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Review article

Hippocampal information processing across sleep/wake cycles

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ABSTRACT

According to a two-stage memory consolidation model, during waking theta states, afferent activity from the neocortex to the hippocampus induces transient synaptic modification in the hippocampus, where the information is deposited as a labile form of memory trace. During subsequent sharp-wave ripples (SPW-Rs), the newly acquired hippocampal information is transferred to the neocortex and stored as a long-lasting memory trace. Consistent with this hypothesis, waking theta states and SPW-Rs distinctly control information flow in the hippocampal–entorhinal loop. Although both waking theta states and rapid eye movement (REM) sleep are characterized by prominent hippocampal theta oscillations, the two brain states involve distinct temporal coordination and oscillatory coupling in the hippocampal–entorhinal circuit. While distinct brain states have distinct network dynamics, firing rates of individual neurons in the hippocampal–entorhinal circuitry follow lognormal-like distributions in all states. Firing rates of the same neurons are positively correlated across brain states and testing environments, suggesting that memory is allocated in preconfigured, rather than tabula rasa-type, skewed neuronal networks. The fast-firing minority and slow-firing majority neurons, which can support network stability and flexibility, are under distinct homeostatic regulations that are initiated by spindles and SPW-Rs during slow wave sleep and implemented during subsequent REM sleep.

Contents

1. Introduction

Distinct brain states involve distinct information processing. Theta and SPW-R (non-theta) states are two prominent brain states recognized by local field potentials (LFP) in the hippocampus (Buzsaki, 1989; Buzsaki, 2002; Buzsaki, 2005; Buzsaki, 2015a). It has been proposed that memory trace formation involves two distinct steps, each of which occurs during the distinct brain state (Marr, 1971; Buzsaki, 1989; Buzsaki, 2015a). According to the proposal, during theta states, afferent activity from the neocortex/entorhinal cortex to the hippocampus induces transient synaptic potentiation in the CA3 hippocampal regions, where the

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newly acquired information is temporally held as a labile form of memory trace (Buzsaki, 1989). During subsequent SPW-R state, the highly synchronous population bursts, initiated in the CA3 recurrent network, induces long-term synaptic reorganization in the circuit, and converts labile trace into a long-lasting form of memory trace (Buzsaki, 1989). The hippocampal memory trace is transferred to the neocortex during post-experience SPW-Rs for long-term storage (Buzsaki, 1989; Buzsaki, 2015a).

During waking theta states, higher levels of neuromodulators, such as acetylcholine, in the hippocampus enhance the influence of external inputs relative to intrinsic activity, likely favoring sensory processing and predominant information flow from the neocortex to the hippocampus (Hasselmo, 1999). Consistent with this notion, waking theta states in rodents are predominantly observed during sniffing, whisking, rearing, and walking periods in which an animal intensely processes sensory inputs (Buzsaki, 2002; Buzsaki, 2005). Place coding in the hippocampus during exploration is the best characterized form of neuronal coding. Hippocampal "place cells" selectively fire when the animal is in a restricted zone of space ("place field") (O'Keefe and Dostrovsky, 1971). When an animal traverses across multiple place fields, the corresponding place cells fire sequentially. Importantly, this firing sequence in a behaviorally relevant time-scale (in the order of seconds) is embedded in the ongoing theta rhythm (in the order of 100 ms) in a time-compressed manner (O'Keefe and Recce, 1993; Skaggs et al., 1996; Dragoi and Buzsaki, 2006; Foster and Wilson, 2007; Diba and Buzsaki, 2008). As a result, cells with overlapping place fields fire sequentially in close temporal proximity, which in turn triggers spike-timing-dependent plastic changes in the synapses between the cells (Skaggs et al., 1996; Mehta et al., 2000), thus providing a cellular mechanism for initial sequence learning in the hippocampus network (Skaggs et al., 1996; Yamaguchi, 2003).

Mammalian sleep consists of two distinct states, rapid eye movement (REM) sleep and slow wave sleep (SWS). During REM sleep, the acetylcholine level is similar or even higher and norepinephrine and serotonin levels are lower when compared with waking (Hasselmo, 1999). However, REM sleep and waking theta states share quite similar electrophysiological properties. Theta oscillations in the hippocampus and low voltage desynchronized LFP in the neocortex are prominent during both REM sleep and waking theta states. Despite the apparent similarity in electrophysiological properties, recent studies revealed that the activity of hippocampal CA1 pyramidal neurons is distinctly coordinated with ongoing theta oscillations during REM sleep and waking theta states (Mizuseki et al., 2011). Moreover, the hippocampal CA1 region receives different spatiotemporal input patterns from the CA3 region and entorhinal cortex during REM sleep and waking theta states (Schomburg et al., 2014; Oliva et al., 2016b; Fernandez-Ruiz et al., 2017). These findings suggest that information is handled differently in the hippocampal–entorhinal loop during REM sleep and waking theta states.

SPW-Rs in the hippocampus are best characterized by the transiently occurring 140–230 Hz ripple oscillations near the CA1 pyramidal cell layer, which are associated with negative polarity deflections known as sharp waves in the CA1 stratum radiatum (Buzsaki, 2015a). SPW-Rs are self-organized patterns that emerge from the extensive excitatory recurrent system of the CA3 region, potentially triggered by activity in the CA2 region (Oliva et al., 2016a), and represent a synchronous population activity in the CA3–CA1–subicular complex and entorhinal cortex (Buzsaki et al., 1983; Buzsaki, 2015a). Although SPW-Rs occur during consummatory behaviors and SWS, the spike content of SPW-Rs is coordinated with replay fragments of waking neuronal sequences in a temporally compressed manner (Buzsaki, 2015a). It has been suggested that SPW-Rs assist in transferring the time-compressed representation from the hippocampus to distributed circuits to support memory consolidation (Buzsaki, 1989; Buzsaki, 2015a; Pennartz et al., 2004; Frankland and Bontempi, 2005; Girardeau et al., 2009; Ego-Stengel and Wilson, 2010; Jadhav and Frank, 2009; O'Neill et al., 2010; Girardeau and Zugaro, 2011; Carr et al., 2011; Csicsvari and Dupret, 2014; Ji and Wilson, 2007; Karlsson and Frank, 2009; Lansink et al., 2009; Bendor and Wilson, 2012; Girardeau et al., 2014; Wu et al., 2017).

Consistent with the hypothesized role of SPW-Rs in memory consolidation, off-line reactivation during SPW-Rs has properties suitable for promoting synaptic plasticity (Buzsaki, 1989; Buzsaki, 2015a; Sadowski et al., 2016). Pyramidal cell–interneuron interactions underlie hippocampal ripple oscillations (Stark et al., 2014), and pyramidal neurons show depolarization with concurrent strong inhibition during SPW-Rs, thus producing an exquisite balance between excitation and inhibition (Maier et al., 2011; English et al., 2014; Buzsaki, 2015a; Hulse et al., 2016; Gan et al., 2017). A recent study showed that neurons activated while mice explore novel environments are preferentially activated during SPW-Rs in hippocampal slice preparations, and reactivated neurons have a higher excitation/inhibition synaptic ratio, suggesting that unbalanced excitation underlies off-line reactivation of behaviorally activated neurons (Mizunuma et al., 2014).

Moreover, hippocampal co-firing patterns associated with spatial novelty or reward learning are reactivated more strongly (O'Neill et al., 2008; Singer and Frank, 2009; McNamara et al., 2014), and this phenomenon is promoted by midbrain dopaminergic neurons (McNamara et al., 2014). SPW-Rs occurrence rates increase during the hour following a training session on an odor-reward association task (Eschenko et al., 2008) and a radial maze task, which is concomitant with a significant improvement in performance (Ramadan et al., 2009).

In support of the information transfer hypothesis, hippocampal SPW-Rs coordinate with neocortical oscillations (Siapas and Wilson, 1998; Sirota et al., 2003; Battaglia et al., 2004; Peyrache et al., 2009). SPW-Rs are more likely to occur at the transition between DOWN and UP states (Sirota et al., 2003; Battaglia et al., 2004; Isomura et al., 2006; Molle et al., 2009; Peyrache et al., 2009; Peyrache et al., 2011) of slow oscillations (Steriade, 2003) and tend to coincide with neocortical spindles during sleep (Siapas and Wilson, 1998; Sirota et al., 2003; Molle et al., 2009; Clemens et al., 2011). Reactivation of ensemble firing patterns in neocortical areas coincide with hippocampal SPW-Rs in a coarser time-scale (Peyrache et al., 2009; Ji and Wilson, 2007; Jadhav et al., 2016). Cell assemblies formed in the medial prefrontal cortex during awake behavior are transiently reactivated during slow wave sleep (SWS) in a time-compressed manner (Euston et al., 2007; Peyrache et al., 2009). Prefrontal reactivation is correlated with DOWN-to-UP state transition density (Johnson et al., 2010) and most often occurs near the beginning and ending of the UP state (Peyrache et al., 2009). Moreover, a recent study showed that as soon as a rat has learned a behavioral rule, prefrontal neurons self-organize into cell assemblies that are coordinated with the hippocampal theta rhythm and that the same assemblies are then preferentially reactivated during sleep (Benchenane et al., 2010). These findings suggest that coordinated hippocampal–prefrontal reactivation participates in selective memory consolidation.

