Received: 15 December 2017 | Revised: 28 May 2018 | Accepted: 4 June 2018

DOI: 10.1002/hipo.22997

WILEY

RESEARCH ARTICLE

Hippocampal ripples as a mode of communication with cortical and subcortical areas

Ralitsa Todorova | Michaël Zugaro

Center for Interdisciplinary Research in Biology, Collège de France, CNRS, INSERM, PSL Research University, Paris, France

Correspondence
Michaël Zugaro, Center for Interdisciplinary Research in Biology, Collège de France, CNRS, INSERM, PSL Research University, Paris, France.
Email: michael.zugaro@college-de-france.fr

Funding information
Agence Nationale de la Recherche, Grant/Award Numbers: ANR-15-CE16-0001-02ANR-17-CE37-0016-01, CE37-0016-01, CE16-0001-02; Collège de France, Grant/Award Number: ATER; École des Neurosciences de Paris; PSL Research University, Grant/Award Number: LabEx MemoLife

Abstract

Hippocampal sharp wave-ripple complexes are transient events of highly synchronous neuronal activity that typically occur during "offline" brain states. This endogenous surge of activity consists of behaviorally relevant spiking patterns, describing spatial trajectories. They have been shown to play a critical role in memory consolidation during sleep and in navigational planning during wakefulness. Beyond their local impact on the hippocampal formation, ripples also exert direct and indirect effects on target cortical and subcortical areas, which are thought to play a key role in information processing and semantic network reconfiguration. We review research into the function of hippocampal sharp waves-ripples, with a special focus on information flow between the hippocampus and its cortical and subcortical targets. First, we briefly review seminal work establishing a causal role of ripple-related activity in cognitive processes. We then review evidence for a functional interplay between hippocampal ripples and specific patterns of cortical and subcortical activity. Finally, we discuss the critical role of the functional coupling between ripples and other sleep rhythms, including the cortical slow oscillation and thalamocortical sleep spindles.

KEYWORDS

learning and memory, memory consolidation, oscillations, replay, sleep

1 | MANIPULATING RIPPLES

The causal relationship between ripples and memory consolidation was demonstrated in two independent studies where sleep ripples were perturbed by precisely timed electrical stimulation of the ventral hippocampal commissure (Ego-Stengel & Wilson, 2010; Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009). In both studies, the rats were trained on a spatial memory task where they learned across days to preferentially visit the correct arms of a maze to get food rewards. In the first hour of sleep following training, ripples were detected online and interrupted by precisely timed single pulse stimulation of the ventral hippocampal commissure, briefly suppressing ongoing neuronal activity and preventing further development of the ripple (Figure 1). This closed-loop protocol impaired subsequent performance on the task (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009) to levels comparable to complete hippocampal lesions (Jarrard, 1995). Importantly, nonspecific effects of the stimulation were ruled out as no impairment was observed in a group of control animals that underwent the same stimulation protocol, but with a random delay between ripple detection and stimulation, thus leaving ripples intact (Girardeau et al., 2009). This established that ripple activity is critical for memory consolidation.

Jadhav, Kemere, German, and Frank (2012) leveraged the same closed loop stimulation protocol for awake ripples during a spatial alternation working memory task. Interruption of awake ripples impaired performance on the task, indicating that awake ripples play a role in navigational decision making, which requires integrating immediate past experience with a known rule. However, there is evidence that awake ripples are not homogeneous: ripples during reward consumption are often accompanied by reverse replay (reversed relative to the behavioral trajectory; Foster & Wilson, 2006), while ripples at trial onset tend to involve forward replay (same order as the behavioral trajectory; Diba & Buzsáki, 2007). Because Jadhav et al. (2012) did not discriminate between ripples, it remains unclear how each replay type specifically contributes to navigational planning.

Ripples may serve a variety of functions and it is plausible that some of these functions take place locally. Roux, Hu, Eichler, Stark, and Buzsáki (2017) directly tested the role of awake ripple activity in

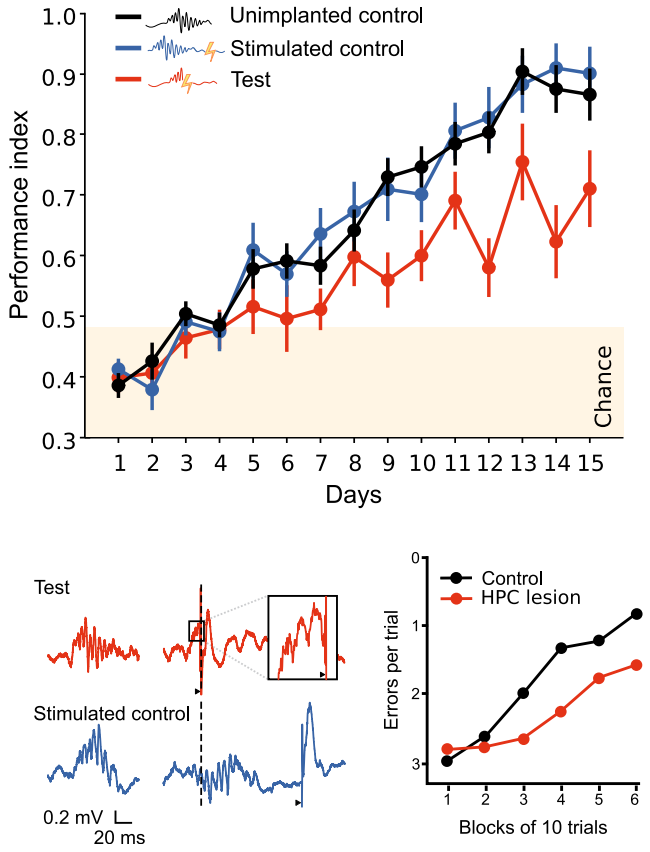

FIGURE 1 Suppression of sleep ripples interferes with memory consolidation. Top: Test rats (red) were significantly impaired in the radial maze task compared with control rats (blue, stimulated; black, unimplanted). Bottom left: In the test condition (red), ripples were immediately disrupted upon detection; in the control condition (blue), a random delay was introduced before stimulation. Unperturbed ripples are shown to the left, example stimulations to the right. Dashed vertical lines, ripple detection; black triangles, stimulation; box inset shows magnified trace. Bottom right: The effect of the complete hippocampal lesion on a radial maze (Jarrard, 1995). Note that the *y*-axis (number of events) is reversed to allow for the comparison with Girardeau et al.'s (2009) results. Adapted from "Selective suppression of hippocampal ripples impairs spatial memory" by Girardeau et al., 2009, Nature Neuroscience 12 (10), pp. 1222–1223 and "What does the hippocampus really do?" by Jarrard, 1995, Behavioural Brain Research, 71(1), pp. 1–10 [Color figure can be viewed at wileyonlinelibrary.com]

the stabilization of place fields. In rats performing a spatial memory task, they optogenetically inhibited hippocampal neurons during awake ripples occurring at goal locations. During subsequent exploration, the place fields of the inhibited neurons were destabilized, while the place fields of the remaining neurons remained stable. Intriguingly, optogenetic inhibition during sleep ripples following exploration of a novel environment does not trigger a similar perturbation of place fields (Kovács et al., 2016), suggesting a specific role of awake ripples in the immediate stabilization of hippocampal spatial representations.

Another potential function of ripples within the hippocampal network is the stabilization of cell assemblies previously established during wakefulness. While Kovács et al. (2016) found awake pairwise firing rate correlations of CA1 pyramidal cells unaffected by sleep ripple suppression, van de Ven, Trouche, McNamara, Allen, and Dupret (2016) reported that neuronal coactivation patterns (cell assemblies detected using independent component analysis of the binned multiunit spiking activity) were considerably less reactivated upon re-exposure to the environment when CA1 pyramidal cells were optogenetically silenced upon ripple detection during intervening sleep epochs. Interestingly, the authors reported two different encoding dynamics during the first exploration of a novel open field. While some assemblies stabilized in the first few minutes of exposure, after which their activity plateaued, other assemblies gradually strengthened—their activity continually increased throughout the first exploration. Ripple suppression selectively altered the reactivation of the gradually stabilized assemblies. The authors suggested that early stabilized patterns might provide a representation of space that is readily available for navigation, while the gradually strengthened assemblies might reflect the memory trace of the experience.

