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The role of slow-wave sleep rhythms in the cortical-hippocampal loop for memory consolidation.

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Abstract

Memory consolidation during slow-wave sleep is supported by slow oscillations (SOs), spindles, and hippocampal ripples. Recent evidence in both rodents and humans has demonstrated that consolidation is mediated by a bidirectional hippocampal-cortical loop. Here, we discuss oscillatory mechanisms by which the interaction of these non-REM oscillations may provide an appropriate neural framework for both the TOP-DOWN and the BOTTOM-UP processes in this loop. We also discuss how non-REM oscillations promote cortical plasticity for new memories, while simultaneously downregulating the representations of information in hippocampal networks. Finally, we point out that not all individual instances of non-REM oscillations play a role in the consolidation process. Instead, the capacity of these rhythms to support memory is determined by a triple SO-spindle-ripple coupling provided by thalamocortical dynamics. Importantly, large, spatially synchronised SOs promote thalamic downstates, and spindles, boosting the probability of this triple coupling.

Introduction

Consolidation of episodic, sequential and spatial memories is largely supported by hippocampal networks. Neural replay of encoded information occurs during post-learning rest and sleep and is commonly concurrent with hippocampal ripples (HC-ripples) within sharp-wave/ripple complexes (SWR)[1]. Memory is impaired when SWR are suppressed during sleep[2] and wakefulness[3], but memory reactivation has different functions in sleep and wake. Thus, wakeful SWRs are thought to support initial memory formation and are implicated in decision making, while sleep SWRs promote long-term memory storage and integration with past information[4]. The sleeping brain therefore offers the necessary physiological conditions for optimal consolidation of recently acquired information. In this review, we focus on the sleep-dependent memory consolidation which is associated with hippocampal replay.

The Active Systems Consolidation (ASC) hypothesis of memory during sleep proposes that information is consolidated by the interaction between hippocampal and cortical structures during non-REM sleep, including slow-wave sleep (SWS) and lighter sleep stages[5]. This hypothesis indicates that the repeated and timed coordination of classical non-REM graphoelements such as HC-ripples (~150-250Hz), thalamocortical spindles (~11-16Hz) and cortical slow oscillations (SO, ~0.5-3Hz) during SWS facilitate the process of reactivation, plasticity, and stabilization of recently encoded memory traces[5].

The process of memory stabilization in the cortex and the directionality of cortico-hippocampal communication during SWS are both matters of current discussion[1]. Based on recent findings[6], Rothschild 2019 proposed that memory consolidation in SWS relies on a bidirectional hippocampal-cortical communication[7]. Further evidence supports this model indicating the role of non-REM oscillations and the ASC theory in this process[8]. Nevertheless, the neural mechanisms for memory consolidation in sleep are still debated[9,10].

Here, we aim to unify the new findings relating to SWS rhythms and discuss possible mechanisms that may support the bidirectional hippocampal-cortical process under the ASC hypothesis. We then consider possible oscillatory interactions of hippocampal and cortical structures within this framework. Building on ASC, we argue that the capability of classical non-REM oscillations to participate in the process of memory consolidation is determined by precise interactions between these and other SWS rhythms. Finally, we briefly consider where techniques for memory manipulation in sleep may lie within this framework.

The role of SWS rhythms in the cortico-hippocampal communication

SWS dependent memory reactivation requires coordination between the hippocampus and sensory, entorhinal, and prefrontal cortices[11]. During wakefulness, information can be simultaneously encoded in the hippocampus and the cortex[12], possibly allocating temporal and spatial context into the hippocampus, while other aspects of the memory are logged to the cortex[7,13] (Figure 1a). Cortico-hippocampal sharing of information during SWS then helps to reorganize and stabilize recent memory traces. Indeed, previous articles have described the memory implications of hippocampo-cortical binding[10,11], whereas the organization of SWS rhythms is linked to this process in the ASC model[5,9],

Oscillatory activity emerges from the distributed interaction of neural assemblies across brain regions. Thus, different dimensions of neural information are combined within the oscillatory activity such as

changes in obvious (amplitude, frequency, wave-shape) and less-obvious (synchrony, coupling) attributes of the oscillations[14,15]. Thus, although non-REM oscillations are graphoelements defined as typical oscillatory patterns with obvious attributes[9], SWS rhythms also carry diverse levels of information regardless of power or frequency (e.g. phase-synchrony, cross-frequency coupling and multifrequency components). Hence, beyond the structured organization of non-REM graphoelements detailed in the ASC[5,9], we argue that these additional attributes of SWS rhythms may support neural mechanisms of consolidation.

