The hippocampus: hub of brain network communication for memory

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A complex brain network, centered on the hippocampus, supports episodic memories throughout their lifetimes. Classically, upon memory encoding during active behavior, hippocampal activity is dominated by theta oscillations (6–10 Hz). During inactivity, hippocampal neurons burst synchronously, constituting sharp waves, which can propagate to other structures, theoretically supporting memory consolidation. This ‘two-stage’ model has been updated by new data from high-density electrophysiological recordings in animals that shed light on how information is encoded and exchanged between hippocampus, neocortex and subcortical structures such as the striatum. Cell assemblies (tightly related groups of cells) discharge together and synchronize across brain structures orchestrated by theta, sharp waves and slow oscillations, to encode information. This evolving dynamical schema is key to extending our understanding of memory processes.

Memory evolution and brain information flow
Memory is a dynamical phenomenon, from the moment of encoding to retrieval and in the intervening time interval. After encoding, labile memories undergo consolidation, that is, they stabilize over time. This process depends on delicate interactions between circuits located in several brain areas. In particular, the hippocampus stands out as a crucial structure for the initial encoding and storage of labile memories involving synaptic plasticity. Gradually, the neocortex becomes involved in memory maintenance.

From a theoretical point of view there are many reasons why this dual memory system, already defined in formal terms by Marr in the 1970s \textsuperscript{[1]}, can be advantageous: there is a division of labor between a fast learner (the hippocampus), capable of rapidly encoding new information, and the neocortex, with its larger storage capacity but more slowly changing connections. This system would alleviate the problems of interference between different memory traces and thus avoid catastrophic memory loss as storage load exceeds a certain ceiling \textsuperscript{[2]}. However, to date, there is no generally accepted theoretical view on memory consolidation. A key point of contention is whether memories ever become completely independent of the hippocampus, and are autonomously supported by the cortex and other structures: the evidence from animal and human lesion studies is equivocal (see \textsuperscript{[3–5]} for reviews articulating diverse positions). However, evidence from human functional magnetic resonance imaging (fMRI) (e.g. \textsuperscript{[6]}) and animal immediate early gene experiments (e.g. \textsuperscript{[7]}) shows strong hippocampal activation at retrieval shortly after encoding and an increasing neocortical role over time. Another issue is the nature of the memory trace and how it evolves with time. Is it transferred from the hippocampus to the neocortex? Is the trace replicated repeatedly during consolidation providing robustness to the memory \textsuperscript{[8]}? Although these issues are still unresolved, it seems clear that these phenomena imply continuous exchanges of information in a network of brain areas centered on the hippocampus and including the neocortex and other key structures such as the amygdala and the striatum.

A key to addressing these issues comes from elegantly designed neurophysiological experiments in behaving animals. In recent years, two methodological breakthroughs have enabled the accumulation of a wealth of new evidence...

Glossary

\textbf{Entorhinal cortex (EC)}: a medial temporal lobe paleocortical area interfacing neocortex and hippocampus: the main input to hippocampus originates in superficial layers (2 and 3) whereas layers 5 and 6 receive hippocampal outputs.

\textbf{Hippocampal subfields}: the hippocampus proper (an archicortex) consists of the dentate gyrus (DG) and CA1 and CA3. The traditional view postulates a ‘tri-synaptic circuit’ in which DG receives EC input, and information flows unidirectionally to CA3 then CA1 that then sends outputs to subiculum that then connects to EC. CA1 also receives direct EC inputs. CA3 is endowed with recurrent connections that render it capable of establishing attractor dynamics (stable configuration of activity to which dynamic networks tend to converge).

\textbf{Oscillatory coherence}: when oscillations in two brain structures keep a constant phase relationship, facilitating possible communication between them.

\textbf{Replay}: the spontaneous reactivation, often during sleep, of neural configurations that occurred during an earlier experience.

\textbf{Ripples}: spontaneous LFP oscillations at 150–200 Hz observed in the hippocampal subfield CA1 during sharp waves correlated with synchronous activity bursts.

\textbf{Sharp waves}: brief (~100 msec) large hippocampal LFPs during quiet wakefulness or SWS.

