Trends in
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Review

Coupled sleep rhythms for memory consolidation

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How do passing moments turn into lasting memories? Sheltered from external tasks and distractions, sleep constitutes an optimal state for the brain to reprocess and consolidate previous experiences. Recent work suggests that consolidation is governed by the intricate interaction of slow oscillations (SOs), spindles, and ripples – electrophysiological sleep rhythms that orchestrate neuronal processing and communication within and across memory circuits. This review describes how sequential SO–spindle–ripple coupling provides a temporally and spatially fine-tuned mechanism to selectively strengthen target memories across hippocampal and cortical networks. Coupled sleep rhythms might be harnessed not only to enhance overnight memory retention, but also to combat memory decline associated with healthy ageing and neurodegenerative diseases.

Highlights

Newly formed memories require strengthening and reorganisation (consolidation) after learning.

The sleeping brain is hallmarked by slow oscillations (SOs), spindles, and ripples. These rhythms drive neuronal firing rates with increasing efficacy and spatiotemporal precision.

While SOs set global windows of excitability and inhibition, nested spindles serve as relays that partially reactivate cortical learning networks, facilitate hippocampal ripples, and bias the content of associated memory reactivation.

Ripples activate local memory circuits and drive hippocampal–cortical pattern completion to strengthen and reorganise memory traces.

SO–spindle–ripple coupling thus governs consolidation processes at the neuronal (synaptic) and brain-wide (systems) level.

Memory consolidation during sleep

What did you eat for dinner last night? The ability to answer this innocuous question unveils one of the most remarkable feats of the human mind: the capacity to mentally travel back in time and relive past experiences with astonishing richness, from the perceptual details to the contextual surroundings that made up an event. Memory traces such as the recollection of last night's dinner evolve through three key stages: (i) the initial acquisition (encoding); (ii) stabilisation of the memory trace during postlearning offline periods (consolidation [1]); and (iii) recall triggered by an internal or external reminder cue (retrieval).

While substantial progress has been made in elucidating the neural mechanisms supporting encoding and retrieval, understanding the principles of memory-related offline processes has proven more challenging. This is because consolidation processes unfold dynamically over extended time spans [2,3], making them less amenable to rigorous experimental assessment and control. Moreover, the myriad of impressions, thoughts, and feelings that constitute wakeful experience all leave some physical trace (**engram**; see Glossary) in the brain [4], but only a fraction of those traces would be adaptive for future behaviour if retained [5]. Memory consolidation thus needs to strike the delicate balance between cleaning the brain of irrelevant traces and selectively strengthening the relevant ones. In short, consolidation is a complex and multifaceted process, with the underlying mechanisms still somewhat elusive.

Sleep, notably, has long been recognised for its role in enhancing the retention of newly acquired memories [6]. Initially, sleep was believed to merely shield new memories from external interference, but it has become increasingly evident that the sleeping brain is far from inactive [7]. Instead, it actively processes and reshapes recent experiences, with leading frameworks emphasising aspects of active enhancement [8] or homeostatic renormalisation [9] of learning networks, respectively. How, then, does the sleeping brain facilitate memory consolidation?

Consolidation is thought to operate on two levels – synaptic consolidation and systems consolidation [10]. During synaptic consolidation, the cellular processes of long-term potentiation

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(LTP) and long-term depression (LTD) mould synaptic connections among learning circuits within minutes to hours after learning [11,12]. The driving force of LTP is short-latency (<~100 ms) cofiring of participating neurons, referred to as **spike-timing-dependent plasticity (STDP)** [13]. Systems consolidation unfolds at a slower time scale and entails the spatial reorganisation and redistribution of memories between the hippocampus and cortical networks [14]. In the course of systems consolidation, memories may also undergo qualitative transformations such as the extraction of the semantic gist or integration into pre-existing schemas [3]. This review highlights recent progress in our understanding of how sleep-specific brain rhythms might contribute to synaptic and systems consolidation, selectively strengthening relevant connections within and across memory circuits.

Sleep rhythms: SOs, spindles, and ripples

The electroencephalogram (EEG) of **non-rapid eye movement (NREM) sleep** is characterised by three cardinal electrophysiological signatures: SOs, sleep spindles, and ripples (Figure 1A). Prior to discussing their interactions, the key roles of each of these sleep rhythms for memory