A causal role of SPW-Rs in memory consolidation during sleep was suggested in studies showing that the perturbation of neuronal activity during SPW-Rs in sleep by electrical stimulation leads to spatial memory impairment (Girardeau et al., 2009; Ego-Stengel and Wilson, 2010). Moreover, induction of delta waves and spindles in the neocortex by SPW-R-triggered electrical stimulation reinforces the coordination between the hippocampus and prefrontal cortex and improves memory performance in a novel object

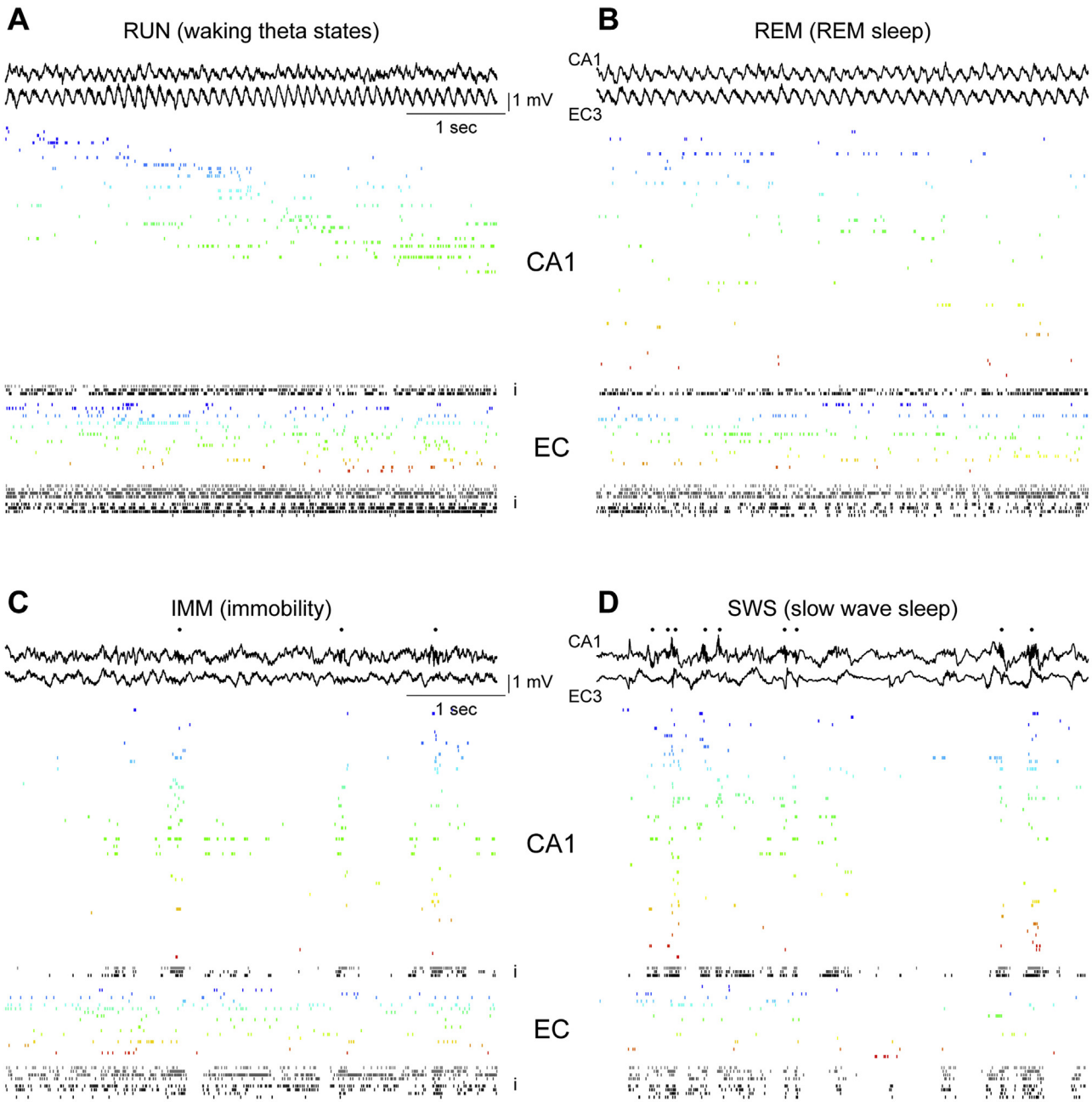

Fig. 1. Local field potentials (LFP) and spiking activity depend on brain state.
LFP and spiking activity of CA1 and entorhinal cortical (EC) neurons. Dots above the CA1 LFP during slow wave sleep (SWS) and waking immobility (IMM) represent sharp-wave ripples (SPW-Rs). Note the strong population synchrony during SPW-Rs. Colored ticks: principal neurons. Gray and black ticks: interneurons. The same neurons were recorded during four different brain states. Principal neurons are sorted according to the timing of the spiking during RUN. Positive polarity is up for LFP.

recognition task, suggesting that fine-tuned coordination between SPW-Rs, delta waves and spindles supports memory consolidation (Maingret et al., 2016). Furthermore, off-line reactivation of newly formed cell assemblies, but not those of previously formed cell assemblies, correlates with future context-dependent reinstatement, and reactivation during SPW-Rs is required for consolidating cell assemblies only when the assemblies are newly formed and gradually strengthened during the first exposure to a novel environment (van de Ven et al., 2016).

Pavlides and Winson (1989) reported that activity of hippocampal place cells in waking states influences the firing characteristics of these cells in subsequent sleep episodes, paving the way for replay research (Wilson and McNaughton, 1994; Skaggs et al., 1996; Kudrimoti et al., 1999; Nadasdy et al., 1999; Hirase et al., 2001). SPW-Rs-associated replay of behavioral trajectory was first reported during SWS (Lee and Wilson 2002) but was later discovered during waking states when an animal pauses in an environment (Foster and Wilson 2006; Diba and Buzsaki, 2007). CA1 pyramidal neuron population bursts during SPW-Rs represent previously experienced behavioral sequences in forward or reverse order (Foster and Wilson, 2006; Diba and Buzsaki, 2007). Forward vs. reverse and centrifugal vs. centripetal replay may be under distinct control by reward (Ambrose et al., 2016; Gomperts et al., 2015). In addition to reactivation of goal locations during SPW-Rs in sleep, the number of waking SPW-Rs that occur at the goal locations in brief pauses of exploration predicts the prefer-

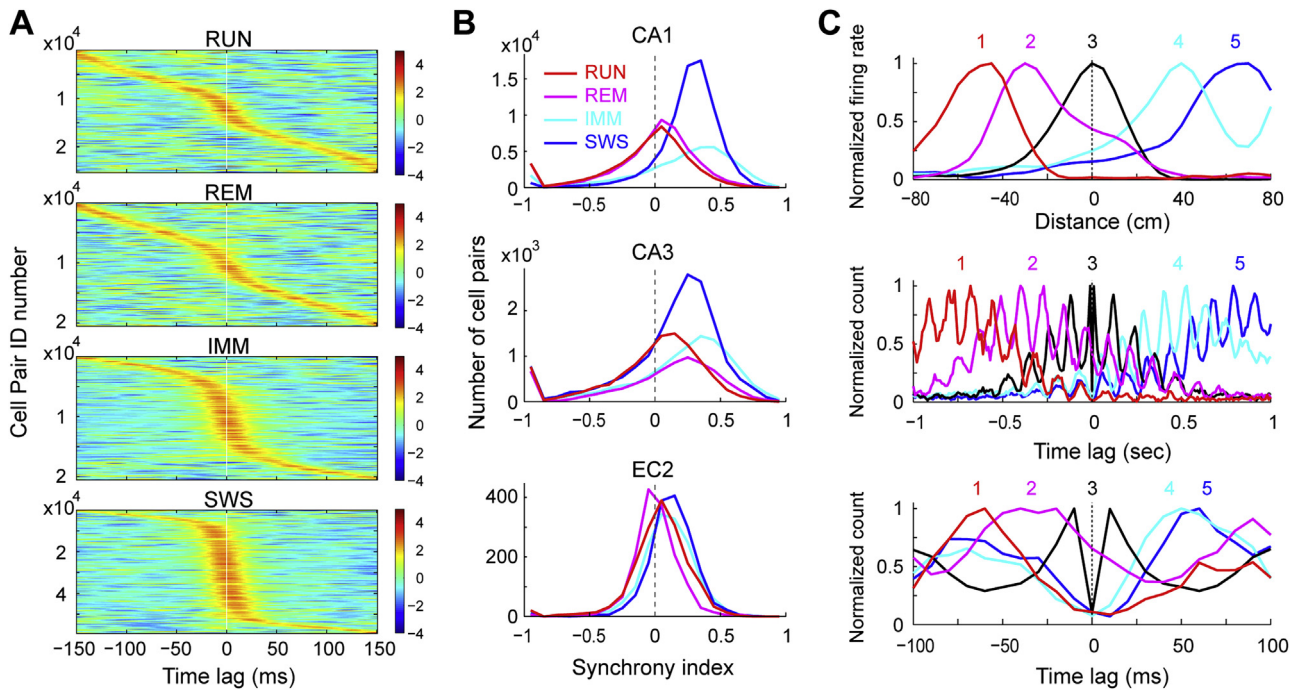

Fig. 2. Synchrony is lower during theta states than non-theta states.
(A) Cross-correlograms (CCGs) of CA1 pyramidal cell–pyramidal cell pairs in different brain states. Each row represents a normalized CCG of a cell pair. CCG height was z-scored and color coded for each cell pair. Neuron pairs were sorted by the timing of the peak of the CCG. (B) Distribution of synchrony index of principal neuron–principal neuron pairs in different brain states. The synchrony index was calculated as the difference between the mean spike counts across bins in [−25, +25] ms and that in [−500, −25] ms and [+25, +500] ms in CCGs divided by the sum. (C) Top: normalized firing rates of five place cells, with neuron 3 as a reference (black trace with peak firing at 0 cm). Middle: normalized cross-correlations between the reference neuron and other place cells (colors) and the autocorrelogram of the reference neuron (black). Temporal offsets between the peaks represent the time needed for the rat to run between the place fields of the neurons. Bottom: Time-expanded versions of the normalized CCGs shown in the middle (theta time-scale). Note that the order of peak activity of place cells 1–5 within the theta cycle is the same as the order of position representation on the track. The dip around time 0 in the autocorrelogram of the reference cell is due to the spike refractory period. (A–C) Reproduced from Mizuseki and Buzsaki, 2014 with permission from Royal Society.

ence of the animal in returning to that location in future probe sessions (Dupret et al., 2010). Furthermore, the perturbation of CA1 pyramidal neuron activity during waking SPW-Rs results in spatial working memory deficits (Jadhav et al., 2012). Moreover, it has been shown that reactivation of behavioral trajectories during SPW-Rs in a W-maze predicts future arm choices (Singer et al., 2013), and reactivated firing sequences during waking SPW-Rs often predict the future trajectory of the animal to reach a desired goal in two-dimensional environments (Pfeiffer and Foster, 2013), suggesting that waking SPW-Rs play a role in navigational planning (Buzsaki 2015a). Replay of firing sequences corresponding to long runs through a large environment can begin at remote locations on the track; extended replay is composed of chains of shorter sequences, which may support the storage of memories of prolonged experiences (Davidson et al., 2009). Further, waking "replay" content includes never and rarely experienced shortcut trajectories, suggesting that hippocampal replay may help in active learning and maintenance of the cognitive map (Gupta et al., 2010).