\textbf{Spindles}: cortical LFP oscillations at 7–14 Hz during early phases of SWS in bouts of a few seconds.
characterizing the encoding of information in and the interactions among brain areas with unprecedented detail, and allowed us to follow memory encoding and consolidation processes in ‘real time’: simultaneous recording of up to hundreds of neurons ([9] for a review see [10]) in multiple brain areas and of multisite local field potentials (LFP). Here we review these new findings. We start from an analysis of the global dynamical processes taking place in hippocampus and neocortex during active behavior and during sleep that provide scaffolding for the interplay between these two structures. A distinction between ‘two-stages’, different dynamical states of hippocampal networks at memory encoding and during consolidation, has been long known [11] and considerably extended in recent years. We describe how information could actually be encoded in these neural circuits by Hebbian cell assemblies ([12], tightly coordinated neuronal groups that can emerge spontaneously), and ‘replayed’ during sleep to support memory consolidation. We discuss how cell assemblies in different brain areas interact, and how the pattern of interactions between the striatum and the hippocampus resembles that between the neocortex and the hippocampus. We indicate how these physiological findings can be integrated in our understanding of memory, and how extensions of this approach might prove themselves instrumental in resolving the current debate in systems consolidation.

Dynamics of cortico–hippocampal interactions
Communication during active states
As previously mentioned, the hippocampus is the major structure involved in memory formation; information must therefore reach the hippocampus during the encoding phase. Active behavior is accompanied by hippocampal theta oscillations driven by generators outside the hippocampus that are located in the medial septum and in the entorhinal cortex (EC; see Glossary) [13] and that possibly interact with autonomous theta oscillators in the hippocampus [14,15]. Most hippocampal cells are entrained by the theta rhythm, that is, they fire preferentially at a certain theta phase (see e.g. [16,17]). Theta oscillations also appear in the medial temporal lobe and other structures closely connected to the hippocampus, and have been posited to regulate information exchange with the hippocampus. A detailed quantitative analysis of population activity across different regions has been made possible only recently.

The prefrontal cortex (PFC) is particularly interesting when considering information transfer between the hippocampus and other regions. The PFC is one of the very few neocortical areas intimately associated to the hippocampus: receiving monosynaptic excitatory, plastic input connections. Hippocampal/PFC communication is important during active behavior and transfer of memory-related information. Electrophysiological studies have also demonstrated coupling between hippocampus and PFC during controlled behavioral tasks [18–21]. However, hippocampally coupled activity extends to a much larger swath of neocortex: surprisingly, neurons many synapses away from hippocampus in sensory and associative areas of parietal cortex are also entrained by theta oscillations [22].

Theta oscillations could be a metronome for the neocortex coordinating information transfer to the hippocampus. In neocortex, faster local gamma (30–140 Hz) rhythms are locked to a preferred phase of the theta cycle [22]. The picture becomes more complex when looking at the role of the EC. In each station along the EC–hippocampal pathway, neurons discharge preferentially at a theta phase ‘different’ from the next one (Figure 1). This casts doubt on whether activity can propagate in a simple feedforward fashion [16] because the latter would optimally benefit from inphase oscillations in all involved structures. In fact, relatively few entorhinal neurons discharge in phase with most of their hippocampal targets. Thus, it seems that the population output from EC layers II and III to the hippocampus mostly provides a ‘seed’ signal triggering intra hippocampal

![Figure 1. Simplified diagram of the interrelationships between the theta rhythm and neuronal activities in the hippocampus, EC and neocortex during the active state. Top: cartoon of hippocampal CA1 pyramidal layer LFP theta oscillations. Below (raster diagrams): firing preferences of the majority of pyramidal cells in EC, hippocampus and neocortex. EC layer 2 feeds input to CA3 that tends to fire maximally at a theta phase at which this input is low. The same pattern is observed between EC layer 3 and CA1. Interestingly, theta phase precession (red arrows) in CA1 and CA3 (observed also in EC layer 2) shifts the firing progressively earlier in the cycle as the animal traverses a place field. Thus, during each place field traversal, the firing phase moves from a phase compatible with the input structure preferred phase, to a phase where the entorhinal inputs are minimal, and most firing can arise from intrinsic hippocampal dynamic processing of previous inputs that occurred much earlier. CA1 projections to neocortex can be multisynaptic, however, in phase locking to the theta rhythm is observed there. (Note that, for simplicity, several structures (e.g. dentate gyrus, subiculum, EC layer 5) in the circuit have been left out of this schematic.) Adapted from [16] and summarizing data from [18,22,37].}
self-organized dynamical processing that develops autonomously in the later phases of the theta cycle (Figure 1).