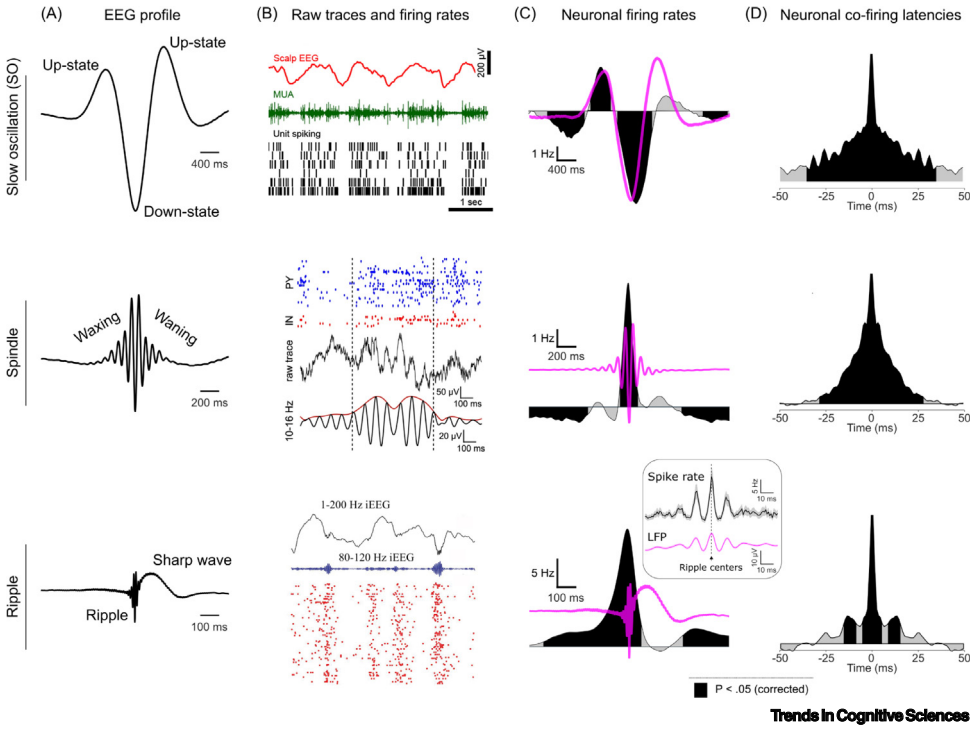

Figure 1. Non-rapid eye movement sleep (NREM) sleep rhythms and their impact on neuronal firing rates. Top to bottom: slow oscillations (SOs), spindles, and ripples. (A) Electroencephalography (EEG) morphologies, highlighting key components of each rhythm. SO and spindle examples originate from scalp recordings (electrodes C3/C4) and ripples from intracranial EEG (iEEG) medial temporal lobe (MTL) recordings [20]. Note that the polarity of iEEG signals is somewhat arbitrary, as it depends on recording site and referencing scheme. (B) Examples of EEG traces, single-unit and multi-unit activity (MUA). Note the increase and decrease of firing rates locked to SO up- and down-states, respectively [16], as well as increases in firing rates locked to spindles [41] and ripples [139]. (C) MUA (black) locked to SOs, spindles, and ripples recorded from the human MTL during NREM sleep, relative to a pre-event baseline window. Grand-average iEEG traces are shown in magenta. Black shading: $P < 0.05$ (corrected for multiple comparisons via cluster-based permutation tests). Note the exponential increase in firing rates across SOs, spindles, and ripples [20]. Inset: Local field potential (LFP) locked to cortical ripple centres (magenta) and associated local interneuron spike rates during NREM sleep (adapted, with permission, from [63]). (D) Cofiring latencies (normalized cross-correlograms) in a 100 ms window centred on SO up-states, spindle maxima, and ripple maxima. Black shading denotes significant increases. Note the stepwise narrowing of cofiring windows across SOs, spindles, and ripples [20].

Glossary

Blood-oxygenation level-dependent (BOLD) signal: reflects indirect and delayed metabolic effects of neuronal activity (leading to certain temporal ambiguity); main dependent measure in fMRI.
Decodability: analytical read-out of stimulus representations based on multivariate pattern analysis of brain activation recorded via M/EEG or fMRI.
Engram: neurophysiological representation of a memory trace underlying its phenomenology.
Hippocampal index: theoretical account positing that hippocampal cell assemblies formed during an experience point to neocortical representations of that experience.
Intracranial electroencephalography (iEEG): invasive recordings of electrical brain activity via cortical grids or depth electrodes.
Microwire recordings: special type of intracranial EEG in which a bundle of microwires protrudes from the tip of depth electrodes, allowing recordings of local field potentials as well as single- and multiunit firing rates.
Non-rapid eye movement (NREM) sleep: cumulative sleep stage consisting of stages N2 and N3, rich in slow oscillations and spindles as observed with scalp EEG; distinct from REM sleep.
Pattern completion: partial reminder cue elicits the reactivation of an entire neuronal ensemble which represents the memory engram.
Replay: special form of neuronal reactivation in which the temporal order of extended learning experiences is preserved.
Spike-timing-dependent plasticity (STDP): biophysical process strengthening synaptic connections among neurons based on the precise, short-latency temporal relationship of pre- and post-synaptic neuronal firing.
Tag: biophysical signal cascades elicited during an experience temporarily render involved synapses more responsive to subsequent stimulation and concomitant induction of plasticity.
Targeted memory reactivation (TMR): experimental protocol in which external auditory or olfactory cues are presented to sleeping participants in order to selectively strengthen particular memory traces.

(re)processing are briefly outlined in the following section, with an emphasis on recent findings on ripples.

Slow oscillations

SOs reflect fluctuations (~0.75 Hz) in cellular excitability, toggling between depolarized up-states and hyperpolarized down-states [15]. Despite the existence of isolated/local SOs [16], SOs tend to act as travelling waves [17], originating in (prefrontal) cortical sites [18] and imposing broad (~500 ms) time windows of neuronal activity (ON periods) and inactivity (OFF periods) on widespread cortical regions, the thalamus and the hippocampus [15,19]. Human **intracranial EEG (iEEG)** studies have confirmed increases and decreases of neuronal firing rates during up- and down-states, respectively, throughout the brain [16,20] (Figure 1B,C). Following a declarative learning task, brain-wide coherence has been found to increase during SO up-states [21]. More recent EEG work using effective connectivity analyses further showed that SOs gate global long-range communication, which in turn predicts retention of associative memories overnight [22].