To date, the relationship between awake and sleep ripples remains unclear. Suppression of awake ripples and associated replay has been shown to leave sleep replay unaffected (Jadhav et al., 2012). This argues for a complementary mechanism to bridge the gap between sequences established during behavior and those consolidated during sleep.

While stabilization of the hippocampal representation of the environment can plausibly take place within the hippocampal formation, decision making, and memory consolidation may require the involvement of multiple brain areas beyond the hippocampus. We next discuss how ripple-related activity impacts numerous target brain areas.

2 | NEURONAL REACTIVATION IN OTHER BRAIN REGIONS

Synchronous hippocampal outputs during ripples strongly depolarize CA1 target regions, including the subiculum, deep layers of the entorhinal cortex, and multiple neocortical and subcortical areas. Both direct and indirect effects of hippocampal ripples have been reported, with hippocampal replay often leading, but in some cases following, neuronal reactivations in other brain areas.

2.1 | Entorhinal cortex

The subiculum and the deep layers of the entorhinal cortex are prominent targets of CA1 outputs. In awake rats, Chrobak and Buzsáki (1994) recorded increased activity in response to ripples in the subiculum and deep (V/VI) but not superficial (II/III) layers of the entorhinal cortex. Chrobak and Buzsáki (1996) extended these findings in awake and sleeping rats, showing that the highly synchronous resultant activity, in both the subiculum and the deep layers of the entorhinal cortex, led to local ripples which followed hippocampal CA1 ripples with a 5–30 ms lag. The authors suggested that this strong depolarization might represent a physiological mechanism for relaying memory traces from the hippocampus to other brain areas such as the neocortex.

Recently, two studies have addressed a possible coupling between entorhinal and hippocampal neuronal activities during replay of memory traces. Ólafsdóttir, Carpenter, and Barry (2016) simultaneously recorded hippocampal place cells and grid cells from deep

layers of the medial entorhinal cortex (MEC). While the number of simultaneously recorded grid cells was limited (in many cases three at a time) due to the challenging nature of the recordings, using clever analyses the authors were able to quantify cross-structural replay. They first detected hippocampal reactivation events and decoded neuronal activity as a spatial trajectory. They then showed that the grid cell representation was spatially coherent with the hippocampal template. The position encoded by the entorhinal cortex lagged behind hippocampal replay by ∼11 ms, which is consistent with monosynaptic propagation delays from CA1. This suggests that hippocampal replay is translated into replay in deep layers of the MEC, possibly relaying spatial information to the neocortex. Interestingly, in a follow-up study, Ólafsdóttir, Carpenter, and Barry (2017) reported that a similar coordination takes place in awake ripples during prolonged (>10 s) but not brief periods of immobility (although the number of recorded replay events was small: prolonged <400; brief <150). They concluded that awake ripples during rest periods might contribute to systems memory consolidation by communicating information to downstream targets through the deep layers of the MEC. On the other hand, "engaged" ripples (during brief periods of immobility) may play a role in navigational planning through a pathway independent of the MEC; this pathway is likely to involve the prefrontal cortex (Jadhav, Rothschild, Roumis, & Frank, 2016).

In a complementary study, O'Neill, Boccara, Stella, Schoenenberger, and Csicsvari (2017) compared reactivations between the hippocampus and the superficial layers of the MEC. While they did report replay in both regions, these were not temporally coupled. Moreover, the decoded spatial representations of the two regions did not overlap. These findings indicate that, unlike cells in deep layers of the entorhinal cortex, neurons in superficial layers replay task-related trajectories independently of the hippocampus. Surprisingly, superficial MEC replay events were not more likely than chance to be preceded or followed by hippocampal ripples. This is puzzling given that the superficial MEC is the main input area of the hippocampus, suggesting that ripples should at least be biased by strong synchronous inputs. Similarly, some of the areas projecting to the MEC respond to hippocampal ripples, so one might expect increased ripple probability preceding MEC events. Neither of these expected relationships was observed, and the authors proposed that superficial MEC replay may represent a parallel reactivation system with a role different from that of hippocampal ripples. Given the extensive multi-regional effects of hippocampal ripples, it is unclear how such a system may remain independent of hippocampal ripples. Investigating the timing of superficial MEC replay relative to prominent field events in its input areas, notably delta waves or spindles, may provide informative cues. Crucially, determining the potential behavioral impairments resulting from blockade of superficial MEC replay may give insight into the possible functions of this hypothesized system.

In summary, while the deep layers of the MEC may relay hippocampal information to the neocortex, the role of reactivations in superficial layers remains unknown. In both cases, experiments manipulating neuronal activity in the respective layers will be required to shed light on the functional roles of these reactivation patterns.

2.2 | Associative cortices

The medial prefrontal cortex (mPFC) receives direct projections from the intermediate and ventral CA1 regions, as well indirect hippocampal projections through the subiculum, the entorhinal cortex, and multiple subcortical areas (Cenquizca & Swanson, 2007). In sleeping rats, Siapas and Wilson (1998) showed increased activity in the mPFC up to a second after the onset of hippocampal ripples. Wierzynski, Lubenov, Gu, and Siapas (2009) found that during sleep a subset of mPFC cells reliably respond to hippocampal firing with a short latency of 11–18 ms, consistent with known monosynaptic delays (Tierney, Dégenètais, Thierry, Glowinski, & Gioanni, 2004) while a larger population response follows ∼100 ms later. Both responses were most prominent for hippocampal spikes during ripples, supporting the notion that ripple activity communicates information to the prefrontal cortex during sleep.

Peyrache, Khamassi, Benchenane, Wiener, and Battaglia (2009) recorded neuronal activity from the mPFC and the hippocampus of rats trained on a set-shifting task and provided the first evidence for a temporal coupling between hippocampal ripples and reactivation of task-related mPFC assemblies. In the mPFC, reactivation strength of task-related co-activity patterns increased around hippocampal sleep ripples, reaching a peak 40 ms after the ripple peak. One can speculate that this is indicative of a polysynaptic response, either within the local prefrontal network, or (this is not mutually exclusive) through the entorhinal cortex or the thalamic nucleus reuniens. The finding that mPFC reactivation (Euston, Tatsuno, & McNaughton, 2007) closely follows hippocampal ripples lends support to the notion that ripples can trigger reinstatement of neocortical assemblies in a process that would underlie the reorganization and stabilization of neocortical memory traces (Frankland & Bontempi, 2005).

A substantial fraction (∼35%, excitatory and inhibitory) of mPFC neurons also respond to awake hippocampal ripples (Jadhav et al., 2016). This coordination might contribute to decision-making and deliberation dependent on awake ripples (Jadhav et al., 2012). In this view, ripples during brief pauses in exploration would select prefrontal representations that are relevant to ongoing behavior, including working memory retrieval and navigational planning. Interestingly, Tang, Shin, Frank, and Jadhav (2017) showed that responses of a prefrontal neuron to awake and to sleep ripples are not correlated, and thus awake and sleep ripples appear to modulate distinct neuronal populations. In light of the results of Ólafsdóttir et al. (2017) presented above, we speculate that the responses to sleep and awake ripples may reach the prefrontal cortex through different pathways. Sleep and prolonged immobility ripples might modulate the prefrontal cortex directly or via the deep layers of the entorhinal cortex, whereas awake ripples might modulate prefrontal neurons through a different pathway, either via direct projections or a relay area such as the nucleus reuniens.

The parietal cortex, although it receives no direct projections from the hippocampus, has also been shown to reactivate task-related activity following sleep ripples. Wilber, Skelin, Wu, and McNaughton (2017) recorded in multiple sites (300 μm apart) in the parietal cortex and found that the multiunit activity on a given site encoded movements as the animals were performing a navigation task. Treating each

parietal recording site as a unit, they found reactivation of compressed (4- to 10-fold) sequences of activity that followed hippocampal ripples by ~100 ms. Their functional role in memory consolidation remains unknown.