This segregation of distinct phases of signal processing along the EC–hippocampal pathway is consistent with the hypothesis that each new encoding as well as retrieval of relevant stored traces take place at different theta phases [23]. This is supported by the synchronization of gamma LFP at different theta phases in the respective afferents converging on hippocampal subfield Cornus Ammonis 1 (CA1) from hippocampal subfield Cornus Ammonis 3 (CA3) and from the EC [24,25]. The EC conveys current sensory information directly to CA1 while CA3, the dynamics of which are dominated by feedback connections, can initiate memory retrieval and then send it to CA1. Indeed, gamma synchronization in the CA3–CA1 pathway, and its segregation to a particular phase of theta, correlates with learning and decision-making performance in a working memory task [26,27].

Communication during sleep
Although a link between hippocampal theta and neocortical dynamics is widely accepted, research on network dynamics during sleep in hippocampus and neocortex have traditionally proceeded independently [28,29]. In neocortex, slow wave sleep (SWS) is associated with widespread slow oscillations between ‘UP’ states when neurons are active and silent ‘DOWN’ states. Sleep spindles powerfully entrain neurons throughout neocortex during UP states [28,29]. Recent evidence suggests that cortical activity powerfully affects hippocampal activity during sleep. The most prominent SWS events of the hippocampus are sharp-wave bursts. Precise temporal analysis has revealed that sharp waves in the hippocampus occur preferentially during cortical UP states [30–32]. Paralleling the theta-orchestrated coordination during the active state described above, during sleep intrahippocampal and entorhinal–hippocampal pathway gamma oscillations are also segregated to different phases of the UP/DOWN cycle [32,33]. Inspired by these observations, one hypothesis posits that hippocampal replay begins with self-organized synchronization of subsets of neurons in the CA3 network during the input-free cortical DOWN state, generating a ‘seed’ for cell assemblies discharging during the ensuing sharp-wave burst, triggered by the arrival of UP-state excitation from the cortex. Sharp-wave induced replay propagates to CA1 and later outside the hippocampus. Thus the cortical excitatory drive associated with UP states can time and, potentially, shape the hippocampal sharp-wave activity [32]. In turn, sharp waves can transiently influence cortical activity [30,31,34].

**Hippocampus and neocortex alternate as information source and receiver**
The functional role of synchronous oscillations in the two-stage model can be theoretically understood as an information source-receiver framework as follows [22,30,32]. During awake state encoding as well as SWS consolidation the network follows slow clock rhythms, theta and slow oscillations, respectively, that create a ‘duty cycle’ of information exchange with the direction of transfer changing according to the oscillatory phase (Figure 2). In this duty cycle, the dynamics of the current information source can be biased to match the ‘receptive’ phase of the receiver. This ‘source-receiver’ hypothesis would thus explain why sharp wave-triggered hippocampal replay occurs less frequently during the DOWN state of neocortical neurons. The same model could also help further understand how multimodal sensory input is integrated during theta oscillations in the hippocampus where network dynamics is strongly segregated to different phases of the theta cycle.

**Information encoding in the hippocampus**
In addition to enabling information transfer, the theta rhythm also has a crucial role in information encoding: shaping the time course of hippocampal cell activity in a very precise way.

**Encoding: theta rhythm and phase precession**
 Theta oscillations can synchronize the encoding of sequential spatial information via ‘phase precession’. Rodent hippocampal ‘place’ cells are principal neurons active as the animal transits its ‘place field’. Across the place field, a neuron will fire at progressively earlier phases of each theta cycle, so that as the rat exits the place field the preferred phase of firing will be 180–360 degrees earlier than it was at the beginning [35]. Thus within each theta cycle, place cells fire in a sequence that recapitulates the immediately previous trajectory, and at a timescale fast enough to trigger spike timing-dependent plasticity (STDP [36]) and hence help store that information. Theta phase precession is ubiquitous throughout hippocampal subregions, and has also been
observed in the EC [37]. We propose that phase precession might also help to bridge the gap between the different preferred phases observed at each station on the entorhinal–hippocampal pathway (Figure 1) by broadening the theta phase ranges at which neurons in each module fire. Combined with the phase shifts between different structures described above, phase precession creates complex patterns of coiring across structures, the significance of which will have to be investigated, for example with respect to the propagation of spatial information between medial EC and the hippocampal subfields.

