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Hippocampal coupling with cortical and subcortical structures in the context of memory consolidation

Ivan Skelin[a,b,*], Scott Kilianski[b], Bruce L. McNaughton[a,b]

[a] Canadian Centre for Behavioural Neuroscience, The University of Lethbridge, Lethbridge, AB T1K 3M4, Canada
[b] Department of Neurobiology and Behavior, University of California, Irvine, CA 92697, USA

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ABSTRACT

Memory consolidation is a gradual process through which episodic memories become incorporated into long-term 'semantic' representations. It likely involves reactivation of neural activity encoding the recent experience during non-REM sleep. A critical prerequisite for memory consolidation is precise coordination of reactivation events between the hippocampus and cortical/subcortical structures, facilitated by the coupling of local field potential (LFP) oscillations (slow oscillations, sleep spindles and sharp wave/ripples) between these structures. We review the rapidly expanding literature on the qualitative and quantitative aspects of hippocampal oscillatory and neuronal coupling with cortical/subcortical structures in the context of memory reactivation. Reactivation in the hippocampus and cortical/subcortical structures is tightly coupled with sharp wave/ripples. Hippocampal-cortical/subcortical coupling is rich in dimensionality and this dimensionality is likely underestimated due to the limitations of the current methodology.

1. Introduction

Prominent learning theories postulate that memory encoding occurs via an interaction between a 'fast learning' hippocampal network, which underlies episodic memory, and a 'slow learning' neocortical network which extracts the statistical regularities of the world (Buzsáki, 1989; Marr, 1971; McClelland, McNaughton, & O'reilly, 1995). The hippocampus receives convergent input from polymodal association cortices (Fig.1) through the superficial layers of medial entorhinal cortex (MEC) and projects to cortical targets either directly or through the deep layers of MEC (Amaral & Witter, 1989; Swanson & Kohler, 1986). Both the hippocampus and neocortex are reciprocally connected with subcortical areas involved in appetitive and aversive learning, such as the amygdala and nucleus accumbens (Khan and Shohamy, 2013; Stein et al., 2007). They also receive inputs from multiple neuromodulatory systems (Lisman & Otmakhova, 2001), which regulate the communication between structures (Benchenane et al., 2010; Goto & O'Donnell, 2001; Roopun et al., 2010) and the hippocampal processing of neocortical inputs during behavior, possibly affecting selection for permanent memory encoding (Redondo & Morris, 2011). Hippocampal connections with neocortical and subcortical structures show a distinct septo-temporal gradient, with the temporal (ventral, anterior in primates) segment of hippocampus connected to prefrontal cortices and medial parts of amygdala/ventral striatum, while more septal (intermediate/dorsal, posterior in primates) segments are connected with progressively more caudal parts of cingulate cortices and lateral parts of amygdala/ventral striatum (reviewed by Strange, Witter, Lein, & Moser, 2014). The combination of recurrent connectivity in hippocampal subfield Cornu Ammonis 3 (CA3) and highly plastic synaptic connections within and between the different hippocampal subfields (Andersen, 2007) enables fast information storage in a large combinatorial space of the hippocampal connectivity matrix (Treves & Rolls, 1994). Furthermore, based on the physiological (i.e. inducible synaptic plasticity in the form of long term potentiation (LTP)) and anatomical characteristics (i.e. reciprocal connectivity with the neocortex), it has been theorized that the hippocampus can store an index to the patterns of neocortical activity representing a particular mnemonic experience or episode. Thus, reactivation of a given hippocampal activity pattern would, in turn, reactivate the indexed neocortical sequence and lead to successful memory retrieval (memory indexing theory; Teyler & DiScenna, 1986).

Whereas the hippocampus has been implicated in rapid memory encoding and retrieval of recent memories, the neocortex appears to play a more gradual and longer-term role in memory processing.

Abbreviations: ACC, anterior cingulate cortex; DHipp, dorsal hippocampus; LFP, local field potential; MFB, median forebrain bundle; non-REM, non-rapid eye movement; PFC, prefrontal cortex; PPC, posterior parietal cortex; RSC, retrosplenial cortex; SO, slow oscillations; SP, sleep spindles; SWR, sharp wave/ripple; VHipp, ventral hippocampus; VS, ventral striatum; VTA, ventral tegmental area

* Corresponding author at: Canadian Centre for Behavioural Neuroscience, The University of Lethbridge, Lethbridge, AB T1K 3M4, Canada.
E-mail addresses: iskelin@uci.edu (I. Skelin), skilians@uci.edu (S. Kilianski), brucemcn@uci.edu (B.L. McNaughton).

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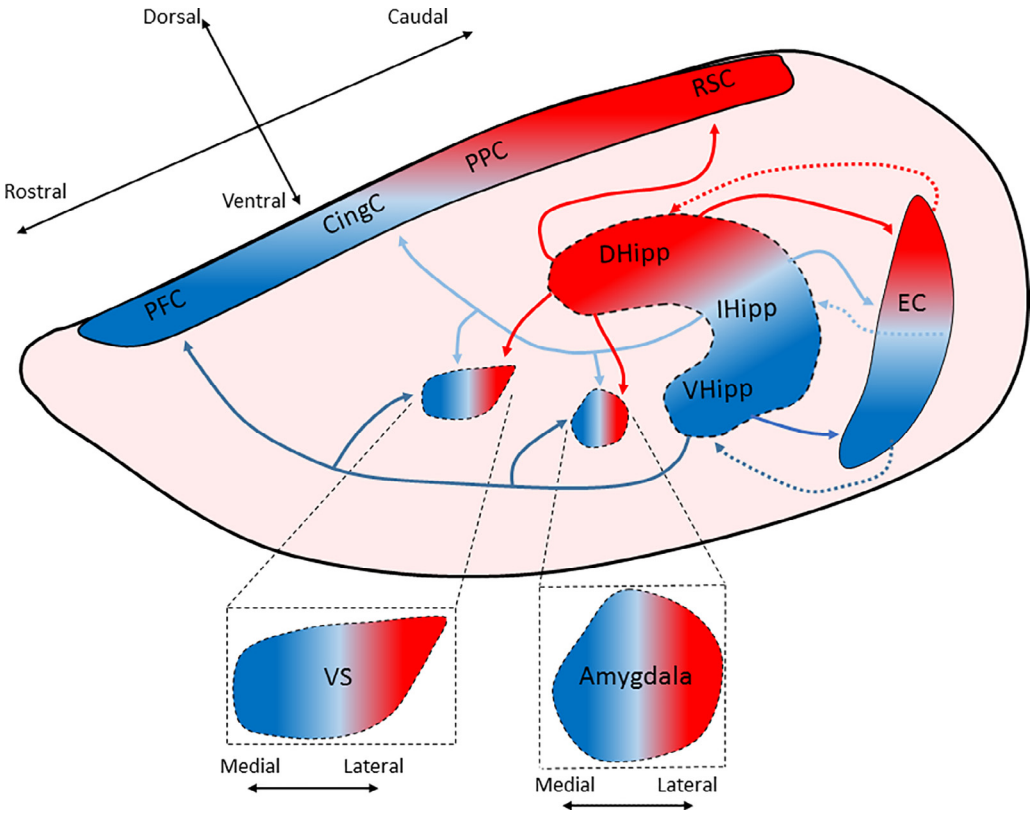