Another cortical area that has received limited attention in its relation to the hippocampus is the retrosplenial cortex, where place cells have been recorded. These have been shown to reflect direct hippocampal inputs (Mao, Kandler, McNaughton, & Bonin, 2017), and are therefore likely to reactivate during ripples, although to our knowledge no studies have yet investigated this.

2.3 | Sensory cortices

While many regions that receive direct CA1 projections respond to hippocampal ripples with brief delays, the temporal relationship between ripples and activity in sensory cortices appears more variable. In the somatosensory cortex, neuronal activity peaks ~100 ms before hippocampal ripples (Sirota, Csicsvari, Buhl, & Buzsáki, 2003). Surges in activity (DOWN-UP transitions, see section 3.1) in the visual cortex lead hippocampal periods of elevated activity (frames) by ~50 ms, and reactivation can be observed simultaneously in the hippocampus and visual cortex (Ji & Wilson, 2007), consistent with the idea that replay-rich periods are initiated by the neocortex, which would provide context and thus bias hippocampal activity; hippocampal replay, via some intermediary region, would then bias cortical activity toward a matching cortical replay, resulting in systems consolidation.

Bi-directional information flow was also documented between the hippocampus and the auditory cortex (Rothschild, Eban, & Frank, 2017). Not only did CA1 activity during sleep ripples predict subsequent cortical activity, but in addition, a subpopulation of cortical neurons elevated their firing rates prior to ripple onset, effectively predicting ripple occurrence and even replay content. To probe this potential cortico-hippocampal communication, task-related sounds were played during sleep. The sounds biased neuronal activity in the auditory cortex as well as subsequent hippocampal ripple activity, supporting the notion that during ripples information can flow from the cortex to the hippocampus. This extends previous results by Bendor and Wilson (2012), who trained rats to retrieve food rewards on the left or right side of a track, depending on instructing sounds. Playing the same instructing sounds during slow-wave sleep biased subsequent reactivation events—for at least 10 s following the sound presentation, replay was ~10% more likely to involve the trajectory associated with the respective sound. Together, these studies provide evidence that cortico-hippocampal communication can affect ripple activity.

While the above studies did not include behavioral readouts of effective memory consolidation, they provide a plausible mechanism for the intriguing phenomenon of targeted memory consolidation. A body of work in humans has established that after a task involving the presentation of cues such as odors (Rasch, Büchel, Gais, & Born, 2007) or sounds (Rudoy, Voss, Westerberg, & Paller, 2009), reexposing subjects to the cues during slow-wave sleep can selectively strengthen cue-associated memories and improve recall performance. Evidence from the rodent studies mentioned above suggests that targeted memory consolidation is related to the ability of sensory cortices to bias hippocampal replay during sleep ripples. Causal studies blocking or enhancing cortical activity assumed to bias ripple content will be required to provide conclusive support for this hypothesis.

2.4 | Subcortical areas

A number of studies have addressed how hedonic values (representations of rewarding vs. aversive stimuli) are integrated into memory traces, and how activity in relevant subcortical areas is related to hippocampal replay during ripples.

2.4.1 | Ventral tegmental area

The ventral tegmental area (VTA) has long been known to be involved in reward associations. During awake behavior, ripples are more prevalent at reward sites (Singer & Frank, 2009), and reward-responding neurons in the VTA fire in coordination with hippocampal ripples, especially during replay of rewarded locations (Gomperts, Kloosterman, & Wilson, 2015). Could such coupling be instrumental in forming reward-place associations? De Lavilléon, Lacroix, Rondi-Reig, and Benchenane (2015) used a closed-loop protocol that paired the activity of one place cell with stimulation of the medial forebrain bundle, known to elicit reward signals, in particular via the VTA. During the subsequent test session, mice headed directly toward the place field of the paired neuron, attesting that a memory trace had been formed during sleep. This indicates that VTA activation during hippocampal ripples is sufficient to establish new associations, most likely involving multiple brain areas. But, does such associative memory consolidation actually take place during natural sleep? While the VTA does reactivate reward-related firing patterns in post-task sleep (Valdés, McNaughton, & Fellous, 2015), it is unclear whether such reactivations are coordinated with hippocampal ripples. On the contrary, Gomperts et al. (2015) reported that the coordination between VTA firing and ripples observed in the awake state is greatly diminished during sleep. They suggested that VTA activity during awake ripples may instead serve to link reward representations across brain regions, thus setting the stage for subsequent consolidation.

2.4.2 | Ventral striatum

The ventral striatum is a candidate region for such a process. Pennartz et al. (2004) showed that activation patterns observed in the ventral striatum during behavior are reactivated in post-task sleep and also that reactivated neurons fire more around sleep ripples. In a follow-up study, Lansink, Goltstein, Lankelma, McNaughton, and Pennartz (2009) reported cross-structural replay on a compressed (10-fold) timescale, where hippocampal place cells fire in sequence, replaying the trajectory leading up to a goal zone, followed by reward-responding cells in the ventral striatum. Such joint reactivation of hippocampal and ventral striatal neurons may underlie the off-line consolidation of memories associating a place with a reward. Awake ripples may play a role in the initial formation of such memories—recently, Sosa, Joo, and Frank (2017) reported neurons in the ventral striatum that respond to awake ripples. These studies are consistent with the hypothesized VTA-dependent mechanism described above. In this proposed scenario, the associative memory is formed as neurons from the hippocampus and the striatum are active together during awake ripples in reward zones, memory-trace formation is

facilitated by the concurrent dopaminergic drive from the VTA, and the linked hippocampo-striatal representations are consolidated in cross-structural replay during sleep ripples. Validating this hypothesis will require testing whether joint VTA–hippocampus–striatum activity during awake ripples is required for cross-structural replay in sleep ripples and whether such cross-structural replay is crucial for memory consolidation and thus future retrieval.

2.4.3 | Locus coeruleus

In addition to memory of reward associations, dopamine mediates the facilitation of synaptic plasticity induced by novelty (Li, Cullen, Anwyl, & Rowan, 2003). This is expected to have an impact on memory consolidation, as optogenetic stimulation of VTA dopaminergic terminals enhances hippocampal ripple reactivations and memory performance (McNamara, Tejero-Cantero, Trouche, Campo-Urriza, & Dupret, 2014). Indeed, mere exposure to a novel environment can promote the retention of recent memories preceding the novel experience (Ballarini, Moncada, Martinez, Alen, & Viola, 2009). While the VTA has long been thought to mediate the effects of novelty, recently Takeuchi et al. (2016) reported that memory enhancement is instead induced by dopamine co-released from noradrenergic terminals of the locus coeruleus (LC). It is not yet known how this activity is related to awake ripples.

2.4.4 | Basolateral amygdala

Finally, the interactions between hippocampal ripples and activity patterns in the basolateral amygdala (BLA) were investigated by Girardeau, Inema, and Buzsáki (2017), who studied the consolidation of aversive associations. They trained rats on a place-threat association task, in which an aversive air puff was delivered at a specific location on a linear track, in one running direction only, resulting in one "air puff" and one "safe" trajectory per complete lap. The location of the air puff was changed every day, and thus the rats had to learn a new location in each recording session. The authors documented hippocampo-amygdalar co-activation patterns during subsequent sleep, coinciding with sleep ripples. Notably, only patterns observed in the "air puff" direction were enhanced relative to pre-task sleep. These results suggest that the hippocampus reactivates contextual information while the amygdala reactivates the emotional value of the memory and that these two components are integrated during ripples to consolidate aversive memories.

In summary, the key role of hippocampal ripples in memory consolidation is supported by a coordination with reactivation in multiple brain areas, including the entorhinal cortex, prefrontal cortex, ventral striatum, and amygdala that provide spatial, appetitive, and aversive context to complement hippocampal signals. How are these reactivations temporally organized? Next we explore the coupling between ripples and prominent sleep rhythms in the brain.

