COMPUTATIONAL NEUROSCIENCE

Insights into hippocampal network function

A new study proposes a full-scale model of the entorhinal cortex–dentate gyrus–CA3 network, providing a conceptual overview of the computational properties of this brain network, to show that it is an efficient pattern separator.

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There is hardly an area in the mammalian brain on which so many experimental facts are known as the hippocampus. Both the anatomy of its network circuitry and the physiology of its constituent neurons and synapses have been characterized in remarkable detail. For many years, the hippocampus has also been the prime target area when studying synaptic plasticity and its role in learning and memory. Yet, despite this wealth of experimental data, there is still no clear understanding about how the specific properties of network circuitry, neurons and synapses contribute to the purported function of the hippocampal network. Writing in *Nature Computational Science*, S. Jose Guzman and colleagues[1] propose a biologically realistic, full-scale network model to show that these various specific properties and their intricate interactions optimize higher-order computations performed in this biological network.

One of the primary components in current theories of hippocampal network function is pattern separation, which denotes the effect that similar input patterns presented to the network result in more dissimilar output patterns from the network (Fig. 1b). Thus, pattern separation helps to distinguish inputs and provides the means to categorize them by downstream networks. This component is conventionally associated with early stages of the three-layer feedforward neuronal network of the entorhinal cortex–dentate gyrus–hippocampal CA3 (Fig. 1a). Another, complementary, component is pattern completion, which describes the effect of having a partial input being completed into a full output: 'half a word suffices' (Fig. 1c). This component is typically associated with later stages of the hippocampal feedforward network.

In their study, the authors focus on pattern separation, but pattern completion is also considered. Specifically, they address the following question: whether and to what extent the three-layer feedforward network provides the anatomical, physiological and biophysical properties to support the computational process of pattern separation. To this end, they developed, implemented and simulated a network model of this brain network, including most of the known cell types in the circuitry, using realistic values of network connectivity, cell properties,

