REVIEW

How rhythms of the sleeping brain tune memory and synaptic plasticity

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Abstract

Decades of neurobehavioral research has linked sleep-associated rhythms in various brain areas to improvements in cognitive performance. However, it remains unclear what synaptic changes might underlie sleep-dependent declarative memory consolidation and procedural task improvement, and why these same changes appear not to occur across a similar interval of wake. Here we describe recent research on how one specific feature of sleep—network rhythms characteristic of rapid eye movement and non-rapid eye movement—could drive synaptic strengthening or weakening in specific brain circuits. We provide an overview of how these rhythms could affect synaptic plasticity individually and in concert. We also present an overarching hypothesis for how all network rhythms occurring across the sleeping brain could aid in encoding new information in neural circuits.

> ### Statement of Significance
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> Sleep is associated with many changes in brain physiology, including the emergence of robust rhythms of activity in multiple brain circuits. These rhythms coordinate the firing pattern of neurons in those circuits and may affect their physiology in numerous ways. Here we discuss how such rhythmic patterns of activity may relate to changes in synaptic strength throughout the brain and, ultimately, to the cognitive benefits of sleep.

Key words: oscillation; resonance; consolidation; synaptic plasticity

Introduction: Crescendo or Diminuendo? The Role of Sleep in Tuning Synaptic Strength in the Brain

More than a century of study has made clear that sleep promotes both declarative memory storage and skill learning.

Such processes are now known to be associated with changes in the strength of connections between neurons in the brain—so-called "synaptic plasticity." Over the past two decades, evidence has accumulated that sleep directly promotes synaptic plasticity. This evidence suggests that sleep

can have differing effects on synaptic strength, depending on the specific brain circuit under study and the animal's prior experience (Figure 1).

For example, proponents of the synaptic homeostasis hypothesis (SHY) cite a number of studies indicating that when animals remain awake for several hours, expression of a number of genes involved in synaptic plasticity (e.g. immediate early genes and neurotrophic factor genes) and synaptic localization of glutamatergic receptors are elevated in the neocortex [1]. When animals are allowed to sleep, levels of these indicators of synaptic strength decline. In support of the idea that glutamatergic synapses are strengthened during wake, firing rates in some neocortical neurons can also increase after a period of extended wake [2]. Recent microanatomical evidence (based on serial transmission electron microscopy) supports the idea that at least some neocortical synapses increase in size during a period of wake, relative to a period of sleep [3] (Figure 1b, top and middle rows). Taken together, these data support the

idea that neocortical synapses undergo relative strengthening across wake, and relative weakening during sleep. However, a number of lines of evidence (some of which are outlined below) suggest that sleep effects on synaptic strength are more diverse and complex than the SHY would predict.

First, recent data characterizing changes in individual neurons' firing rates over time show that sleep has heterogeneous effects within neural circuits (Figure 1a). Spontaneous firing rates of individual neurons in both cortex and hippocampus vary over several orders of magnitude, and multiple studies have found that across a period of sleep, higher-firing neurons undergo firing rate reductions, whereas sparsely firing neurons show increases [4–6]. Critically, our recent experiments have shown that firing rate changes in both directions (i.e. increases and decreases) are blocked by a period of sleep loss [5].

In addition, a number of recent biochemical and anatomical studies indicate that in brain areas such as the hippocampus, sleep-dependent shifts in plasticity-related markers often
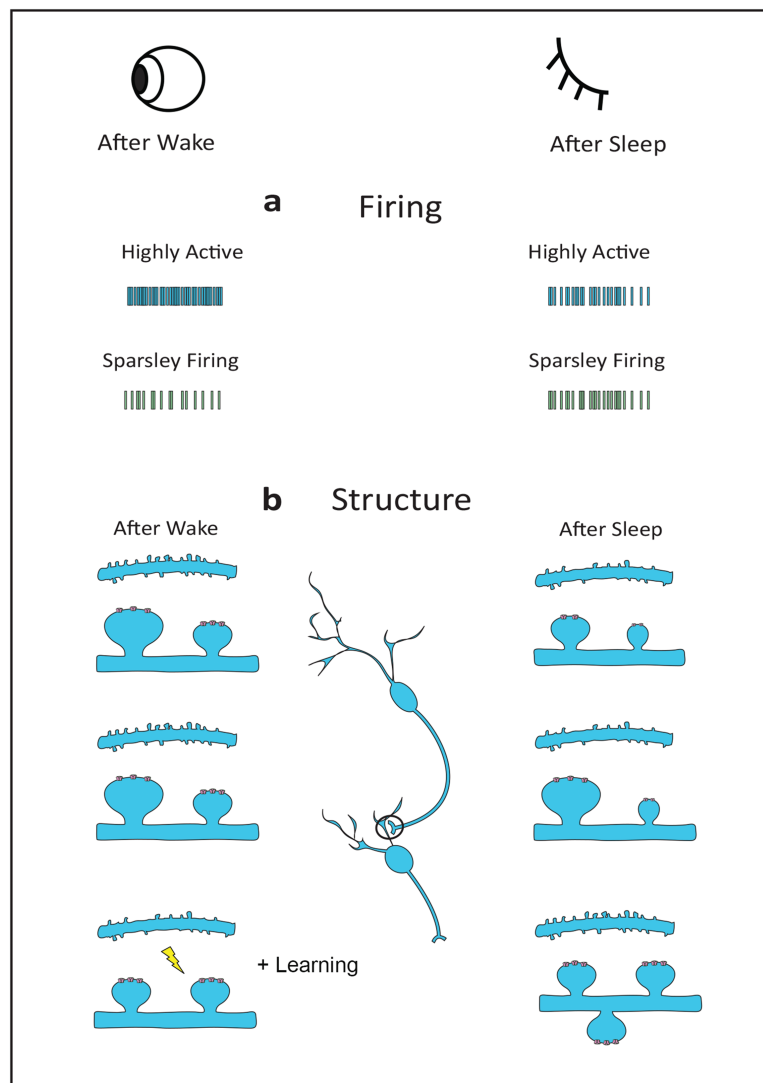

Figure 1. Overview of observed and hypothetical changes to neurons across sleep. Sleep-associated changes in firing rate (a) are heterogeneous, with highly active neurons (top left) undergoing sleep-dependent decreases in rate, and sparsely firing neurons (bottom left) undergoing sleep-dependent firing rate increases. Changes in synaptic structure across sleep (b): as predicted by SHY (global synaptic downscaling; top row), as seen in ultrastructural studies in nonlearning animals (selective decreases in the size of smaller boutons; middle row), and as seen in cortical areas activated during prior learning (increases in synapse number and stability; bottom row).

diverge from what SHY would predict. For example, anatomical data in both area CA1 and DG show that sleep loss reduces (rather than increases) the number of dendritic spines in pyramidal neurons [7, 8]. Prolonged wake also leads to reduced cAMP levels in the hippocampus, which in turn disrupts the strengthening of glutamatergic synapses through long-term potentiation (LTP) [9]. Furthermore, expression of the immediate-early gene Arc, which is required for LTP, long-term depression (LTD), and homeostatic plasticity, is simultaneously increased in neocortex and decreased in hippocampal structures following a period of extended wake [10].

