Review

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 [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 [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 [3–5] for reviews articulating diverse positions). However, evidence from human functional magnetic resonance imaging (fMRI) (e.g. [6]) and animal immediate early gene experiments (e.g. [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 [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

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.
Hippocampal subfields: the hippocampus proper (an archicortex) consists of the dentate gyrus (DG) and CA1 and CA3. The traditional view postulates a 'trisynaptic 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).
Oscillatory coherence: when oscillations in two brain structures keep a constant phase relationship, facilitating possible communication between them.
Replay: the spontaneous reactivation, often during sleep, of neural configurations that occurred during an earlier experience.
Ripples: spontaneous LFP oscillations at 150–200 Hz observed in the hippocampal subfield CA1 during sharp waves correlated with synchronous activity bursts.
Sharp waves: brief (~100 msec) large hippocampal LFPs during quiet wakefulness or SWS.
Spindles: cortical LFP oscillations at 7–14 Hz during early phases of SWS in bouts of a few seconds.

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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 intrahippocampal

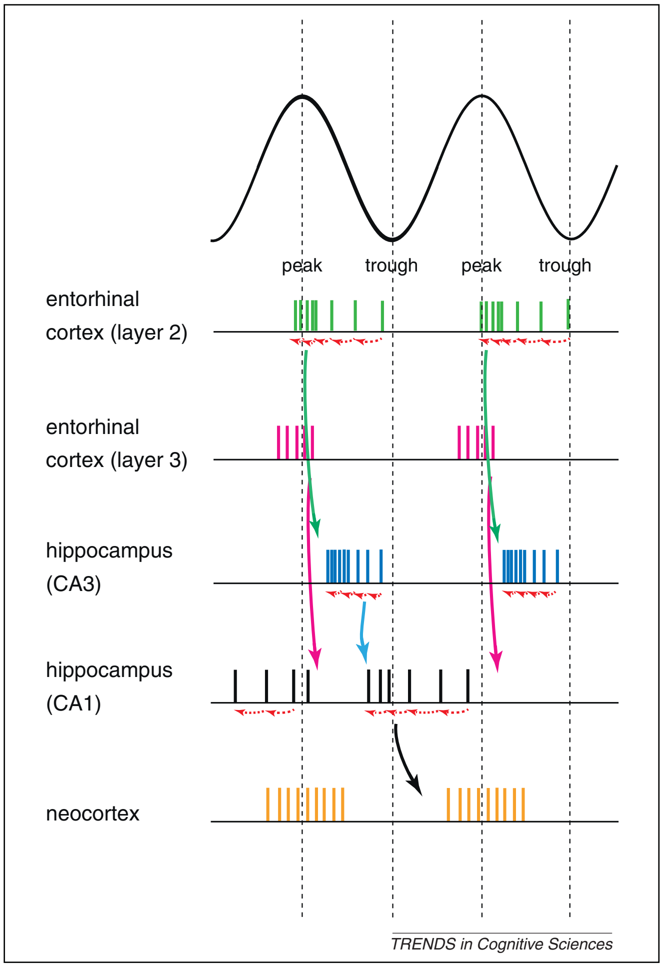

Figure 1. Simplified diagram of the interrelationships between the theta rhythm and neuronal activities in the hippocampus, EC and neocortex during the active state. Top: cartoon of hippocampal CA1 pyramidal layer LFP theta oscillations. Below (raster diagrams): firing preferences of the majority of 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].