Spindles

Sleep spindles are ~12–16 Hz oscillations of waxing and waning amplitude and 0.5–2 s duration, generated and sustained through reticular thalamic and thalamocortical neurons [23] and projected widely to cortex and the hippocampus [24–27]. Note that ~12–16 Hz fast spindles can be distinguished from ~8–12 Hz slow spindles, which are not further considered here as they not only differ in topography and function [28], but are also less likely to occur in the hippocampus [26]. Various features of spindles (e.g., density and amplitude) have been linked to sleep-dependent memory consolidation [29–32]. Importantly, spindles show high degrees of local specificity [16,33–35] and converging evidence suggests that spindles during postlearning sleep are more prevalent at brain sites involved in prior learning [36–38]. For instance, a recent study [39] showed that participant-specific topographies of spindle amplitudes during sleep track EEG topographies of prior learning (manifested as alpha power (~8–12 Hz) decreases). Moreover, participants with greater extents of spindle-learning overlap showed greater behavioural levels of memory consolidation (i.e., less forgetting from pre- to postsleep), corroborating the functional significance of region-specific spindle expression. In terms of neuronal processing, two recent iEEG studies in humans showed that spindles not only increase neuronal firing rates as previously shown in rodents [40] (Figure 1B,C), but that they also enhance cofiring among pairs of neurons within ~25 ms [20,41] (Figure 1D); that is, within the window of STDP. The corresponding molecular induction of synaptic plasticity is likely driven by Ca^{2+} influx into neuron dendrites, shown to be gated by spindles *in vivo* and *in vitro* [42–44]. In summary, spindles show regional specificity as a vestige of prior learning and facilitate structural remodelling at the synaptic level.

Ripples

Ripples are brief (~50–100 ms) high-frequency oscillations (110–200 Hz). They are best characterised in the rodent hippocampus [45], where they emerge from CA3–CA1 subfield interactions and are superimposed on high-amplitude sharp waves, culminating in sharp-wave–ripple (SW-R) complexes (for brevity referred to as ripples henceforth). They can also be readily observed in the human hippocampus and surrounding medial temporal lobe (MTL) regions during NREM sleep via intracranial recordings, albeit at slightly lower frequencies (~80–120 Hz) [26,46–48]. Perhaps the most striking feature of ripples is that they reliably accompany reactivation of cell assemblies involved in prior learning (**replay** for the reactivation of sequential patterns) [49], placing them front and centre for mediating hippocampal memory processes during offline periods [50]. Indeed, experimental suppression of ripples during sleep in rodents has been shown to impair subsequent memory performance [51] as well as subsequent levels of reinstatement for newly learnt environments [52], while experimental ripple enhancement bolsters later memory performance [53]. Human evidence linking ripples with memory

consolidation is still scarce. One study showed a positive correlation between entorhinal cortex ripples during a daytime nap and subsequent memory performance [46] and more recent iEEG work provided tentative evidence for reinstatement of distributed learning/daytime patterns during hippocampal ripples [54,55].

Despite their transient nature and relatively small amplitude, hippocampal ripples significantly impact both local as well as brain-wide extrahippocampal cell circuits, rendering them viable candidates for supporting synaptic and systems consolidation. For instance, a recent study using iEEG and **microwire recordings** showed not only that neuronal firing rates exponentially increase during ripples compared to SO up-states and spindles (Figure 1B,C), but that windows of neuronal cofiring (thought to underly STDP) are narrowest around ripples, with the majority of pairwise firing occurring within 5 ms of each other [20] (Figure 1D). Corroborating their role for synaptic consolidation, rodent work has shown that LTP associated with replay of place cells is contingent on the presence of ripples [56]. At the same time, ripples have recently been shown to induce LTD among neurons presumably less relevant for a given memory trace [57], together suggesting that ripples may shape local cell circuits in service of memory refinement.

On a brain-wide level, simultaneous recordings of local field potentials and whole-brain **blood-oxygenation level-dependent (BOLD)** activity in non-human primates have shown widespread increases and decreases in cortical and subcortical areas around hippocampal ripples [58], which has recently been extended to electrophysiological recordings in the rodent [59,60] as well as human [61] brain. Moreover, a magnetoencephalography (MEG) study linked high gamma MTL activity (presumably reflecting ripples) and associated replay with activation in default mode and parietal networks [62]. Finally, using invasive recordings in humans, local ripples were found to drive firing rates across the entire MTL [20]. Taken together, ripples have the capacity not only to potentiate local cell circuits, but also to synchronise and orchestrate brain-wide neuronal interactions, thereby likely supporting processes of systems consolidation. Of note, ripples do not seem to be confined to the hippocampus or the wider MTL network, but can also be observed in an array of cortical regions [63,64]. Interestingly though, recall-related ripples in lateral temporal cortex (and associated replay of learning patterns) have been found to be preceded by MTL ripples [65]. This finding dovetails with recent rodent work showing that ripples recorded from retrosplenial cortex originate from the hippocampus [66]. Collectively, these observations suggest that hippocampal ripples may directly propagate to specific cortical regions where they facilitate reactivation and refinement of memory engrams.