Fig. 1. Outline of major afferent and efferent hippocampal connections (based on Strange et al., 2014). Arrows denote the direction of projections. The red-to-blue gradient represents the connectivity of each structure to dorsal (posterior) or ventral (anterior) hippocampus, respectively. The dorsal (posterior) hippocampus (DHipp) is connected with posterior neocortical areas, such as retrosplenial (RSC) and posterior parietal cortices (PPC), while the ventral (anterior) hippocampus (VHipp) is connected with prefrontal (PFC) and more anterior parts of cingulate cortices (CingC). DHipp is predominantly connected with medial and VHipp with lateral parts of amygdala and ventral striatum (VS). Most of DHipp input and output connections are relayed through dorsolateral portions of both medial and lateral entorhinal cortex (MEC and LEC), while most of VHipp connections are relayed through ventromedial MEC and LEC. Superficial layers of EC receive input from hippocampus (solid lines), while deep layers of EC project to hippocampus (dotted lines).

Cortical representations of different aspects of experience are stored in widely distributed areas, characterized by sparse connectivity over longer anatomical distances and denser connectivity and functional homogeneity within small patches of neocortex, often referred to as "modules" (Felleman & Van Essen, 1991; Mountcastle, 1978; Tsunoda, Yamane, Nishizaki, & Tanifuji, 2001). The hub-like anatomical position of hippocampus allows it to orchestrate a wide range of cortical and subcortical networks and thus link various aspects of a given experience that are represented in distributed neocortical modules. In this way, activity in the hippocampus can trigger the reactivation of neocortical patterns resulting in the retrieval of a memory in which the various aspects of the memory are coherently recalled (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011; Teyler & DiScenna, 1986). It has been thought that, over time and/or with sufficient repetition, memory retrieval that is initially hippocampus-dependent can become hippocampus-independent (Frankland & Bontempi, 2005; Squire, 1992). However, more recent studies question this simple view (see Sutherland, Sparks and Lehmann (2010) and Ocampo et al. (2017)), and it is becoming more widely accepted that most memories never become independent of hippocampus. Rather, as was evident already in the classic case of HM, what is independent of the hippocampus is the semantic knowledge (categories, schemas etc.) that is constructed from the amalgamation of many episodic experiences.

The main proposed mechanism supporting this shift in hippocampal-dependence and recoding of memory is hippocampal-cortical interaction during offline periods, such as sleep and quiet rest, when the brain is largely isolated from external sensory interference (Buzsáki, 1989; Marr, 1971; McNaughton 2010). During these periods, synchronized memory trace reactivation occurs in hippocampus and multiple cortical/subcortical structures, facilitating the formation and/or rearrangement of horizontal connections between neuronal populations encoding different aspects of experience, possibly through plasticity mechanisms depending on relative timing of pre- and postsynaptic activation (Levy & Steward, 1983). Different plasticity mechanisms are proposed to operate on a variety of timescales, ranging from tens of milliseconds (Dan & Poo, 2004; Markram, Lübke, Frotscher, & Sakmann, 1997) to several seconds (Bittner, Milstein, Grienberger, Romani, & Magee, 2017). The latter plasticity rule, known as behavioral timescale synaptic plasticity (BTSP; Bittner et al., 2017), was recently demonstrated in vivo, accounting for a rapid formation of place fields during behavior. Hippocampal and neocortical memory reactivation occurs mostly during non-REM sleep (Johnson, Euston, Tatsuno, & McNaughton, 2010; Nadasdy, Hirase, Czurkó, Csicsvari, & Buzsáki, 1999; Wilson & McNaughton, 1994), either emerging from the intrinsic dynamics of hippocampal or neocortical networks or biased by subcortical inputs (de Lavilléon, Lacroix, Rondi-Reig, & Benchenane, 2015). Alternatively, as horizontal connectivity among neocortical modules is altered, neocortical modules, with their dense recurrent connectivity, can likely act as attractor networks allowing them to reactivate stored memory traces and trigger subsequent reactivation in other areas (Rolls, 2010). The shift in dependence of memories from hippocampal to the neocortical is accompanied by removal of contextual background, extraction of statistical regularities and incorporation into schema-like relational network, ultimately manifesting in the acquisition of semantic memory or "knowledge" (Takehara-Nishiuchi & McNaughton, 2008; McClelland et al., 1995; Tse et al., 2007; McNaughton, 2010). It should be noted that memory reactivation also occurs during behavioral immobility periods (awake reactivation; Jadhav, Kemere, German, & Frank, 2012). Awake memory reactivation differs from sleep reactivation in several aspects, such as the relative timing of hippocampal-cortical communication (Tang, Shin, Frank, & Jadhav, 2017), and it has a possible role in decision-making (Jadhav et al., 2012). The focus of the present review is on hippocampal-cortical/subcortical interactions during non-REM sleep; readers interested in awake memory reactivation are referred to recent reviews covering that topic (Atherton, Dupret, & Mellor, 2015; Roumis & Frank, 2015).

Memory encoding and consolidation are characterized by distinct network activity modes. During behavior (encoding phase), the hippocampal local field potential (LFP) is dominated by theta oscillations (5–10 Hz), which modulate the firing probability of hippocampal

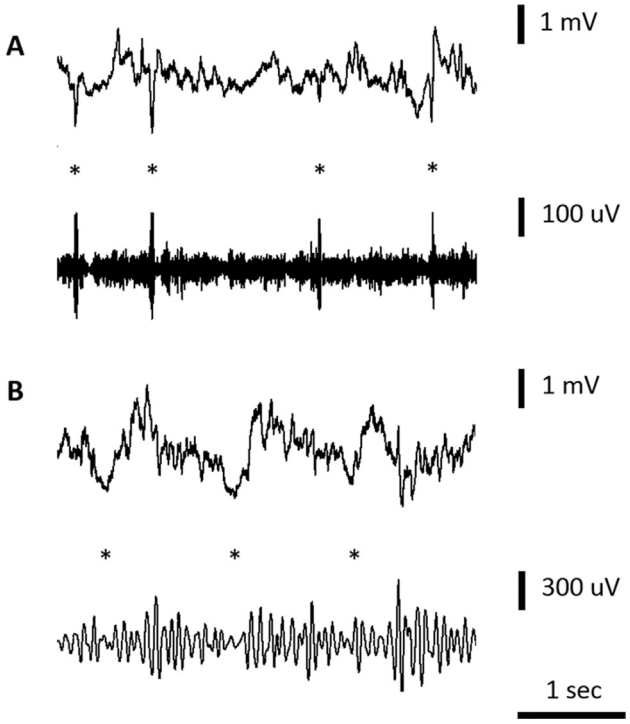

Fig. 2. Electrophysiological characteristics of non-rapid eye movement (non-REM) sleep recorded from the rat brain. A. Hippocampus – dorsal Cornu Ammonis 1 (CA1). *Top*: Raw hippocampal local field potential (LFP) trace. Bottom: Hippocampal LFP trace filtered in the sharp wave/ripple (SWR) range (100-300 Hz). Stars denote the occurrences of sharp wave/ripples. B. Cortex – medial prefrontal cortex. Top: Raw LFP showing slow oscillations with nested spindles. *Bottom*: LFP filtered in the spindle range (10–20 Hz), showing increased spindle power during peaks of slow oscillations, which correspond to up-states. Stars denote the occurrences of slow oscillation troughs, corresponding to down-states (Skelin and McNaughton, unpublished).