Recent findings suggests that consolidation may be a cortical-hippocampal-cortical process[7] (Figure 1b). Thus, a study in rodents revealed that external sensory triggering first reactivates encoded information in cortical areas[6]. This cortical activity then predicts hippocampal reactivation during ripples, then subsequently, this hippocampal reprocessing modulates the cortical reactivation[6]. These findings led Rothschild to propose a model where memory strengthening is supported by a bidirectional loop which is time-aligned to HC-ripples during sleep[7]. Under this new framework, cortical areas first reactivate encoded information (e.g. in the sensory cortex) in a TOP-DOWN manner. Memory is then processed in the hippocampus where spatiotemporal context is integrated with cortical related memory elements (e.g. sensory information). Finally, The integrated representation is reinstated BOTTOM-UP into the cortex[7]. Although this model is compelling, it is hard to infer causation between these regions, regardless of the temporal association of cortical-hippocampal reactivations[6].

New evidence in humans supports Rothschild's framework[8], further establishing that this bidirectional loop is coordinated by SWS rhythms. In this study on intracortical implanted subjects, medial-temporal lobe (MTL) ripple activity (including hippocampus) was predicted by broad frequency TOP-DOWN cortical activation, and a directed BOTTOM-UP exchange of information from the hippocampus to the prefrontal cortex was then generated after MTL-ripples[8]. Hence, the degree of inter-region connectivity and information sharing was coordinated by the strength of SO-spindle coupling, while the transfer of information peaked after spindle-ripple activity modulated by SOs[8].

Rothschild[7] proposed that either spontaneous or sensory induced reactivation during sleep can trigger a cortico-hippocampal volley of information that integrates sensory and spatiotemporal context. However, the neural mechanisms involved in this TOP-DOWN process remain unclear[7]. Cortical reactivation of memories in sleep has been suggested to relate to the salience of the memory representation, with cortical reactivation inducing hippocampal replay of the linked memory representation[16]. In rodents, cortical reactivation is supported by the similarity of cell firing templates between learning and sleep periods, predicting subsequent hippocampal replay associated with slow waves[17,18]. Because of methodological constrains, it is difficult to verify the same cooperative cell activation within deep local networks in human intracortical recordings[19]. Nevertheless, recent findings in humans showed non-obvious stimulus-specific oscillatory patterns such as phase-synchrony[20] or amplitude similarity[21] during SWS mirroring cortical activity in learning. These attributes were further linked to memory performance and coupled to HC-ripples[21]. Based on these findings, we propose that hippocampal replay may be triggered by such oscillatory interactions in cortical reactivation around SOs, and that these mirror cortical activity during learning, initiating the TOP-DOWN link. Notably, cortical reprocessing associated with the BOTTOM-UP process might rely on a different process from that used in this TOP-DOWN link.

The BOTTOM-UP process of memory consolidation is facilitated by the interaction of ripples with SOs and spindles and has been well described in the ASC. During SOs, cortical down-states (synchronized neural hyperpolarisations) isolate neural inputs to the prefrontal, entorhinal and hippocampal areas, coordinating the temporal patterns of neural firing that establish connectivity between these

regions[22]. Hippocampal CA3-CA1 ripples associated with down-to-up transitions of cortical activity mark periods of replay, promoting cortical plasticity[17,23]. Thalamocortical spindles contribute by inhibiting superficial layers of cortical pyramidal cells, possibly protecting them from interference so that recently altered cortico-cortical synapses can be stabilised[17,24]. HC-ripples may simultaneously help to stabilize the hippocampal information while promoting cortical synapses[10]. A reverberant process in the hippocampal-cortical loop may thus readjust hippocampal-cortical binding, while hippocampal reactivation gradually decreases as the associated representations within cortical schemas are strengthened[16] (Figure 2).