Here, we review recent progress in the knowledge of hippocampal information processing across sleep/wake cycles with an emphasis on (1) brain state-dependent firing patterns and network dynamics, (2) comparison of information flow during waking theta states and SPW-Rs, (3) comparison of information processing during REM sleep and waking theta states, (4) distribution of firing rates during distinct brain states, (5) distribution of SPW-R-related firing patterns and magnitude of population synchrony, (6) firing rate correlation across brain states and testing conditions, and (7) regulation of neuronal firing rate by sleep.

2. Brain state-dependent firing patterns and network dynamics in the hippocampus

The hippocampus is comprised of laminar structures in which projections from different brain areas terminate in distinct layers (Andersen et al., 2006). Due to the laminar anatomy, hippocampal LFP patterns reflect various behavior-dependent network dynamics. Two prominent brain states that can be classified by hippocampal LFP are theta and SPW-R (non-theta) states (Buzsaki, 1989; Buzsaki, 2002; Buzsaki, 2006; Buzsaki, 2015a). During exploration and REM sleep, theta oscillations are prominent in the hippocampus and entorhinal cortex (Buzsaki, 2002; Fig. 1). In contrast, during waking immobility, consummatory behavior (grooming, eating, drinking, etc.), and slow wave sleep, SPW-R events are prominent in the hippocampal CA1 field (Buzsaki, 2015a, Fig. 1). As described earlier, it has been hypothesized that the theta/non-theta switch supports a two-stage memory trace formation with an "on-line" rapid information acquisition stage during waking theta states, followed by repeating "off-line" reactivation of acquired information in post-experience SPW-Rs during non-theta states (Buzsaki, 1989).

In addition to LFP, neuronal spiking patterns depend on brain states. During active exploration, a fraction of neurons (e.g., place cells) occasionally increase their firing rates for a short period (~1 s) with a low level of population synchrony in the hippocampal CA1 field (Figs. 1 and 2). Similar spiking activity is observed during REM sleep, in which a given neuron increases its firing rate occasionally and temporally, but synchrony, as measured by co-activation of principal cell pairs, is low (Mizuseki and Buzsaki,

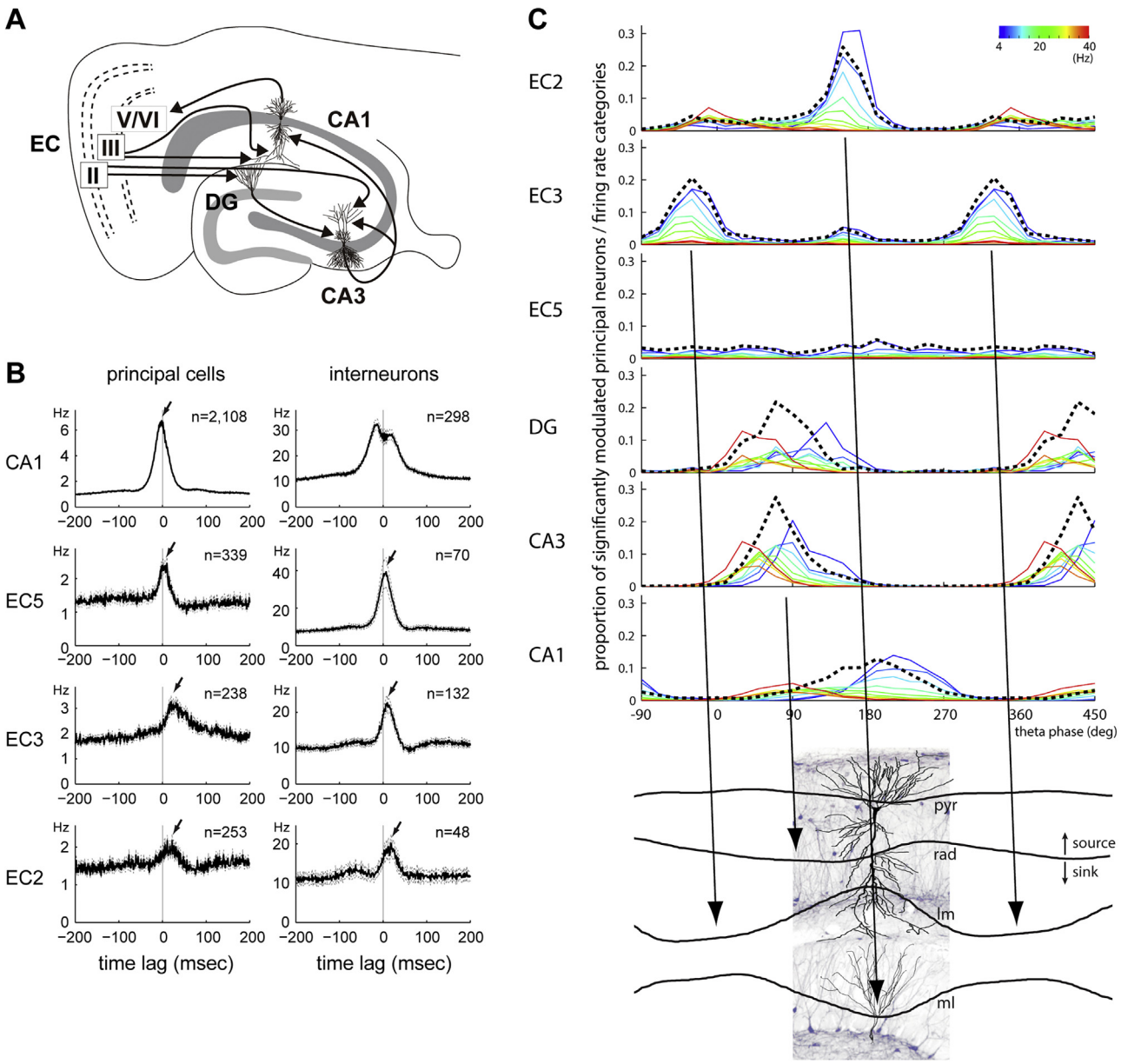

Fig. 3. Temporal relationship between layer-/region-specific firing patterns in the hippocampal–entorhinal loop during SPW-Rs and waking theta states.
(A) Simplified connectivities in the hippocampal–entorhinal circuit. Only major excitatory connections are shown. Principal neurons in the entorhinal cortex layer 2 (EC2) project to the dentate gyrus (DG) and synapse on granule cells. EC2 principal neurons also project to the CA3 field and innervate CA3 pyramidal neurons. CA3 pyramidal neurons project to the CA1 and synapse with CA1 pyramidal neurons. Principal neurons in the entorhinal cortex layer 3 (EC3) principal neurons directly project to the CA1 field and synapse with CA1 pyramidal neurons. CA1 pyramidal neurons send axons to deep layers of the EC. Therefore, the entorhinal-hippocampus loop is often regarded as a unidirectionally connected feed-forward excitatory loop.
(B) Sharp wave/ripple-triggered discharge patterns of hippocampal and EC neurons. Neuronal discharges were aligned to the ripple peak determined by the power peak of filtered LFP (140–230 Hz), and mean (±SEM) firing rates are shown. n = number of cells. Note the increasing onset and peak delays of both principal cells and interneurons (~15 ms) in the CA1-EC5-EC3-EC2 axis. EC5, entorhinal cortex layer 5.
(C) Temporal relationship between layer/region-specific firing patterns and theta current sinks in the hippocampus. Top: distribution of preferred theta phase. The height of the histograms reflects the proportion of principal neurons significantly modulated in each firing rate category (reference = EC3 theta oscillations). Black dashed line, population mean. The instantaneous rate (color coded) was quantified for each spike in ten increments (1, 2, 3, . . . ≥10 spikes per 250 ms, corresponding to 4, 8, 12, . . . ≥40 Hz). Bottom: current-source density theta traces are superimposed on a histological section in the CA1–DG axis with highlighted pyramidal and granule cells. Note the phase-reversed sinks in the CA1 stratum lacunosum-moleculare (lm) and dentate molecular layers (ml), and phase-shifted sink (relative to lm sink) in the stratum radiatum (rad). pyr, CA1 pyramidal layer. Arrows indicate the temporal (phase) offsets between the peak of population firing in upstream layers and the theta sinks in the target layers with the expected delays based on axonal conduction velocity. Note that while the population peak of an upstream layer correctly predicts the timing of the dendritic sink in its target layer, the spiking activity in the downstream target population is substantially delayed.
(B) and (C) Reproduced from Mizuseki et al. (2009) with permission from Elsevier.

2014; Figs. 1 and 2). In contrast, when an animal is immobile or in SWS, a fraction of neurons in the CA1 fire synchronously during SPW-Rs (Buzsaki, 2015a; Figs. 1 and 2). Thus, synchrony is lowest during waking theta states and REM sleep, associated with theta oscillations, and highest during SWS (Mizuseki and Buzsaki, 2014).