Although phase precession can synchronize the encoding of sequential spatial information, to support episodic memory the hippocampus must also associate nonspatial and nonsequential information (for example, about objects or sensory experiences) with its spatial and temporal context. A second level of temporal organization of neural activity might subserve this task. Groups of hippocampal CA1 neurons repeatedly activate synchronously in a very narrow time window (~30 msec, roughly corresponding to a gamma cycle) at the theta trough, possibly corresponding to Hebbian assemblies [38]. Cell assembly activations might reflect the association of nonspatial information to a spatial representation or (note that the two possibilities are not mutually exclusive) transient switches between different hippocampal spatial representations [39,40]. In any event, the strong concurrent signal from members of the assembly could exert a powerful influence on another assembly of downstream neurons that could then ‘read’ and act on the information conveyed [41]. Once again, synchronous activation in a small time window could help to trigger STDP and leave a trace of the assembly in the synaptic matrix effectively storing it in long-term memory.

**Hippocampal–PFC communication, cell assemblies, dopamine and the selection of relevant memories**

Further research has pointed to the possible functional significance of cell assembly activations and interstructure communication. Of particular interest is the rat medial PFC (mPFC, to some extent anatomically and functionally reminiscent of the primate dorsolateral PFC) because it receives direct hippocampal inputs. The oscillatory coherence between hippocampal and prefrontal LFP theta rhythms depends on behavioral state: for example it is enhanced during periods with high working memory demands in rats and mice [19,42,43] in a performance-dependent way, and it correlates with anxiety [44]. Such coherence would facilitate communication between these structures [45]. However, hippocampal–PFC communication could be implicated in other cognitive functions, in particular long-term memory encoding. At the choice point in a Y-maze task where the rat must learn new rules to obtain a reward, theta coherence between these structures is increased and rises further after a rule has been reliably acquired [21]. This is accompanied by the synchronization of PFC cell assembles to the hippocampal theta rhythm, possibly through reinforced efficacy of inhibitory interneurons. These synchronous prefrontal patterns might contribute to long-term memory traces through STDP-based plasticity processes. Because prefrontal assemblies arise at the same theta phase as do hippocampal assemblies [38], storage could be implemented in global hippocampal/PFC assemblies by reinforcing interstructure connections. These cortico-hippocampal assemblies might support hippocampal ‘index’ representations: rapidly forming associations of hippocampal and cortical representation by which the hippocampus would link together different components, residing in multiple cortical areas, of an episodic memory [46].

However, what triggers these synchronization effects within and between structures? Once a new rule has been acquired in the Y-maze the rat can confidently predict the upcoming reward: the choice point where the crucial information for solving the task is likely to be processed. It would thus be highly advantageous for that information to be stored in long-term memory. Dopamine could trigger this because it conveys reward information. Findings that dopamine infusions in PFC of anesthetized animals reinforce LFP theta coherence with hippocampus, as observed in Y-maze learning, support this hypothesis. Dopamine infusion also triggers synchronization of mPFC principal neurons to hippocampal theta, as observed in learning animals, and this could facilitate cell assembly formation and lead to long-term storage. Furthermore, reward-associated patterns are more strongly replayed during the following sleep period in mPFC [34] and ventral striatum [47]. Similarly, hippocampal reward-related neural patterns are replayed disproportionately more frequently during immobile wakefulness [48]. The mechanisms might not be limited to mPFC because reward-dependent theta phase locking of neural activity was also observed in orbitofrontal cortex [49].