In summary, SOs, spindles, and ripples have all been implicated in memory-related processes on behavioural and physiological levels, but seem to play distinct roles. In line with the gradual increase in spatiotemporal resolution from slower to faster oscillations [67], SOs set the coarse time frame for brain-wide neuronal interactions. Spindles can promote structural brain changes and display greater spatial versatility, being preferentially expressed at sites involved in prior learning and thereby apt to select and shape relevant memory networks. Finally, ripples have the most pronounced impact on neuronal firing rates and communication, further driving plasticity within and across localised target circuits. How though does the brain – during the unsupervised state of natural sleep – integrate these distinct functions to selectively upregulate specific memory representations?

Coupled sleep rhythms

A ubiquitous observation across species is that SOs, spindles, and ripples exhibit a particular temporal relationship. As elaborated in the following section, this tripartite coupling constitutes a viable mechanism to drive synaptic and systems consolidation in a controlled fashion.

SO–spindle coupling

Human scalp EEG recordings have consistently shown that spindles systematically nest in SO up-states [68] (see [27] for an in-depth description of the underlying connectivity between cortex and thalamus). Providing early (indirect) evidence for a role of SO-spindle coupling for memory consolidation, spindle density during slow-wave sleep (where spindles and SOs can co-occur) was found to be a better predictor for postsleep memory performance than spindle density in general [69]. More recent work has confirmed that not only the coarse co-occurrence, but the exact SO phase at which spindles occur impacts memory. For instance, the closer spindles aligned with the peak of the SO up-state, the better overnight retention in a declarative memory task [70]. Moreover, a recent study showed that reinstatement of learning patterns (object or scene representations) during postlearning sleep was time-locked to SO–spindle complexes [71]. Importantly, individuals whose spindles clustered closer to the SO up-state showed greater levels of memory reinstatement which, in turn, was predictive of post-sleep memory performance. Likewise, work in rodents has shown that memory reactivation and behavioural expressions of consolidation are linked to the precision of SO–spindle coupling [72,73] and that conditions for plasticity (Ca^{2+} activity in pyramidal neurons) are augmented when spindles are nested in SOs [74]. On the flipside, misalignment of spindles with respect to SO up-states has been associated with behavioural consolidation deficits and accompanies age-related memory decline [75–77] (Box 1).

Spindle–ripple coupling

Given the relatively broad time window of SO up-states (~500 ms for a 1 Hz oscillation), however, greater temporal precision is arguably needed to forge memory engrams within the tight time constraints of STDP. Mounting evidence from invasive recordings in animals and humans suggests that spindle–ripple coupling might fulfil this role. Specifically, hippocampal ripples not only preferentially occur during the waxing phase of cortical or hippocampal spindles, but nest in individual spindle half cycles (troughs; ~30–40 ms for a 12–16 Hz oscillation) [20,26,47,48,78–84]. Beyond the fine-tuned temporal co-occurrence of ripples and spindles, their functional link has been corroborated by showing that longer-duration ripples (associated with enhanced memory reactivation [53]) are more strongly coupled with spindles [78,85] and that stronger hippocampal ripple

Box 1. (Mis)alignment of sleep rhythms: biomarker and opportunity for intervention in cognitive decline?

Age-related memory decline, mild cognitive impairment (MCI), Alzheimer's disease (AD), and dementia pose tremendous burdens for individuals, their loved ones, and healthcare systems worldwide [125]. These conditions are strongly associated with irregularities in sleep macro- and microarchitecture [126–128]. Critically, a series of recent human sleep EEG studies has pinpointed the precision of SO–spindle coupling (i.e., the mean direction and consistency of SO phase angles at which spindle maxima are detected) as a strong predictor of age-related memory decline. Specifically, studies have found that SO–spindle coupling is misaligned in the elderly, with the extent of misalignment paralleling consolidation deficits compared to young controls [75–77,129]. In fact, SO–spindle misalignment has been directly linked to brain atrophy [75] and amyloid-β burden (a marker of AD neuropathology [130]), as well as with blood plasma glial fibrillary acidic protein (GFAP) levels (a potential marker for astrocyte activation and neuroinflammation [129]). SO–spindle misalignment has also been observed in patients with hippocampal damage [131] and in animal models of stroke [132], with the latter study showing that coupling is restored as recovery proceeds.

Can SO–spindle coupling – apart from being a powerful potential early biomarker for age-related cognitive decline and memory erosion – be harnessed as an opportunity for intervention? Recent years have seen an exciting surge in noninvasive brain stimulation tools, particularly during sleep. For example, one study used transcranial direct current stimulation during sleep to experimentally bolster SO activity in MCI patients and found that a resulting increase in SO–spindle coupling was linked to improved memory consolidation [133]. An even less-invasive (and therefore arguably more feasible) method [134] is closed-loop auditory stimulation, in which brief sound bursts (clicks) are delivered to the sleeping participant during SO up-states in an effort to prolong endogenous SO trains. This protocol has been shown to enhance SOs and SO–spindle coupling alongside behavioural improvements in memory consolidation in healthy participants [135] and MCI patients [136], albeit with less success in another study in elderly participants [136,137]. Despite apparent room for improvement [138] (see Outstanding questions), these novel tools hold great promise to provide a portable and cost-effective means to combat memory deficits associated with ageing, neurodegenerative diseases, and disrupted sleep microarchitecture.

bursts correlate with greater cortical spindle power [86]. Thus, spindle-mediated synchronisation between hippocampus and cortex [48,85] allows nested ripples to potentiate hippocampal–cortical connections well within windows of STDP. Experimental manipulations in rodents have shown that disruption of spindle-ripple coupling leads to diminished hippocampal–cortical interactions [87] and impaired behavioural expressions of memory consolidation [88,89].