3 | COUPLING WITH SLEEP RHYTHMS

Ripple occurrence is irregular, yet it is coupled with other recurrent brain rhythms. Most notably, ripple timing is influenced by the neocortical slow oscillation and by thalamocortical sleep spindles (Figure 2),

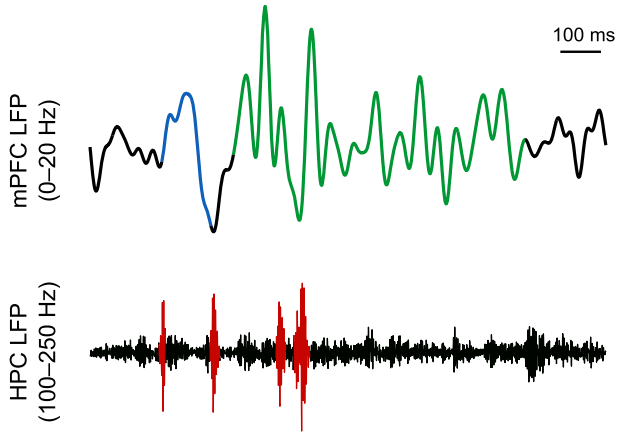

FIGURE 2 A representative example of hippocampo-cortical coupling, showing low-pass filtered (0–20 Hz) prefrontal LFP and simultaneously recorded hippocampal LFP filtered in the ripple band (100–250 Hz, ripples are highlighted in red). Note the first ripple preceding the delta wave (blue), the second ripple following the delta wave while preceding the spindle (green), and the last two ripples embedded in the spindle oscillation [Color figure can be viewed at wileyonlinelibrary.com]

possibly because inputs to the hippocampus may advance or delay the occurrence of forthcoming ripples (Buzsáki, 2006). In turn, ripple activity may influence the timing of these two sleep rhythms. We hypothesize that this dialogue plays an important role in systems memory consolidation.

3.1 | Slow oscillation

Perhaps the most prominent sleep rhythm is the cortical slow oscillation—the generalized alternation between a depolarized (UP) state and a hyperpolarized (DOWN) state of synchronized cortical neurons (Steriade, Nunez, & Amzica, 1993). The DOWN state is characterized by a transient cessation of firing and a positive deflection of the local field potential in deep cortical layers, known as a delta wave (Sirota & Buzsáki, 2005).

Evidence for a causal role of the slow oscillation in memory consolidation has been provided in several studies. Transcranial stimulation in sleep at the frequency of the slow oscillation was reported to enhance memory consolidation of declarative memory (Binder et al., 2014; Marshall, Helgadottir, Molle, & Born, 2006). However, more recent studies have failed to replicate this effect (Eggert et al., 2013; Sahlem et al., 2015) and questioned whether transcranial stimulation can entrain the slow oscillation (Lafon et al., 2017). Still, a different technique—closed-loop auditory stimulation in phase with the ongoing slow oscillation—reliably boosts the slow oscillation and enhances declarative memory retention (Ngo, Martinetz, Born, & Mölle, 2013), confirming that the slow oscillation plays a critical role in memory consolidation. The authors have suggested that this could be mediated by increased slow wave amplitude as well as temporal alignment of sleep spindles. In light of our own findings (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016), we propose an alternative interpretation based on the temporal coupling between the slow oscillation and hippocampal ripples (section 3.3).

Because both ripples and delta waves are recurring events, it is difficult to infer causal relationships between the two activity patterns based on their relative timing. Delta waves tend to follow hippocampal ripples, suggesting that ripples might facilitate a forthcoming UP-DOWN transition. There are also reports of ripples immediately following delta waves; this is likely related to the surge of cortical activity during the DOWN-UP transition, as discussed below.[1]

3.1.1 | Ripples preceding delta waves

The first systematic study of a temporal coupling between delta waves and ripples was provided by Sirota et al. (2003), who showed that while ripples follow periods of elevated activity in the somatosensory cortex, they precede somatosensory delta waves by 50–150 ms. The authors suggested that this coupling could mediate coordinated information transfer between the hippocampus and the neocortex.

A possible mechanism for ripple-delta coupling is that the surge of excitatory activity serves as a "kick" that destabilizes the UP state and thus biases the transition from an UP to a DOWN state (Jercog, Roxin, Barthó, Luczak, & Compte, 2017). Consistently, hypersynchronous recruitment of hippocampal neurons through strong electrical stimulation of the ventral hippocampal commissure leads to a decrease in prefrontal activity lasting ~200 ms (Girardeau et al., 2009), comparable to the duration of a DOWN state, as well as to an increase in delta power (Gelinas, Khodagholy, Thesen, Devinsky, & Buzsáki, 2016), consistent with a contribution of ripples in facilitating the emergence of delta waves.

Evidence for a possible role of ripple-delta coupling in memory consolidation was provided by Peyrache et al. (2009), who performed simultaneous recordings in the hippocampus and the prefrontal cortex of rats trained on a set-shifting task. The authors detected prefrontal coactivation patterns during the task and measured their reactivation in post-task sleep. Both the hippocampal ripple incidence and the reactivation strength of prefrontal ensembles peaked before delta waves. Moreover, prefrontal reactivation tended to closely follow (by ~40 ms) hippocampal ripples. This suggests that a hippocampo-cortical information transfer might be preferentially initiated briefly before delta waves. We propose that a possible role for the delta wave (neural silence) might be to avoid interference with other, unrelated inputs (although see section 3.3).

3.1.2 | Ripples following delta waves

Battaglia, Sutherland, and McNaughton (2004) reported a higher ripple rate around DOWN-UP transitions in multiple cortical areas. A fine timescale analysis further revealed that cortical firing rates decreased 400–200 ms before sharp wave ripples; the authors attributed this decrease to a consistent occurrence of delta waves before ripples. In recordings of the prefrontal electroencephalogram (EEG) of sleeping rats, Mölle, Yeshenko, Marshall, Sara, and Born (2006) showed ripples following delta waves by 140–480 ms and suggested that the cortical UP state following the delta wave may promote hippocampal ripples via efferent pathways.

A thorough assessment of the influence of neocortical slow oscillations on hippocampal activity in anesthetized and sleeping rats was provided by Isomura et al. (2006), who reported that prefrontal DOWN-UP transitions were closely followed by entorhinal DOWN-UP transitions and increased activity in the dentate gyrus and CA1. Most ripples occurred ~100 ms after entorhinal DOWN-UP transitions and ~200 ms after prefrontal DOWN-UP transitions. The authors proposed that the upsurge of activity in the dentate gyrus associated with the entorhinal UP state may activate selected populations of CA3 and suppress the rest by feed-forward inhibition, thus biasing hippocampal ripple occurrence as well as the identity of the participating neurons.

Recently, Khodagholy, Gelinas, and Buzsáki (2017) recorded neural activity from the surface of the brain in sleeping rats and reported cortical oscillations in the ripple band in association cortices, including parietal, retrosplenial, anterior cingulate, and medial prefrontal cortex. These events took place at the DOWN-UP transition, preceding spindles, and occurred synchronously with hippocampal ripples. The coupling between cortical and hippocampal ripples increased in sleep following training on a cheeseboard maze task, suggesting a potential role in memory consolidation. The authors hypothesized that such joint events might be a substrate of communication in the hippocampo-cortical dialogue, although it remains to be investigated in which direction information might flow. Alternatively, this concurrence might result from a common drive orchestrated by the cortical slow oscillation, and the ripple event in each region might consolidate relevant information locally.

3.2 | Sleep spindles

Sleep spindles are thalamocortical waxing-and-waning oscillatory events (10–15 Hz; Berger, 1933; Steriade, McCormick, & Sejnowski, 1993), which are known to promote synaptic plasticity (Sejnowski & Destexhe, 2000; Steriade & Timofeev, 2003). Generated by bursting neurons in the thalamic reticular nucleus, spindles are associated with massive calcium entry in neocortical neurons (Contreras, Destexhe, & Steriade, 1997; Seibt et al., 2017). Applying spindle stimulation patterns in vitro induces long-term potentiation in cortical synapses via an NMDA receptor-dependent process (Rosanova & Ulrich, 2005). Spindles are embedded in the cortical slow oscillation, occurring early in the UP state as they closely follow delta waves (Amzica & Steriade, 1997; Peyrache, Battaglia, & Destexhe, 2011).