As the hippocampus interacts with a range of cortical areas encoding different types of information (e.g. sensory, motor or associative information). Memory consolidation could potentially differ depending on the cortical regions involved. However, the bidirectional cortical-hippocampal loop has been observed in both primary sensory[6] and prefrontal[8] cortices, suggesting similar SWS consolidation mechanisms in different sleep-dependent memories with hippocampal engagement. This includes spatial, associative and semantic memories as well as language learning[5]. Therefore, it seems probable that only the timing and cortical reactivation that initiates the TOP-DOWN cortico-hippocampal link differ for different memory types.

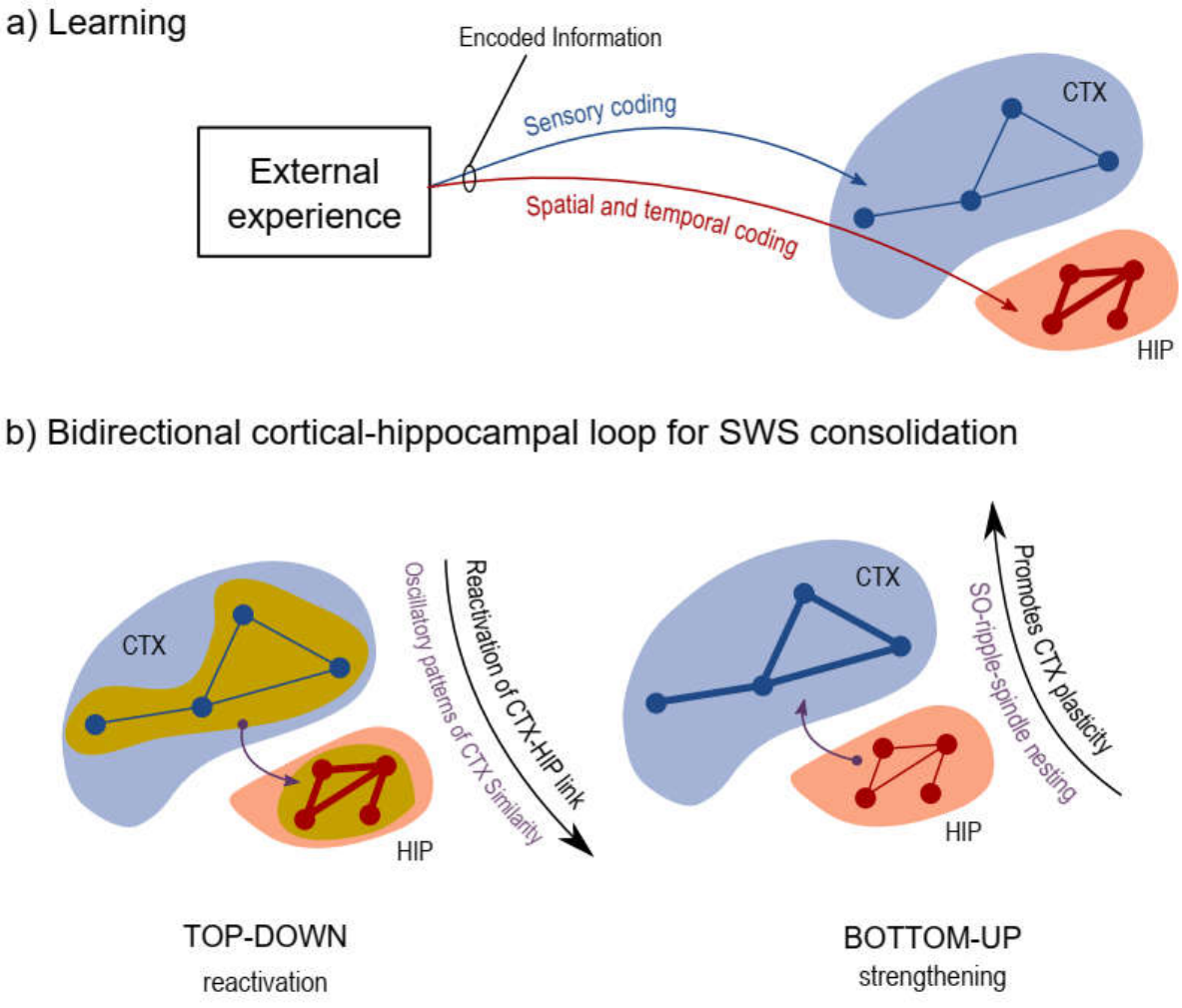

Figure 1. Dynamics of the memory consolidation process. a) During learning, experience encodes neural representations in both cortical (CTX) and hippocampal (HIP) networks. Spatial and temporal information from the experience are strongly coded within the hippocampus whereas sensory representations are stored in the cortex. b) During SWS, spontaneous or cued information is reactivated in the cortex triggering hippocampal replay (TOP-DOWN). This reactivation of CTX-HIP link may be indexed by the reactivation of non-obvious oscillatory patterns such as phase or amplitude similarity mirroring cortical activity during learning. Hippocampal reactivation promotes strengthening of cortical synapses supported by the nesting of slow oscillations (SO), ripples and spindles (BOTTOM-UP).

Memory stabilization in hippocampal and cortical regions during SWS

Sleep not only facilitates the strengthening of single events, but also contributes to integrating this information with previous knowledge in broader schemas[25] and to hippocampal downscaling[26]. Memory representations become more dependent on cortical schemas over time, and hippocampal activation is no longer essential for retrieval[26]. These functional changes suggest that memory consolidation may proceed in different but complementary ways in the cortex and hippocampus. Systems consolidation suggests that the repetitive action of SWS graphoelements provides a basis for the neural dynamics leading to this memory reorganization[5].

HC-ripples may simultaneously contribute for both hippocampo-cortical communication and hippocampal stabilization. Ripples, modulated by spindles, are broadly believed to mark periods of hippocampal-cortical communication and replay[27]. However, both rodent[17,28] and human[29] studies show that ripple-related cortical reactivation is stronger prior to spindles. Both HC-ripples in down-to-up SO transitions and HC-ripples that are non-coupled to spindles may help to mark cortical reactivation[30], whereas HC-ripples during spindles and cortical up-states might also help newly reconfigured information to be integrated into hippocampal networks[10]. Spindles shape the inhibition of upper cortical layers, briefly imposing a synchronous functional deafferentation of upper layers from hippocampal