These mechanisms might be part of more general processes that control which information gets stored in memory. In some experiments, intensity of replay was found to correlate with the relative incidence of the experience (visit to a location) replayed [50,51]. However, this was not the case in a more complex environmental and behavioral context where intensity of replay did not reflect amount of experience with a given trajectory [52]. A possibility is that less visited trajectories could elicit more ‘novelty’ signals (conveyed by neuromodulators) that might give rise to more synchronized activity [53] and therefore stronger storage that evens out the effects of experience. This would have the advantageous consequence of establishing a memory representation of environmental elements of uniform strength throughout the maze.

Dopamine in PFC influences many cognitive functions, for example working memory. The data reviewed here lead to the hypothesis that this control might be exerted, at least partly, by modulating cortico-hippocampal coherence [19,42,43] and assembly synchronization.

**Hippocampal–striatal communication and online evaluation of behavioral valence**

The reward-processing network includes other areas, most notably the ventral striatum (nucleus accumbens), also intimately connected with the hippocampus. Hippocampal subfield CA1 and the subiculum send substantial unidirectional projections to the ventral striatum [54,55].

Interestingly, the mechanisms of hippocampal–striatal communication present many similarities with cortico–hippocampal interactions described above. During active locomotion and other attentive behaviors, hippocampal
 theta rhythm co-occurs and is coherent with theta activity in dorsal and ventral striatum, especially during decision making [56–58]. Hippocampal theta activity is relevant for local striatal processing (as it is for the neocortex) as evidenced by phase locking of substantial subsets of ventral striatal neurons [58,59]. Ventral striatal neurons generate firing patterns correlating to task events such as rewards, sensory stimuli predicting rewards and approach responses to goal locations [47,60–62]. Strong evidence has been raised for outcome anticipation there [63]: notably, a subset of ventral striatal neurons expressed an incremental ‘ramp’ in firing rate as an animal approached reward in time and space [47] probably reflecting the value attached to an animal’s current state with respect to reaching a goal state. These ‘ramping’ anticipatory neurons show phase precession to hippocampal theta rhythm, similar to hippocampal place cells [64], hinting that hippocampal spatial representations are tightly coupled to a moment-to-moment updating of expected reward value. A related but different form of hippocampal-striatal communication has been identified during ‘forward sweeps’ of hippocampal activity mentioned above. Ventral striatal neurons that normally fire close to or at reward sites on a maze are briefly active during hippocampal forward sweeps at decision points; this suggests a tight coordination of prospective coding of information about future possible positions and coding of expected reward [62].

Neural sequences can be replayed forwards and backwards
During active behavior spontaneously emerging hippocampal assemblies can also replay sequences related to previous experience, either in a forward [65,66] or in reverse order [67]. Forward and reverse replay can coexist during wakefulness: the former mostly observed at the beginning of a run, the latter more at its endpoint [68]. Buzsáki’s excitation-spread mechanism is still a contending hypothesis for reverse replay when the replay sequence begins at the current animal position [11,66–68] (Figure 3). Note however that Gupta and colleagues [52] observe many reverse replay events at locations far away from the current animal location, which cannot be explained by this model, suggesting additional mechanisms. Forward replay can be explained by asymmetric synaptic potentiation as predicted by STDP [36]: if cells A and B activate in sequence, only the synapse from A to B will be activated but not from B to A. The role of ‘awake replay’ and assembly activations for memory encoding is supported by other findings: first, synchronous activations are more frequent during exploration of novel environments [53], and they are accompanied by high frequency oscillations (100–300 Hz) resembling ‘ripple’ oscillations observed in CA1 during sharp waves. Second, at reward sites or during short pauses while running on the maze, neural activity configurations of a previous running episode on a different maze are replayed [50,69] or might ‘recapitulate’ the trajectories run only a few moments earlier or to be run imminently [66,70]. Third, in a spatial memory task, cells encoding the memorized goal location are preferentially synchronously active, and the intensity of activation predicts successive memory performance [71].

Assembly activations in the awake state might contribute to online information processing
Assembly synchronization might also have an impact on working memory encoding. In inactive delay periods in spatial working-memory tasks, hippocampal cells showed activity correlated with previous or planned running trajectories [72]. Sequences of activations of transient hippocampal cell assemblies occur also when running in a wheel in the delay period of a spatial working memory task [73]. The identity and the temporal ordering of the cells active during this delay period predicted the rat’s choice at the end of the delay period, so that transient, sequential assembly activation could be part of the machinery supporting working memory.