SO–spindle–ripple coupling

These findings suggest that by joining forces to open and exploit windows of global and local excitability, triple coupling of SOs, spindles, and ripples might optimise the regulation of neuronal firing rates and plasticity in target memory circuits. A large body of work in rodents and humans has demonstrated temporal coupling of these three sleep rhythms [20,26,47,48,63,80,82,83,90,91]. Figure 2 shows recent iEEG examples of intra- and inter-regional SO–spindle–ripple coupling, illustrating how spindles nest in SO up-states and in turn group ripples in individual cycles during their waxing phase. Of note, spindles can last up to 2 s. The ~1 s waxing phase (where ripples tend to occur) of such long spindles would thus span both the 0.5 s up-state as well as the 0.5 s down-state of a 1 Hz SO. Importantly though, the vast majority of spindles are <1 s long [92,93], ensuring that the <0.5 s waxing phase (and associated ripples) comfortably fits in the ~0.5 s SO up-state.

While reported numbers vary as a function of event detection criteria across studies, it deserves explicit mention that coupled SO–spindle–ripple events are relatively rare phenomena across a whole night's sleep. Nevertheless, SO–spindle–ripple co-occurrences reliably exceed rates that would be expected by chance given the raw numbers of each event type [26]. In fact, recent data point to cross-contingencies of SOs, spindles, and ripples beyond mere co-occurrence. That is, ripples are more likely to co-occur with spindles when spindles are coupled to SOs than when they occur in isolation [47]. Likewise, ripples are more likely to cluster in SO up-states and neuronal firing rates during up-states are further increased in the joint presence of spindles (compared to solitary SOs) [20,91] (Figure 2A), pointing to a relay function of spindles between SO up-states and ripples (Figure 3). Providing compelling evidence for the added benefit of SO–spindle–ripple coupling, animal work has further shown that spindle–ripple coupling is most beneficial for behavioural expressions of memory consolidation when induced during SO up-states [94] and that electrical reinforcement of triple SO–spindle–ripple coupling boosts memory consolidation [95]. The latter observation has recently been extended to human iEEG recordings, showing that cortical electrical stimulation time-locked to SO up-states recorded in the MTL bolsters crossregional SO–spindle–ripple coupling alongside improved postsleep memory performance [96].

In summary, converging evidence suggests that coupling of SOs, spindles, and ripples serves synaptic and systems consolidation in hippocampal–cortical networks, regulating neuronal firing rates and communication with increasing efficacy and spatiotemporal precision (Figure 3). In particular (and as further elaborated in the following section), SOs and spindles might provide the temporal and spatial scaffold upon which ripples can selectively strengthen target memories.

Cortical–hippocampal–cortical interactions: a night in the life of a memory

How do SO–spindle–ripple dynamics sculpt memories, from their inception during learning to their reorganisation during sleep? The framework outlined in the following section synthesises recent findings to suggest how coupled sleep rhythms might facilitate hippocampal–cortical interactions for systems consolidation (Figure 4).

During learning, constituent elements of our experience activate dedicated cortical modules (exemplified in three nodes representing the learning experience in Figure 4A). These surges in local activation lead to temporary molecular changes at the synaptic level and result in enhanced