inputs, while in deep layer pyramidal cells are driven mainly by ripples rather than spindles[28]. By silencing competing inputs in superior layers, spindles are thought to protect newly minted cortico-cortical plasticity[24,31]. Simultaneously, HC-ripples may also reorganise integrated representations both in cortical deep layers and in the hippocampus during modulated periods of cortical inhibition on superior layers[28]. It has been suggested that hippocampal downscaling occurs mainly during REM sleep[9,26]. However, we propose that this local reorganization driven by HC-ripples could potentially help both in promoting cortical consolidation and in downscaling the hippocampal content of the memory representation, indicating thus the end of replay of a consolidated memory[16] (Figure 2b). Indeed, a recent study demonstrated that HC-ripples regulate hippocampal synaptic depression, and that spontaneous down-scaling is impaired after optogenetic ripple silencing during SO periods[32].

Post spindle cortico-cortical interactions may also help to integrate cortical representations into schemas (Figure 2c). Hippocampal-cortical shared information in the cortex, defined by ripple mediated mutual dependence, peaks after spindles[8]. This increase coincides with periods of spindle refractoriness which have been suggested to facilitate memory reprocessing[33]. As this is a statistical measure, it would be an oversimplification to consider this peaking of mutual dependence between cortical and hippocampal activity as evidence of neural connectivity or reactivation. Nevertheless, mutual dependence may indicate more complex cortical dynamics triggered by the spindle-ripple binding, including the cortical integration of memory representations.

Consolidation requires both local and network dynamics for cortical integration. Therefore, locally restricted cortico-cortical slow-waves (see BOX 1) may reinstate specific information by selecting independent cortical regions[34]. Cortical integration may also be facilitated by the gamma modulation of cortico-cortical links. Gamma activity (40-120Hz) is associated with memory encoding and retrieval[35,36]. Coherence of gamma oscillations has also been proposed to underpin connections between both nearby and distant cortical regions [14,37]. High gamma events (>80Hz) coupled to SOs indicate increases of local neural firing[38]. In rodents, the coupling between high gamma events and HC-ripples is strengthened during SWS following learning[39]. In humans, these events are triggered by HC-ripples and modulated by spindles in both superior and deep cortical areas[28,38]. High gamma events are also phase-coupled to SOs during SWS and mainly synchronized within middle and short distance connections (< 5cm), suggesting an active process of information processing within local cortical circuits[40]. However, the interactions of spindles and gamma oscillations, and the role of gamma activation during the process of integration of encoded information is yet to be determined using additional memory paradigms.