Spindle activity has been shown to play a role in memory consolidation. The rate of spindle occurrence increases in sleep after learning a declarative memory task in both humans (Gais, Mölle, Helms, & Born, 2002) and rats (Eschenko, Mölle, Born, & Sara, 2006). Moreover, pharmacologically enhancing sleep spindle occurrence improves declarative memory performance in healthy humans (Mednick et al., 2013).

Reports of ripple-spindle coupling span multiple timescales. On the timescale of seconds, spindles tend to follow hippocampal ripples. On a finer timescale, ripples are phase-locked to individual spindle

[1]Due to the traveling nature of cortical delta waves (with a tendency to propagate from anterior to posterior areas), the precise timing between delta waves and hippocampal ripples may vary between regions. However, given the estimated speeds of delta wave propagation (1.2–7 m/s) (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004) and the duration of a typical delta wave (~200 ms), the order of events (ripple-delta versus delta-ripple) is not expected to be affected by delta propagation.

cycles. The implications of these coupling relations on memory consolidation are discussed below.

3.2.1 | Ripples preceding spindles

Siapas and Wilson (1998) first documented the tendency of hippocampal ripples to precede spindles in the prefrontal cortex. Later studies have shown that the ripple rate tends to peak ~0.5 s before prefrontal spindles (Mölle et al., 2006; Peyrache et al., 2009).

Sirota and Buzsáki (2005) proposed that the slow oscillation might orchestrate both hippocampal ripples and thalamocortical spindles—ripples tend to precede (or closely follow) cortical delta waves, which are in turn followed by spindles. It is therefore plausible that the slow oscillation may explain the coupling of these events on this long timescale.

When do neocortical reactivations take place with respect to ripple-spindle events? Peyrache et al. (2009) showed that the highest spiking probability of prefrontal units occurred during the second half of spindles. However, prefrontal reactivation of task-related patterns peaked much earlier, before spindle onset (coinciding with ripple activity). Memory-related cell assemblies would therefore be reinstated a few hundred milliseconds before the high spiking activity associated with spindles.

A classical account of how a hippocampo-cortical dialogue involving ripple-spindle events can lead to memory consolidation is therefore the following: ripple-related activity facilitates the resurgence of cortical cell assemblies relevant to a given memory trace; this is then followed by the strong synchronized spindle activity that induces synaptic plasticity. However, a caveat in this scenario is that these events typically take place hundreds of milliseconds apart, which is not consistent with classical forms of long-term potentiation.[2] A recent study reported a long timescale form of synaptic plasticity, where a calcium plateau potential in CA1 dendrites can potentiate inputs offset by seconds (Bittner, Milstein, Grienberger, Romani, & Magee, 2017). While it is not yet known whether a similar mechanism might take place during sleep in the neocortex, one could speculate that during spindles, the bursting of neocortical pyramidal cells combined with the massive calcium influx may retroactively potentiate synapses activated ~0.5 s earlier, and that as a result ripple-triggered reactivated cortical traces are consolidated during the following sleep spindles.

Ripples nested in spindle cycles

Ripples can also occur phase locked to individual spindle cycles, both in rats (somatosensory cortex, Sirota et al., 2003) and mice (prefrontal cortex, Phillips et al., 2012). Ripples are also phase locked to spindles in humans (Clemens et al., 2011; Staresina et al., 2015).

Coordination on such a fine timescale indicates a thalamocortical influence on the timing of hippocampal ripples, possibly via the entorhinal cortex (Sullivan, Mizuseki, Sorgi, & Buzsáki, 2014) or via the nucleus reuniens (Varela, Kumar, Yang, & Wilson, 2014). It is possible that the mechanism which promotes ripple nesting might also bias which specific neuronal populations participate in the ripple, although this remains to be investigated.

How would spindle-nested ripples participate in memory consolidation? In one view, this coupling could be a substrate for unidirectional cortico-hippocampal communication. Because ripple-associated cortical reactivation is high before but not during spindles (Peyrache et al., 2009), spindles could correspond to a period of reorganization and plasticity at the level of cortico-cortical synapses. Ripples embedded in spindles might then integrate this newly reconfigured information into the hippocampal network, while the cortical network would remain dominated by local interactions (Peyrache et al., 2011).

Alternatively, it is possible that this phenomenon allows for a bidirectional information transfer, where in addition to cortical inputs biasing replay activity in ripples nested in spindles, hippocampal outputs in turn modulate cortical activity during spindles. Indeed, while hippocampal inputs would have to compete with local inhibition to discharge prefrontal neurons during spindles (Peyrache et al., 2011), they may nevertheless bias activity at the population level (Wierzynski et al., 2009). Moreover, because during spindles calcium entry into the dendrites can be decoupled from somatic firing (Seibt et al., 2017), the absence of cortical spikes should not be interpreted as evidence that cortical networks are unaffected by hippocampal ripples occurring during spindles.

3.3 | Causal role of ripple-delta-spindle coupling

Maingret et al. (2016) proposed that memory consolidation critically depends on a temporal coordination between ripples, delta waves and spindles, rather than on the prevalence or strength of each of these oscillations independently. They first showed that, consistent with this view, hippocampo-cortical coupling in sleep does increase during memory consolidation periods. To then demonstrate a causal link, they designed a stimulation protocol to induce delta-spindle sequences timed on the online detection of hippocampal ripples, thus boosting the coordination between these rhythms. In order to determine whether this could potentially improve memory consolidation, they used a modified version (Ballarini et al., 2009) of a classical spatial memory task: rats were first placed in a rectangular arena with two identical objects in adjacent corners (sampling); on the following day (recall), they were returned to the arena, where one of the two objects had been displaced; the critical modification compared to the classical version of the task was that the sampling period was much briefer, actually too brief for the animals to memorize the configuration of the objects and notice the change during recall. Yet, following a period of stimulation enhancing hippocampo-cortical coupling during sleep, the rats reacted to the altered arrangement of the objects, demonstrating that the transient memory traces formed during sampling had now been consolidated (Figure 3). Furthermore, the authors showed that induced coupling resulted in functional reorganization of prefrontal cortical networks, and increased responsivity of prefrontal cells to the task. Importantly, these improvements were not observed in a control condition where a brief random delay (~200 ms) was introduced between ripples and triggered delta-spindles, indicating that the underlying mechanism was a remarkably fine temporal precision of ripple-delta-spindle coupling.

In particular, these results indicate that memory consolidation could not be accounted for by increased occurrences of delta waves

[2]A further complication is that ripple-spindle sequences are often interrupted by delta waves (see section 3.3).