Finally, available data suggest that in both hippocampus and neocortex, following a learning experience, synapses can be strengthened in a circuit-specific manner during sleep. In hippocampus, both neuronal firing rates and cellular indicators of synaptic strengthening increase during sleep in the hours following spatial or contextual learning [11–17]. In the motor cortex of adult mice, dendritic spine growth occurs in a sleep-dependent manner immediately following motor learning [18] (Figure 1b, bottom row). In the visual cortex of juvenile cats and adult mice, biochemical and electrophysiological indicators of synaptic strengthening are present during sleep in the hours following a novel visual experience [19–25].

An unanswered question is how plastic changes to brain circuitry come about during sleep. A plausible hypothesis (and one increasingly discussed among neuroscientists) is that the neuronal and network activity patterns that characterize sleep play a critical role in promoting specific types of synaptic plasticity [26]. Here, we review recent evidence that specific rhythms present in the mammalian brain during nonrapid eye movement (NREM) (Figure 2) and rapid eye movement (REM) sleep (Figure 3) promote synaptic plasticity underlying the cognitive benefits of sleep.

A Symphony of NREM Sleep Rhythms, and Their Role in Synaptic Plasticity

NREM sleep is a symphony of rhythms (Figure 2a). Some of these rhythms, such as slow-wave activity (SWA; comprising delta [1–4 Hz] and slow oscillation [<1 Hz]), are continuous and present for prolonged periods throughout much of NREM sleep. Others, such as thalamocortical spindle (7–14 Hz) and hippocampal sharp wave ripple (SWR) (>100 Hz) oscillations, occur in discrete bursts at intervals and are more prominent in particular phases of NREM. How these rhythms are coordinated with one another, and their function in processes such as memory consolidation, are areas of active investigation. Here we discuss how specific rhythmic patterns of NREM brain activity participate in regulating synaptic plasticity.

Adagio: slow-wave activity

Numerous studies published over the past two decades have linked one of the most prominent NREM sleep rhythms, SWA (used to refer to rhythms ≤ 4 Hz; Figure 2a, right), to consolidation of both declarative and procedural memories in human subjects. Often treated as a unified phenomenon, SWA is an amalgamation of two rhythms: a thalamically generated delta (1–4 Hz) rhythm and the cortically generated slow (<1 Hz) oscillation. Both total amounts and intensity (i.e. amplitude or

temporal density) of SWA across a sleep interval have been positively correlated with some forms of declarative memory retention [27] or improvement on a wide range of procedural (e.g. sensorimotor) tasks [28–31]. An intriguing feature of SWA is that it in addition to being homeostatically regulated (i.e. augmented across the brain after a period of prolonged wake), it also appears to be regulated by brain activity during cognitive tasks in prior wake. Task-related increases in SWA in turn appear linked to task improvement [32]. For example, "local" SWA (where SWA is augmented over a particular region of cortex activated during prior waking experience) has received a great deal of attention and appears to predict individuals' sleep-associated improvements on some tasks [29, 31, 33]. More recently, studies using noninvasive brain stimulation techniques have provided additional evidence for a causal role of SWA in promoting cognitive functions. Enhancing SWA in NREM (through auditory closed-loop stimulation or transcranial direct current stimulation [tDCS]) leads to improvements in declarative verbal memory [34–40]. Furthermore, it was demonstrated that SWA augmentation through tDCS can lead to functional (i.e. motor) improvements during recovery from stroke [41], and memory consolidation improvements in patients with mild cognitive impairment [42]. Conversely, disruption of SWA during NREM sleep can interfere with sleep-associated memory consolidation [43]. Together these data suggest a causal role for SWA in promoting neurobiological events underlying cognition.

What are the neurobiological underpinnings of SWA's benefits for cognition? SWA displays numerous phenomenological features that are useful for consolidating plastic changes initiated in neural circuits during wake. Its homeostatic regulation means that slow-wave intensity and amplitude are greatest immediately following wake, and particularly following prolonged wake. The local nature of this homeostasis means that areas highly active in wake (e.g. during learning) experience even greater subsequent SWA. Slow waves propagate across the cortex, often along the rostro-caudal axis [44, 45], an ideal scenario for plasticity between neighboring cortical regions, and possibly specifically in the regulation of top-down feedback circuits. Recent data suggest that temporal coordination of activity between adjacent cortical regions may play a critical role in promoting sleep-dependent memory processes. Miyamoto et al. [46] found that NREM-targeted optogenetic inhibition of top-down cortical feedback to primary somaotosensory cortex disrupted sleep-dependent consolidation on a texture discrimination task in mice. Moreover, rhythmically stimulating somatosensory and motor cortices synchronously (but not asynchronously) at a delta frequency (2 Hz) was sufficient to rescue memory consolidation deficits associated with sleep loss [46]. Finally (as we discuss in detail below), SWA coordinates other NREM rhythms to optimally synchronize neuronal activity across a number of brain circuits.