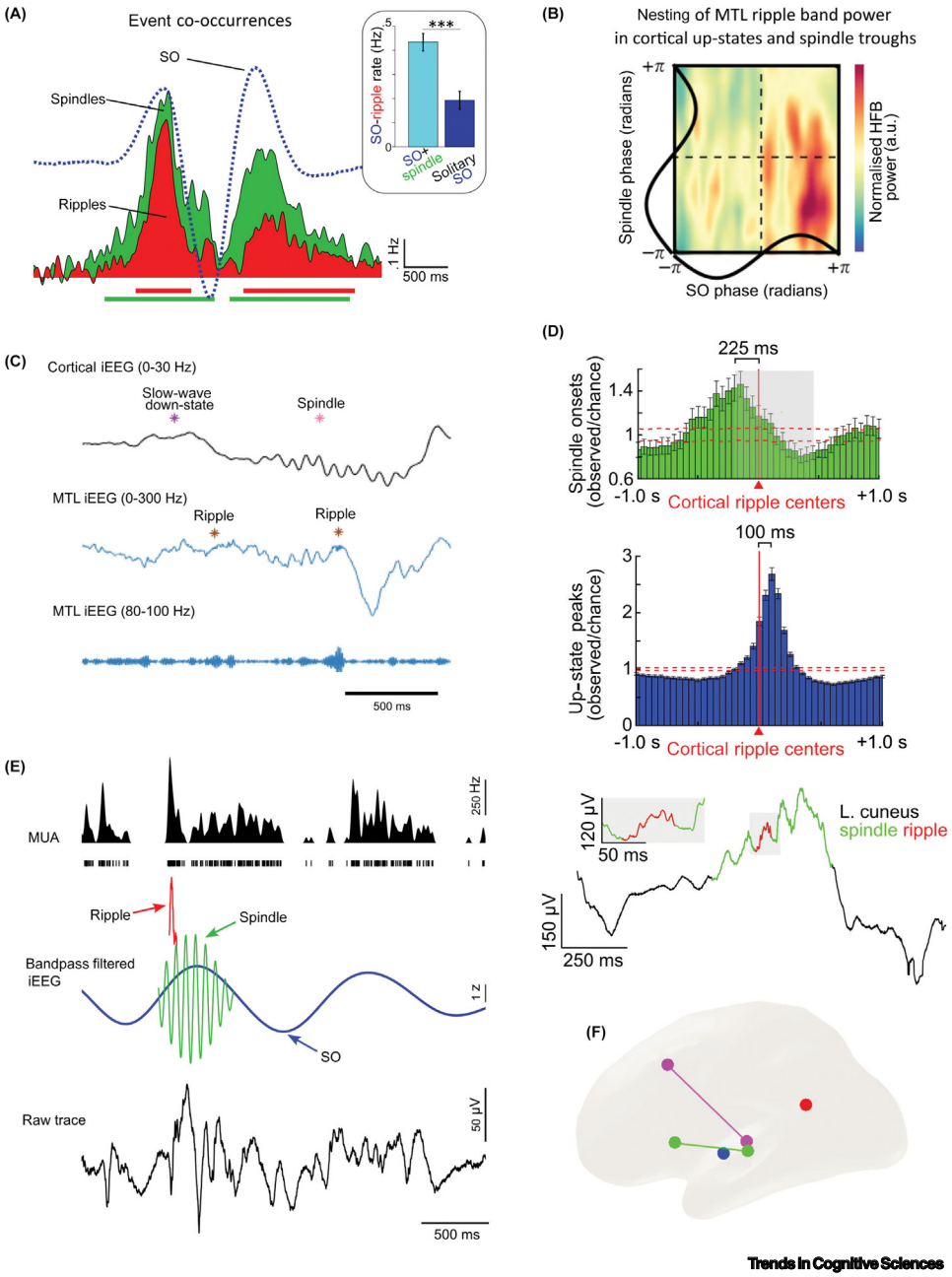

Figure 2. Slow oscillation (SO)–spindle–ripple coupling. (A) Nesting of spindles and ripples in SO up-states. Data show relative rates (Hz) of spindles and ripples with respect to a pre-event baseline period. Horizontal lines: $P < 0.05$ (corrected for multiple comparisons via cluster-based permutation tests) for spindle (green) and ripple (red) increases. Inset: SO–ripple coupling is enhanced in the joint presence of spindles [20]. (B) Medial temporal lobe (MTL) ripple-band power [high-frequency band (HFB), 80–100 Hz] is nested in prefrontal SO up-states and spindle troughs (magenta recordings sites in F) [47]. (C) Example crossregional coupling between prefrontal cortex SOs/spindles and MTL ripples (green recording sites in F) [96]. (D) Example raw trace (bottom) and peri-event time histograms of spindles (top) and SO up-states (middle) with respect to ripples (red recordings site in F) [63]. (E) Example MTL trace (bottom: raw trace, middle: bandpass filtered trace) and multiunit activity (top, MUA) during a coupled SO–spindle–ripple event (blue recordings site in F) [20]. (F) Recording sites from B–E rendered on a template in MNI space.

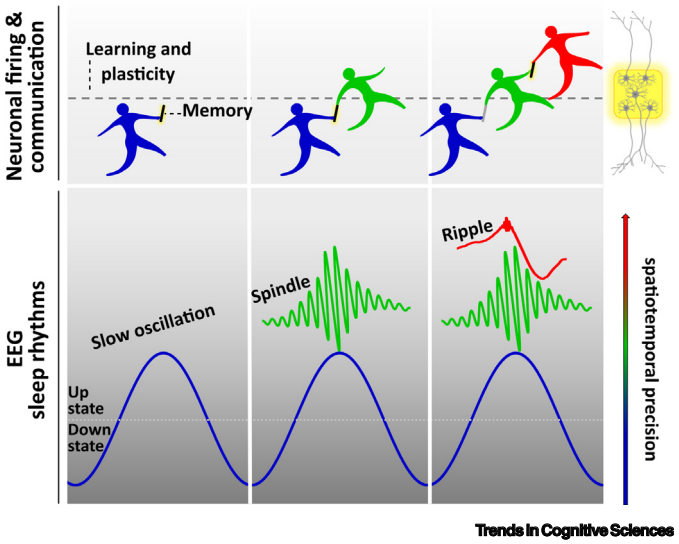

Figure 3. Coupled sleep rhythms promote synaptic consolidation. Slow oscillations (SOs), spindles, and ripples regulate – with increasing efficacy and spatiotemporal precision – neuronal firing rates and communication in service of learning and plasticity. SOs enhance brain-wide excitability during up-states. Nested spindles serve as relays, further elevating neuronal firing rates in learning networks and facilitating the emergence of ripples. Ripples are most effective in driving neuronal firing rates and communication, thereby sculpting engrams in local target memory circuits.

sustained excitability, akin to a biophysical **tag** [8,97,98]. Theoretical models suggest that in parallel, the hippocampus retains pointers (indices) to these cortical nodes, resulting in a cortical and a hippocampal copy of a specific memory trace (engram) [99]. Tentative empirical support for the existence of **hippocampal indices** in humans comes from iEEG studies showing that firing of single hippocampal neurons represents memories in an episode-specific manner [100] and precedes firing rates and memory reinstatement in adjacent entorhinal cortex [101].