neurons (Csicsvari, Hirase, Czurkó, Mamiya, & Buzsáki, 1999; Whishaw & Vanderwolf, 1973). In addition, some neurons and LFP oscillations in cortical (prefrontal and cingulate cortices) and subcortical structures (nucleus accumbens) are phase-locked to hippocampal theta (Benchenane et al., 2010; Jones & Wilson, 2005; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009; Remondes, Wilson, 2015), suggesting a possible hippocampal-cortical communication mechanism during encoding. The presumed consolidation phase is characterized by three major LFP patterns: cortical/subcortical slow oscillations (SOs), hippocampal sharp wave/ripples (SWRs) and neocortical sleep spindles (SPs) (Fig. 2; Amzica & Steriade, 1997; Siapas and Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsáki, 2003; Isomura et al., 2006; Staresina et al., 2015), as well as time-compressed (4–10×) reactivations of neuronal activity patterns present during behavior (Wilson & McNaughton, 1994; Skaggs & McNaughton, 1996; Nádasdy et al., 1999; Euston, Tatsuno, & McNaughton, 2007). Initially, memory reactivation was assessed by quantifying the effects of experience on firing rates of individual cells during subsequent sleep (Pavlides & Winson, 1989). The advancement of recording hardware and simultaneous recordings of tens or hundreds of neurons (Battaglia, Sutherland, & McNaughton, 2004; Pfeifer & Foster, 2013; Wilson & McNaughton, 1994), paved the way towards discerning coordinated reactivation of larger neuronal ensembles in multiple brain structures and revealed the fine temporal dynamics of cross-structure interactions during memory reactivation (Ji & Wilson, 2007; Lansink et al., 2009; Rothschild, Eban, & Frank, 2016). However, despite the decades of research on brain dynamics underlying memory consolidation, the factors initiating and regulating this process are still unclear. The aim of this review is to summarize the rapidly-growing literature on hippocampal communication with cortical/subcortical structures during non-REM sleep in the context of memory consolidation, identify the emerging patterns, and highlight open questions in this field of research.

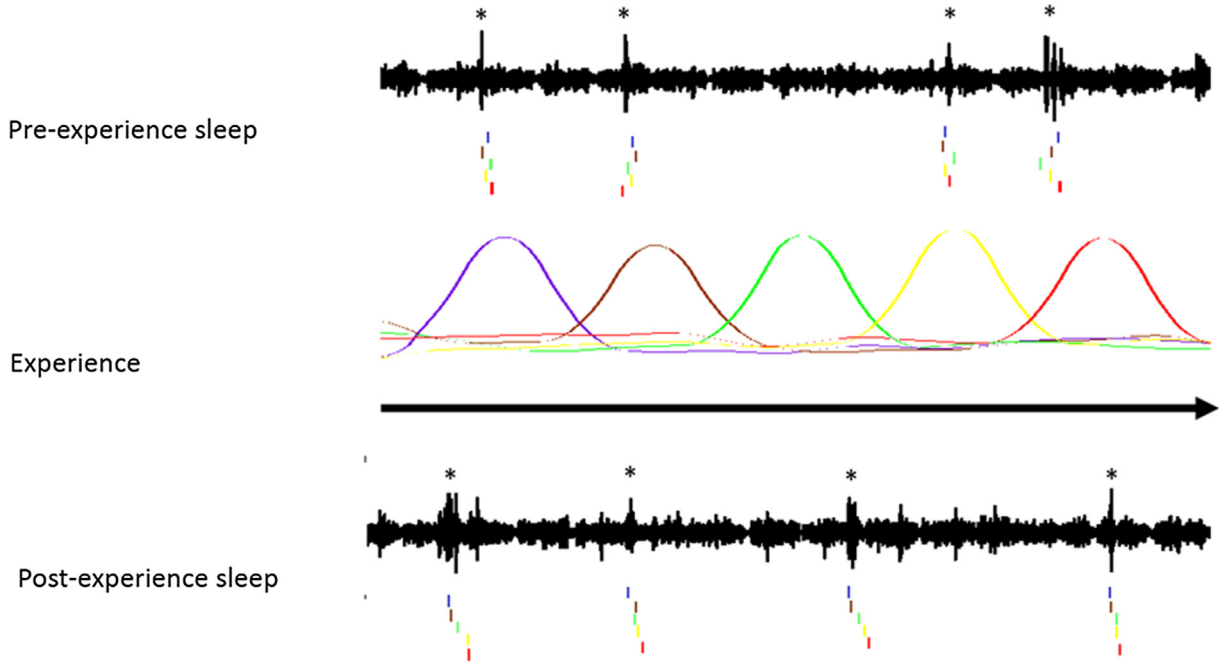

Fig. 3. Schematized example of hippocampal place cell reactivation. Top: Prior to experience, the subset of place cells shows no distinct sequential activity. Black trace denotes hippocampal local field potential (LFP) filtered in sharp wave/ripple (SWR) range (100-300 Hz), with SWR events marked by stars. Colored tick marks denote spikes with neuron identities denoted by different colors. Middle: During the experience, place cells form a sequence that reflects their place field positions in the environment. Colored curves denote average firing rates of different neurons at different subsets of linear trajectory (black arrow). Bottom: After the experience, the sequential activity established during experience is preserved during memory reactivation events, which occur during SWRs, denoted by stars.

2. Place cells and major LFP oscillations in memory consolidation

2.1. Place cells

Most research on memory consolidation at the cellular level has focused on hippocampal place cells (Fig. 3), as their high spatial tuning allows precise decoding of spatial aspects of experience reactivated during sleep and quiet rest (Diba & Buzsáki, 2007; Ji & Wilson, 2007; Skaggs & McNaughton, 1996). Place cells fire in limited portions of the environment, called place fields, and they represent a large fraction of hippocampal neurons (O'Keefe & Dostrovsky, 1971), and properties of individual place cell fields may reflect the environmental topology (Alvernhe, Save, & Poucet, 2011). Individual place cells vary widely in their mean firing rates and propensity to form multiple fields (Rich, Liaw, & Lee, 2014), and place cell field diameter varies with the anatomical location along the septo-temporal axis, ranging from ~0.25 m in dorsal to ~5 m in ventral hippocampus (Jung, Wiener, & McNaughton, 1994; Kjelstrup et al., 2008). In addition, place cells conjunctively encode the non-spatial aspects of experience, such as the salience and task contingencies (Bower, Euston, & McNaughton, 2005; Eichenbaum, 1996; Karlsson & Frank, 2009; Leutgeb, Ragozzino, & Mizumori, 2000). Based on the estimates from immediate early gene studies, ~ 40% of dorsal hippocampal pyramidal cells are active in a single environment of about 1 m^2 (Guzowski, McNaughton, Barnes, & Worley, 1999).