During exploration, a significant fraction of pyramidal cell pairs have negative spike count correlations (Mizuseki and Buzsaki, 2014), implying that neurons prefer different phases within a given

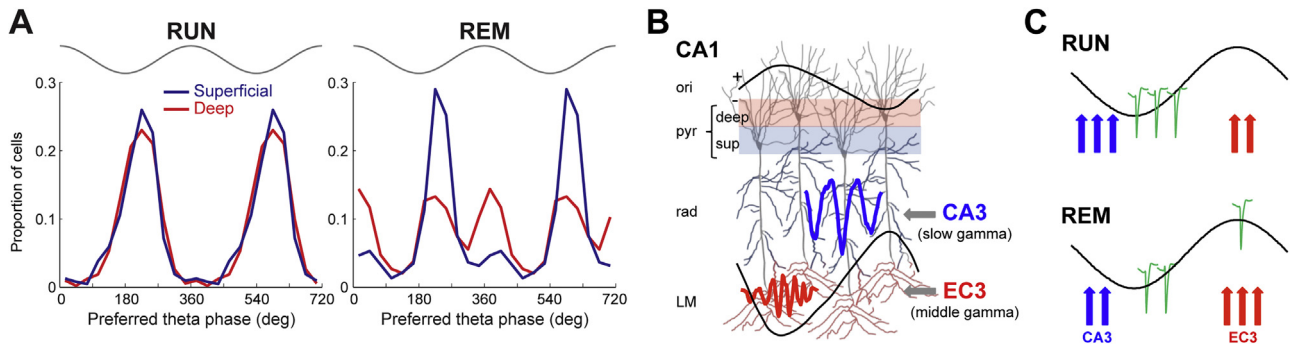

Fig. 4. Entorhinal–CA3 dual-input control of spike timing in the hippocampus during waking theta states and REM sleep.
(A) Distribution of the preferred theta phase of CA1 pyramidal cells in the superficial and deep layers during maze running (RUN) and REM sleep. Note the unimodal distribution of theta phase preference in the deep layer group during RUN and bimodal distribution during REM sleep. Top gray traces indicate the idealized reference theta cycle in the CA1 pyramidal layer. Positive polarity is up. (B and C) Diagrams summarizing the entorhinal–CA3 dual-input control of spike timing of CA1 pyramidal cells. (B) Entorhinal layer 3 (EC3) middle gamma input (60–100 Hz) modulates distal dendrites in stratum lacunosum moleculare (LM) at the positive peak of CA1 pyramidal layer theta, followed by CA3 slow gamma (30–60 Hz) input in stratum radiatum (rad) on the descending theta phase. Deep CA1 pyramidal cells receive stronger EC3 input than superficial ones. pyr; CA1 pyramidal cell layer. ori; stratum oriens. Black traces, theta oscillations in CA1 pyramidal cell layer and in stratum lacunosum moleculare. Positive polarity is up. (C) The relative strengths of phase-separated CA3 and EC3 inputs are hypothesized to determine the theta phase of CA1 pyramidal cells spiking. During REM sleep, CA3 drive is weaker and EC3 drive is stronger compared with those during exploration (RUN). As a result, the preferred phase of a significant fraction of CA1 pyramidal cells (green) moves toward the peak during REM. Black traces, theta oscillations in CA1 pyramidal cell layer. Positive polarity is up.
Reproduced from (A) Mizuseki et al. (2009); (B) Fernandez-Ruiz et al. (2017), and (C) adapted from Fernandez-Ruiz et al. (2017), with permission from Elsevier.

theta cycle (Dragoi and Buzsaki, 2006; Diba and Buzsaki, 2008). Indeed, hippocampal principal neurons discharge at progressively earlier theta phases as the rat moves through the place field of the neuron, a phenomenon known as phase precession (O'Keefe and Recce, 1993). As a result, the cell assembly representing the current location of the animal is active at the trough of the theta cycle, whereas assemblies representing the previously and subsequently visited locations are activated on the descending and ascending phases, respectively, thus spanning almost the entire cycle (Skaggs et al., 1996; Dragoi and Buzsaki, 2006; Diba and Buzsaki, 2008; Geisler et al., 2010). While place cells do not discharge synchronously, their activities are temporally coordinated and separated with orderly delays. This is illustrated by the spatial and temporal relationships of CA1 place cells during linear track walking (Fig. 2C). The sequential firing of place cells, with time lags commensurate with the distance between their place fields, appears in a time-compressed manner in a theta time-scale (Skaggs et al., 1996; Dragoi and Buzsaki, 2006; Foster and Wilson, 2007; Fig. 2C). The behaviorally relevant longer time-scale (~1 s) pattern of sequential activity is faithfully reflected within a theta cycle (~100 ms). Thus, theta oscillations can generate non-synchronous yet coordinated firing patterns (Mizuseki and Buzsaki, 2014).

Perturbations of the theta time-scale spike-timing coordination by the administration of a cannabinoid receptor agonist (Robbe and Buzsaki, 2009) and inactivation of the medial septum (Wang et al., 2015) result in spatial memory deficits, suggesting that the precise theta time-scale coordination of hippocampal activity is necessary for memory processing. Furthermore, loss of CA3 input abolishes the precise theta time-scale coordination at the ensemble level in CA1, despite the persistence of phase precession at a single cell level, implying that temporal coordination at single cell and population levels can be dissociable (Middleton and McHugh, 2016), as previously suggested (Dragoi and Buzsaki, 2006). In line with this notion, phase precession of individual cells exists at the first traversal of the novel liner track, whereas theta sequence (Foster and Wilson, 2007) develops through experience (Feng et al., 2015).

3. Comparison of information flow during waking theta states and SPW-Rs

Theta oscillations are believed to play an important role in the coordination of neuronal firing in the entorhinal and hippocampal system (Buzsaki, 2002; Buzsaki, 2005), temporal packaging and transfer of neuronal information (Skaggs et al., 1996; Hasselmo, 2005; Dragoi and Buzsaki, 2006), encoding and retrieval of episodic and spatial memories (Hasselmo, 2005; O'Keefe and Burgess, 2005; Jensen and Lisman, 2005), and synaptic plasticity (Pavlides et al., 1988; Huerta and Lisman, 1995; Holscher et al., 1997). Consistent with these hypotheses, interfering with theta rhythms results in spatial memory deficits in rats (Winson, 1978; Mizumori et al., 1990; Robbe and Buzsaki, 2009; Wang et al., 2015). However, physiological mechanisms that give rise to theta oscillations and theta-mediated temporal coordination of individual neurons across anatomically successive sub-regions are not well understood. Recently, the simultaneous recording of neurons in multiple regions of the hippocampal–entorhinal loop revealed that theta-coordinated spiking of entorhinal cortex principal cell populations predicts the timing of current sinks in target layers of the hippocampus (Mizuseki et al., 2009; Fig. 3C). However, principal neurons in monosynaptically connected upstream and downstream layers/regions fire with significantly longer temporal delays (typically half of a theta cycle) than would be expected from axon conduction velocity, synaptic delays, and passive synaptic integration (Mizuseki et al., 2009; Fig. 3C; Cutsuridis and Poirazi, 2015). Therefore, it has been hypothesized that population activity in downstream layers/regions is not merely driven by the upstream passively, but rather a local circuit mechanism plays a significant role for the precise temporal coordination of neuronal activity during waking theta states (Mizuseki et al., 2009). From this perspective, it has been proposed that the temporal windows set by theta cycles allow for local circuit interaction and provide a considerable degree of computational independence in subdivisions of the hippocampal–entorhinal loop (Mizuseki et al., 2009). Other slower oscillations, such as slow oscillations during sleep, may also provide local autonomy for computation (Isomura et al., 2006).

Grid cells (Hafting et al., 2005) in the entorhinal cortex layer 2 (EC2), but not in layer 3 (EC3), show phase precession (Hafting et al., 2008). However, the proportion of phase precessing cells is much larger in hippocampal CA1 and CA3 pyramidal neurons and granule cells in dentate gyrus (DG) than in the entorhinal cortical neurons (Mizuseki et al., 2009). Furthermore, at place field onset, CA1 place cells fire preferentially near the peak of theta oscillations in which EC3 input affects the CA1 region the most, but at the middle of the field, CA1 place cells fire at the trough of theta oscillations

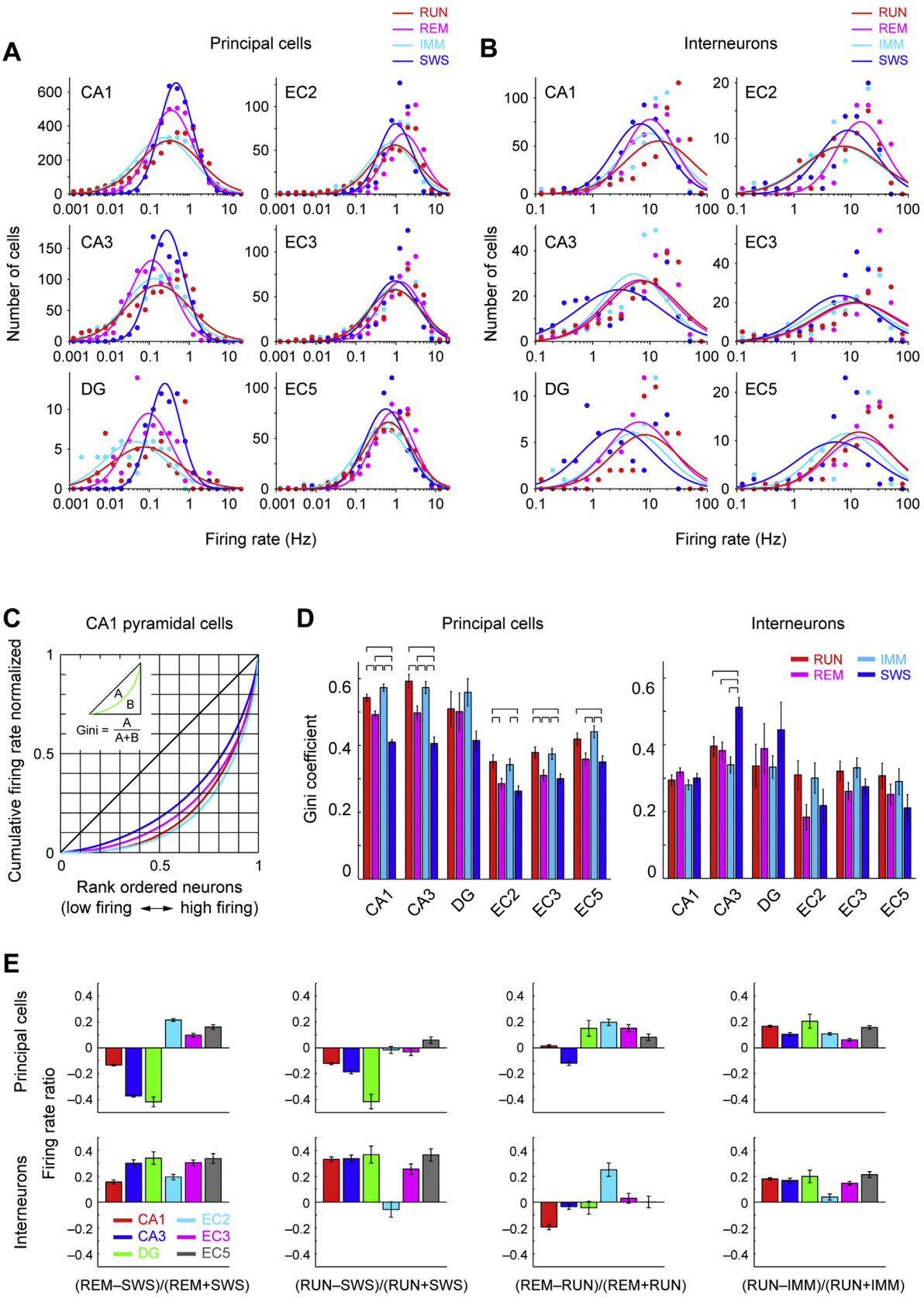

Fig. 5. Firing rate distribution in different brain states.
Firing rate distribution of principal cells (A) and interneurons (B) in the hippocampus and entorhinal cortex. Dots, data; Lines, lognormal fit. Note the similar brain state-dependent changes of rate distributions in the various hippocampal regions and EC layers. (C) Lorenz plots of the distribution of firing rates. Inset: Illustration of the Gini coefficient, which is determined by dividing A (the area between the line of equality and the Lorenz curve) by the areas marked by A and B. (D) Gini coefficients in different hippocampal regions and EC layers in different brain states (mean ± SEM). Brackets indicate significant differences ($p < 0.05$; ANOVA, followed by Tukey's test). The same color code is used for (A) ~ (D). (E) Firing rate changes of individual neurons across different brain states (mean ± SEM). The firing rate ratio of each neuron was calculated