An unanswered question, and one that is vigorously debated in the field, is whether SWA promotes consolidation primarily via synaptic weakening, synaptic strengthening, or both [26]. Proponents of SHY have suggested that SWA in particular may lead to overall reductions in synaptic strength due to highly co-incident spike timing between neurons, coupled with altered spike timing-dependent plasticity (STDP) rules that bias synapses toward depression during NREM sleep [47]. However, it is unclear whether invoking the precise alteration proposed in those studies is warranted. As reviewed elsewhere [26], available
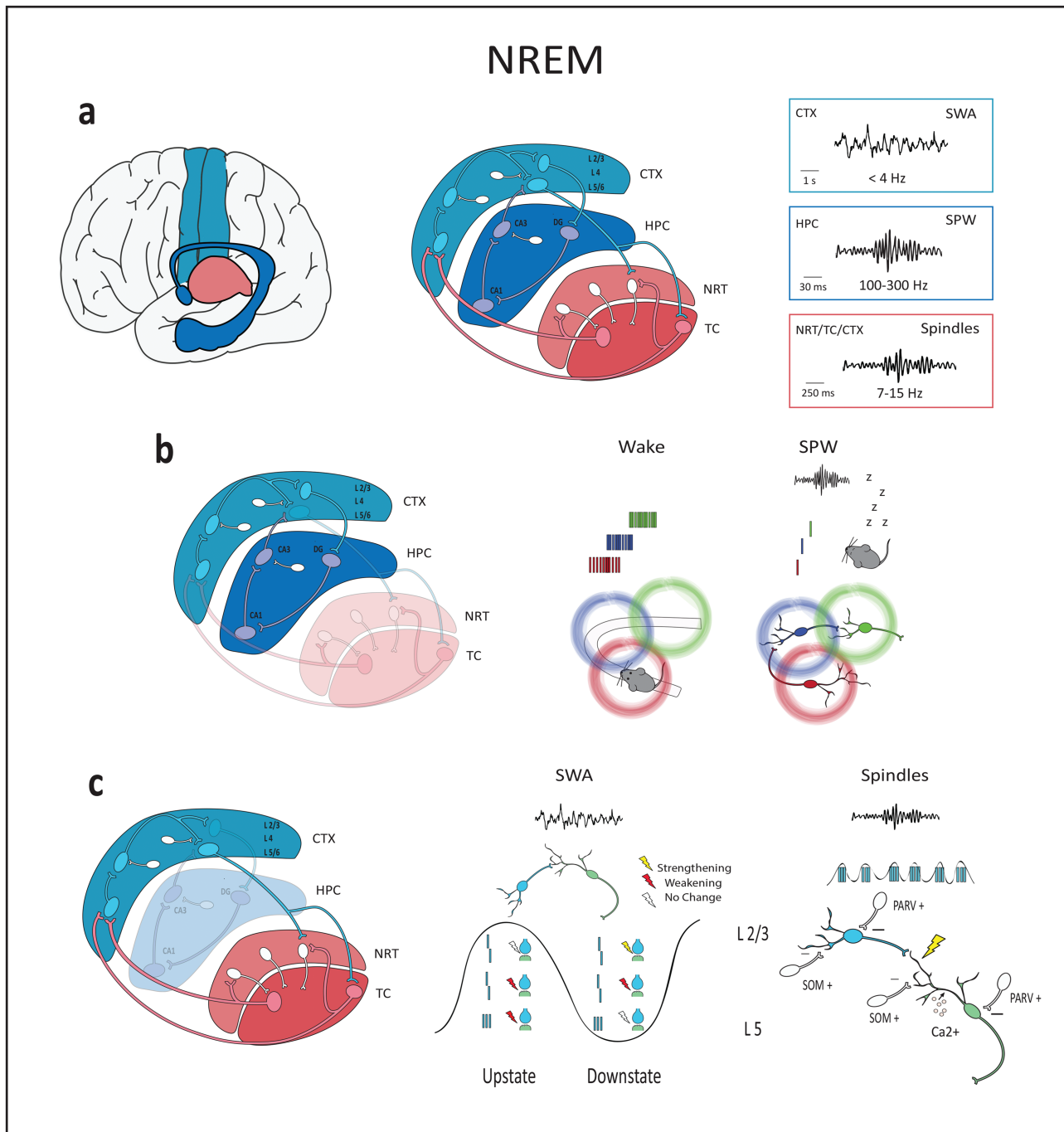
Figure 2. Rhythms of NREM sleep, and their effects on neural circuits. Sleep associated rhythms are expressed in memory-subserving hippocampal (indigo), cortical (cyan), and thalamic (red) circuits (a, left and middle). Various NREM-associated rhythms affect different subsets of these circuits (a, right). CTX =cortex; HPC = hippocampus; NRT = thalamic reticular nucleus; TC = thalamocortical relay nucleus. During NREM sleep SPWs, sequential replay of activity patterns among neurons activated sequentially during wake has been reported (b), in both hippocampal and cortical circuits. Additional NREM rhythm-specific mechanisms have been proposed to mediate plasticity in intracortical and thalamocortical circuits (c). These include selective depression and potentiation based on phasing of correlated neuronal activity during upstates and downstates of SWA in NREM (c, middle), intracortical changes in inhibitory interneuron activity during NREM spindles (c, right). SOM+ = somatostatin-expressing interneuron; PARV+ = parvalbumin-expressing interneuron; Ca2+ = calcium.

data suggest that NREM-associated changes in neuromodulation may limit STDP (either potentiation or depression) during SWA. In addition, STDP rules appear to vary substantially based on pre- and postsynaptic neurons' firing frequency and their pattern of firing (i.e. tonic vs. bursting) [48, 49]. There are limited physiological data addressing STDP rules during SWA (Figure 2c,

middle). Gonzalez-Rueda et al. optogenetically stimulated (presynaptic) layer 4 cortical neurons and carried out whole-cell current clamp recordings from (postsynaptic) layer 2–3 neurons in the barrel cortex during SWA in urethane-anesthetized mice. The authors found a general lack of STDP-based synaptic strengthening when pre- and postsynaptic neurons' firing was
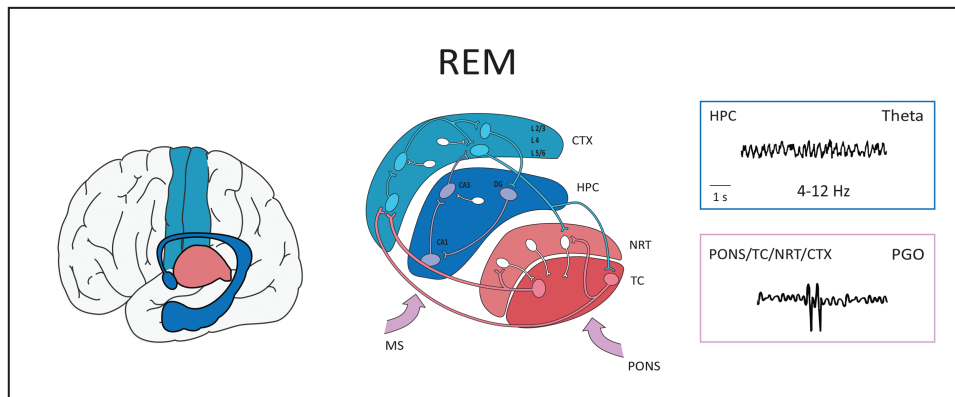
Figure 3. Rhythms of REM sleep. REM-associated rhythms (including REM sleep theta and PGO waves) are expressed in memory-subserving hippocampal (indigo), cortical (cyan), and thalamic (red) circuits and are modulated by input from the pons and medial septum (MS). CTX = cortex; HPC = hippocampus; NRT = thalamic reticular nucleus; TC = thalamocortical relay nucleus; MS = medial septum.