The critical role of place cells in hippocampal-dependent memory encoding and consolidation is supported by multiple lines of evidence, including pharmacological, electrical and optical manipulations of place cells during behavior or subsequent sleep. Systemic application of NMDA antagonists prevents the induction of long-term potentiation (LTP) at hippocampal synapses (reviewed by Nakazawa, McHugh, Wilson, & Tonegawa, 2004). Although the NMDA antagonism does not produce large effects on place cell spatial tuning during behavior, it abolishes place field stabilization across sessions (Kentros et al. 1998; Silva, Feng, & Foster, 2015), experience-induced place field expansion (Ekstrom, Meltzer, McNaughton, & Barnes, 2001), place cell sequence reactivation during subsequent sleep (Silva et al., 2015), and hippocampal-dependent learning (Morris, 1989). The NMDA antagonism paradigm revealed another interesting aspect of hippocampal memory reactivation dynamics – prolonged reactivation of place cell sequences experienced prior to NMDA antagonist application, possibly enabled by a lack of reactivation of place cell sequences experienced after the NMDA application that might otherwise compete/interfere with reactivation of those earlier sequences (Silva et al., 2015). Optically-induced dopamine release during exploration of new environment increases reactivation of place cell ensembles encoding the environment (McNamara, Tejero-Cantero, Trouche, Campo-Urriza, & Dupret, 2014). In addition, closed loop pairing of online-detected spikes from a single place cell with median forebrain bundle (MFB) stimulation, known to enhance the dopamine release in forebrain structures (Millar, Stamford, Kruk, & Wightman, 1985), induced a place preference for the MFB stimulation-paired place cell field, effectively 'backdating' the place – reward association (De Lavilléon et al., 2015). Perturbation of place cell activity could result in the opposite effect – abolishment of experimentally-induced cocaine place-reward association – demonstrated by optically silencing place cells encoding the cocaine-associated environment during re-exposure. This manipulation resulted in the emergence of a new map for the same environment, encoded by the previously silent population of hippocampal neurons and the abolishment of place preference (Trouche et al., 2016).

2.2. Sharp wave/ripples

SWRs are discrete and short (30–120 ms) LFP events occurring in the hippocampal area Cornu Ammonis 1 (CA1) during non-REM sleep and awake immobility (Buzsáki, 2015; Karlsson & Frank, 2009; O'Keefe, 1976; Roumis & Frank, 2015). In addition, SWRs occur in primate hippocampus during visual search (Leonard & Hoffman, 2015). SWRs consist of a sharp wave – deflection of CA1 LFP reflecting the volley of synaptic input from CA3 and ripples – 10–20 fast oscillation cycles (100–300 Hz). SWR occurrence is stochastic, typically at ~0.5–1 Hz in rodents and at an order of magnitude lower rates (~0.05–0.1 Hz) in macaque (Skaggs et al., 2007) and human hippocampus (Bragin, Mody, Wilson, & Engel, 2002; Staresina et al., 2015). This difference might be due to increased size of hippocampal network in primates, combined with limited SWR propagation distance, resulting in recording of only a relatively localized minority of SWRs, compared with a more synchronized rodent hippocampal network. In addition, it is possible that neurons in primate hippocampus are less densely packed, which could result in lower SWR amplitudes and consequently lower detection rates.

SWRs are the windows of largest non-pathological population synchrony in the brain (Buzsáki, 1986), with an estimated up to 6-fold activity gain (Csicsvari et al., 1999), and a large variation in the extent of spatial synchronization (Patel, Schomburg, Berényi, Fujisawa, & Buzsáki, 2013). Although most place cell sequences generated during SWRs do not significantly resemble the sequences present during recent behavior (Lubenov & Siapas, 2008), this apparent dissociation could be due to sparse sampling of hippocampal neuronal activity. This question could be addressed by recording larger CA1 populations with emerging methods, such as two-photon calcium imaging (Malvache, Reichinnek, Villette, Haimerl, & Cossart, 2016; Mao, Kandler, McNaughton, & Bonin, 2017). Several studies have reported increases in SWR density following learning sessions (Axmacher, Elger, & Fell, 2008; Eschenko, Ramadan, Mölle, Born, & Sara, 2008; Ramadan, Eschenko, & Sara, 2009), but the finding is not consistent (Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009). These discrepancies might reflect the differences in task design and learning dynamics, as well as recording locations in the hippocampus. Regardless of the presence or absence of increased SWR density following learning, the importance of SWRs in memory consolidation was convincingly demonstrated by several studies using closed loop online detection/suppression of SWRs during awake immobility (Jadhav et al., 2012) or post-learning sleep (Ego-Stengel & Wilson, 2010; Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009), which transiently impaired subsequent memory performance. The transient nature of SWR disruption effects on memory consolidation was explained by the effect of the initial SWR portions preceding suppression (first ~20 ms of each suppressed SWR), as well as the presence of small amplitude SWRs, which were not detected/suppressed. It is also possible that SWR suppression triggered by SWR detection at single site in hippocampal network is not sufficient to suppress the overall hippocampal output to cortex, as a significant proportion of SWRs do not propagate across large parts of hippocampus and thus could not be detected (Patel et al., 2013). Similarly, suppression of SWRs induced by optical stimulation of non-serotonergic neurons in median raphe resulted in abolition of fear memory (Wang et al., 2015). Ripple-like oscillations have been described in the rodent and primate temporal cortices (Bragin, Engel, Wilson, Fried, & Buzsáki, 1999; Kandel & Buzsáki, 1997) and recently in the rodent association cortices, such as the medial prefrontal and parietal (Khodagoly et al., 2017). Although the functional role of the cortical ripple-like oscillations is still poorly understood, they have shown positive correlation with learning in humans (Clemens et al., 2007), as well as learning-induced coupling with hippocampal SWRs (Khodagoly et al., 2017).