when the direct input from the EC3 is minimum (Mizuseki et al., 2009; Fernandez-Ruiz et al., 2017). The same situation is found in CA3 place cells. At place field onset, CA3 place cells spike at the preferred theta phase of EC2 input, whereas at the middle of the field, CA3 place cells fire at the theta phase when the direct input from the EC2 is minimum (Mizuseki et al., 2009; Fernandez-Ruiz et al., 2017). Therefore, it has been suggested that hippocampal phase precession is not simply inherited from the entorhinal cortex but rather reflects intra-hippocampal local circuit computation (Mizuseki et al., 2009). When perisomatic inhibition of CA1 pyramidal cells is reduced by silencing parvalbumin-positive interneurons optogenetically, the disinhibited pyramidal neurons show reduced phase precession and tend to fire in synchrony with other disinhibited pyramidal neurons (Royer et al., 2012). This finding suggests that local inhibition plays a significant role in precisely coordinating the temporal activity of pyramidal cells within a theta cycle.

In contrast to waking theta states, SPW-R-associated synchronous CA1 activity rapidly propagates to the entorhinal cortex within 10–15 ms during non-theta states (Chrobak and Buzsaki, 1994; Mizuseki et al., 2009; Fig. 3B). Therefore, information embedded in synchronous firing in the hippocampus is transmitted immediately to the downstream entorhinal cortex during SPW-Rs (Mizuseki et al., 2009; Buzsaki, 2015a). Indeed, place cells in the hippocampal CA1 region and grid cells in the deep layers of the entorhinal cortex show spatially coherent and temporally coordinated replay during population bursts associated with SPW-Rs (Olafsdottir et al., 2016). Namely, during replay entorhinal grid cells encode locations with ~10 ms delay relative to hippocampal place cells, suggesting that the entorhinal cortex cooperates with the hippocampus to consolidate spatial memory (Olafsdottir et al., 2016). However, it was also reported that cell assemblies in superficial layers of the entorhinal cortex replay trajectories independently of the hippocampus and SPW-Rs (O'Neill et al., 2017). Thus, it is under debate to what extent reactivations of the entorhinal cortex and hippocampus are spatially coherent and temporally correlated.

During SPW-Rs, inhibition is markedly elevated concurrently with strong excitation (Csicsvari et al., 1999; Buzsaki, 2015a). The firing of CA1 pyramidal cells increases ~6-fold and the firing of CA1 interneurons increases ~3-fold during SPW-Rs (a two-fold gain of excitability in CA1; Csicsvari et al., 1999; Mizuseki et al., 2009; Buzsaki, 2015a; Fig. 3B). In contrast, SPW-Rs recruitment of entorhinal principal cells is weaker than recruitment of entorhinal interneurons in all layers (gain of inhibition) (Mizuseki et al., 2009; Buzsaki, 2015a; Fig. 3B). This 'dampening' mechanism ensures the transfer of hippocampal information to neocortical targets via neurons in deep layers of the entorhinal cortex without reverberating excitation in the hippocampal–entorhinal loop (Chrobak and Buzsaki, 1994; Mizuseki et al., 2009; Buzsaki, 2015a).

4. Comparison of information processing during REM sleep and waking theta states

Accumulating evidence suggests that REM sleep plays essential and distinct roles in memory processing (Crick and Mitchison, 1983; Giuditta et al., 1995; Datta, 2000; Louie and Wilson, 2001; Walker et al., 2003; Wetzel et al., 2003; Datta et al., 2004; Stickgold, 2005; Ishikawa et al., 2006; Datta et al., 2008; Nishida et al., 2009; Diekelmann and Born, 2010; Gujar et al., 2011; Rasch and Born, 2013; Fogel et al., 2009; Watts et al., 2012; Stickgold and Walker, 2013; Ravassard et al., 2016; Boyce et al., 2016; Li et al., 2017a). REM sleep is characterized by muscle atonia, saccadic eye movement, and, at least in humans, dreaming (Aserinsky and Kleitman, 1953; Dement and Wolpert, 1958; Berger and Oswald, 1962; Llinas and Pare, 1991; Hobson and Pace-Schott, 2002). REM sleep is considered a paradoxical state because, despite the high behavioral threshold to arousing perturbations, the gross physiological patterns in the forebrain during REM sleep resemble those observed during waking. Indeed, LFPs in the hippocampus during waking theta states and REM sleep are quite similar (Buzsaki, 2002; Montgomery et al., 2008; Fig. 1).

One of the noticeable differences between REM sleep and waking theta states is the theta frequency; theta pacing is faster during waking than REM sleep (Montgomery et. al., 2008). Moreover, theta and gamma synchrony between the DG and CA3 is higher during REM sleep than waking theta states. In contrast, gamma power in CA1 and CA3–CA1 gamma coherence significantly decrease during REM sleep when compared with waking theta states (Montgomery et al., 2008). Furthermore, during phasic bursts of activity in REM sleep, theta and gamma synchrony among the DG, CA3, and CA1 regions as well as the firing of CA1 pyramidal neurons transiently and significantly increase (Montgomery et al., 2008). Therefore, it has been hypothesized that information processing within the DG and the DG–CA3 network is enhanced but CA3–CA1 coordination is limited during REM sleep with brief windows of opportunity to synchronize the hippocampal tri-synaptic loop and increase output to cortical targets during phasic bursts of activity in REM sleep (Montgomery et al., 2008).

Another difference between waking theta states and REM sleep involves the preferred theta phase of CA1 pyramidal neurons (Poe et al., 2000; Mizuseki et al., 2011). It was previously shown that CA1 pyramidal cells active in novel places fire at the troughs of theta waves during both exploration and subsequent REM sleep, whereas cells active in familiar places during waking exhibit a reversal of firing phase, i.e., they discharge at the troughs of theta during exploration and fire at the peaks of theta waves during subsequent REM sleep (Poe et al., 2000). A recent study could not detect a noticeable effect of familiarity on theta phase preference (Mizuseki et al., 2011). Instead, it was found that there is a strong correlation between the preferred theta phase and position of the soma of CA1 pyramidal neurons relative to the pyramidal cell layer (Mizuseki et al., 2011; Fig. 4A). Accumulating evidence indicates that deep and superficial pyramidal neurons in the CA1 have distinct morphologies (Schaffer, 1892; Lorente de Nó, 1934; Bannister and Larkman, 1995), timing of neurogenesis (Bayer, 1980), zinc content (Slomianka, 1992), molecular expression (Baimbridge et al., 1991; Thompson et al., 2008; Dong et al., 2009; Cembrowski et al., 2016), anatomical connectivity (Slomianka et al., 2011; Deguchi et al., 2011; Kohara et al., 2014; Lee et al., 2014; Li et al., 2017b), and physiological functions (Stark et al., 2014; Valero et al., 2015; Maroso et al., 2016; Danielson et al., 2016; Geiller et al., 2017a; Geiller et al., 2017b; Li et al., 2017b). Superficial pyramidal neurons, whose cell bodies are closer to the stratum radiatum than to the stratum oriens, fire at the trough of theta oscillations during both waking theta states and REM sleep (Mizuseki et al., 2011; Fig. 4). In contrast, deep pyramidal cells, whose cell bodies are located closer to stratum oriens than to stratum radiatum, fire at the trough of theta during waking theta states but shift their firing phase to the peak of theta during REM, which is the phase when EC3 input to the CA1 is maximum (Mizuseki et al., 2011; Fig. 4).

as the difference between firing rates of two brain states divided by the sum. Note the unique constellations of rate shifts in principal cells and interneurons across states. Direction of firing rate changes in upstream principal neurons (e.g., EC2 and EC3) does not predict direction of firing rate changes in downstream targets (CA1, CA3, and DG). Note that the brain-state-related firing rate changes of principal cells (top) and interneurons (bottom) within the same layer were mostly uncorrelated.

