learning

Bursting activity, particularly, through its dependence on global $Ca^{2+}$ spiking, can modify synaptic strength and intrinsic cellular excitability in these network domains to stabilize and regulate ongoing slow oscillations. Temporal coincidences between bursting activity in post synapses and slow wave oscillatory activity can then enhance or depress potentiation according to spike timing dependent plasticity rules. Hence, they can potentially contribute to the optimization of information processing for future learning capacity or the retention of learned behaviors. By virtue of the rhythmic LTS-dependent, somatodendritic depolarization and large-scale alterations in Ca concentration, there is made available a homeostatic regulation of thalamic circuits with downscaling of strength across a wide swath of synapses during sleep together with neocortical synapses [68,69]. Significantly, it has also been shown that spike-timing-dependent-plasticity (STDP) additionally yields a differential homeostatic process allowing the preservation of potentiation in some circuits. For example, classification of visual images for memory recall is enhanced, apparently by the

intersectioning of activities between thalamocortical projections and corticothalamic predictions onto the slow wave [70]. In these classification studies, this may be understood as the formulation of a prediction in the thalamus during the slow wave UP state that activates a thalamic pattern corresponding to learned event. The projection of these patterns to the cortex then activates neuronal populations having learned similar input patterns. This sequence promotes connections between populations of neurons coding for the same class of visual images according to STDP. It also suggests that there is a specific enhancement of connections among groups of neurons associated with the same class of stimulation. Randomly potentiated synapses created by the training, on the other hand, are renormalized.

Although the specific molecular and physiological events have yet to be clarified, modulation from different oscillations offer a likely mechanism. For example, GABAergic TRN-TC synapses may be either potentiated or depressed, depending on whether the postsynaptic cell is preferentially expressing LTSs at slow (<1 Hz) oscillations [66] or nested delta waves [71] frequency, respectively. Such a bidirectional plasticity could allow TC neuron slow oscillations to either strengthen TRN-TC synapses or rescale and weaken them to ensure continuous optimal transmission, a phenomenon likely to be similarly found in cortical zones. This implies that two forms of plasticity exist at GABAergic TRN-TC synapses that can potentiate or depress them as a function of TC neuron burst-firing frequency.

## Conclusion

While the SHY hypothesis may be interpreted as a non-specific, globally directed process for renormalization of synapses that have experienced substantial neuroplastic change, also implicit in the proposal is the incorporation of mechanisms that assist the nervous system in overcoming thermodynamic constraints to achieve greater behavioral versatility for survival. It is increasingly clear that the role of the thalamus is crucial in this regard and has evolved to be a central hub overseeing sleep dependent, neuroplastic restoration and learning. The broadscale evolution of thalamic intrinsic as well as cell circuit mechanisms that subserve control over the modulation of cortical neuroplasticity reveals that external behavioral requirements are determinative in shaping this evolution and that the targeting of the thalamus is indicative of its operational relevance to optimizing learning efficiency. The future analysis of the mechanisms that have emerged in this structure can be expected to illuminate not only how but also why this is so.

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