2.3. Slow oscillations

SOs are the hallmark of the neocortical LFP during non-REM sleep (Steriade, Nuñez, & Amzica, 1993), reflecting the alternation of cortical networks between down- and up-states. SOs described in this review include both the typical SOs (0.5–2 Hz), as well as delta waves (1–4 Hz). Down-states are brief periods (50-400 ms) of membrane hyperpolarization and virtual absence of cortical spiking activity,

separated by up-states, periods of membrane depolarization and increased cortical spiking activity (Battaglia et al., 2004; Isomura et al., 2006; Steriade et al., 1993). Presence of SOs in cortical slices (Sanchez-Vives & McCormick, 2000) suggests that they represent a cortically-generated phenomenon. Thalamic spontaneous activity can trigger cortical up-states, but is incapable of large scale cortical synchronization, suggesting a critical role of intracortical connectivity in this process (Steriade et al., 1993). SO amplitude positively correlates with homeostatic sleep pressure (Finelli, Borbély, & Achermann, 2001) and decreases over successive non-REM episodes (Vyazovskiy et al., 2009). In addition, SO amplitude shows experience dependence on both short and long timescales, reflected by the selectively increased SO amplitude in cortical areas involved in recent learning (Huber, Ghilardi, Massimini, & Tononi, 2004) and selectively decreased SO amplitude in visual cortex following visual deprivation (Heynen et al., 2003). SOs typically emerge in frontal cortex, propagate as travelling waves (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Nir et al., 2011) along the major anatomical pathways towards the visual cortex (Murphy et al., 2009), and invade temporal lobe structures (Isomura et al., 2006; Nir et al., 2011). SOs are present in the hippocampal LFP, but the membrane potential of hippocampal neurons does not show the bimodality characteristic of cortical neuron membrane potentials during up/down-states (Isomura et al., 2006). The initial phase of an up-state is a period of rather stereotypical cortical neuronal activity patterns (Luczak, Barthó, Marguet, Buzsáki, & Harris, 2007), which can be modulated by experience and subsequently reactivated (Bermudez-Contreras et al., 2013; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Peyrache et al., 2009).

2.4. Sleep spindles

SPs are transient (~ 1-3 s) bouts of oscillations in the 7-20 Hz range, occurring in thalamus and neocortex (Kandel & Buzsáki, 1997; Loomis, 1935; Steriade et al., 1993) during non-REM sleep. Cortical SP generation depends on input from thalamic reticular nucleus (Steriade, Deschenes, Domich, & Mulle, 1985), but intracortical connectivity is required for synchronized emergence of SPs across the cortical mantle (Contreras, Destexhe, Sejnowski, & Steriade, 1996; Kandel & Buzsáki, 1997). Similar to SOs, SPs in the human brain also tend to occur locally (Andrillon et al., 2011). SWRs, as well as the spiking of many cortical neurons, are significantly phase-locked to SP troughs (Peyrache et al., 2009; Steriade, 2006). SP densities are positively correlated with learning in rats (Eschenko, Mölle, Born, & Sara, 2006) and humans (Clemens, Fabo, & Halasz, 2005; Gais, Mölle, Helms, & Born, 2002). One hypothesized model explaining the mechanistic role of SPs in memory consolidation (Sejnowski & Destexhe, 2000) involves the cascade of events, starting with subthreshold dendritic depolarization of cortical pyramidal neurons by the thalamic inputs, followed by massive calcium entry into dendrites and activation of perisomatic inhibition (Contreras, Destexhe, Sejnowski, & Steriade, 1997), which functionally isolates dendrites from soma and triggers molecular plasticity pathways. This scenario was recently corroborated by the demonstration of increased dendritic, but not somatic calcium levels, in layer V pyramidal neurons *in vivo* during SPs (Seibt et al., 2017). Although in most studies SPs were analyzed as a single entity, they could be classified into two categories with potentially different mechanistic roles in memory consolidation. Faster, low voltage spindles (LVSP; 10–20 Hz) follow the K-complexes with short latency and positively correlate with memory reactivation (Johnson et al., 2010), while slower, high voltage spindles (HVSP; 7-12 Hz), occur independently of K-complexes (Andrillon et al., 2011; Zeitlhofer et al., 1997) and slightly negatively correlate with memory reactivation (Johnson et al., 2010).

3. Hippocampal-cortical LFP coupling

SOs are hypothesized to orchestrate the SWRs and SPs, facilitating their temporal coupling (Staresina et al., 2015). SWRs show bimodal coupling to SOs, with the highest SWR probability around the up-state onsets and offsets, and lowest during down-states (Battaglia et al., 2004; Peyrache et al., 2009; Wilber, Skelin, Wu, & McNaughton, 2017), while SPs typically follow the up-state onsets (Fig. 2; Siapas et al., 1998; Sirota et al., 2003). Increased SWR probability at both the down-to-up-state and up-to-down-state transitions (Battaglia et al., 2004; Peyrache et al., 2009; Wilber et al., 2017) led to the conceptualization of SWRs as “toggle-switches”, which facilitate cortical network state transitions (Genzel, Kroes, Dresler, & Battaglia, 2014). However, up-states in the entorhinal cortex persist for much longer and undergo fewer state transitions than the rest of the cortex (Hahn, Sakmann, & Mehta, 2006), despite the entorhinal cortex being more directly exposed to large and synchronized volleys of hippocampal activity during SWRs. In addition, SWRs that occur during cortical down-states are capable of transiently activating cortical neurons, but this does not result in sustained up-states, as the membrane potentials quickly revert to hyperpolarized levels (Isomura et al., 2006). Widespread coupling between SWRs and cortical/subcortical activity was demonstrated by Logothetis et al. (2012), who recorded SWR-triggered brain-wide blood oxygen level – dependent (BOLD) signal in macaque monkeys, revealing two distinct patterns of SWR-triggered response – cortical/limbic activations and subcortical deactivations. These results are broadly consistent with higher SWRs probability during periods of cortical activations (Ji & Wilson, 2007; Sirota et al., 2003). In addition, subcortical deactivations are consistent with decreased neuronal activity in medial raphe nuclei during SWR windows (Wang et al., 2015) and generally low activity of subcortical monoaminergic nuclei during non-REM sleep (reviewed by Watson, Baghdoyan, & Lydic, 2010).

Functional significance of SWR-SO temporal coupling was demonstrated using a closed loop approach with online detection of SWRs and application of SWR-contingent SO-inducing cortical electrical stimulation during post-learning sleep. This procedure increased both SWR/SO coupling, as well as the subsequent performance on an object recognition task (Maingret et al., 2016). This approach was efficacious only if the SOs were induced within 250 ms following SWR detection; delayed SO induction had no effect on memory performance. Interestingly, SOs were induced by stimulation of motor cortex and propagated in the posterior-anterior direction, opposite from the typical spontaneous SO propagation direction (Massimini et al., 2004), suggesting that the direction of sequential activation of cortical areas is not critical for memory consolidation. Furthermore, disruption of SWR-SP coupling by optical activation of the locus coeruleus, the source of noradrenergic input to forebrain, also impairs memory consolidation (Novitskaya, Sara, Logothetis, & Eschenko, 2016). Similarly, disruption of SWR-SP coupling between the medial PFC and CA1, by chemogenetic inhibition of parvalbumin-positive interneurons in either structure, was sufficient to impair fear conditioning memory consolidation (Xia et al., 2017).