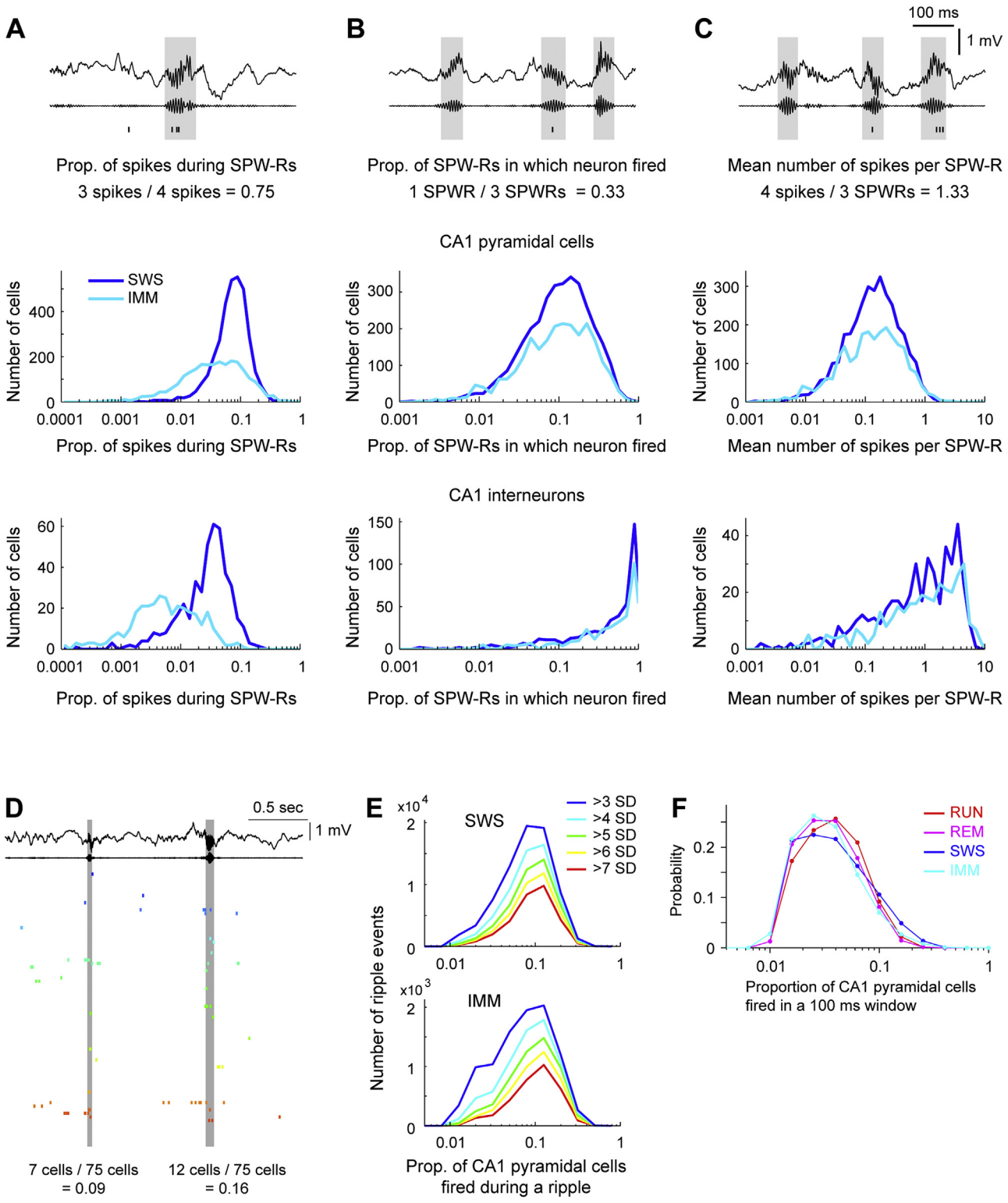

Fig. 6. Distribution of SPW-R-related firing patterns and magnitude of population synchrony.
(A–C) Top, example of wide-band and ripple-band filtered (140–230 Hz) signals (positive polarity is up), and spiking activity of a CA1 principal neuron. Ripple epochs are shadowed. Middle and bottom, distribution of CA1 pyramidal neurons (middle) and interneurons (bottom) during SWS and IMM.
(A) The proportion of spikes during SPW-Rs, defined as the number of spikes during SPW-Rs divided by the number of all the spikes during SWS/IMM.
(B) The proportion of SPW-Rs in which each neuron fired, calculated as the fraction of SPW-Rs in which the neuron fired at least once.
(C) The mean number of spikes per SPW-R. The number of spikes within SPW-Rs was divided by the total number of SPW-Rs in SWS/IMM.
(D and E) Skewed distribution of the magnitude of population synchrony during SPW-Rs.
(D) Wide-band and ripple-band (140–230 Hz) filtered LFP (top, positive polarity is up) and spiking activity of 75 simultaneously recorded CA1 pyramidal cells. Two SPW-R events with relatively low (0.09) and high (0.16) fractions of neurons firing synchronously during SPW-Rs.
(E) Distribution of the population synchrony of CA1 pyramidal cells' firing during SPW-Rs using various ripple detection thresholds (from small [>3 SD] to large [>7 SD]) during SWS and IMM.
(F) Distribution of the population synchrony, measured as a proportion of CA1 pyramidal cells fired in a 100 ms sliding window, in different brain states.
(A–F) Reproduced from Mizuseki and Buzsaki (2013) under the terms of the Creative Commons Attribution License.

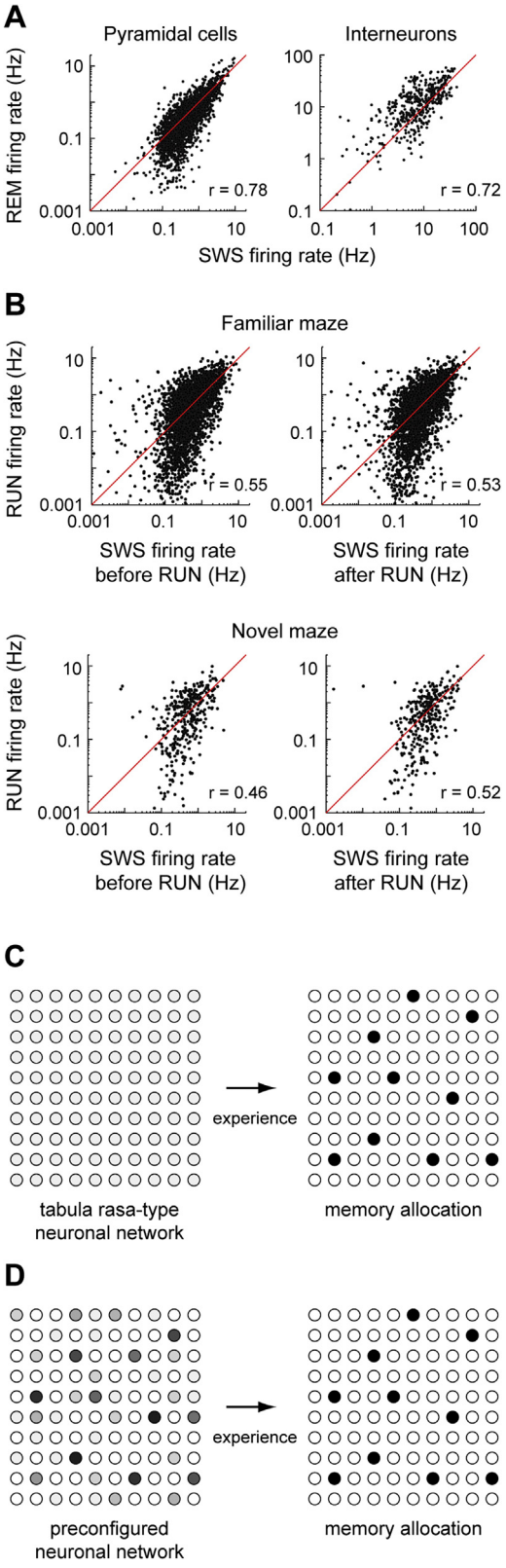

Fig. 7. Preserved firing rates of hippocampal neurons across brain states and distinct environments.
(A) Comparison of firing rates of the same CA1 pyramidal neurons (left) or interneurons (right) during SWS and REM sleep. Each dot represents a single neuron. (B) Firing-rate comparison between RUN in a familiar maze and SWS in the home cage either before or after the maze session (top), and comparison between firing rates during exploration of a novel maze (RUN) and SWS in the home cage either before or after the maze session (bottom). Each dot represents a single CA1 pyramidal cell. (A and B) R values are the correlation coefficients of log firing rates. All correlations were significant ($p < 0.00001$). Red lines, identity lines. (C and D) Two hypothesized mechanisms of memory allocation. Each circle represents a single neuron. Activity is coded in gray scale. Black color; active high-firing neurons. White; quiet low-firing neurons. (C) 'Tabula rasa-type neuronal network' hypothesis states that the memory of a new experience is allocated to randomly selected neurons of a homogenous cell population. (D) 'Preconfigured neuronal network' hypothesis states that some neurons are already active and others are relatively silent before any experience. When we have a new experience, memory is preferentially allocated to highly active neurons in the network at the time.
(A) and (B) reproduced from Mizuseki and Buzsaki (2013) under the terms of the Creative Commons Attribution License.

The hippocampal CA1 region is under the dual control of direct input from the EC3 and CA3. Compared with waking theta states, the firing rate of EC3 principal neurons increases during REM sleep, whereas the firing rate of CA3 pyramidal neurons decreases (Mizuseki et al., 2012; Mizuseki et al., 2013; Schomburg et al., 2014; Fig. 5E). Gamma power in the target layers is a reliable indicator of the firing rates of their upstream neurons (Schomburg et al., 2014; Berenyi et al., 2014; Fernandez-Ruiz et al., 2017). Consistent with the firing rate changes in the CA3 and EC3 between waking theta states and REM sleep, low frequency gamma oscillations (30–60 Hz) in the stratum radiatum, whose power is maximum at the descending phase of the CA1 pyramidal cell layer theta oscillations, decreases during REM sleep when compared with the waking theta state (Schomburg et al., 2014; Fernandez-Ruiz et al., 2017; Fig. 4B and C). In contrast, middle frequency gamma oscillations (60–100 Hz) in the stratum lacunosom-moleculare, whose power is maximum at the peak of CA1 pyramidal layer theta oscillations, increase during REM sleep when compared with waking theta states (Schomburg et al., 2014; Fernandez-Ruiz et al., 2017; Fig. 4B and C). Because EC3 principal neurons preferentially fire at the peak of theta and CA3 pyramidal neurons preferentially fire at the descending phase during both REM sleep and waking theta states (Mizuseki et al., 2011; Oliva et al., 2016b), it has been suggested that deep pyramidal cells, relative to superficial pyramidal cells, in the CA1 area are more strongly influenced by direct EC3 input (Mizuseki et al., 2011; Fernandez-Ruiz et al., 2017; Fig. 4B and C). Consistent with this hypothesis, deep cells, relative to superficial cells, are more strongly phase-locked by slow oscillations, associated with UP and DOWN states of cortical neurons, in SWS, suggesting that deep cells are under stronger control of direct EC3 input (Mizuseki et al., 2011).

Deep and superficial CA1 pyramidal neurons fire at the same theta phase during waking theta states and fire at different theta phases during REM sleep, thus influencing their targets jointly or differentially depending on the brain state. The behavioral importance of such state-dependent integration and segregation of neuronal information by theta oscillations remains unknown (Mizuseki et al., 2011).