restricted to SWA up-states. In contrast, conventional STDP (with both strengthening and weakening occurring depending on the order of pre- and postsynaptic neurons' firing) was present during down-states [50]. The authors also found that, when restricted to up-states, presynaptic stimulation alone elicited postsynaptic LTD. Another study carried out by Bartram et al. found weakening of synapses among layer 3 neurons in medial entorhinal cortex slices when subthreshold presynaptic inputs were paired with induced postsynaptic up-states. However, this same study also found that during up-states, presynaptic inputs paired with suprathreshold postsynaptic bursts of firing underwent LTP [51]. An important caveat is that, like many studies linking sleep to reduction in synaptic strength (reviewed in [26]), these two studies were carried out in juvenile (i.e. 2–3 week old) mice, where rates of synapse elimination are developmentally upregulated. An unresolved question is thus whether the same STDP rules are present in NREM up-states later in life.

Several recent studies suggest that under some circumstances, coordinated firing between neurons during SWA induces synaptic potentiation. Optogenetic disruption of SWA during NREM is associated with impaired plasticity in the adult mouse visual cortex [24]; this form of plasticity is initiated by experience in prior wake and is associated with synaptic potentiation [25, 52]. Similarly, a recent study found that evoked potentials in the cat cortex were enhanced selectively across periods of NREM sleep (but not across periods of wake or REM). They also found that presynaptic stimulation patterned to mimic that seen in SWA (but not that seen in wake) increased cortical neurons' excitatory postsynaptic potential (EPSP) amplitude [53]. Finally Kruskal et al. used in vivo imaging of calcium transients to identify neuronal ensembles activated in a stereotyped fashion and consistently recruited during SWA up-states [54]. The authors found that within this ensemble, LTP was consistently induced by canonical STDP rules (i.e. following pre-before-post spike pairings). They also found that the amplitude of LTP reflected the level of neuronal activation over tens of ms prior to the pre-before-post firing, rather than at the moment of pairing. The same pairing protocol outside of the ensemble (and where prior neuronal activation was low) led to LTD [54]. Together, these studies suggests that subthreshold synaptic inputs to cortical neurons may induce synapse-specific weakening during SWA up-states, whereas suprathreshold inputs (i.e. those

eliciting postsynaptic spiking) are simultaneously preserved or strengthened.

Messa di voce: thalamocortical sleep spindles

Another characteristic feature of NREM sleep is the occurrence of discrete waxing-and-waning events (sleep spindles) comprised of 7–15 Hz rhythmic activity (Figure 2a). The occurrence of sleep spindles in NREM sleep has been extensively linked to cognitive function in human subjects [55]. A number of studies have found that postencoding spindle density increases predict sleep-associated declarative memory consolidation [56, 57]. Pharmacological interventions that augment or decrease spindling activity in NREM have enhancing or disruptive effects on the consolidation process, respectively [58]. Sleep-associated improvements on a number of sensorimotor tasks are also predicted by task-associated increases in spindle density and amplitude [59–61]. Similar to reports for SWA, spindle activity appears to have topological specificity—increasing specifically over cortical areas previously involved in task acquisition during wake [62–64]. These task-associated increases in "local" spindling are predictive of sleep-dependent task improvement [65]. As is true for SWA, auditory or tDCS interventions that increase spindling following memory encoding or procedural task acquisition improve subsequent performance [35, 36, 38, 39, 42, 66].

What circuit-specific events might mediate the effects of spindling on cognitive performance? As is true for SWA, in vivo, spindles occur as traveling waves, where spindle up-states are present in physically adjacent regions of cortex in close temporal proximity. However, unlike slow-wave oscillations which propagate along the rostrocaudal axis linking frontal, parietal, and occipital cortices, spindles instead tend to progress along a curving path connecting temporal, parietal, and frontal cortex, temporally linking activity between these regions [67]. In addition, available data from animal models suggest that spindle oscillations induce coherent phase-locked activity in thalamic and cortical neurons, which may be particularly important for sleep-associated plasticity in sensory and motor systems. For example, functional plasticity in neurons of the primary visual cortex (V1) of both developing cats [21] and adult mice [23] is correlated with the strength of phase-locking of individual

neurons' firing to spindle oscillations. Both forms of plasticity involve augmentation of neuronal firing rate responses to visual input and are mediated by the same intracellular pathways involved in LTP at cortical glutamatergic synapses [19, 25, 52]. In the latter system, orientation tuning of mouse V1 neurons is altered in a sleep-dependent manner following exposure to a visual stimulus of a specific orientation (orientation-specific response potentiation; OSRP) [23–25]. Available data suggest that potentiation of thalamic (i.e. LGN) input to V1 is an essential mediator of OSRP. Specifically, thalamocortical LTP induced between LGN and V1 occludes OSRP in vivo, and vice versa, suggesting a common underlying cellular mechanism [52]. Recent data from our lab show that OSRP is initiated during waking sensory experience, leading to orientation-selective response changes in LGN (but not V1) neurons. During subsequent NREM sleep spindles, coherence of activity between LGN neurons and V1 is augmented in an experience-dependent manner [24]. Coherence of V1 neurons' spiking with network activity during spindle oscillations predicts the extent of OSRP in individual mice [23]. Because OSRP is measurable across cortical layers in V1, this suggests that plastic changes throughout the thalamocortical circuit could be driven by spindle frequency activity.