4. Hippocampal-cortical/subcortical coupling at the neuronal level

Although the LFP coupling between the different structures provides important clues about the timing and extent of their communication in the context of memory consolidation (Colgin et al., 2009; Fries et al., 2005), the most temporally precise insight into communication between the hippocampus and cortical/subcortical structures can be obtained by simultaneous recording of spiking activity (Girardeau, Inema, & Buzsáki, 2017; Lansink et al., 2009; Rothschild et al., 2016). Hippocampal-cortical/subcortical coupling at the neuronal level was assessed based on two main approaches: (a) the timing of cortical/subcortical single neuron or population activity relative to hippocampal single neurons, population activity, or SWRs (Ji & Wilson, 2007; Siapas & Wilson, 1998; Sirota et al., 2003; Tang et al., 2017; Wang & Ikemoto, 2016; Wierzynski, Lubenov, Gu, & Siapas, 2009) or (b) the timing of cortical/subcortical memory reactivation relative to hippocampal

memory reactivation or SWRs (Ji & Wilson, 2007; Peyrache et al., 2009; Rothschild et al., 2016; Ólafsdóttir, Carpenter, & Barry, 2016; O'Neill, Boccara, Stella, Schoenenberger, & Csicsvari, 2017; Tang et al., 2017).

4.1. Medial entorhinal cortex

MEC is the cortical structure anatomically most proximal to hippocampus, showing distinct dynamics during non-REM sleep, with up-states persisting over several SO cycles in the rest of neocortex (Hahn et al., 2006). In addition, the MEC LFP is characterized by brief ripple-like high frequency oscillations (Chrobak & Buzsáki, 1996), following hippocampal SWRs with short delay (5-30 ms). A substantial fraction of MEC neurons are classified as grid cells, based on spatial tuning patterns in the form of regular hexagonal lattice. Unlike hippocampal place cells, grid cells' correlation structure is stable across different environments (Hafting, Fyhn, Molden, Moser, & Moser, 2005), although the redistributions of grid field peak firing rates (Fyhn, Hafting, Treves, Moser, & Moser, 2007) and shifts in individual grid cell field locations are observed between recordings in different rooms (Diehl, Hon, Leutgeb, & Leutgeb, 2017). This phenomena might underlie hippocampal global remapping – change in composition of place cell ensemble encoding a given environment (Diehl et al., 2017). Two recent studies found reactivation of maze trajectories during non-REM sleep, based on Bayesian spatial decoding of entorhinal population activity (Ólafsdóttir et al., 2016; O'Neill et al., 2017; but see Trimper, Trettel, Hwaun, and Colgin (2017) for methodological concerns regarding spatial decoding based on grid cell activity). Reactivation in superficial layers, which provide input to hippocampus, was not temporally coupled with hippocampal reactivation (O'Neill et al., 2017), while reactivation in deep layers followed hippocampal reactivation, with short time lag (~10 ms) and short space lag of the reactivated spatial trajectory (Ólafsdóttir et al., 2016). This dichotomy is consistent with the up-modulation of deep, but not superficial MEC neuronal activity by hippocampal SWRs (Chrobak & Buzsáki, 1994). It is somewhat puzzling that reactivation in superficial MEC was not coupled with hippocampal reactivation (O'Neill et al., 2017), while the primary auditory cortex reactivation content was both temporally coupled and significantly predictive of the hippocampal reactivation content (Rothschild et al., 2016), despite the much more indirect connectivity of the early sensory regions with hippocampus (Felleman & Van Essen, 1991).

4.2. Association cortices

Association cortices are involved in processing multimodal sensory information and include the PFC, cingulate, retrosplenial, posterior parietal (PPC), perirhinal and postrhinal cortices (Goldman-Rakic, 1988). PFC is the cortical structure most extensively studied in the context of hippocampo-cortical communication (Maingret et al., 2016; Peyrache et al., 2009; Peyrache, Battaglia, & Destexhe, 2011; Siapas and Wilson, 1998; Wierzynski et al., 2009), due to monosynaptic and highly plastic inputs from ventral hippocampus (Laroche, Davis, & Jay, 2000; Swanson et al., 1981), and the hypothesized cooperation with hippocampus on various memory tasks (Doyere et al., 1993; Jones & Wilson, 2005). The extensive connectivity of PFC with hippocampus and the range of cortical/subcortical structures (Fuster, 1988), as well as the selective activation of PFC during remote, but not recent memory retrieval (Maviel, Durkin, Menzaghi, & Bontempi, 2004), suggest that the PFC might gradually take over the hub position in the organization of remote memories, as they are progressively integrated with cortical schemas (Frankland & Bontempi, 2005; Tse et al., 2007; Holleman & Battaglia, 2015). Simultaneous hippocampal-PFC recordings, which typically included infra/prelimbic parts of medial prefrontal cortex (mPFC), have shown asymmetric SWR-triggered population activity peri-event time histograms (PETH), with increases from baseline up to 200 ms prior to SWR that persisted for 1-2 s following SWR (Peyrache et al., 2009; Siapas & Wilson, 1998; Wierzynski et al., 2009). Similar pre-SWR activation, but shorter persistence of SWR-triggered response was reported by Tang et al. (2017), which could be due to the construction of SWR-triggered PETH selectively from neurons showing significant SWR-modulation. At the level of single neuron cross-structure timing, for two thirds of significantly correlated hippocampal-mPFC pairs, the activity of hippocampal pair member on average preceded mPFC member, while the remaining hippocampal-mPFC neuron pairs showed the opposite pattern (Wierzynski et al., 2009). The size of the prefrontal response to SWRs was correlated with hippocampal population activity magnitude (Wierzynski et al., 2009), but was attenuated during SPs (Peyrache et al., 2011), which could reflect the presence of lateral inhibition, as a potential mechanism for selection of reactivated cortical ensembles (Goldman-Rakic, 1995). Reactivation strength in mPFC peaked ~40 ms after SWR (Peyrache et al., 2009), while showing a broad increase from baseline within ± 1 s from SWR, possibly reflecting the tendency of SWRs to occur within short intervals (doublets or triplets). This notion is supported by the similar decay time constants of SWR-triggered reactivation strength and SWR autocorrelograms (~150 ms). Interestingly, joint reactivation of hippocampal-mPFC neuron pairs was observed during sleep SWRs, but the probability of joint reactivation did not correlate with spatial correlation of pair members' activity during the behavior (Tang et al., 2017). The stereotyped prefrontal firing sequences following up-state onsets were modified in parallel with learning on an object recognition task, dependent on interaction between hippocampus and PFC (De Vito et al., 2010). This process likely reflects the rearrangement of local functional connectivity and it was facilitated by artificially enhanced coupling of up-states with SWRs (Maingret et al., 2016).