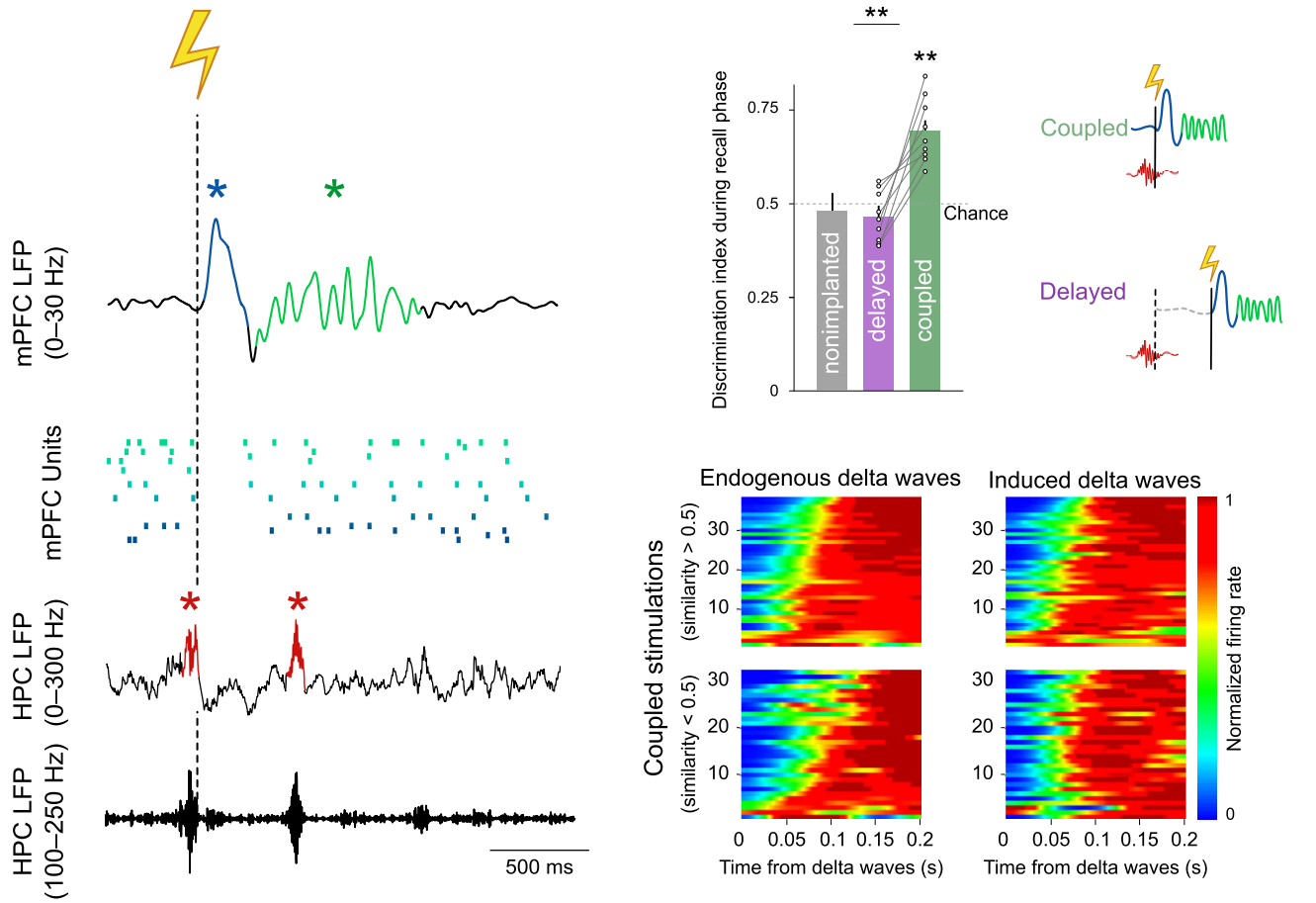

FIGURE 3 Ripple–delta coupling boosts memory consolidation. Left: an example of a ripple-triggered stimulation (lightening icon) followed by a delta wave (blue) and a spindle (green) in the prefrontal cortex. Top right: Stimulation coupled to ripples (green) resulted in memory recall on the next day, while delayed (control) stimulation (purple) did not enhance memory consolidation. Note that non-implanted animals performed at chance levels. Bottom right: Peri-event time histograms for average mPFC firing rate during up states following endogenous (left) and induced (right) delta waves coupled to ripples. Cells are divided into a subpopulation of high (top) and low (bottom) similarity indices. Note that the subpopulation with low similarity changed their activity profiles following induced hippocampo-cortical coupling (lower right panel), reflecting a selective functional reorganization of prefrontal subnetworks. Adapted from "Hippocampo-cortical coupling mediates memory consolidation during sleep" by Maingret et al., 2016, Nature Neuroscience, 19(7), pp. 959–964 [Color figure can be viewed at wileyonlinelibrary.com]

or spindles since the number of these events were unchanged between test and control conditions. This appears to be at odds with previous studies documenting a direct role for delta waves in memory consolidation (see section 3.1). We propose that in previous studies, boosting the slow oscillation incidentally increased its coupling to hippocampal ripples and that this coupling, rather than the reinforced slow oscillations per se, was instrumental in triggering improvements in memory performance.

Consistent with these findings, Novitskaya, Sara, Logothetis, and Eschenko (2016) applied a closed-loop stimulation protocol in post-task sleep, where the LC was electrically stimulated upon ripple detection. While stimulation did not affect the ongoing ripple, ripple-spindle coupling was reduced and memory consolidation was impaired. Although one cannot rule out that the noradrenergic release following LC stimulation had widespread uncontrolled effects beyond disrupting hippocampo-thalamic coupling, this remains consistent with a potential role of ripple-spindle coupling in memory consolidation.

Additional support comes from a recent study in mice, where thalamic activity was manipulated in sleep after contextual fear conditioning, a classical hippocampus-dependent task (Latchoumane, Ngo, Born, & Shin, 2017). In this closed-loop stimulation protocol, detection of frontal delta waves triggered optogenetic stimulation in the thalamic reticular nucleus simulating spindle activity. The stimulation entrained cortical networks in the UP state, resulted in hippocampal ripples phase-locked to the stimulation, and improved memory performance relative to nonstimulated mice. A control version of the protocol involved stimulating during the DOWN state when cortical networks are silent. Memory performance was not improved, although ripples were still locked to the stimulation. One caveat however is that light pulses were delivered at 8 Hz, rather than at spindle frequency (10–15 Hz), making mechanistic interpretations in terms of underlying brain rhythms more challenging.

In summary, a hippocampo-cortical dialogue orchestrated by fine-tuned ripple-delta-spindle coupling mediates memory consolidation during sleep. Following learning, ripples increase in rate and amplitude, and synchronous hippocampal outputs replaying wake experiences trigger reactivation and functional reorganization of selected cell ensembles in target areas, including the prefrontal cortex. Concurrently, ripples may facilitate a transition to the next cortical DOWN state. The precise timing of this DOWN state relative to the ripple is

instrumental to the consolidation of the memory trace, but the exact underlying mechanism remains unknown. One possibility is that the synchronous DOWN state may isolate local cortical networks from competing inputs before undergoing intracortical consolidation during the following UP state, possibly during sleep spindles (Peyrache et al., 2011; Siapas & Wilson, 1998; Sirota et al., 2003). While this scenario proposes a convincing computational role for delta waves, how information processed during the preceding hippocampal replay and the cortical response would remain available in a silent cortical network remains to be elucidated (Todorova, Maingret, Fayat & Zugaro, 2017).

4 | PERSPECTIVES

Ripples are not isolated hippocampal events, but a vital component of a process spanning multiple brain regions. Awake ripples are followed by responses in the VTA, the ventral striatum, the prefrontal cortex, but not in the entorhinal cortex (except during prolonged periods of immobility). Sleep ripples, possibly biased by cortical inputs, may initiate reactivations of cortical ensembles, and even cross-structural reactivations involving other areas including the ventral striatum, the deep layers of the entorhinal cortex, and the amygdala. Further, sleep ripples may precede delta waves, follow delta waves, precede spindles, or occur during spindles phase-locked to individual cycles. With few exceptions, (correlational) reactivation studies have typically ignored ongoing brain rhythms, and (causal) coupling studies have typically ignored reactivation patterns. While cross-structural communication is thought to be orchestrated by the slow oscillation, it remains to be explored how the ripple-associated activity in different areas is timed with respect to delta waves and spindles and if the direction of information flow is affected by (or reflected in) the ongoing rhythms.

One promising line of inquiry would involve investigating the downstream effects of ripple activity while taking into account the relative timing with respect to delta waves and spindles. Large-scale recordings of multiple brain regions would reveal the fine timescale responses to ripples, and how these responses interact across brain areas. This could help delineate the specific communication streams involving the diverse ripples reviewed here. Future studies may also consider enhancing or suppressing specific ripples based on their timing — in particular, sleep ripples relative to delta waves and thalamocortical spindles, or awake ripples relative to the behavior of the animal.

A second area of future interest would be to investigate how ripple activity affects synaptic plasticity in downstream areas, taking brain state into account. Novel imaging techniques at the level of synaptic boutons, combined with field recordings, may shed light on how ripple timing affects synaptic plasticity, and in particular on the long-hypothesized influence of thalamocortical spindles.