Recent experiments have aimed to test the causal role of sleep spindles in promoting synaptic plasticity. Hypnotic agents that tend to suppress spindle activity (while sparing other rhythms such as SWA) disrupt sleep-dependent V1 plasticity in developing cats, whereas those that preserve these rhythms support plasticity [68, 69]. Similarly, optogenetic manipulations that disrupt coherent firing during thalamocortical rhythms in NREM sleep disrupt sleep-dependent plasticity in the adult mouse visual system [24]. In support of the idea that entrainment of neuronal firing patterns by spindles drives synaptic plasticity, repetitive delivery of patterns of neuronal activity recorded from rat cortex during spindles in vivo is sufficient to drive LTP between cortical pyramidal neurons in vitro [70]. Pulsatile stimulation delivered to the cortex at a frequency consistent with spindle oscillations (10 Hz), but not at lower frequencies, can also evoke LTP in vitro [70] and enhanced sensory-evoked potential amplitudes in vivo [71].

How might spindle-frequency activity drive synaptic strengthening in cortical and thalamocortical circuits? Two recent findings suggest potential underlying mechanisms. An in vivo imaging study by Seibt et al. recently described high levels of dendritic calcium influx (which occurred in a synchronized manner among neighboring cortical neurons) which was tightly linked to spindle frequency EEG activity [72]. Insofar as increasing dendritic calcium is a consistent correlate of (and indeed prerequisite for) LTP [73], this finding is completely consistent with other results linking spindle-frequency activity to synaptic potentiation in thalamocortical circuits. Critically, this increase in dendritic calcium was not associated with a concomitant increase in neuronal spiking during spindle-rich sleep [72]—suggesting a non-Hebbian form of EPSP-driven plasticity, dependent on intra-EPSP timing [74, 75] during spindling. An explanation of the unique conditions found during spindles in the Seibt et al. study (i.e. high-dendritic calcium influx without an increase in somatic calcium or neuronal spiking) may be best explained by a second recent study using in vivo calcium imaging to study activity in specific cortical cell populations during NREM sleep. In that study, Niethard et al. found that specifically in the context of spindle oscillations, somatostatin-positive

(SOM+) interneurons (which target inhibition to cortical pyramidal neurons' dendrites) show decreases in activity, whereas parvalbumin-positive (PV+) fast-spiking interneurons (which target inhibition to pyramidal neurons' cell bodies) simultaneously show increased activity [76] (Figure 2c, right). The latter finding is intriguing in light of the finding that at least some forms of sleep-dependent cortical plasticity are preceded by cortical column-dependent changes in the activity level of fast-spiking interneurons [21]. Together these data suggest that a circuit-specific mechanism involving alterations in inhibitory neuronal populations could drive the augmented dendritic calcium influx seen in pyramidal neurons during spindling.

Molto vivace: hippocampal sharp wave ripples

A third network rhythm occurring characteristically during NREM sleep is the hippocampal SWR (Figure 2, a and b). SWRs consist of large, synchronized-onset (i.e. sharp) waves of hippocampal network activity which initiate subsequent high-frequency (100–300 Hz) oscillations or ripples. Work carried out primarily in rodent models has shown that (as is true for SWA and spindles) the frequency of occurrence and amplitude of SWRs in the hippocampus during NREM increase after a learning experience in wake [12, 77–79]. SWRs have also been observed in the temporal lobes of human subjects [80] where their frequency of occurrence has been linked to successful memory consolidation [81]. Critically, experimental models that disrupt SWR occurrence—either in genetic models of dementia [82, 83] or in animals with experimental disruption of hippocampal circuit activity during SWRs [12, 13, 84, 85]—memory consolidation deficits have been reported.

How might these rhythms support memory consolidation? NREM SWRs have received intensive study over the past two decades due to their capacity to induce temporally patterned activity in neuronal ensembles that reflect activity patterns in prior wake [86] (Figure 2b, right). This so-called "replay" has been proposed as a critical mechanism of memory consolidation [87]. Replay events in SWRs have been proposed to reflect sequential spatial information (i.e. transiting through "place fields" which activate specific hippocampal "place cells") [88], learned associations [89], and emotional valence [90], suggesting that these events reflect multiple facets of wake experiences. Available data suggest that replay events are linked to Hebbian plasticity mechanisms occurring during prior wake. O'Neil et al. found that pairs of hippocampal neurons whose place fields overlap more (and thus show more co-firing within 200 ms of one another) during exploration show greater co-firing during subsequent NREM SWRs [91]. As reviewed elsewhere [26], it is unclear whether sequential replay in the hippocampus (i.e. reflecting prior place field transiting in wake) is essential for circuit plasticity underlying sleep-dependent consolidation, or is simply a reflection of a well-established memory. Other features of hippocampal network dynamics during posttraining sleep (such as network stabilization, which also correlates with ripple occurrence) might be better indicators of plasticity during consolidation of new memories [11–13]. However, during SWR replay, large hippocampal ensembles are co-activated within compressed time frames that are ideal for STDP [92] and the high-frequency bursts occurring during SWRs mimic tetanic stimulation protocols used to induce

hippocampal LTP [51, 93–95]. Thus, it is reasonable to assume that SWRs can and do promote hippocampal circuit plasticity.

SWRs have also been implicated in information transfer from hippocampus to cortex during sleep (Figure 2b). Evidence in support of this idea has come from simultaneous recordings from the two structures, which demonstrated high levels of time-locked cortical neuronal activity triggered by NREM SWRs [92, 96]. Indeed, recent work suggests that SWR-associated hippocampal-cortical communication is a general feature within the association cortices [97] and sensory cortices [98]. There are also data to suggest that co-activation of the two structures could reflect prior experience. For example, reactivation of cortical neuronal ensembles co-activated during prior spatial task learning were triggered by SWRs [89]. Future studies will be needed to determine whether this SWR-linked communication induces plastic changes in circuits outside the hippocampus, and whether this it is necessary for sleep-dependent memory storage.