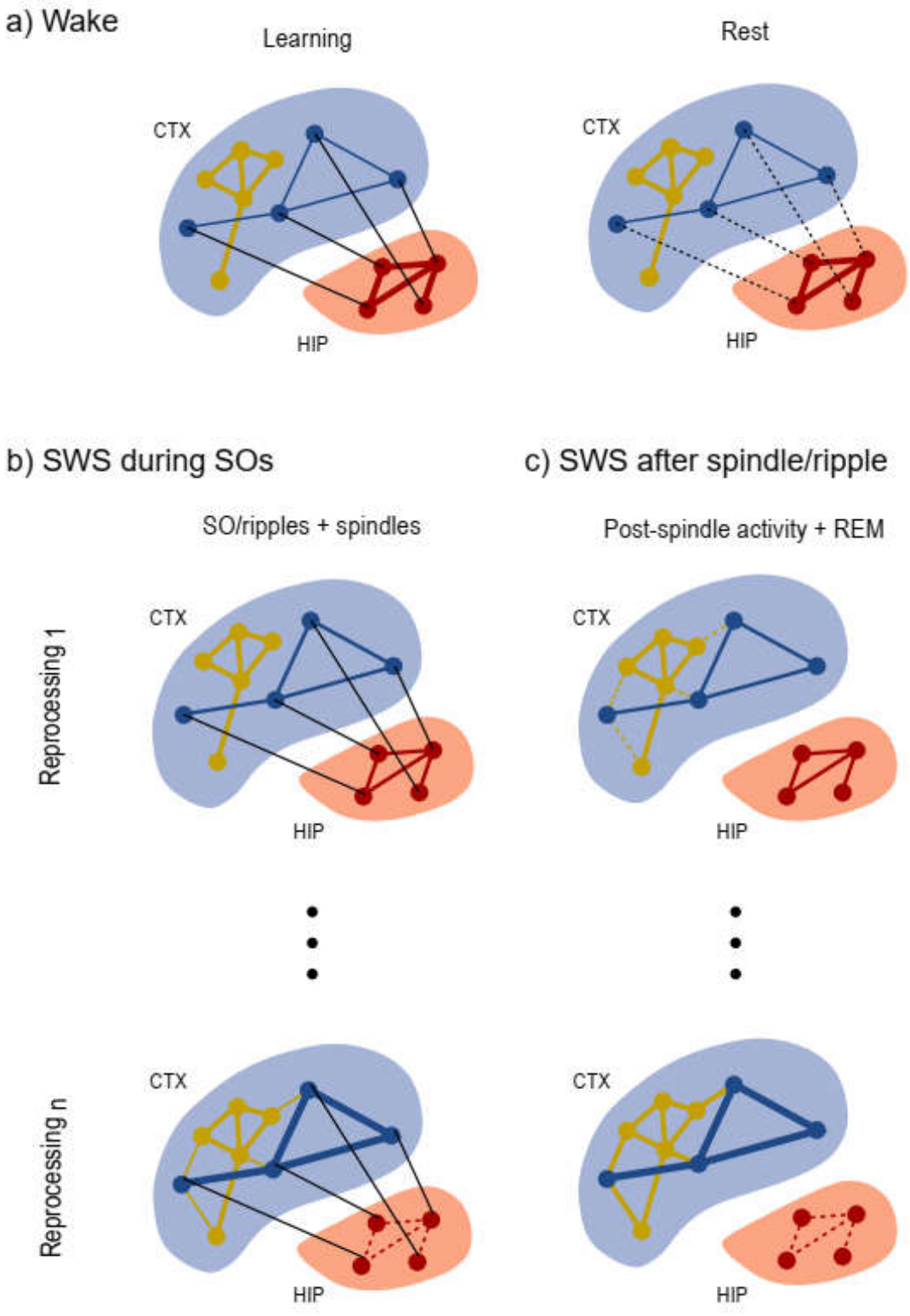

Figure 2. SWS dependent memory stabilization. a) During learning, cortical (CTX) and hippocampal (HIP) representations of the same memory create links to map the encoded information. Cortical networks (blue links) which are firstly weak rely on hippocampal connections (red links) to trace encoded memories, while learned schemas are previously consolidated (Yellow links). b) During non-REM sleep, the nesting of slow oscillations (SOs), ripples and spindles facilitates memory reprocessing. The strengthening of cortical synapses reinforces cortical neural representations, while in hippocampal areas, hippocampal links are reorganised to promote neural down-scaling. c) Post-

spindle activity further promotes cortical reorganization by integrating newly formed links into broader schemas.