Finally, to get a better mechanistic understanding of the dialogue between the hippocampus and the neocortex, it will be crucial to determine how the dynamics in distributed networks bias each other. This could involve relay areas such as the entorhinal cortex or the nucleus reuniens or neuromodulatory areas such as the VTA or the LC. Suppressing specific neuronal activity patterns in these intermediary areas would be expected to affect ripple-associated reactivation in areas such as the prefrontal cortex or the ventral striatum, and potentially impair memory consolidation.

ACKNOWLEDGMENTS

We thank S.I. Wiener, C. Drieu, and N. Benabdallah for comments on an earlier version of the manuscript. This work was supported by the Agence Nationale de la Recherche (ANR-15-CE16-0001-02, ANR-17-CE37-0016-01), Collège de France (to R.T.), and a joint grant from École des Neurosciences de Paris Île-de-France and LabEx MemoLife (ANR-10-LABX-54 MEMO LIFE, ANR-10-IDEX-0001-02 PSL*; to R.T.)

ORCID

Michaël Zugaro https://orcid.org/0000-0002-6199-2635

REFERENCES

Amzica, F., & Steriade, M. (1997). Cellular substrates and laminar profile of sleep K-complex. *Neuroscience*, *82*(3), 671–686.

Ballarini, F., Moncada, D., Martinez, M. C., Alen, N., & Viola, H. (2009). Behavioral tagging is a general mechanism of long-term memory formation. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(34), 14599–14604.

Battaglia, F. P., Sutherland, G. R., & McNaughton, B. L. (2004). Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. *Learning & Memory*, *11*(6), 697–704.

Bendor, D., & Wilson, M. A. (2012). Biasing the content of hippocampal replay during sleep. *Nature Neuroscience*, *15*(10), 1439–1444.

Berger, H. (1933). Über das Elektrenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten*, *98*(1), 231–254.

Binder, S., Berg, K., Gasca, F., Lafon, B., Parra, L. C., Born, J., & Marshall, L. (2014). Transcranial slow oscillation stimulation during sleep enhances memory consolidation in rats. *Brain Stimulation*, *7*(4), 508–515.

Bittner, K. C., Milstein, A. D., Grienberger, C., Romani, S., & Magee, J. C. (2017). Behavioral time scale synaptic plasticity underlies CA1 place fields. *Science*, *357*(6355), 1033–1036.

Buzsáki, G. (2006). *Rhythms of the brain*. New York: Oxford university Press.

Cenquizca, L. A., & Swanson, L. W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Research Reviews*, *56*(1), 1–26.

Chrobak, J. J., & Buzsáki, G. (1994). Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. *Journal of Neuroscience*, *14*(10), 6160–6170.

Chrobak, J. J., & Buzsáki, G. (1996). High-frequency oscillations in the output networks of the hippocampal–entorhinal axis of the freely behaving rat. *Journal of Neuroscience*, *16*(9), 3056–3066.

Clemens, Z., Mölle, M., Eross, L., Jakus, R., Rásonyi, G., Halász, P., & Born, J. (2011). Fine-tuned coupling between human parahippocampal ripples and sleep spindles. *The European Journal of Neuroscience*, *33*(3), 511–520.

Contreras, D., Destexhe, A., & Steriade, M. (1997). Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo. *Journal of Neurophysiology*, *78*(1), 335–350.

De Lavilléon, G., Lacroix, M. M., Rondi-Reig, L., & Benchenane, K. (2015). Explicit memory creation during sleep demonstrates a causal role of place cells in navigation. *Nature Neuroscience*, *18*(4), 493–495.

Diba, K., & Buzsáki, G. (2007). Forward and reverse hippocampal place-cell sequences during ripples. *Nature Neuroscience*, *10*(10), 1241–1242.

Eggert, T., Dorn, H., Sauter, C., Nitsche, M. A., Bajbouj, M., & Danker-Hopfe, H. (2013). No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. *Brain Stimulation*, *6*(6), 938–945.

Ego-Stengel, V., & Wilson, M. A. (2010). Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus*, *20*(1), 1–10.

Eschenko, O., Mölle, M., Born, J., & Sara, S. J. (2006). Elevated sleep spindle density after learning or after retrieval in rats. *Journal of Neuroscience*, *26*(50), 12914–12920.

Euston, D. R., Tatsuno, M., & McNaughton, B. L. (2007). Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. *Science*, *318*(5853), 1147–1150.

Foster, D. J., & Wilson, M. A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature*, *440*(7084), 680–683.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience*, *6*(2), 119–130.

Gais, S., Mölle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *Journal of Neuroscience*, *22*(15), 6830–6834.

Gelinas, J. N., Khodagholy, D., Thesen, T., Devinsky, O., & Buzsáki, G. (2016). Interictal epileptiform discharges induce hippocampal-cortical coupling in temporal lobe epilepsy. *Nature Medicine*, *22*(6), 641–648.

Girardeau, G., Benchenane, K., Wiener, S. I., Buzsáki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. *Nature Neuroscience*, *12*(10), 1222–1223.

Girardeau, G., Inema, I., & Buzsáki, G. (2017). Reactivations of emotional memory in the hippocampus–amygdala system during sleep. *Nature Neuroscience*, *20*(11), 1634–1642.

Gomperts, S. N., Kloosterman, F., & Wilson, M. A. (2015). VTA neurons coordinate with the hippocampal reactivation of spatial experience. *eLife*, *4*, e05360.

Isomura, Y., Sirota, A., Özen, S., Montgomery, S., Mizuseki, K., Henze, D. A., & Buzsáki, G. (2006). Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations. *Neuron*, *52*(5), 871–882.

Jadhav, S., Rothschild, G., Roumis, D., & Frank, L. (2016). Coordinated excitation and inhibition of prefrontal ensembles during awake hippocampal sharp-wave ripple events. *Neuron*, *90*(1), 113–127.

Jadhav, S. P., Kemere, C., German, P. W., & Frank, L. M. (2012). Awake hippocampal sharp-wave ripples support spatial memory. *Science*, *336*(6087), 1454–1458.

Jarrard, L. E. (1995). What does the hippocampus really do? *Behavioural Brain Research*, *71*(1), 1–10.

Jercog, D., Roxin, A., Barthó, P., Luczak, A., Compte, A., & de la Rocha, J. (2017). UP-DOWN cortical dynamics reflect state transitions in a bistable network. *eLife*, *6*, e22425.

Ji, D., & Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature Neuroscience*, *10*(1), 100–107.

Khodagholy, D., Gelinas, J. N., & Buzsáki, G. (2017). Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. *Science*, *358*(6361), 369–372.

Kovács, K. A., O'Neill, J., Schoenenberger, P., Penttonen, M., Ranguel Guerrero, D. K., & Csicsvari, J. (2016). Optogenetically blocking sharp wave ripple events in sleep does not interfere with the formation of stable spatial representation in the CA1 area of the hippocampus. *PLoS One*, *11*(10), e0164675.

Lafon, B., Henin, S., Huang, Y., Friedman, D., Melloni, L., Thesen, T., … Liu, A. (2017). Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nature Communications*, *8*(1), 1199.

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., McNaughton, B. L., & Pennartz, C. M. A. (2009). Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biology*, *7*(8), e1000173.

Latchoumane, C.-F. V., Ngo, H.-V. V., Born, J., & Shin, H.-S. (2017). Thalamic spindles promote memory formation during sleep through triple phase-locking of cortical, thalamic, and hippocampal rhythms. *Neuron*, *95*(2), 424–435.e6.

Li, S., Cullen, W. K., Anwyl, R., & Rowan, M. J. (2003). Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nature Neuroscience*, *6*(5), 526–531.

Maingret, N., Girardeau, G., Todorova, R., Goutierre, M., & Zugaro, M. (2016). Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nature Neuroscience*, *19*(7), 959–964.

Mao, D., Kandler, S., McNaughton, B. L., & Bonin, V. (2017). Sparse orthogonal population representation of spatial context in the retrosplenial cortex. *Nature Communications*, *8*, 243.

Marshall, L., Helgadottir, H., Molle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610–610, 613.