Polymeter: nested NREM rhythms

A growing body of evidence suggests that SWA coordinates other oscillation to facilitate the cognitive benefits of sleep and underlying synaptic plasticity. Many human-subject studies in which SWA is augmented through noninvasive means found that generation of spindles in coordination with slower oscillations (i.e. at a specific and consistent phase relative to up-states) appears to be a consistent correlate of sleep-dependent task improvement [39, 66]. This suggests that SWA could act as a "carrier wave," coordinating the timing of other oscillations generated in interconnected circuits (e.g. spindles in thalamocortical circuits, SWRs in the hippocampus) throughout the brain. In support of this idea, dual-site recordings of the hippocampus and prefrontal cortex show that hippocampal sharp waves reliably emerge during the onset and offset of cortical SWA up-states [99, 100]. Thalamocortical spindles are similarly locked to SWA up-states [100], and rhythmic optogenetic activation of cortical neurons at frequencies associated with SWA leads to phase-locked spindle occurrence [24]. This results in fairly ordered temporal relationship of nested rhythms, wherein hippocampal SWRs occur in tight temporal coordination with spindles, with peak spindle- and ripple-frequency activity occurring simultaneously between cortex and hippocampus [100–102], and ripples occurring selectively in spindle troughs [101, 103, 104]. This temporal coordination of the three rhythms has been established in human subjects undergoing exploratory invasive recording [101, 105] as well as in rodents [98, 100, 106].

It has been hypothesized that the phase–amplitude coupling of these rhythms constitutes an interregional dialogue between thalamocortical and hippocampal circuits during which correlated firing drives plasticity and information transfer between brain areas. The precise phase relationship of activity between interconnected brain regions may play an essential role in interregional communication and coordinated sequential replay of neuronal firing patterns coordinated between hippocampal and cortical ensembles, resembling those occurring during prior experience. For example, Rothschild et al. recently found that neural activity patterns during NREM sleep in the rat auditory cortex predicted CA1 (hippocampal) SWR patterns, and vice versa, following learning of an auditory

task [98]. A similar phenomenon has been reported to occur between rodent hippocampus and visual cortex during NREM sleep following visuo-spatial tasks [107]. This coordination appears to be a reliable correlate of sleep-dependent consolidation. A recent study demonstrated that successful training on a spatial object recognition task (i.e. one that led to consolidation of spatial memory across subsequent sleep) led to increased spindle-delta-ripple coupling during posttraining NREM sleep. The authors also found that when brain stimulation triggering delta-spindle sequences was applied in coordination with SWRs (but not when it was applied out of phase with SWRs) consolidation of spatial memory across sleep improved significantly [108].

Taken together, recent data suggest that coordination of various circuit-specific (e.g. SWR activity generated in the hippocampus, spindling in the thalamus) oscillatory activities between brain regions may play a critical role in promoting brain plasticity. This coordination would not only optimize spike timing between brain areas, thus promoting STDP, it may also optimize information transfer between brain areas—a mechanism that has long been discussed with regard to attentional mechanisms during wake [109]. In other words, adaptive temporal coordination of activity among various oscillating circuits during NREM could provide a basis for informative plasticity between neurons in various brain structures, similar to plasticity driven by sensory experience in wake. Although this coordination appears to be mediated by SWA, future studies will be needed to better understand: (1) the precise circuit-level mechanisms involved, (2) how these mechanisms might be affected by learning and by sleep pressure, and (3) whether some of the functions attributed to SWA are mediated by its role in coupling rhythms across brain structures.

Cambiare: REM

Available data suggest that REM sleep is beneficial for a number of cognitive functions, including consolidation of episodic and emotional memory [110, 111], creative problem solving [112], perceptual learning [113, 114], and restoration of perceptual learning after interference [115]. However, the mechanisms through which REM could facilitate these processes are largely unknown. REM is associated with a variety of changes in brain physiology, including unique patterns of neuromodulation and network activity [26]. Recent findings suggest that various forms of synaptic plasticity occur throughout the brain during REM sleep. For example, following a novel experience during wake, expression of mRNAs [15], proteins [116], and phosphoproteins [22] associated with synaptic plasticity is upregulated in hippocampal and neocortical neurons during subsequent REM. Recent studies using continuous in vivo electrophysiological recording have shown that following sensory experience in wake that initiates cortical plasticity, neuronal firing rates are selectively augmented across bouts of REM in sensory cortex [5, 25]. This REM-associated increase selectively affects sparsely firing neurons that encode sensory stimulus features more precisely; in contrast, high-firing neurons with low-feature selectivity show either no change or reduced activity across periods of REM [5]. One possibility is that the highly active neuronal population includes fast spiking interneurons—an inhibitory cortical neuron population exhibiting high spontaneous firing rates, and whose firing (compared with pyramidal cells) selectively

declines across periods of sleep [2, 21]. Thus, the phenomenon of augmented firing in sparsely active neurons across bouts of REM may be related to cell type-specific effects on neurons' overall activity, and/or changes in excitatory/inhibitory balance during REM sleep [117]. Long-term calcium imaging has demonstrated that, as is true during NREM spindles, during REM sleep, dendrite-targeting SOM+ interneurons show decreases in activity, whereas cell body-targeting PV+ interneurons' activity is augmented [118]. As described above, this alteration may provide an ideal circumstance for non-Hebbian synaptic potentiation (which may selectively affect lower-firing pyramidal neurons) during REM. It might also relate to a seemingly contradictory finding. Structural studies using longitudinal two-photon imaging to characterize layer 5 cortical dendritic spines following learning on a sensory motor task showed synaptic pruning during REM sleep (which selectively affected newly formed dendritic spines) [119]. This may be explained if dendrite-targeted inhibition is significantly reduced during REM, leading to increased dendritic remodeling (e.g. strengthening of stronger and pruning of weaker synapses). Interestingly, and in contrast to studies of firing rate changes occurring across REM in the cortex, studies of firing in the hippocampus have shown that mean firing rates in that circuit are selectively decreased across REM bouts [120]. Thus, one possibility is that REM may have circuit-specific effects on different brain areas.

Clearly, REM has the potential to alter synaptic strength, although debate about REM sleep's role in regulating synaptic strength is ongoing [117, 121, 122]. Resolving this issue will ultimately come down to a better understanding of causal mechanisms—i.e. what features unique to the REM sleep state contribute to specific types of plasticity. Recent studies have approached this question by focusing on the role played by rhythms prominent in the brain during REM sleep (including the hippocampal theta rhythm and pontine–geniculate–occipital [PGO] waves) in promoting long-term memory formation.

Alla marcia: hippocampal theta rhythm

The hippocampal theta rhythm (which depending on the study is either defined as a relatively broad [4–12 Hz] or narrow [e.g. 6–8 Hz] frequency band) is one of the most consistent and pronounced features of REM sleep (Figure 3, right). Driven by medial septal input to the hippocampus [123–126], this rhythm is mediated intrahippocampally by parvalbumin-expressing (PV+) fast spiking interneurons [12, 13, 127].