Memory consolidation is determined by the mechanistic features of sleep oscillations

Neural oscillations contain overlapped information from multiples sources, providing a broad and blurry picture of the fluctuation in excitability of large cell populations. It is therefore inappropriate to set an absolute functional role to each non-REM oscillation based only on its frequency. Indeed, the neural mechanisms of non-REM oscillations underpinning regulation of the consolidation process are debated[10,11]. While memory consolidation benefits from HC-ripples, spindles and SOs, each individual instance of these graphoelements does not contribute equally in the hippocampo-cortical association (BOX 1). For instance, graphoelements from the same family may be involved in different physiological functions depending on their neural sources[41]. The potential of each graphoelement to participate in hippocampal-cortical communication also depends on its network of interactions with other SWS rhythms[8,23].

Optimal hippocampo-cortical association relies on the precise timing of cortical activation within thalamocortical and hippocampal networks. Previously, it has been common to discuss individual increments of SO and spindle density or power as markers of increased consolidation[5]. However, it is now clear that temporal synchronization between SWS rhythms is the critical factor in the consolidation of hippocampus-dependent memories into cortical networks[9]. Indeed, a timed and structured coupling between hippocampal and thalamocortical activities catalyses appropriate hippocampo-cortical communication[8,23]. In one important study[42], the authors manipulated the temporal coordination of hippocampo-cortical structures in sleeping rodents. Their findings suggest that it is not the individual occurrence rate, duration, or amplitude of the HC-ripples, spindles or SOs that predicts post-sleep performance, but rather the timed coupling between these activities[42].

The crucial role of temporal coupling in memory consolidation stems from its role in the generation, protection, and strengthening of cortical synapses. The protective role of spindles is maximized within strong phase locked SO-spindle pairs[8,42], and the strength, timing and level of SO-spindle coupling is determined by the convergence of highly-synchronized thalamocortical down-states into thalamic-networks[43]. Therefore, an optimal hippocampo-cortical binding is established during thalamocortical SOs that are highly synchronized across cortical regions (Figure 3a). Accordingly, a recent study found different protective roles on memory performance and spindle coupling for larger, more spatially synchronized, SOs compared to more local and faster delta oscillations through inhibition of the neural activation within stereotypical oscillations [44]. Although not all spindles may be involved in consolidation, the hippocampo-cortical communication is optimized during SO-spindle pairs because plasticity is facilitated. If SO-spindle phase locking is decreased, the protector role of spindles is reduced then so is the effect of consolidation (Figure 3b)[42]. Increased density of these SWS rhythms should therefore increase the probability of optimal coupling, thereby promoting memory consolidation.