During subsequent sleep, SO up-states ignite the thalamocortical release of spindles [27]. One conceivable scenario (Figure 4B) is that spindles are initially broadcast at random, but resonate more strongly (i.e., oscillate with greater amplitude and/or duration) at those (now more excitable) learning sites that were tagged or primed during prior learning. Alternatively, the same thalamic circuits gating thalamocortical dynamics during learning [102] might more readily reactivate during SO up-states, thereby reinstating learning patterns via spindles [103]. Either way, as mentioned already, the preferential expression of spindles at cortical learning sites has been established in several human M/EEG studies [36–39].

As spindle activity spreads from the activated cortical node to the hippocampus (along the same pathways used for cortical–hippocampal input at encoding), the corresponding part of the hippocampal engram (the index) gets reactivated. Indeed, simultaneous EEG–fMRI studies in humans have shown that time-locked to cortically recorded spindles, BOLD activation is enhanced in cortical regions engaged in a prior learning task as well as in the hippocampus [104,105]. Owing to the temporal ambiguity of the BOLD signal, those studies remained agnostic on the exact timing of spindle-mediated cortical–hippocampal interactions. However, a recent iEEG study confirmed a top-down influence by showing that cortical spindles precede hippocampal spindles and drive cortical–hippocampal spindle coherence [85]. Once arrived in the hippocampus, spindles elevate neuronal firing rates and contribute to the emergence of ripples [20,91]. The notion that spindle-mediated reactivation in cortex leads to ripple-mediated reactivation in the hippocampus is corroborated by multiple rodent studies demonstrating that activation in learning-related cortical regions precedes hippocampal ripples and biases associated memory reactivation in the hippocampus [60,81,106–108]. Hippocampal circuit synchronisation facilitated by ripples may then lead to intra-hippocampal **pattern completion** of the corresponding engram (Figure 4C).

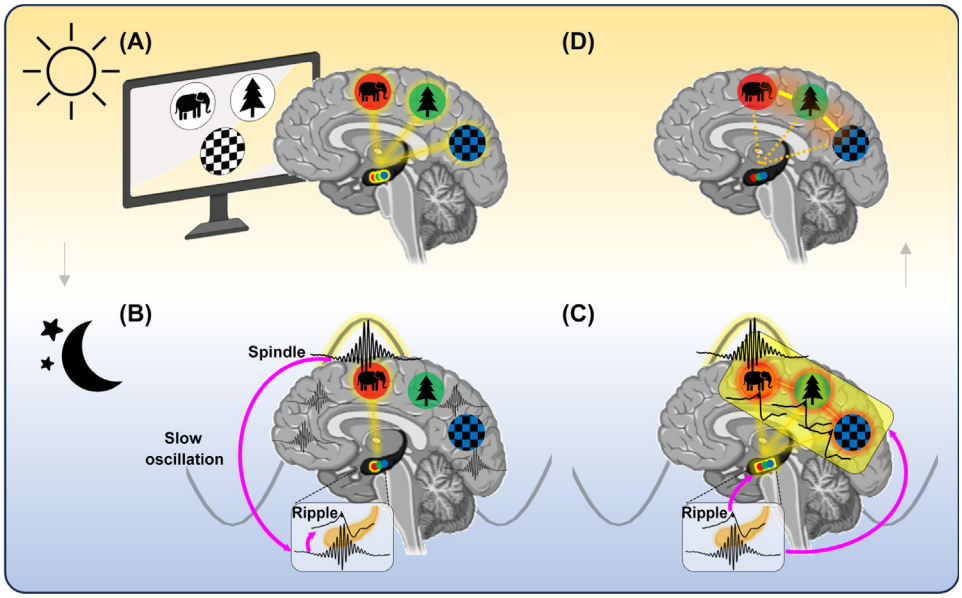

Figure 4. A night in the life of a memory. Figure depicts how coupled sleep rhythms might promote hippocampal–cortical systems consolidation. (A) During learning, cortical nodes that represent different elements of our experience are synaptically tagged. Activation spreads to the hippocampus, where pointers (indices; small circles) to the cortical nodes are retained. (B) During sleep, spindles are broadcast widely during SO up-states and resonate most strongly at tagged sites engaged in prior learning (large spindle). This entrains hippocampal spindles which reactivate the corresponding hippocampal index and trigger ripples. (C) Hippocampal ripples facilitate intrahippocampal pattern completion of the engram and activate/propagate to corresponding (indexed) cortical target sites, triggering cortical pattern completion and strengthening cortical–cortical connections of the participating nodes. (D) Consolidated memories are reflected in strengthened cortical connections. Hippocampal contributions likely diminish with time (broken lines) but can be reintroduced by alterations to the memory trace.