5. Distribution of firing rates during distinct brain states

The dominant communication across neurons occurs via spikes. Despite the central role of spiking activity in transmitting information, only limited data about the firing rates of an unbiased neuronal population in intact networks are available. Moreover, it is largely unknown how the firing rates of individual neurons and their distribution in a given brain region change as a function of brain states and situations. A recent report shows that the firing rate of principal neurons in the hippocampus and entorhinal cortex shows a skewed distribution with a heavy tail and typically follows a lognormal-like distribution in all brain states (Mizuseki and Buzsaki, 2013; Fig. 5). The firing rate distribution of principal neurons is narrowest during SWS (Fig. 5A–D). In the hippocampus and entorhinal cortex, firing rates of interneurons also show a skewed distribution, but the skewness is generally higher in principal neurons than in

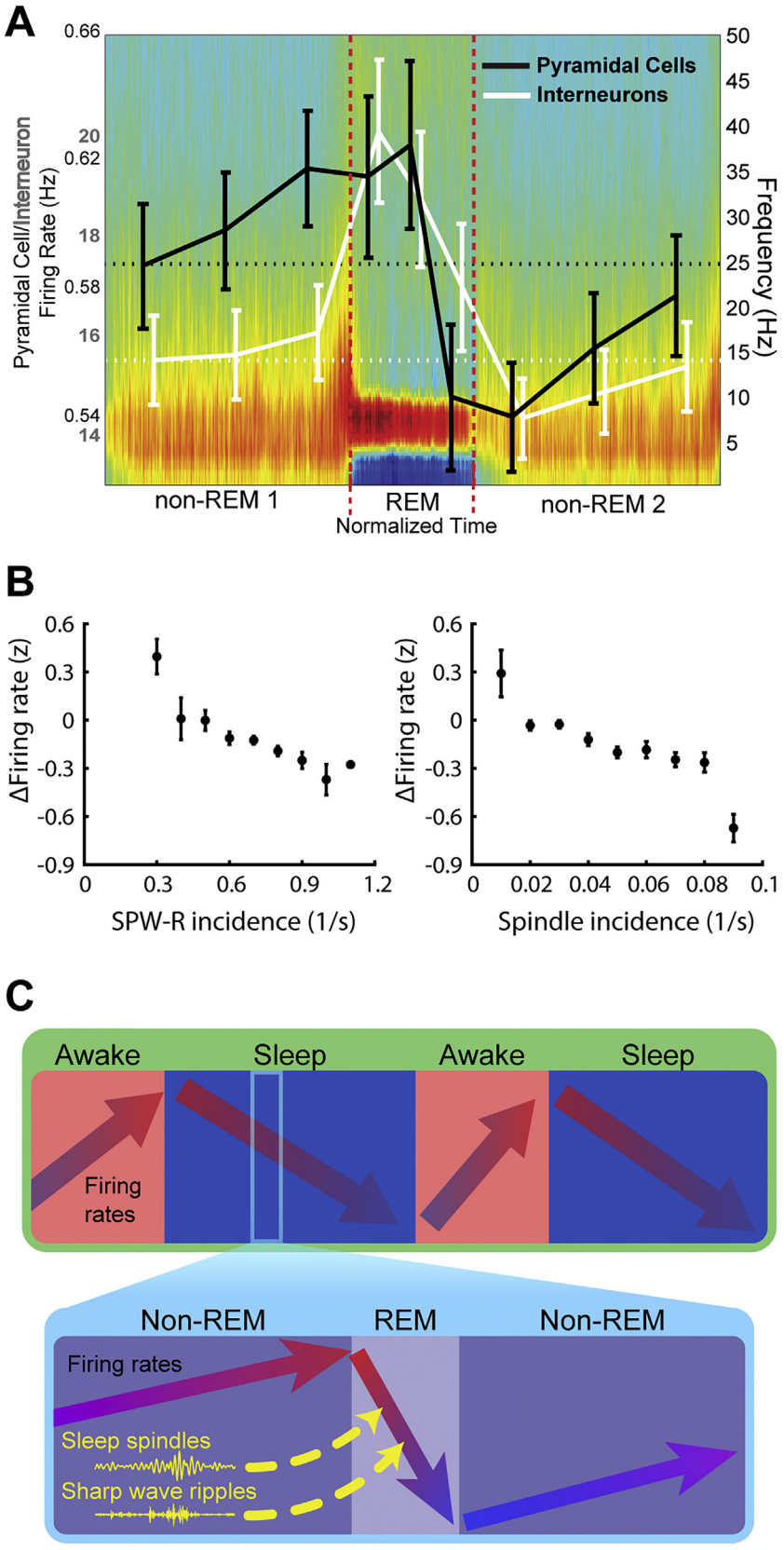

Fig. 8. Regulation of firing rates across sleep/wake cycles.
(A) Time-normalized power spectra of adjacent non-REM$_n$/REM/non-REM$_{n+1}$ episodes (mean of n = 45 non-REM$_n$/REM/non-REM$_{n+1}$ cycles) and corresponding firing rates (±SEM) of pyramidal cells (black) and interneurons (white) shown within thirds of non-REM and REM episodes. Note that firing rates gradually increase within non-REM episodes and rapidly decrease within REM episodes, resulting in a net decrease in firing rate across sleep. Horizontal lines represent mean rates at the beginning of the non-REM$_n$/REM/non-REM$_{n+1}$ cycle. (B) Incidence rates of SPW-Rs (left) and sleep spindles (right) in non-REM$_n$ are predictive of changes in firing rates across non-REM$_n$/REM/non-REM$_{n+1}$ sequences. A total of 306 sequences were sorted into 10 groups based on the incidence of SPW-Rs (left) or spindles (right), and the mean and SEM

interneurons (Fig. 5A–D). Mean and peak firing rates within place fields of CA1 and CA3 pyramidal neurons also follow lognormal-like patterns, indicating that only a small fraction of place cells fire at a high firing rate, whereas most place cells are relatively quiet even in their place fields (Mizuseki and Buzsaki, 2013). In addition to firing rate, burst probability also shows a lognormal-like distribution with a handful of super-bursters and the majority of neurons bursting only occasionally (Mizuseki and Buzsaki, 2013). Such a skewed distribution of hippocampal principal neurons creates a rate spectrum with a wide dynamic range spanning from a majority of very slow-firing neurons to a small fraction of fast-firing cells (Mizuseki and Buzsaki, 2013; Panas et al., 2015; Slomowitz et al., 2015). A small subnetwork of highly active and stable neurons may endow neuronal networks with the flexibility to continuously remodel without compromising stability and function (Panas et al., 2015).

A skewed distribution of firing rate prevails in the neocortex as well. Recent quantifications of the firing patterns of neocortical principal neurons in the intact brain have shown that both mean spontaneous and stimulus-evoked firing rates of individual neurons span at least three orders of magnitude and that their distributions obey a long-tailed, typically lognormal pattern (Buzsaki and Mizuseki, 2014; Battaglia et al., 2005; Shafi et al., 2007; Hromadka et al., 2008; O'Connor et al., 2010; Peyrache et al., 2012; Wohrer et al., 2013; Schwindel et al., 2014; Hengen et al., 2016; Watson et al., 2016). The firing rate of individual neurons in lumbar spinal circuits of turtle during rhythmic movements also follows lognormal distribution (Petersen and Berg, 2016). Although cataloging rate distributions in multiple neuronal types in various regions of the nervous system will require further data collection, the existing data obtained from various brain regions clearly indicate a substantial deviation from Gaussian rate distribution (Buzsaki and Mizuseki, 2014). Theoretical works suggest that skewed populations have beneficial features for network performance (Izhikevich et al., 2004; Gilson and Fukai, 2011; Teramae et al., 2012; Ikegaya et al., 2013; Hiratani et al., 2012; Panas et al., 2015). Network hubs composed of high-firing active neurons (Yassin et al., 2010) may facilitate information transfer between subnetworks (Jahnke et al., 2014; Shimono and Beggs, 2015).

Interestingly, brain state changes differentially affect EC and hippocampal neurons. The firing rates of EC and hippocampal principal cells increase together in waking theta states relative to waking immobility, whereas they change in opposite directions between REM and SWS (Mizuseki and Buzsaki, 2013; Fig. 5E). Thus, brain-state-related firing rate changes of principal cells in upstream regions are not predictive of discharge rate changes in the downstream region (Mizuseki and Buzsaki, 2013; Fig. 5E). Similarly, brain-state-related firing rate changes of principal neurons and interneurons within the same layer/region are mostly uncorrelated, illustrating that brain state changes can drastically alter the balance between excitation and inhibition in a layer/region-specific manner (Mizuseki and Buzsaki, 2013; Fig. 5E). Such changes may be brought about by neuromodulatory systems acting at various targets (McCormick, 1992; Freund, 2003) and may control the routing of information flow within the circuit.

6. Distribution of SPW-R-related firing patterns and magnitude of population synchrony

In addition to the firing rates of single neurons, the participation of CA1 pyramidal neurons in SPW-Rs also shows a lognormal-like pattern (Mizuseki and Buzsaki, 2013; Omura et al., 2015; Malvache et al., 2016; Fig. 6A–C). A small fraction (~1%) of CA1 pyramidal cells dominate by participating in 50% of SPW-R events, whereas half of all neurons fire in <10% of SPW-Rs (Mizuseki and Buzsaki, 2013; Fig. 6A). Importantly, a small minority of active neurons contributing to SPW-R events with a higher probability in a given day are more likely to remain active across consecutive days (Malvache et al., 2016). The proportion of spikes during SPW-Rs (Fig. 6A) is negatively correlated with the overall spike rate, indicating that slow-firing CA1 pyramidal cells emit action potentials predominantly during SPW-R events (Mizuseki and Buzsaki, 2013), when the overall excitability of the EC-hippocampal networks is high (Csicsvari et al., 2000).

The magnitude of population synchrony, as measured by the proportion of CA1 pyramidal cells that fire during a SPW-R event, also shows a lognormal-like distribution (Mizuseki and Buzsaki, 2013; Nadasdy et al., 1999; Taxidis et al., 2013; Omura et al., 2015; Fig. 6D and 6E). Such a skewed distribution of population synchrony is not constrained to SPW-Rs but prevails during hippocampal theta oscillations as well (Mizuseki and Buzsaki, 2013; Buzsaki and Mizuseki 2014; Fig. 6F). Further, the magnitude of the correlation coefficient between neuron pairs also follows a lognormal-like distribution (Mizuseki and Buzsaki, 2014; Buzsaki and Mizuseki, 2014). These findings suggest the existence of a general rule in neuronal synchrony. The behavioral importance of skewed distributions of magnitude of neuronal synchrony remains unknown.