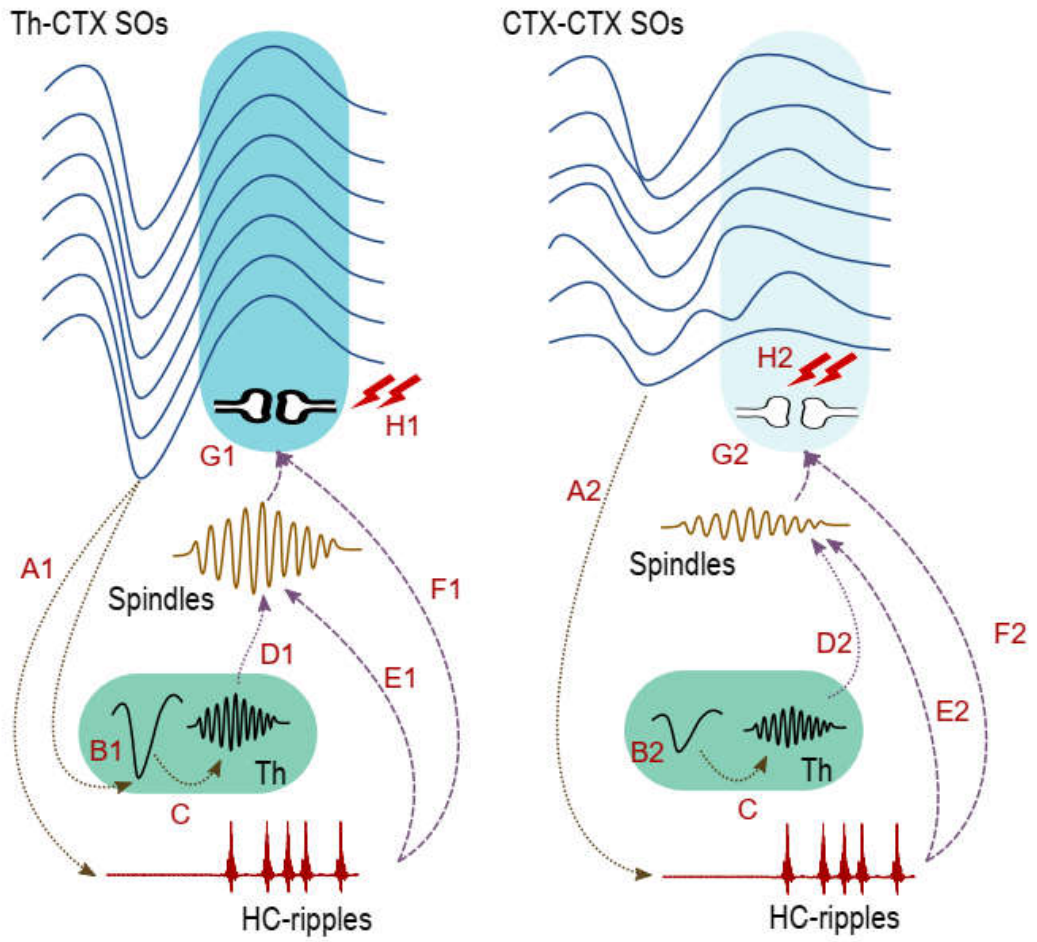

Figure 3. Cortical plasticity is promoted by the precise coupling of slow oscillations (SOs), ripples and spindles. Largely synchronized down-states created by the ongoing inhibition of thalamocortical SOs (Th-CTX SOs) coordinate hippocampal activity (A1). Simultaneously, convergent cortical down-sates promotes down-states in the thalamus (Th) (B1), which then facilitates spindles coupled to CTX-SO (C). Thalamic activity thus promotes precisely timed spindles coinciding with SO up-states (D1) and favouring the ripple-spindle coupling (E1) and hippocampal-cortical sharing of information (F1). This triple ripple-spindle-SO coupling underpins the protective role of spindles on cortical synapses (G1), preventing noisy interference of other inputs (H1). Less synchronized cortico-cortical SOs (CTX-CTX SOs) still may coordinate hippocampal activity (A1). However, the decreased synchronization with thalamic down-states (B2) may generate uncoupled SO-spindles pairs (D2). This asynchrony reduces the protective role of spindles (G2), and the hippocampal-cortical sharing of information (E2 and F2). Hence, any new formed synapse is more susceptible to noise (H2), preventing an optimal memory processing.

Manipulation of memory reactivation

The framework described above has important implications for the mechanisms for sensory interventions of memory manipulation during sleep. For instance, Targeted Memory Reactivation (TMR) has been suggested to depend on the level to which sensory stimuli influence reactivation[16]. In the context of memory consolidation as a reverberation between hippocampus and neocortex, memory reactivation can be considered as the first reactivation initiated by the sensory stimulation, but also as the echoing restructuring of cortico-hippocampal networks after transfer of information[7].

Indeed, in line with this model, recent evidence of neocortical replay in TMR displays re-occurring[20] or delayed[45] patterns of memory processing during SWS.

In comparison, other techniques for memory manipulation may act over other levels of our proposed framework. During closed-loop acoustic stimulation (CLAS), the precise phase-locked stimulation of SOs has been shown to improve memory performance, presumably by increasing SO strength and spindle coupling[46]. CLAS may therefore be successful because the phase-locked stimulation of SOs generates large thalamocortical network activations shown in the synchronous coordination of cortical down-states. Successful CLAS then generates adequate thalamocortical neural dynamics, driving a triple ripple-spindle-SO coupling which provides the perfect conditions for consolidation.