In another experiment on a Y-maze, as the rat briefly stops at the fork, ensemble activity in the hippocampal CA3 subfield spontaneously replays sequences (‘forward sweeps’) of activity corresponding to the two choices of maze arms [70]. This activity could contribute to a decision-making system weighing the consequences of either alternative. The idea that this short duration, awake replay might contribute to route planning is reinforced by the finding that replay can ‘sweep’ physically possible trajectories that have never been followed by the animal before [52], indicating that spontaneous activity at encoding time is not constrained to reproduce previously stored configurations of activity.

Consolidation
While the animal is asleep, or is otherwise inactive, brain dynamics changes radically [11], and becomes dominated by sharp-wave bursts (in the hippocampus) and by slow oscillations and spindles (in the cortex during sleep). During sleep the same activity configurations that occurred during preceding active behavior are reactivated spontaneously, a phenomenon thought to be very important for information exchange across brain structures, resulting in systems consolidation. We review below some of the recent advances in sleep replay research, in particular the results in interstructure communication.

Dynamics of sleep replay
Early demonstrations of sleep replay in rat hippocampal place cells were made in the 1990s by several researchers, notably Bruce McNaughton and colleagues [74], and later extended to cortex [75] and striatum [47,58,76]. These experiments showed that pairs of neurons that repeatedly activated simultaneously during active behavior also spontaneously coactivated during following sleep, preserving the temporal ordering, that is, which cell tended to fire before the other (review [77]). Most reports concern sleep replay during SWS, although a few show replay during rapid eye movement (REM) sleep (see e.g. [78]). The synchronized patterns of SWS (in particular, sharp waves) might be more suited for spontaneous replay. Nevertheless, REM could play a different role in consolidation, for example facilitating stabilization at the synaptic level [79].

Although initial reports gave accounts of sleep replay in terms of the average correlation between cell pairs over relatively long time periods (e.g. [74]), later research has
concentrated on the precise structure of replayed ensemble activity. Lee and Wilson [65] showed that hippocampal place cells replay firing sequences mirroring the ordered activation that took place as the rat previously traversed place fields of different cells in succession on a track. Both the simpler reactivation measures and sequence replay are strongest during sharp waves. Sequence replay takes place in visual [80] and PFC [81] as well, during sleep after performing a task that requires memorizing and re-enacting of serial body movements. The replay was so precise that in some cases it preserved the detailed features of the crosscorrelograms between neurons [58,65,81]. In hippocampus, PFC as well as in the ventral striatum, sequence replay took place at a temporally compressed rate with the
sequence activating as much as 7–10 times faster than during the original behavior [58,65,81]. As is the case for theta phase precession, this accelerated replay would lead to pre- and postsynaptic cells firing in a sequence rapid enough to induce STDP, hence favoring long-term memory storage.

However, sequences are not the only form of ensemble replay: similar to during active behavior, transient and simultaneous (and not necessarily ordered) coactivations of neuronal groups are also observed, which last 30–100 msec. These 'cell assembly activations' were observed in neural populations in the rat mPFC [34] in sleep after training in a task involving flexible rule selection on a Y-maze (a task that requires the involvement of the PFC). In fact, these assembly activations are equivalent to those observed in active behavior in the same experiment [21].

Influence of pre-existing neuronal network state on reactivation

Simultaneous and sequential assembly activations characterize both active and inactive states theoretically supporting memory (encoding and consolidation) and online processing of information to instruct behavior. During sleep, assembly activation is ascribed to the endogenous dynamics of neural circuits because external signals are rare. However, even during the active state, intrinsic mechanisms driving the predisposed state of neurons and their connections could play a crucial role. For example, in mice traversing a completely novel track, the same sequences of hippocampal place cells activations appear as observed in a ‘preceding’ rest episode (‘preplay’) suggesting that the neurons discharging together were already predisposed to do so [82]. Furthermore, in an anesthetized preparation the patterns of spontaneous cortical activity are similar to the activity recorded in the cortex after thalamic or sensory stimulation [83]. Thus, as new inputs are processed, the brain can engage ensembles already preconfigured in the synaptic matrix. This leads to the suggestion that learning does not act on a tabula rasa in brain circuits; rather, it adapts to the current state of the system.