7. Firing rate correlations across brain states and testing conditions

Although a given neuron fires at different rates in different brain states, the firing rates of the same neuron are robustly and positively correlated across brain states (waking theta states, IMM, SWS, and REM sleep) (Hirase et al., 2001; Mizuseki and Buzsaki, 2013; Fig. 7 A). Furthermore, the mean firing rates of the same neuron in different situations during waking exploration remain positively correlated (Mizuseki and Buzsaki, 2013; but see Leutgeb et al., 2004). Namely, the same subset of neurons tends to be active in different environmental contexts and mazes when firing rates are plotted on a log scale (Mizuseki and Buzsaki, 2013; Buzsaki and Mizuseki, 2014). Recent evidence suggests that low- and high-firing neurons display different plasticity and dynamics. Highly active hippocampal neurons are more likely to be assigned place fields (Mizuseki and Buzsaki, 2013; Rich et al., 2014; Alme et al., 2014; Buzsaki, 2015b; Witharana et al., 2016). The coexistence of high-firing rigid neurons and low-firing plastic neurons may be beneficial for both system stability and mnemonic function (Grosmark and Buzsaki, 2016).

A relatively "fixed" firing rate of individual neurons is also reported in the neocortex (Buzsaki and Mizuseki, 2014; Okun et al., 2016), and overall within-cell variability in firing rate over time is smaller than the variability of mean firing rates over the population. In mouse visual cortex, firing rates of regular spiking neurons differ by several orders of magnitude, and after recovery from long-term perturbation by visual deprivation, a given neuron returns to its firing rate set-point (Hengen, 2016). Together, these observations suggest that the skewed distribution of intrinsic firing rates reflects a fundamental biophysical heterogeneity in neuronal populations, and that the skewed distribution is actively maintained by homeostatic mechanisms (Hengen et al., 2013; Hengen, 2016).

of firing rate changes in each group are shown. (C) Schematic diagram of firing rate changes across wake/sleep cycles (top) and within sleep (bottom). Overall, firing rates increase during waking and decrease during sleep. Within sleep, firing rates gradually increase during non-REM sleep and rapidly decrease during REM sleep. Importantly, SPW-Rs and sleep spindles occur during non-REM sleep and their incidences predict firing rate decreases during subsequent REM sleep. (A) Reproduced from Grosmark et al. (2012); (B) and (C) reproduced from Miyawaki and Diba (2016) with permission from Elsevier.

Furthermore, it has been reported that even novel experiences do not have a drastic effect on the firing rate of individual hippocampal neurons. When an animal is moved from a familiar maze to a novel maze, the log firing rates of individual hippocampal CA1 neurons remain significantly positively correlated between the two situations (Mizusekie and Buzsaki, 2013). The log firing rates of individual neurons during SWS in the home cage and those during subsequent exploration in a novel environment show a reliable positive correlation, demonstrating that log firing rates remain relatively preserved across situations that involve changes in brain states, environmental input, and novelty (Mizuseki and Buzsaki, 2013; Fig. 7B). Thus, the mean firing rate of individual neurons is relatively fixed, at least for a short time (~within a day) (Mizuseki and Buzsaki, 2013). In addition to the mean firing rate of individual cells, the sequence of hippocampal neuronal activity is relatively "fixed" (Dragoi and Tonegawa, 2011; Villette et al., 2015; Malvache et al., 2016). The neuronal trajectory existing in internally-generated spontaneous activity before a new experience is statistically similar to that observed during a subsequent behavioral experience (Dragoi and Tonegawa, 2011; but see Silva et al., 2015), which likely reflects constraints by anatomical connectivity among neurons (Luczak et al., 2009; Dragoi and Tonegawa, 2014).

The observed relatively fixed firing rate scenario may have implications in mechanisms of memory. One extreme hypothesis regarding memory allocation postulates that the memory of a new experience is allocated to randomly selected neurons of a homogenous cell population in a tabula rasa-type neuronal network (Fig. 7C). However, we suggest that the observed relatively fixed firing rate of individual neurons supports an alternative opinion (Fig. 7D). In this model, before any experience, a preconfigured network pattern exists where some neurons are already active and others are relatively silent. When we have a new experience, memory is preferentially allocated to highly active neurons in the network at the time. In line with this hypothesis, in the lateral amygdala, eligible neurons are recruited to a memory trace based on their relative CREB activity and neuronal excitability at the time of learning (Han et al., 2007; Zhou et al., 2009; Yiu et al., 2014). The postulated preconfigured network pattern may change at a slow time-scale (e.g., days, weeks, or months). Recent calcium imaging in the CA1 reported that a fraction of place cells is active at the same location in the same maze across days, but a significant fraction of cells' place fields appears and disappears in the same maze over days (Ziv et al., 2013; Rubin et al., 2015). Furthermore, overlap of active neuronal ensembles in two contexts is higher if the timing at which the animal is exposed to the environment/context is closer, which may be the mechanism by which memories that are acquired near in time are linked (Cai et al., 2016; Rashid et al., 2016). The gradual change of preconfigured network patterns at longer time scales (e.g., days, weeks, or months) may be the mechanism by which memories of similar experiences at different times can be stored in different constellations of neuronal activity. The speed of gradual changes in a preconfigured neuronal network may be different in different hippocampus subfields (Mankin et al., 2012; Mankin et al., 2015) and between different memory structures, such as hippocampus vs. amygdala (Cai et al., 2016; Rashid et al., 2016; Eichenbaum, 2016; Manns et al., 2007).

8. Regulation of neuronal firing rate by sleep

The influential synaptic homeostasis hypothesis (SHY) postulates that synaptic potentiation during waking increases the firing rates of neuronal populations, and homeostatic mechanisms that globally downscale all synapses decrease the firing rates to baseline during subsequent sleep (Tononi and Cirelli, 2006; Olcese et al., 2010; Tononi and Cirelli, 2014; de Vivo et al., 2017; Diering et al., 2017). Consistent with the SHY, it has been reported that the firing rate of neurons in the rat barrel cortex increases during waking and decreases during sleep in parallel with the decreasing amplitude of slow waves (Vyazovskiy et al., 2009).

Similarly, hippocampal neurons decrease firing activity over sleep and increase upon waking across the circadian cycle (Miyawaki and Diba, 2016; Fig. 6C). Interestingly, higher- and lower-firing cells change their firing differently across sleep/wake cycles. Lower-firing neurons in the hippocampus decrease more during sleep. On the other hand, moderate firing cells in the hippocampus increase the most during wakefulness (Miyawaki and Diba, 2016). Recently it was also reported that in the neocortex, excitabilities of low- and high-firing neurons are modulated differentially during sleep (Watson et al., 2016; Levenstein et al., 2017).

Importantly, the neuronal firing rate in the hippocampal CA1 field gradually increases within SWS episodes but rapidly decreases during interleaved REM episodes, resulting in a net decrease in firing rate across sleep (Grosmark et al., 2012; Fig. 8A and C). The magnitude of decrease in firing rate between SWS epochs is correlated with the power of theta oscillations during interleaved REM epochs; therefore, it has been proposed that an important role of REM sleep is to downregulate the firing rate of neurons, at least in the hippocampal CA1 region (Grosmark et al., 2012; Fig. 8A). It was recently reported that the incidence of sleep spindles and SPW-Rs during SWS correlates with a decrease in the firing rate of hippocampal CA1 pyramidal neurons during subsequent REM sleep (Miyawaki and Diba, 2016; Fig. 8B). Interestingly, the correlation between sleep spindle/SPW-R incidence and decrease of firing rate is significantly stronger than the correlation between theta power during REM sleep and decreases of firing rate; however, firing rate decreases during REM sleep. Based on these observations, it has been proposed that the homeostatic changes in hippocampal firing are initiated by spindles and SPW-Rs during SWS and implemented during subsequent REM sleep (Miyawaki and Diba, 2016; Fig. 8C).

9. Summary and future perspectives

In summary, we discussed the following points regarding hippocampal information processing across sleep/wake cycles.

(1) Neuronal synchrony is much lower during theta states than non-theta states.
(2) During waking theta states, principal neurons in monosynaptically connected upstream and downstream regions in the entorhinal–hippocampal loop fire with long theta phase offsets and temporal delays (typically half of a theta cycle, or >60 ms), suggesting that the activity of each region is not simply inherited from upstream regions but is mainly coordinated by local circuit mechanisms. In contrast, SPW-R-related synchronous activity is transmitted immediately from the hippocampus to the downstream entorhinal cortex during non-theta states.
(3) Hippocampal CA1 is under the dual control of direct input from the EC3 and CA3. During REM sleep, pyramidal neurons in deep sublayers of the CA1 area, relative to those in superficial sublayers, are more strongly influenced by direct EC3 input.
(4) The firing rate of principal neurons in the hippocampus and entorhinal cortex follows a lognormal-like distribution in all brain states.
(5) The distribution of SPW-R-related firing patterns of individual neurons and the distribution of the magnitude of population asynchrony in the CA1 area follow a lognormal form.
(6) The firing rate of individual neurons in different brain states and conditions are significantly positively correlated. In other words, the firing rates of individual neurons are relatively fixed, at least in a short time period (~within a day).

(7) Firing rates of high- and low-firing neurons are differentially regulated by sleep. Homeostatic changes in hippocampal firing are initiated by spindles and SPW-Rs during SWS and implemented during subsequent REM sleep.

A lot of intriguing questions regarding hippocampal information processing across sleep/wake cycles remain. We suggest that it is important to address the following questions in the future.

(1) Sleep is hypothesized to mediate both memory consolidation and homeostatic functions. How does sleep implement both the selective plasticity necessary for memory consolidation and general homeostatic plasticity required to maintain a functioning neural system?
(2) What are the intrinsic and network mechanisms that maintain the skewed distribution of mean firing rates of individual neurons, and which brain states (waking theta states, SWS, REM sleep, etc.) support these mechanisms?
(3) Are sleep-dependent changes in firing rate and synaptic weight in the hippocampus different from those in other brain regions, such as the neocortex, amygdala, and subcortical regions? If so, what mechanisms underlie regional differences?
(4) How long do individual neurons maintain their rank in the firing rate? Is there a brain-region-specific "life-time" of the preconfigured neuronal network?

Conflict of interest

The authors declare that they have no conflict of interest.

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