Rodent work further indicates that this cortical top-down signal is followed by a hippocampal return signal (closing a cortical–hippocampal–cortical loop), with the resulting activation pattern in cortex reflecting a specific subset of the initial activation [81,106,107]. Notably, the reactivation of cortical learning engrams has been directly linked to hippocampal ripples [109], suggesting that ripple-mediated pattern completion in the hippocampus drives reinstatement of the full cortical memory trace (Figure 4C). This scenario of a cortical–hippocampal–cortical loop is reminiscent of wake cued recall in humans, where a partial cortical cue precedes a hippocampal pattern completion process (associated with high gamma/ripple activity), which in turn leads to reinstatement of the full cortical memory trace [110–112]. The tacit assumption is that during natural sleep, the initial activation of a cortical node is not driven by an external reminder cue, but by spindles. Support for the idea that cortical memory signals can spread to the hippocampus (and back) during sleep comes from **targeted memory reactivation (TMR)** studies, in which external reminder cues are presented to sleeping participants. Specifically, these perceptual cues were shown to elicit hippocampal BOLD [113] and spindle band [114] increases. However, increases in spindle power and enhanced **decodability** of the learning material typically do not set in until the next up-state [115–117], possibly reflecting hippocampal pattern-completion occurring in the interim [118]. Recent rodent work has shown that hippocampal ripples are coupled to and precede ripples in cortical regions, where they coincide with cortical spindles [119]. In fact, ripples can directly propagate from the hippocampus to cortex [66], thereby likely to synchronise and potentiate – in tandem with coupled spindles – the corresponding cortical nodes of the engram as part of the hippocampal-cortical pattern completion process (Figure 4C). Consistent with the notion that ripples help forge engrams across cortical

nodes, a recent human iEEG study showed that cortical ripples (preceded by hippocampal ripples) synchronise neuronal firing rates across widespread cortical areas [64].

Given the strong capacity of hippocampal discharges to reinforce brain-wide networks [45], checks and balances need to be in place to avoid overexcitation and strengthening of detrimental circuits [120]. Sequential SO–spindle–ripple coupling (as depicted in Figure 4B,C) is well suited to achieve this balance between potentiation and inhibition, ensuring that the right circuits are potentiated to the appropriate degree. First, SO down-states (and associated global neuronal silence) put regular breaks on local and crossregional interactions, which is an effective means for avoiding overexcitation and for increasing the signal-to-noise ratio between more and less relevant circuits [9,19,121]. Second, the local specificity of spindles ensures that further activity increases during SO up-states are restricted to target areas involved in prior learning. Finally, the proposed mechanism of (spindle-mediated) top-down bias to activate the corresponding hippocampal index [85,106] ensures that bottom-up potentiation via hippocampal–cortical connections retains regional specificity; that is, selectively pattern completes the cortical target engram.

As these cortical–hippocampal–cortical interactions are repeatedly facilitated by the numerous up-states during a single night or across multiple nights, the cortical nodes will eventually be strengthened to a point where the hippocampal bottom-up signal becomes less crucial (Figure 4D). Indeed, recent work in rodents has revealed that hippocampal–cortical coupling during sleep diminishes once a task is behaviourally consolidated, giving way to cortical–cortical SO coupling [122]. Intriguingly, introducing a slight modification to the task brought back hippocampal–cortical interactions, in line with the notion that (re)consolidation is a dynamic process adaptively incorporating our everchanging environment [2,3,123].

Despite the outlined advantages of coupled sleep rhythms, there are of course many instances of solitary SOs, spindles, and ripples throughout the night. While this might be a byproduct of events missed by automated detection algorithms or mishaps due to inherent noise in the sleeping brain, it may also indicate that SO–spindle–ripple coupling is not necessary in all instances. For example, it is conceivable that particularly salient learning experiences (conferring, e.g., high levels of novelty or reward) establish more potent tags during learning [97], rendering isolated postlearning SOs and/or spindles sufficient to promote synaptic consolidation. Likewise, if a learning experience can be embedded in a pre-existing schema, new cortical nodes might be readily incorporated in existing engrams with less need for ripple-mediated hippocampal contributions [124].

Concluding remarks

How did your brain preserve the memory for last night's dinner throughout the night? Accumulating evidence from human and animal work indicates that the sleeping brain utilises a triad of coupled endogenous rhythms to orchestrate neuronal processes in service of learning and memory. Specifically, recent discoveries suggest that SOs act as a global temporal pacemaker whereas spindles reactivate and synchronise learning networks in a more region-specific manner, serving as relays between up-states and ripples. Ripples are most effective at driving firing rates to induce LTP within and across target memory circuits. Sequential SO–spindle–ripple coupling thus controls consolidation processes with increasing spatiotemporal precision, facilitating reactivation, refinement, and redistribution of memory engrams across hippocampal–cortical networks. Future work will harness the dynamic interactions of sleep rhythms across the brain not only to better understand the mnemonic fate of our experiences over time, but also to combat memory decline in healthy ageing and neurodegenerative disease (see Outstanding questions).

Outstanding questions

How does SO–spindle–ripple coupling rise and fall across the lifespan and is (SO–)spindle–ripple coupling a better biomarker for cognitive health than SO–spindle coupling alone?

Can SO–spindle alignment be better entrained by using crossmodal noninvasive brain stimulation; for example, independently controlling SOs with transcranial direct current stimulation and spindles with closed-loop auditory stimulation?

(How) is SO–spindle–ripple coupling governed by other, slower pacemakers; for example, respiration, heartbeat, or gastric rhythms?

What role does REM sleep and associated reactivation during dreaming play for memory consolidation?

Are structural brain changes underlying memory consolidation, captured for example via diffusion MRI, linked to particular (coupled) sleep rhythms?

Can representational transformations of memory traces (e.g., semantisation) be linked to specific electrophysiological phenomena during sleep?

Do all memories benefit equally from SO–spindle–ripple coupling or are effects differentially linked to declarative/hippocampus-dependent tasks (as opposed to, e.g., procedural learning)?

How are synaptic and systems consolidation facilitated during wake offline periods; that is, in the general absence of SOs and spindles?

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Declaration of interests

No interests are declared.

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