Replay in brainwide networks

During sleep, neocortex and hippocampus engage in an intense dialogue punctuated by cortical UP/DOWN state transitions and hippocampal sharp waves. This choreographs interactions among cell assembly activations (embodying replay and preplay) across the brain. Sequence replay in the visual cortex and the hippocampus are coordinated in UP state events [80], and replay in the PFC follows hippocampal sharp waves at short latencies [34], demonstrating possible hippocampal influence on cortical activity. A similar pattern holds for the ventral striatum where hippocampal sharp waves precede augmented firing activity and replay lasting several hundreds of milliseconds [76].

Cortical replay also correlates with cortical UP states: the average intensity of replay covaries with the frequency of UP/DOWN state transitions (an indicator of SWS depth) [84]. In the mPFC, during early SWS stages, replay tends to peak at the beginning of an UP state, or preceding onset of a DOWN state [34], when the cortex would be most receptive, according to the source-receiver model. By contrast, sharp waves can trigger cortical replay [34], and can act as a toggle for the bistable dynamics of slow oscillations [85], increasing the probability of both onset and termination of UP states. UP state onsets impose a sequential ordering completely unrelated to replay: as neurons recover from the depressed DOWN state the most excitable ones (those with the highest overall activity rate) resume firing first, then less excitable ones follow up [86] regardless of their encoding properties.

Sleep spindles and hippocampal–neocortical communication

The other major cortical event during SWS is the sleep spindle. It has been suggested that spindles, occurring at the beginning of an UP state and synchronized to sharp wave occurrence [87], represent the ideal dynamical state for cortical replay and hippocampo–cortical communication ([30], cf. [79]). By contrast, in the PFC, replay peaks immediately before spindle occurrences (rather than simultaneously) [34]. This suggests the possibility that spindle activity, rather than directly enabling replay, could increase intradendritic calcium in a relatively nonspecific way, and in this way facilitate plasticity phenomena triggered by replay and, ultimately, memory consolidation [88].

Replay in the inactive state and memory: functional implications

Memory consolidation, as mediated by spontaneous activity and replay during the inactive state, should affect the strength of the memory trace as measured both by behavioral performance and by the neural activity at retrieval time. Indeed, electrical stimulation aimed at selectively disrupting sharp waves, and therefore replay, impairs memory retention [89,90]. In an aversive conditioning paradigm, involving a time delay between the cue and the negative stimulus, sustained delay activity in PFC appears only after an idle consolidation period after training [91]. In humans, hippocampal/prefrontal correlations, as measured by fMRI blood-oxygen-level dependent (BOLD) signals, are correlated with memory retention [92]. Striatal replay is also likely to be connected with memory consolidation: behavioral studies have indicated an instrumental role for the Ventral Striatum in offline memory consolidation of Pavlovian approach responses [93].

Concluding remarks

In this brief presentation of the complexities of the interaction between the hippocampus and the cortex (and the ventral striatum), we saw how ideas that emerged in the 1980s in hippocampal physiology have gradually evolved to a two-stage dynamical model involving communication between many brain structures. In the future, we will need to include in this schema other brain structures, such as the amygdala, that are crucial for memory consolidation and for valence computation, and that are closely connected to the hippocampus. Indeed, some relevant initial data are coming in [94]. Structures such as the hippocampus and the PFC, discussed here, are part of the default mode network identified in neuroimaging experiments. A dynamical understanding of the default network might
arise from electrophysiological experiments in humans [95] as well as in animals.

We also showed how massive multichannel electrophysiological recordings, in combination with contemporary data analysis techniques and behavioral manipulations, provide insight into mechanistic processes crucial to understanding memory mechanisms. The future will probably bring even more detailed dissections of the same brain circuitry with new genetic, interventional [96], electrophysiological and imaging techniques allowing us, for example, to discriminate precisely different neuronal species and cortical layers, and taking us closer to the essence of the stages of memory processing. This physiological approach might prove to be a key factor in solving the long-standing debate on system consolidation. New experiments will explore the differential encoding in the brain for recent and remote memories, and how the transition between episodic and semantic memory (see e.g. [97]) could take place.

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