Anterior cingulate cortex (ACC) is a more caudal frontal cortical structure, characterized by sparse direct connectivity with dorsal hippocampus (Cenquizca & Swanson, 2007), and implicated in consolidation of different aspects of memory, such as contextual fear memory (Frankland & Bontempi, 2005). SWR-triggered neuronal responses in ACC show both similarities and differences to typical mPFC responses. In both structures, population activity increased up to ~200 ms prior to SWR, but unlike the typically right-shifted SWR-triggered PETH in mPFC (Peyrache et al., 2009; Siapas & Wilson, 1998; Tang et al., 2017; Wierzynski et al., 2009), neuronal activity in ACC decayed shortly after the SWR (Wang & Ikemoto, 2016). Another similarity between the SWR-triggered PETH in ACC and mPFC was the presence of sharp activity peaks following SWR with short latencies (up to 60 ms), likely reflecting the local populations of neurons sensitive to hippocampal input during SWRs.

PPC is an association cortical structure characterized by connections with thalamus, various sensory and association cortices, and indirect hippocampal inputs through MEC (reviewed by Whitlock, Sutherland, Witter, Moser, & Moser, 2008). This structure encodes movement-related parameters (McNaughton et al., 1994; Nitz, 2006; Wilber et al., 2017; Wilber, Clark, Forster, Tatsuno, & McNaughton, 2014) and supports spatial cognition and decision-making (Driscoll, Pettit, Minderer, Chettih, & Harvey, 2017; Harvey, Coen, & Tank, 2012; Szczepanski, Konen, & Kastner, 2010; Whitlock et al., 2008). Multiple reports implicated PPC coupling with hippocampus in the context of memory reactivation (Qin, McNaughton, Skaggs, & Barnes, 1997; Wilber et al., 2017, Khodagoly et al., 2017). Specifically, Qin et al. (1997) found that experience-induced correlation structure between the hippocampal and PPC neurons was preserved in subsequent sleep, suggesting cross-structure reactivation. The reactivation of multineuronal clusters in PPC, consisting of all the spikes recorded from a single electrode, also peaked around the time of hippocampal SWRs (Wilber et al., 2017). Finally, oscillations that correspond to SWRs based on frequency content and duration were found in PPC, showing experience-dependent increase in coupling with hippocampal SWRs (Khodagoly et al., 2017).

4.3. Sensory cortices

Neural activity in early sensory cortices tends to precede both hippocampal SWRs and associated hippocampal neuronal activity (Ji & Wilson, 2007; Rothschild et al., 2016; Sirota et al., 2003). Sirota et al. (2003) reported that the somatosensory cortex population activity precedes hippocampal population activity and SWRs, while at the level of cross-structural significantly correlated neuronal pairs, somatosensory neurons activate on average ~50-100 ms prior to hippocampal neurons during non-REM sleep. This pattern was confirmed by Ji and Wilson (2007), who demonstrated that visual cortical 'frames', periods of higher population activity likely corresponding to cortical up-states, tend to initiate ~50 ms prior to hippocampal 'frames' during non-REM sleep. The relative cross-structure reactivation timing of cortical 'templates', consisting of visual cortical neurons active in certain part of maze during behavior, and hippocampal 'templates', consisting of place cells encoding the same portion of the maze, suggested that hippocampal reactivation preceded visual cortical reactivation, but due to very sparse occurrence of temporally overlapping cross-structure reactivation events, the results were inconclusive (Ji & Wilson, 2007). A convincing line of evidence suggesting that hippocampal memory reactivation could be initiated by the primary sensory cortices was obtained using a targeted memory reactivation paradigm. Following behavioral studies showing that presentation of task-associated sensory cues during post-learning sleep enhances task performance (Rasch, Büchel, Gais, & Born, 2007; Rudoy, Voss, Westerberg, & Paller, 2009), Bendor and Wilson (2012) paired two distinct spatial trajectories on the maze (left and right arm) with trajectory-specific auditory stimuli. Selective presentation of a single auditory cue during subsequent sleep selectively increased the reactivation probability for the place cell sequence encoding the cue-associated trajectory. Finally, Rothschild et al. (2016) have shown that the activity increase in auditory cortex during non-REM sleep starts up to 200 ms prior to onset of SWRs. In addition, neuronal content of hippocampal reactivation events could be predicted based on the preceding auditory cortex reactivation content, when the reactivation was cued by auditory stimulus or occurred spontaneously. Also, post-SWR neural activity in auditory cortex was predictable based on the hippocampal activity pattern during a given SWR, revealing the existence of a functional loop connecting the early sensory cortex and hippocampus. The bias induced by auditory stimulation on hippocampal reactivation content could be detected up to 15 s following the stimulation. Overall, activity in early sensory cortices during non-REM sleep tends to precede and potentially bias hippocampal SWRs and reactivation events, although the communication is likely bidirectional.

4.4. Subcortical structures

Coordinated memory reactivation during non-REM sleep has also been demonstrated between the hippocampus and subcortical structures involved in appetitive and aversive learning, such as the ventral tegmental area (Gomperts, Kloosterman, & Wilson, 2015), nucleus accumbens (Lansink et al., 2008, 2009) and basolateral amygdala (Girardeau et al., 2017). Simultaneous recordings from hippocampus and nucleus accumbens revealed the joint reactivation, preferably involving hippocampal neuron-leading pairs. The direction of this temporal bias was preserved during sleep, and the pair-wise cross-correlation indicated that accumbens neurons fired ~50 ms after hippocampal neurons (Lansink et al., 2009). The strongest predictor of an individual neuron's involvement in reactivation was the degree of spatial and/or reward tuning (Lansink et al., 2008, 2009). Finally, reactivation peaks were observed within a 200 ms window following SWRs (Lansink et al., 2008). In contrast to joint reactivation of place-reward information by the nucleus accumbens and hippocampus during sleep, reward-modulated neurons in the ventral tegmental area (VTA) were mostly negatively modulated by SWRs and did not exhibit coordinated reactivation with hippocampal spatial trajectories during sleep (Gomperts et al., 2015). A large fraction of VTA neurons show reward-sensitivity and release dopamine from their terminals in forebrain structures, signaling the degree of positive mismatch between the expected and obtained reward (Schulz, 1998). The functional advantage of the VTA/hippocampal decoupling during sleep (Gomperts et al., 2015) could be to prevent the interference of reward signal with ongoing memory consolidation, as the electrically induced dopamine release during sleep could introduce place-reward associations not experienced during behavior (de Lavilleon et al., 2015). Reactivation of stimulus-sensitive putative dopaminergic VTA neurons has been demonstrated during post-task SWS (Valdés, McNaughton, & Fellous, 2015), but without the temporal compression typically characteristic of hippocampal or cortical reactivation (Euston et al., 2007; Nadasdy et al., 1999; Wilson and McNaughton, 1994).

Aversive learning involves the association of aversive stimuli with spatial location and is mediated by interaction between amygdala and hippocampus (Selden, 1991). Similarly to joint reactivation of place-reward information during appetitive learning (Lansink et al., 2008, 2009), memory reactivation underlying aversive memory consolidation occurs simultaneously in dorsal hippocampus and basolateral amygdala (Girardeau et al., 2017). Basolateral amygdala neurons recruited in this process typically develop correlated firing with a subset of hippocampal neurons during learning of aversive stimulus (air puff) location and show up-modulation by SWRs during subsequent sleep. Although nucleus accumbens and basolateral amygdala receive projections from ventral hippocampus (Strange et al., 2014), coordinated reactivation of these structures with dorsal hippocampus may be explained by the fact that neuronal ensembles can become synchronized over the entire hippocampus during some large amplitude SWRs (Patel et al., 2013). In conclusion, joint reactivations of hippocampal spatially tuned neurons with neurons encoding positive or negative valence of stimuli located within a portion of the environment could potentially support memory consolidation in both positive and negative reinforcement learning paradigms.