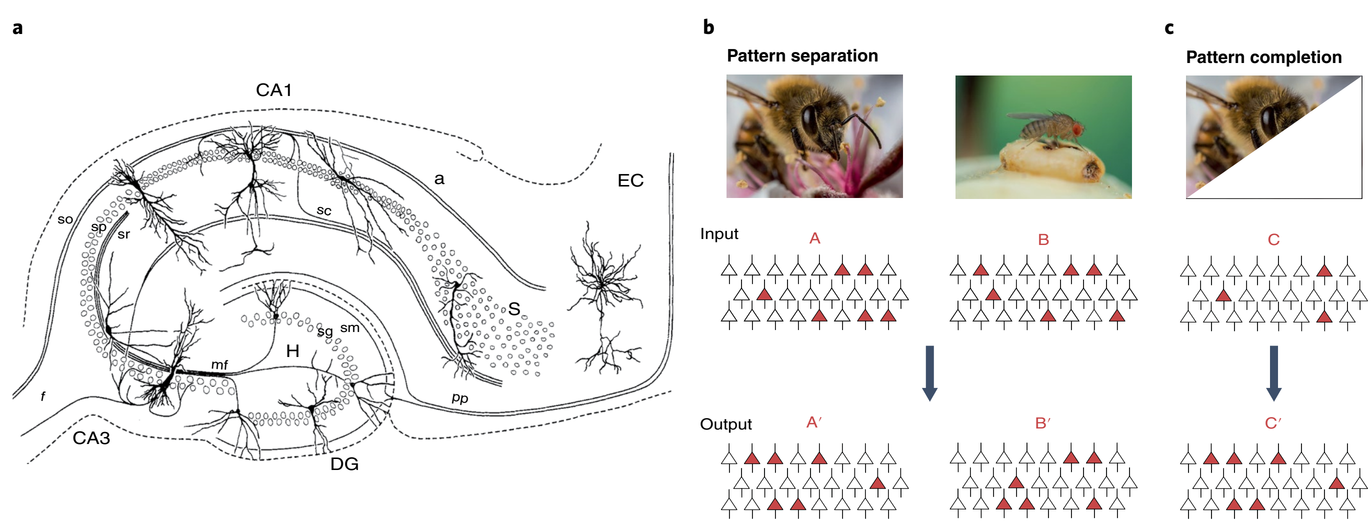

Fig. 1 | Pattern separation and pattern completion in the hippocampal network. a, Basic circuitry of the rodent hippocampus. Schematic drawing of the hippocampal formation, demonstrating the main cell types, laminae and subfields. The figure is a modification from Cajal's famous original drawing[10]. The excitation enters the dentate gyrus (DG) by the perforant path (pp), runs along the mossy fibers (mf) and the Schaffer collaterals (sc) and leaves the hippocampus via the alveus (a) or the fimbria (f). so, stratum oriens; sp, stratum pyramidale; sr, stratum radiatum; sg, stratum granulosum; sm, stratum moleculare; H, hilus; EC, entorhinal cortex; S, subiculum. **b**, Schematic illustration of pattern separation. Neuronal activity at the input (top) and the output level (bottom) in response to two similar input stimuli (top). Cells active in patterns A and B are colored red. Highly overlapping input patterns (A, B; top) are converted into weakly overlapping output patterns (A′, B′; bottom). **c**, Schematic illustration of pattern completion. Neuronal activity at the input (top) and the output level (bottom) in response to a partial input stimulus (top). Cells active in pattern C are colored red. A partial input pattern (C; top) is converted into a completed output pattern (C′; bottom; compare to pattern A′ in **b**). Credit: adapted with permission from ref. [11], Wiley (**a**); Anand Varma/Getty (**b**, left); Benjamin Fabian (**b**, right).

synaptic dynamics and other biophysical properties — many of them stemming from their own experimental work[2–5]. Importantly, the authors chose to make a full-scale model of the network, thereby avoiding the complex issues involved with scaling connectivity, neuronal and synaptic properties with network size.

Over the years, a number of different ingredients for pattern separation have been proposed in the context of different brain networks. These include divergent feedforward excitation in the cerebellum[6,7], lateral inhibition in the insect olfactory system[8], plasticity-dependent detonation properties of mossy fiber synapses in the hippocampus[3], and Hebbian synaptic plasticity in the input pathway to the hippocampus[9]. Thus, the authors access the role of each of these ingredients in the separation performance of their network model. They compare and unravel the contributions of external, gamma-modulated inhibition and internal, lateral inhibition to the separation performance of the network. Likewise, they compare and quantify the contributions of global versus local connectivity to the separation performance. They also compare the contributions of divergent and convergent projections in the network and the importance of sparse connectivity and fast signaling and plasticity in mossy fiber synapses. To each of these questions and sub-questions, the authors present an array of simulation studies, upon systematic variation of the relevant network, cellular and synaptic parameters, together with careful quantitative analyses of the effects of these parameter variations on the network's pattern separation performance, using three well-established, complementary quantitative measures for this performance.

The authors found that pattern separation was primarily generated between the first two layers of the network, but, surprisingly, was further enhanced in the transition to the third layer. In contrast to Marr's work on the cerebellum[6], the authors found that divergent connectivity was not strictly required for pattern separation in the hippocampal network. Instead, pattern separation represents a distributed network computation, involving multiple layers of the feedforward network. They found that a critical role in the pattern separation process was played by the combination of gamma-modulated inhibition and lateral inhibition in the early network layers. In addition, local inhibition was found to support pattern separation more effectively than global connectivity, by avoiding longer delays and, thereby, facilitating more rapid lateral inhibition. Interestingly, sparse connectivity of mossy fiber synapses decreased, rather than increased, pattern separation performance. Finally, Hebbian plasticity of the mossy fiber synaptic inputs to the hippocampal network was found to be able to shift the hippocampal network from pattern separation to pattern completion. Likewise, Hebbian synaptic plasticity at the perforant path synapses from entorhinal cortex to granule cells shifted the network from pattern separation to pattern completion.

Taken together, the paper provides a comprehensive and innovative conceptual overview of the computational properties of an important brain network, on which the literature up till now has been riddled with many isolated experimental facts and numbers, without a clear view regarding the functional role of these various facts and numbers. Interesting questions remain, though. For instance, the finding that plasticity in the mossy fiber input synapses may shift the overall network function from pattern separation to pattern completion begs the question: how may learning affect the functional role of the hippocampal network in guiding behavior? In this context, the authors hypothesize that inhibition-based pattern separation could dominate at early times, with novel input patterns, whereas plasticity-based pattern completion might prevail at later times, with more familiar input patterns. Appropriately designed behavioral experiments, combined with recordings of the involved synaptic physiology could help resolve this issue. Also, it would seem helpful to study whether this hippocampal network is able to perform other computations, besides pattern separation and pattern completion. Finally, the authors suggest that these new insights may help improve machine learning approaches in technical multi-layer networks. Currently, the intricate details of neural network dynamics have been overlooked and remain to be fully explored in machine learning, which may open new avenues in the field. ❐

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Competing interests
The author declares no competing interests.