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A single microcircuit with multiple functions: State dependent information processing in the hippocampus

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Abstract

Many neural circuits process information in multiple distinct modes. For example, the hippocampus is involved in memory encoding, retrieval, and consolidation processes. These different mnemonic computations require processing of differing balances of current sensory input and previously stored associations. Here we explore patterns of activity in hippocampal output area CA1 associated with different information processing states. We discuss the evidence linking these patterns to specific inputs to CA1 and describe behavioral factors that are related to the balance of synaptic drive. We suggest that understanding the factors that influence information flow in the hippocampal circuit could provide important new insights into how neural circuits are reconfigured on the fly to perform different functions at different times.

Like many brain regions, the hippocampal circuit supports multiple modes of information processing. The hippocampus and adjacent structures in the medial temporal lobe are essential for rapidly encoding new memories, retrieving stored memories and consolidating memories for long-term storage. These memory processes differ in their requirement for external (arising in the cortex) and internal (arising within the hippocampus) information. During the encoding of new memories, highly processed sensory information from the entorhinal cortex (EC) drives the development and expression of new representations throughout the hippocampal circuit. In contrast, consolidation is thought to depend primarily on internal drive, with stored information broadcast out of the hippocampus to engrain memories in distributed hippocampal-neocortical circuits. The pathways supporting retrieval are less clear, but we suggest that external and internal drive are likely to be balanced, with external input serving as a cue to reinstate internally stored patterns. Here we discuss recent evidence bearing on the encoding, retrieval, and consolidation of spatial representations and how these processes may differentially engage internal and external drive to hippocampal output area CA1.

Neural activity associated with encoding and consolidation

Encoding of new spatial information within the hippocampus is thought to depend on the development of new representations during exploration. When an animal first moves through a novel environment, about 50% of CA1 pyramidal neurons are active [1] and each neuron's activity is generally restricted to a portion of the environment referred to as the

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cell's "place field." These place fields develop quickly with experience [1–3], consistent with the importance of the hippocampus for the rapid encoding of new information.

The subsequent consolidation of these spatial representations has been hypothesized to occur primarily during sleep. In particular, hippocampal network events known as sharp-wave ripple (SWR) oscillations are prevalent in sleeping animals, and during these events representations of previous behavioral experiences are reactivated [4,5], often replaying entire behavioral sequences [6]. This repetition is thought to engrain representations in distributed hippocampal-neocortical circuits, a hypothesis that has received recent support from experiments showing that disrupting SWRs following learning impairs subsequent behavioral performance [7,8].

However, SWRs and the replay of past experiences also occur frequently in the awake state [9–12]. Furthermore, while SWRs are most prevalent when animals are still, SWRs and reactivation can be seen during periods of exploration that are traditionally associated with place field activity [13,14]. Awake SWRs may play an additional role in memory retrieval [12,15–17]. Recently we tested this hypothesis by interrupting awake SWRs as animals learned a spatial alternation task. We found that selective disruption of awake SWRs impaired learning and performance in the aspect of the task that required the animal to use specific past experiences to guide subsequent choices [51]. This disruption had no detectable effect on place cell activity, suggesting that disruption of awake SWRs leads to a specific deficit in memory retrieval while leaving memory encoding intact.

Taken together, these findings demonstrate that CA1 shows distinct types of population activity that include place coding and memory replay. These patterns are thought to reflect memory encoding and consolidation / retrieval processes respectively, but how can one circuit support these multiple patterns of activity?

Distinct patterns of inputs to CA1

CA1 is the primary output of the hippocampal circuit and is most frequently discussed as having two main excitatory inputs: a weak input from EC layer 3 (EC3) which terminates in the outer 1/3rd of the dendrites and the strong input from upstream hippocampal subfield CA3 which terminates in the proximal 2/3rds of the CA1 apical dendrites (Figure 1) [18]. Here we consider how these two main inputs can differentially influence activity in CA1.

The superficial layers of the EC receive convergent input from virtually all of the associational regions of the cortex. Neurons in EC3 show generalized tuning properties, firing in response to head direction, environmental borders, and with geometric grid patterns [19–22]. This generalized spatial input from EC3 is sufficient for sustaining place cell activity in CA1 [23] and plays an important role in the encoding, but not retrieval, of contextual memories [24]. However, the inputs from EC3 to CA1 synapse on the most distal CA1 dendrites and *in vitro* studies have consistently reported that these inputs are very weak and in fact lead to feed-forward inhibition of CA1 pyramidal cells [25]. Therefore it is unclear how the weak synapse between EC3 and CA1 can support place coding and the memory functions attributed to the EC3 input to CA1 [26–29]. Understanding hippocampal area CA2, a small region between CA1 and CA3, may resolve this issue. Recent reports of strong EC3 drive of CA2 and CA2 drive of CA1 *in vitro* [30] suggest that CA2 may serve to amplify the weak EC3 input to effectively drive CA1 [31]. While future work is needed to establish the role of CA2 *in vivo*, this amplification by CA2 may explain how the external input from EC3 can drive place coding in CA1.