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *The Journal of Neuroscience*, *24*(31), 6862–6870.

McNamara, C. G., Tejero-Cantero, A., Trouche, S., Campo-Urriza, N., & Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nature Neuroscience*, *17*(12), 1658–1660.

Mednick, S. C., McDevitt, E. A., Walsh, J. K., Wamsley, E., Paulus, M., Kanady, J. C., & Drummond, S. P. A. (2013). The critical role of sleep spindles in hippocampal-dependent memory: A pharmacology study. *Journal of Neuroscience*, *33*(10), 4494–4504.

Mölle, M., Yeshenko, O., Marshall, L., Sara, S. J., & Born, J. (2006). Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *Journal of Neurophysiology*, *96*(1), 62–70.

Ngo, H.-V., Martinetz, T., Born, J., & Mölle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron*, *78*(3), 545–553.

Novitskaya, Y., Sara, S. J., Logothetis, N. K., & Eschenko, O. (2016). Ripple-triggered stimulation of the locus coeruleus during post-learning sleep disrupts ripple/spindle coupling and impairs memory consolidation. *Learning & Memory*, *23*(5), 238–248.

Ólafsdóttir, H. F., Carpenter, F., & Barry, C. (2016). Coordinated grid and place cell replay during rest. *Nature Neuroscience*, *19*(6), 792–794.

Ólafsdóttir, H. F., Carpenter, F., & Barry, C. (2017). Task demands predict a dynamic switch in the content of awake hippocampal replay. *Neuron*, *96*(4), 925–935.e6.

O'Neill, J., Boccara, C. N., Stella, F., Schoenenberger, P., & Csicsvari, J. (2017). Superficial layers of the medial entorhinal cortex replay independently of the hippocampus. *Science*, *355*(6321), 184–188.

Pennartz, C. M. A., Lee, E., Verheul, J., Lipa, P., Barnes, C. A., & McNaughton, B. L. (2004). The ventral striatum in off-line processing: Ensemble reactivation during sleep and modulation by hippocampal ripples. *Journal of Neuroscience*, *24*(29), 6446–6456.

Peyrache, A., Battaglia, F. P., & Destexhe, A. (2011). Inhibition recruitment in prefrontal cortex during sleep spindles and gating of hippocampal inputs. *Proceedings of the National Academy of Sciences*, *108*(41), 17207–17212.

Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S. I., & Battaglia, F. P. (2009). Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. *Nature Neuroscience*, *12*(7), 919–926.

Phillips, K. G., Bartsch, U., McCarthy, A. P., Edgar, D. M., Tricklebank, M. D., Wafford, K. A., & Jones, M. W. (2012). Decoupling of sleep-dependent cortical and hippocampal interactions in a neurodevelopmental model of schizophrenia. *Neuron*, *76*(3), 526–533.

Rasch, B., Büchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-save sleep prompt declarative memory consolidation. *Science*, *315*(5817), 1426–1429.

Rosanova, M., & Ulrich, D. (2005). Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *The Journal of Neuroscience*, *25*(41), 9398–9405.

Rothschild, G., Eban, E., & Frank, L. M. (2017). A cortical-hippocampal-cortical loop of information processing during memory consolidation. *Nature Neuroscience*, *20*(2), 251–259.

Roux, L., Hu, B., Eichler, R., Stark, E., & Buzsáki, G. (2017). Sharp wave ripples during learning stabilize the hippocampal spatial map. *Nature Neuroscience*, *20*(6), 845–853.

Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science*, *326*(5956), 1079–1079.

Sahlem, G. L., Badran, B. W., Halford, J. J., Williams, N. R., Korte, J. E., Leslie, K., … George, M. S. (2015). Oscillating square wave transcranial direct current stimulation (tDCS) delivered during slow wave sleep

does not improve declarative memory more than sham: A randomized sham controlled crossover study. *Brain Stimulation*, *8*(3), 528–534.

Seibt, J., Richard, C. J., Sigl-Glöckner, J., Takahashi, N., Kaplan, D. I., Doron, G., … Larkum, M. E. (2017). Cortical dendritic activity correlates with spindle-rich oscillations during sleep in rodents. *Nature Communications*, *8*(1), 684.

Sejnowski, T. J., & Destexhe, A. (2000). Why do we sleep? *Brain Research*, *886*(1), 208–223.

Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron*, *21*(5), 1123–1128.

Singer, A. C., & Frank, L. M. (2009). Rewarded outcomes enhance reactivation of experience in the hippocampus. *Neuron*, *64*(6), 910–921.

Sirota, A., & Buzsáki, G. (2005). Interaction between neocortical and hippocampal networks via slow oscillations. *Thalamus and Related Systems*, *3*(4), 245–259.

Sirota, A., Csicsvari, J., Buhl, D., & Buzsáki, G. (2003). Communication between neocortex and hippocampus during sleep in rodents. *Proceedings of the National Academy of Sciences*, *100*(4), 2065–2069.

Sosa, M., Joo, H., Frank, L.2017. Reactivation of nucleus accumbens neurons during awake dorsal and ventral hippocampal sharp-wave ripples. *Society for Neuroscience Abstracts*, *84*, 07.

Staresina, Bergmann, Bonnefond, van der Meij, Jensen, Deuker, Elger, Axmacher, & Fell (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature Neuroscience*, *18*(11), 1679–1686.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, *262*(5134), 679–685.

Steriade, M., Nunez, A., & Amzica, F. (1993). A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: Depolarizing and hyperpolarizing components. *Journal of Neuroscience*, *13*(8), 3252–3265.

Steriade, M., & Timofeev, I. (2003). Neuronal plasticity in Thalamocortical networks during sleep and waking oscillations. *Neuron*, *37*(4), 563–576.

Sullivan, D., Mizuseki, K., Sorgi, A., & Buzsáki, G. (2014). Comparison of sleep spindles and theta oscillations in the hippocampus. *The Journal of Neuroscience*, *34*(2), 662–674.

Takeuchi, T., Duszkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., … Morris, R. G. M. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature*, *537*(7620), 357–362.

Tang, W., Shin, J. D., Frank, L. M., & Jadhav, S. P. (2017). Hippocampal-prefrontal reactivation during learning is stronger in awake as compared to sleep states. *Journal of Neuroscience*, *37*(49), 11789–11805.

Tierney, P. L., Dégenètais, E., Thierry, A.-M., Glowinski, J., & Gioanni, Y. (2004). Influence of the hippocampus on interneurons of the rat prefrontal cortex. *The European Journal of Neuroscience*, *20*(2), 514–524.

Todorova, R., Maingret, N., Fayat, R., & Zugaro, M. (2017). Communication between the hippocampus and the neocortex underlying memory consolidation during slow wave sleep. *Society for Neuroscience Abstracts*, *751*, 11.

Valdés, J. L., McNaughton, B. L., & Fellous, J.-M. (2015). Offline reactivation of experience-dependent neuronal firing patterns in the rat ventral tegmental area. *Journal of Neurophysiology*, *114*(2), 1183–1195.

van de Ven, G. M., Trouche, S., McNamara, C. G., Allen, K., & Dupret, D. (2016). Hippocampal offline reactivation consolidates recently formed cell assembly patterns during sharp wave-ripples. *Neuron*, *92*(5), 968–974.

Varela, C., Kumar, S., Yang, J. Y., & Wilson, M. A. (2014). Anatomical substrates for direct interactions between hippocampus, medial prefrontal cortex, and the thalamic nucleus reuniens. *Brain Structure and Function*, *219*(3), 911–929.

Wierzynski, C. M., Lubenov, E. V., Gu, M., & Siapas, A. G. (2009). State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. *Neuron*, *61*(4), 587–596.

Wilber, A. A., Skelin, I., Wu, W., & McNaughton, B. L. (2017). Laminar Organization of Encoding and Memory Reactivation in the parietal cortex. *Neuron*, *95*(6), 1406–1419.e5.

How to cite this article: Todorova R, Zugaro M. Hippocampal ripples as a mode of communication with cortical and subcortical areas. *Hippocampus*. 2018;1–11. https://doi.org/10.1002/hipo.22997