Concluding Remarks

Recent finding in both rodents and humans support a cortico-hippocampo-cortical movement of information during memory consolidation in SWS. The Active Systems Consolidation framework focuses on the role of NREM oscillations in consolidating hippocampally represented information into the cortex, and these same oscillations could also participate in the bidirectional interaction between these structures. We explain why the temporal coordination of these oscillations is critical, with a triple ripple-spindle-SO coupling providing the best conditions for cortical consolidation, while also supporting hippocampal downscaling. We further argue that a high spatial synchronization across SO troughs increases the likelihood that such triple coupling will occur since it drives the thalamocortical relay that produces spindles.

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BOX 1

Multiple functions of the same face: differential specialization of SWS patterns

Increasing evidence suggests that similar electrophysiological rhythms can have quite different functions. This is true for both SOs and spindles.

For SOs, the main differences are in extent and origin. SOs are traditionally described as periods of neural silence that recruit large neural populations[47]. Delta oscillations (0.5 – 4Hz) originate in cortico-cortical networks of primary and association cortices, but they are also seen in the thalamus. Slower and larger amplitude waves (<1Hz) are also expressed in cortical and thalamic neurons. These slow oscillations originate from cortico-cortical activations, but they are fully expressed in amplitude, extent, and synchrony only with active thalamic contribution[48]. Importantly, delta and slow waves involve different neural interactions depending on whether they originate in the cortex or the thalamus. Both can nest faster rhythms (e.g. spindles) regardless of their origin. Interestingly, intra-thalamic GABAergic synapses can be potentiated or depressed depending on whether thalamocortical neurons are modulated by slow (<1Hz) oscillations or delta rhythms, showing differentiated functions on thalamic plasticity[41]. Depending on their spreading, other SO subdivisions have also been characterized[49]. Similarly, these SO types indicate different global dynamics from cortico-cortical and thalamocortical SOs, as well as the different implication for localized and widespread SOs in physiological[50] and learning[34] processes. Furthermore, a recent article described how the characteristics of spindle-SO coupling are determined by the cortical SOs[43] with the convergent effect of cortical down-states on thalamic-networks found to be the determining factor that specifies the strength, timing and level of coupling within the SO activity[43].

SWS also imposes differentiated dynamics for sleep spindles. Spindles are generated in the thalamus by intrinsic network dynamics of thalamic-reticular generators, and their functionality has been described according to their frequency, location and coupling. Traditionally, human spindles can be sub-classified as fast (~12-16Hz) and slow (~9-12Hz)[51]. Centroparietal fast-spindles are associated with post-learning periods and memory consolidation[52], while slow spindles may be part of cortico-cortical dynamics[53]. Likewise, new evidence suggests a distinctive role for spindles according to their intracortical laminar profiles and thalamocortical projections. Because of their characteristics, the authors suggest that spindles contained in middle layers could be associated in the integration of sensory processing, whereas spindles within only upper cortical layers might engage associative aspects of memory[54].

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References annotations:

6 [**] This work shows for first time the bidirectional cortical-hippocampal transfer of information in rodents

8 [**] Using statistical technics, the authors demonstrate that a bidirectional cortical-hippocampal transfer of information in humans and support the role of sleep oscillation to maintain this link

21 [*] This work presents how cortical memory reactivation is associated to hippocampal ripples in humans

24 [**] In this study the authors demonstrate the protective role of spindles in synaptic plasticity

30 [**] A study in humans demonstrating the time development of SOs, spindles and their association with ripples from posterior and anterior regions from the hippocampus. This work showed different dynamics for posterior and anterior ripples suggesting differentiated functional mechanisms in memory consolidation.

31 [**] The findings of this work evidence the dendritic strengthening influenced by spindle activity

43 [**] In this study the authors evidence the driving role of highly synchronized SOs on the thalamic down-states for the generation and timed modulation of sleep spindles.

44 [**] In this work the authors used optogenetic techniques to inhibit neural activity targeted to highly synchronized SOs and delta oscillations showing in this way differentiated functionalities of these oscillations on the process of memory consolidation