Although the relationship of hippocampal theta activity to waking functions (e.g. for encoding spatial information during navigation) has received extensive study, there is a growing body of evidence that REM theta may play a role in sleep-associated cognitive functions. Early reports from napping human subjects indicated that theta activity recorded over prefrontal cortex during REM was a predictor of emotional memory improvement [111]. Available data also suggest a link between REM theta and memory consolidation in studies using animal models. Early work suggested that the phase of hippocampal neurons' firing with respect to REM theta rhythms could be modified as a function of their activation during prior waking experience [128]. More recently, cued fear learning in rats was shown to increase theta coherence between hippocampus and amygdala during subsequent REM sleep, and this increase in coherence predicts

the success of associative memory consolidation (i.e. increases in coherence are proportional to offline associative gains) [129]. A growing body of data indicates that theta frequency activity is increased for several hours following single-trial contextual fear conditioning (CFC) in hippocampal area CA1, across both REM and NREM sleep [11–13], and that this increase predicts successful contextual fear memory (CFM) consolidation. Other studies have experimentally tested whether hippocampal theta can itself drive improvements in performance. An early study found that augmentation of theta activity (via medial septal stimulation) immediately following training on a spatial visual discrimination task improved rats' task performance 24 hr later [130]. Consistent with this, a more recent study disrupting septal input to the hippocampus optogenetically in the hours following CFC led to a reduction in REM theta in CA1, and impaired CFM consolidation [123]. Two related studies inhibited hippocampal theta activity locally (within CA1), in the hours following CFC, leading to similar deficits in CFM consolidation [12, 13]. Conversely, optogenetically generating a theta rhythm in CA1 throughout a period of post-CFC sleep deprivation is sufficient to rescue CFM consolidation (which normally requires uninterrupted sleep) [13].

At the cellular level, why might REM theta (or hippocampal theta rhythms in general) support memory storage? Theta is known to support replay of hippocampal place cell sequences, following their sequential activation during experience [131]. Computational work suggests that: (1) the precise phasing of neuronal firing during replay can be modified as a function of learning-associated plasticity [132, 133], and (2) replay could emerge naturally from resonance with subsequent network oscillations [132]. Electrophysiological data suggest that CA1 pyramidal neurons resonate selectively at theta frequency, in response to rhythmic activity in parvalbumin-expressing (PV+) fast spiking interneurons [12]. This resonance is associated with increased consistency of spike timing relationships between neurons, an ideal scenario for driving STDP throughout the CA1 circuit [12, 13, 132]. Indeed, recent studies using CFM as a model of sleep-dependent memory consolidation have consistently found that long-term (i.e. over the time scale of several hours) stabilization of spike timing relationships among CA1 neurons is a robust predictor of consolidation [11–13]. Following CFC, pharmacogenetic or optogenetic disruption of theta rhythms leads to destabilization of CA1 spike timing relationships, and disruption of CFM consolidation [12, 13]. Optogenetic generation of theta oscillations increases the stability of CA1 spike timing relationships and preserves memory in the face of sleep loss [12, 13]. Thus available evidence suggests that the highly regular theta-frequency activity that paces hippocampal neurons' firing during REM drives network plasticity and plays a critical role for hippocampally mediated memory consolidation.

Bravura: pontine–geniculate–occipital waves

PGO waves, like NREM spindles, occur as discrete biphasic wave events during sleep (as intermittent single waves during certain phases of NREM, and as repeating motifs throughout REM; Figure 3, right) [134, 135]. These high waves of activity propagate (as the name implies) through the pons, the lateral geniculate nucleus of the thalamus, and the occipital cortex of

species with highly developed visual systems, and propagate from the pons to apparently communicate with numerous brain structures (and are thus simply called "P waves") in rodents [136]. A role of this wave in sleep-dependent memory consolidation (particularly for hippocampus- and amygdala-dependent memories) has been extensively investigated in rodents. These studies have demonstrated an increase in P wave occurrence during REM following training on fear and avoidance memory tasks [137, 138]. Studies manipulating the generation of these waves following learning have demonstrated a clear causal role in promoting consolidation [139], which may be linked to P wave-dependent upregulation of kinase pathways and transcriptional activation of plasticity-mediating genes in target structures (such as the hippocampus and amygdala) in the hours following learning [14, 140, 141]. How these cellular events come about during and after PGO waves occurrence is an unanswered question, although it is clear that these waves can generate massive, highly synchronous depolarization among neurons in the circuits they propagate through. Thus, it is not surprising that they tend to act as "carrier waves" that initiate other network rhythms (e.g., beta oscillations in the occipital cortex). In this respect, their behavior is very much analogous to sharp waves, which by virtue of generating synchronous depolarization, kick off ripple oscillations in CA1. During REM, PGO waves also occur with a specific phase relationship to theta rhythms occurring in the hippocampus [142]. Thus as is true in NREM sleep, in REM multiple rhythms harmonize activity across the brain. Such interregional synchrony, comprising rhythms of different cadences, may play a critical role in REM-associated plasticity and the cognitive benefits of REM sleep.

How the Brain Listens to Sleep's Symphony of Rhythms—Toward a Unifying Theory for Sleep's Role in Synaptic Plasticity

Numerous hypotheses have been proposed for the function of sleep-associated rhythms in mediating the cognitive benefits of sleep [26, 47, 86, 109, 136, 143]. And while oscillations at specific bands are clearly important for plasticity across brain regions, we hypothesize that they can also influence synaptic plasticity in a broadly universal manner. We argue that during wake, new information is initially encoded in circuits based on experience-dependent changes in their firing rate (Figure 3a). Rate coding (in which information is encoded based on how rapidly individually neurons fire) is frequently used by neurons during wake, e.g. to encode specific features of sensory stimuli. The idea that new information is encoded in the firing rates of specific neurons during experience has become widely accepted in recent years [144]. However, information encoding based on firing rate alone has several limitations. When neurons fire with a wide range of rates, plasticity based on STDP can be very ineffective. Furthermore, a purely rate-based readout should limit the contribution of sparsely active neurons, which provide important sensory information and are highly plastic [5], to an engram. Finally, the limited dynamic range over which individual neurons can vary their firing puts a limit on new information encoding in a purely rate-based system. For optimal information encoding and storage, nonrate-based information encoding strategies must be invoked.