While EC3 inputs are sufficient to drive place coding in CA1, CA3 plays a central role in driving SWRs and the associated memory replay in CA1 [34,35]. In particular, memory

reactivation in CA1 requires CA3 input [37] and in the intact circuit memory reactivation is of higher fidelity in CA3 than in CA1. The importance of CA3 for reactivation brings up another puzzle: if EC3 plays a central role driving place cell activity by itself, how does CA3 drive coherent sequences of place cells during reactivation? Or, put another way, how is it that both EC3 and CA3 can drive coherent spatial representations at different times?

One clue may come from the importance of CA3 for one-trial learning [32] and the very rapid development of CA3 place fields in a novel environment [1]. These findings suggest that CA3 undergoes rapid plasticity in new situations. In contrast, stabilization of place coding in CA1 takes days [1]. Therefore, we suggest that the slower plasticity in CA1 reflects a reconciliation process whereby synaptic plasticity tunes both EC3 and CA3 inputs such that the same CA1 place cell can be driven by either external drive from EC3 during place coding or internal CA3 inputs during memory replay.

Dynamic Coupling of CA1-CA3 and CA1-EC

In order to understand how CA1 might transmit different mnemonic information to downstream structures at different times we need to understand how the inputs to CA1 are dynamically balanced in the behaving animal. There have been two main approaches to investigate the relative influence of an input on downstream targets: directly by measuring the field excitatory post-synaptic potentials (fEPSPs) following electrical stimulation and indirectly by measuring the properties of the local field potential (LFP). Electrical stimulation of the Schaffer collateral pathway from CA3 to CA1 *in vivo* evokes strong fEPSPs in CA1. Direct measurements show that the effective strength of the CA3-CA1 synapse can vary as a function of behavior, with strongest influence of CA3 on CA1 when animals are still and weakest when animals are moving [38]. More recently we found that this pathway was best described as varying continuously as animals move more through their environment, with the largest fEPSPs seen when animals are still and progressively smaller fEPSPs observed as animals move more quickly (C Kemere, MF Carr, MP Karlsson, F Zhang, K Deisseroth, and LM Frank, abstract in Soc Neurosci Abstr 2010, 100.8). Thus, the influence of CA3 on CA1 is graded and can change very rapidly.

The balance between internal, CA3 drive, and external EC drive of CA1 has also been examined by examining oscillations in the local field potential (LFP). These oscillations are thought to reflect synchronized synaptic inputs and to entrain the timing of firing within neural circuits. Specific patterns of oscillatory activity can be used to infer coupling of a region with various inputs. For example, SWRs in CA1 are characteristic of CA3-CA1 coupling [34]. In addition, exploratory locomotion is associated with a prominent ~8Hz oscillation known as the theta rhythm and intermittent periods of 30–100Hz gamma oscillations in CA1 [39,40]. While theta oscillations are relatively coherent across CA1, CA3, and EC, the properties of the gamma rhythm in CA1 can reveal which of the two main inputs to CA1 is dominant. In particular, the presence of power in the slow gamma band (~30–50 Hz) in CA1 is predictive of coupling between CA3 and CA1, while the presence of power in the fast gamma band (~50–100Hz) is predictive of coupling between the EC and CA1 [40,41]. Thus, coherent gamma oscillations between CA3 and CA1 or EC3 and CA1 may indicate facilitated transmission of information [42].

We recently examined the relationship between ongoing behavior and the coupling of CA3-CA1 and of EC3-CA1 during learning as a function of movement speed. CA3-CA1 coupling was inversely correlated with movement speed: slow gamma and SWR power were largest at very low speeds and decreased as speed increased (MF Carr, C Kemere, MP Karlsson, F Zhang, K Deisseroth, and LM Frank, abstract in Soc Neurosci Abstr 2010, 100.7). In contrast, EC3-CA1 coupling was positively correlated with movement speed: fast gamma

power increased with increasing speed (see also [43]). This shift towards external, cortical drive (EC input) at faster speeds is consistent with observations of stronger sensory responses during increased movement speed [45,46] and suggests that the strength of EC drive to the hippocampus may be inherited from other cortical areas. Thus during learning there is a continuously changing balance between CA3 and EC3 drive to CA1 as a function of behavioral state. As a result, at slow speeds there is strong internal drive and at fast speeds there is strong external drive. This trade-off may enable switching between consolidating or retrieving recently acquired information when still and accurately representing new locations when moving quickly. At the intermediate speeds associated with exploratory behaviors such as scanning the surrounding environment there is a relative balance between CA3 and EC3 driven patterns, suggesting that balanced input may be particularly important for reconciling the CA3 and EC3 representations to accurately encode new information.