5. Summary and open questions

A consistent pattern from a multitude of studies shows that neuronal activation and/or memory reactivation in cortical (PFC, ACC, PPC, deep layers of MEC, visual, somatosensory and auditory cortices) and subcortical structures (nucleus accumbens, basolateral amygdala) during non-REM sleep is coordinated with hippocampal activation and/or memory reactivation, peaking in close temporal proximity to hippocampal SWRs (Siapas & Wilson, 1998; Peyrache et al., 2009; Wierzynski et al., 2009; Wang and Ikemoto, 2016; Qin et al., 1997; Wilber et al., 2017; Ólafsdóttir et al., 2016; Sirota et al., 2003; Rothschild et al., 2016; Lansink et al., 2008; Lansink et al., 2009; Girardeau et al., 2017). A few notable exceptions from this pattern are VTA (Gomperts et al., 2015) and superficial layers of MEC (O'Neill et al., 2017), structures which show memory reactivation during non-REM sleep, but without the obvious temporal coordination with hippocampal reactivation. Population activity across many neocortical structures tends to increase from baseline prior to hippocampal population activity or SWRs, with some regional differences with respect to characteristics of SWR-triggered PETHs (Peyrache et al., 2009; Rothschild et al., 2016; Sirota et al., 2003; Wang and Ikemoto, 2016). Persistent cortical activity increases surrounding SWRs could be due to higher likelihood of SWR occurrence during cortical up-states, and the degree of SWR-triggered PETH asymmetry could reflect the relative probability of SWR occurrence closer to up-state onset or offset. More direct evidence of potential interactions between structures is based on cross-correlations or cross-covariances between spike trains of individual neurons from different structures. For a majority of significantly correlated mPFC-hippocampal cross-structure pairs the hippocampal neurons tend to fire prior to mPFC neurons (Wierzynski et al., 2009), while sensory cortical neurons tend to fire prior to hippocampal neurons (Sirota et al., 2003).

It should be noted that this reflects the overall tendency, but significant interactions in the opposite direction are also present and some of these effects could be recent or remote experience-dependent. Finally, comparisons of relative cross-structure reactivation timing were either inconclusive due to small number of simultaneously detected reactivation events in visual cortex and hippocampus (Ji and Wilson, 2007) or show auditory cortical reactivation starting earlier than hippocampal reactivation (Rothschild et al., 2016). Based on available reports, it is difficult to establish a clear directionality pattern in hippocampal-cortical communication during non-REM sleep.

One of the most interesting open questions pertains to the mechanisms that trigger and regulate memory consolidation. Clear evidence of sensory cortical structures' ability to bias the content of hippocampal replay was shown by Rothschild et al. (2016). Application of similar experimental design in other cortical/subcortical areas could reveal the generality of this phenomenon, which suggests that reactivation could be triggered by the cortical structures that recently accumulated a large degree of synaptic plastic changes. This scenario seems especially plausible for structures involved in recent learning, such as the motor cortex following motor skill learning (Huber et al., 2004; Ramanathan, Gulati, & Ganguly, 2015), visual cortex following exploration of environment rich in visual cues (Ji and Wilson, 2007) or auditory cortex following auditory discrimination learning (Rothschild et al., 2016). Another interesting question pertains to potential functional differences between SWRs occurring at onsets or offsets of cortical up-states. These time windows are characterized by differences in cortical output to hippocampus, which could possibly affect the content of hippocampal reactivation. Similarly, cortical receptivity to hippocampal input also differs during those time windows, due to ensuing changes in cortical neurons' membrane potential. Also, it is unclear how the wide range of SWR propagation distances and trajectories in the hippocampal network (Patel et al., 2013) is biased by cortical inputs or to what degree is it reflected in the hippocampal output to cortex.

Finally, an important caveat for the interpretation of hippocampal-cortical/subcortical coupling is that recordings are typically done from a limited portion of hippocampus and single cortical or subcortical structure at the time. SWRs in ventral hippocampus occur largely asynchronously with SWRs in intermediate and dorsal segments, except for the largest amplitude SWRs, during which the entire septotemporal axis may become more synchronous (Patel et al., 2013). Even within different functional segments of the hippocampus (ventral and intermediate-dorsal), only ~30–40% SWRs synchronize a major portion of the segment and ~20% of SWRs remain localized to ~1 mm from the site of origin (Patel et al., 2013). Moreover, different combinations of local neurons could be recruited during different SWR events at the same location, as evident from the reactivation of different spatial trajectories during different SWR events (Bendor & Wilson, 2012). Similarly, SOs show a continuum between local events involving a limited part of cortex and global events that sweep across the cortical mantle (Massimini et al., 2004; Nir et al., 2011). The spatiotemporal pattern of SO propagation might have functional significance, as it determines the relative timing of excitability windows in different cortical structures and constrains the potential membership of cortical cell ensembles currently receptive for hippocampal input (Buzsáki, 2010). Therefore, interpretations about the dynamics of hippocampal-cortical/subcortical functional connectivity supporting memory consolidation are necessarily limited by the recording configuration. The full dimensionality of this process could possibly be revealed by large scale unimodal or combined electrophysiological recordings and wide field imaging recordings from multiple structures (Bermudez-Contreras et al., 2017; Greenberg et al., 2017; Jun et al., 2017; Khodagoly et al., 2017; Pachitariu et al., 2016). Even with the advance of such technology, however, the actual role of hippocampal-cortical coupling during memory reactivation on the rearrangement of the cortical synaptic matrix that presumably underlies memory consolidation remains largely in the domain of theory.

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Glossary

Place cells: hippocampal neurons showing spatial tuning to portions of the environment
Sharp wave ripples: fast (100-300 Hz) and short (~30-100 ms) oscillation in the stratum pyramidale of hippocampal CA1, occurring during quiet wakefulness and non-REM sleep. Hypothesized mediators of hippocampal communication with cortical/sub-cortical structures and memory consolidation.
Slow oscillations: slow (0.5 - 4 Hz) oscillations occurring in cortex during non-REM sleep and pacing the excitability of cortical neurons.
Sleep spindles: episodes of oscillations in 7-20 Hz range (1-3 s), occurring in cortex during the up states of slow oscillations during non-REM sleep.
Up- and down-states: oscillating periods of high and low cortical neuronal excitability, corresponding to troughs and peaks of slow oscillation in deep cortical layers, respectively.
Memory reactivation: process of reactivation of neural activity patterns present during experience, during offline periods
Memory consolidation: process of gradual strengthening of memory during post-experience offline periods.