We argue that sleep rhythms allow neurons to switch from a rate-coding mode, in which information is encoded based primarily on how rapidly each neuron in an ensemble fires, to a phase-coding mode, in which spike timing becomes critical for information storage [145]. We hypothesize that as the brain transitions from wake to sleep, it dynamically switches between rate and phase coding schemes (Figure 3b). Sleep is well positioned to promote this switch for several reasons. The lack of incoming information to the brain during sleep leads to internal regulation of network dynamics. Changes in neuromodulatory milieu simultaneously modify the excitability of neurons, increasing their capacity for synchronization [146–148]. Finally, in many circuits, oscillatory neuronal activities during sleep drive the phase locking of neuronal activity across the network. This in turn leads to formation of stable spike timing relationships (the basis for phase coding and an ideal mechanism for STDP) across large networks.

Here we focus on one mechanism that relies on resonance, a biophysical property in which neurons have a heightened response to input of a specific frequency [149–151]. This mechanism alone can account for instructive plastic changes to network connections, based on prior experience. A neuron's resonant frequency shifts as a function of depolarization [152–154], meaning that neurons receiving larger synaptic inputs at higher rates, i.e. those which are more depolarized, will fire at an earlier phase. This general mechanism establishes a reliable input versus phase relationship across the network. During sleep-associated rhythms, neurons receiving more or larger excitatory synaptic inputs (based in part on prior experience during wake) will fire at earlier phases of a driving network oscillation (Figure 3b). This patterning can lead to the frequently reported phenomenon of temporally compressed replay of activity patterns occurring during prior wake [145]. Because during oscillations, these neurons will consistently fire prior to their postsynaptic partners, their excitatory inputs to other neurons (firing later in the rhythm, with a delayed phase) will be strengthened through STDP. Any reciprocal connections back to the phase-leading neuron will be weakened through STDP. Thus, when neurons within a network resonate with an oscillation, the input versus phase relationship paired with STDP will selectively strengthen connections from recently activated "engram neurons" to the rest of the network—an optimal scenario for systems memory consolidation.

A similar resonance-based mechanism would also act in the absence of prior learning. In this case, it would lead to differential phasing of highly active and sparsely firing neurons, with highly active cells leading. Assuming similar STDP-mediated effects, this would act to weaken inputs to neurons with initially high-firing rates, and strengthen inputs to neurons with initially sparse firing. This phenomenon could underlie the rescaling of firing rates that appears to happen across neural circuits in a sleep-dependent manner [5]. This idea is similar to one recently put forth by Levenstein et al., who recently proposed NREM slow oscillations as a mechanism by which STDP rules could be optimized to promote heterogeneous firing rate changes among highly active and sparsely firing neurons in a network [6]. Critically, however, we argue that resonance is a general feature of neural circuits, not limited to slow oscillations. According to our model, any oscillation can drive synaptic changes so long as neurons resonate with its particular frequency band. Importantly, this
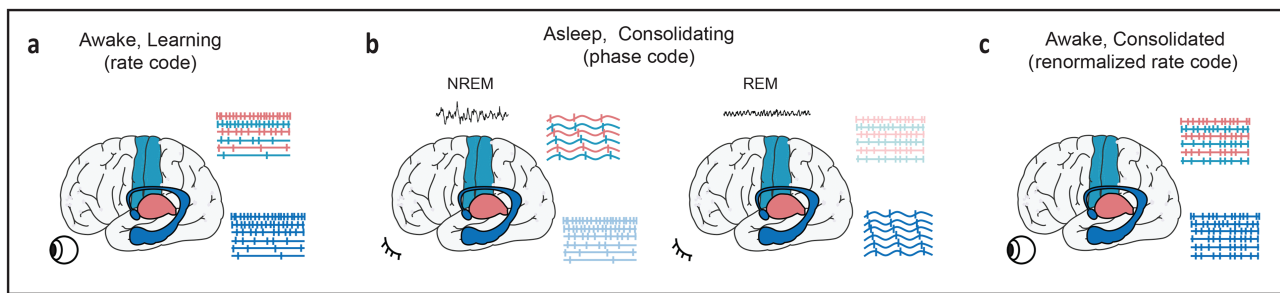
Figure 4. Resonance-based mechanisms for sleep-dependent plasticity. General mechanism for resonance-based plasticity. During wake, ensembles of neurons can encode new information, leading to selective changes in some neurons' firing rate and excitability (a). During subsequent network oscillations in sleep, resonance (wherein relative phasing is based on excitability) generates consistent spike-timing relationships between the neurons in the ensemble (b). Prominent rhythms present in thalamocortical networks during NREM sleep (b, right), and subsequently in the hippocampal network during REM sleep (b, left), can selectively bring these circuits into resonance based on circuit wiring and the intrinsic properties of circuit neurons. Spike-timing dependent plasticity among neurons in resonance leads to: (1) relative strengthening of synapses from highly activated neurons to the rest of the network, and (2) renormalization of firing rates (i.e. highly active neurons show reductions in rate, whereas sparsely firing neurons show increases, relative to prior wake). These changes are evident during subsequent wake (c).

resonance-based mechanism could account for instances of both synaptic weakening and synaptic strengthening across sleep, as well as more idiosyncratic phenomena such as forward and reverse replay (Figure 4) [145].

For the reasons outlined above, we anticipate that the state-dependent switch between rate and phase coding would optimize information storage over widely distributed, heterogeneous circuits across the brain. We predict that any rhythm (in any brain state) can drive synaptic changes so long as neurons' firing can resonate at its frequency. The wiring of specific neural circuits, and neurons' intrinsic properties, will predispose them to resonance with oscillations of particular frequencies, which are naturally augmented during particular brain states. Thus, during NREM sleep, thalamic and cortical neurons will naturally resonate with high-amplitude SWA and spindle oscillations generated in thalamocortical circuits (Figure 3b, left). During REM sleep, hippocampal neurons will resonate with regular, high-amplitude hippocampal circuit rhythms at theta frequency (Figure 3b, right). Thus, it may be that the symphony of sleep-associated rhythms acts in concert, sharing a general mechanism by which they can weaken and strengthen synapses throughout the interconnected circuits of the brain.

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