We found that the dynamic tradeoff between CA3 and EC3 drive of CA1 as a function of movement speed was strongest during novelty, when new learning is required. In more familiar environments, other behavioral factors may alter the relative strength of CA3 and EC3 influence on CA1 output. For example, CA3-CA1 coupling may be necessary to reinstate stored memories to make informed decisions. Indeed, CA3-CA1 coupling has been found to be enhanced when animals approached a position in a maze where they needed to make a memory guided decision [44], consistent with the hypothesis that CA3 drive of CA1 is important for memory retrieval. We suggest that behaviors which require the engagement of the hippocampus such as new learning and memory retrieval lead to a shift in the dynamic balance of inputs towards greater internal drive (CA3 input). Finally, it is important to note that CA3 and EC3 may lead to different patterns of network activity in CA1 through additional mechanisms. For example EC3 and CA3 may modulate their relative timing to the ongoing theta oscillations or differentially target sub-networks of CA1 neurons. Recent evidence that neurons in CA1 vary in their firing properties as a function of depth have raised that possibility that EC3 preferentially targets the deep CA1 pyramidal layer and CA3 preferentially targets superficial CA1 [47].

Modulating the dynamic balance of inputs

Taken together these findings suggest that CA1 supports memory encoding and retrieval / consolidation by dynamically altering the balance between EC3 and CA3 input respectively. While we do not yet understand how this dynamic balance of inputs is controlled in the behaving animal, neuromodulatory influence on this microcircuit could sculpt the relative strength of these two inputs. For example, CA1 receives cholinergic inputs from the medial septum and acetylcholine *in vitro* differentially suppresses the CA3 and EC3 inputs to CA1 in a dose dependent manner, with significantly greater suppression of the CA3 input as compared to the EC3 input [48]. Furthermore, it has recently been discovered that there is a functional feedback loop between the hippocampus and the ventral tegmental area (VTA). Activity in CA3 leads to multisynaptic disinhibition of dopaminergic neurons in the VTA and disruption of this feedback pathway disrupts memory retrieval [49]. CA1 in turn receives dopaminergic input from the VTA and dopamine reduces the threshold for LTP at the CA3 – CA1 synapse [49]. Previously we have shown that SWR activity in CA3 is enhanced following reward [50] suggesting that the positive feedback loop between CA3 - VTA - CA1 may enhance the encoding of salient memories and rewarding contexts.

Possible roles of dynamic coupling

We suggest that the relative strengths of the CA3 and EC3 inputs to CA1 govern, to a large extent, the ongoing information processing state of the hippocampal circuit. One possible

scheme is shown in Figure 2. When external EC3 input dominates, CA1 can reliably reflect information about the state of the external world. When internal CA3 input dominates, output region CA1 will transmit information about stored associations to downstream structures, supporting the consolidation of memories in distributed neocortical circuits. Finally, balancing internal and external inputs to CA1 may be important for both memory encoding, where internal and external representations must be aligned to produce consistent and informative outputs [1] as well as during memory retrieval, where sensory cues can trigger the reinstatement of stored memories.

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Highlights

- The hippocampal circuit is critical for multiple memory functions.
- These functions depend on different patterns of drive to output area CA1.
- Patterns of drive change on a moment-by-moment basis during learning.
- The balance of EC/CA2 and CA3 drive of CA1 may set network state and function.

Figure 1.

Major excitatory inputs to hippocampal output area CA1. Information about the external world reaches CA1 directly via the temporoammonic pathway from EC3 (red). EC3 synapses on the distal apical dendrites in CA1 in stratum lacunosum moleculare. EC3 influences CA1 disynaptically via input to CA2 (orange). CA2 synapses in both the proximal apical dendrites in stratum radiatum and in the basal dendrites. The highly recurrent hippocampal area CA3 (blue) rapidly stores associations and sends strong projections to stratum radiatum in CA1.

Figure 2.

Dynamic balance among inputs to CA1 may subserve distinct mnemonic functions. Color represents relative input strength, with more opaque colors representing stronger inputs. In this scheme, strong CA2 and EC3 input drives spatial representations during exploration, balanced EC3, CA2 and CA3 inputs drive both retrieval and reconciliation of EC3/CA2 and CA3 inputs and strong CA3 inputs drive consolidation.