FOREFRONT REVIEW

WHAT IS THE MAMMALIAN DENTATE GYRUS GOOD FOR?

A. TREVES,[a,b]* A. TASHIRO,[a] M. P. WITTER[a] AND E. I. MOSER[a]

[a]*Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory, Norwegian University for Science and Technology, Trondheim, Norway*

[b]*International School for Advanced Studies, Cognitive Neuroscience Sector, via Beirut 4, I-34014 Trieste, Italy*

Abstract—In the mammalian hippocampus, the dentate gyrus (DG) is characterized by sparse and powerful unidirectional projections to CA3 pyramidal cells, the so-called mossy fibers (MF). The MF form a distinct type of synapses, rich in zinc, that appear to duplicate, in terms of the information they convey, what CA3 cells already receive from entorhinal cortex layer II cells, which project both to the DG and to CA3. Computational models have hypothesized that the function of the MF is to enforce a new, well-separated pattern of activity onto CA3 cells, to represent a new memory, prevailing over the interference produced by the traces of older memories already stored on CA3 recurrent collateral connections. Although behavioral observations support the notion that the MF are crucial for decorrelating new memory representations from previous ones, a number of findings require that this view be reassessed and articulated more precisely in the spatial and temporal domains. First, neurophysiological recordings indicate that the very sparse dentate activity is concentrated on cells that display multiple but disorderly place fields, unlike both the single fields typical of CA3 and the multiple regular grid-aligned fields of medial entorhinal cortex. Second, neurogenesis is found to occur in the adult DG, leading to new cells that are functionally added to the existing circuitry, and may account for much of its ongoing activity. Third, a comparative analysis suggests that only mammals have evolved a DG, despite some of its features being present also in reptiles, whereas the avian hippocampus seems to have taken a different evolutionary path. Thus, we need to understand both how the mammalian dentate operates, in space and time, and whether evolution, in other vertebrate lineages, has offered alternative solutions to the same computational problems. © 2008 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: hippocampus, memory storage, memory retrieval, neurogenesis, spatial representation, mossy fibers.

Contents

*Correspondence to: A. Treves, SISSA, Cognitive Neuroscience Sector, via Beirut 4, I-34014 Trieste, Italy. Tel: +39-040-3787623; fax: +39-040-3787615.
E-mail address: ale@sissa.it (A. Treves).
Abbreviations: ACh, acetylcholine; DG, dentate gyrus; MAM, methylazoxymethanol acetate; MF, mossy fiber/fibers.

An appreciation of the role of the hippocampus in memory began to diffuse half a century ago thanks to the work of Brenda Milner (Scoville and Milner, 1957). Gradually her findings stimulated a renewed interest in trying to understand the beautifully regular internal structure of the hippocampus, described by classical anatomists, in terms of memory function. A prominent feature of that structure, common to all mammals, is the dentate gyrus (DG), whose main neuronal population of granule cells comprises a sort of side-loop to the pyramidal cells of the next hippocampal region, CA3. Cells in CA3 receive on their apical dendrites direct projections from layer II in entorhinal cortex, but those projections also make synapses, on the way as it were, onto the dendrites of the granule cells, which in turn send the so-called mossy fibers (MF) to CA3, where the fibers make strong and sparse synapses near pyramidal cell somata. What is the function of this side-loop, which amounts to duplicating afferent inputs to CA3?

Over the 50 years since the report by Brenda Milner, the overall function of the hippocampus in human memory has been understood much better and it has been related to its function in other mammals (O'Keefe and Nadel, 1978; Squire, 1991; Moser et al., in press). Why the mammalian hippocampus should need a DG is still an open question, despite intense research on this subfield during the past decade (reviewed e.g. in the recent volume edited by Scharfman, 2007).

MARR'S 'SIMPLE' MEMORY

After elaborating his grand memory theories of the cerebellum and of the neocortex, the young David Marr turned

to what he regarded as little more than a straightforward exercise, and developed a theory for archicortex, i.e. the hippocampus (Marr, 1971). He put together in brilliant mathematical form a general view of what the hippocampus does in memory, a view condensed from the neuropsychological studies, and took this as the basis to understand the internal structure of the hippocampus. This theoretical research program, of understanding the design principles of the structure starting from the function, or reverse engineering the hippocampus, has been enormously influential. Nevertheless, the articulated internal structure which anatomists and physiologists describe is somewhat strident with Marr's notion of the hippocampus as a 'simple' memory that is further characterized as 'free,' i.e. which can be accessed from an arbitrary fraction of its content, as opposed to 'directed' (a label which, incidentally, would have perhaps resonated more with the classical notion of the 'trisynaptic' circuit; Andersen et al., 1971). Moreover, the details of his modeling approach are difficult to appraise, let alone to assess. Marr thought in terms of discrete memory states, and devoted an entire section of his paper to 'capacity calculations,' which indicates that he realized the importance of a quantitative approach; yet, his own capacity calculations, when taking into account how sparse neuronal activity is in the real brain, would lead to a rather dismal capacity of only about $p_c \approx 100$ memories (see e.g. Papp and Treves, 2007). To effectively retrieve each of these memories from partial cues, Marr eloquently emphasized, in words, the 'collateral effect' i.e. the potential role in pattern *completion* of recurrent connections, prominent among CA3 pyramidal cells (Amaral et al., 1990); but his own model was not really affected by the presence of such collaterals, as shown later by careful meta-analysis (Willshaw and Buckingham, 1990).

Marr did not conceive of any interesting role for the DG (Fig. 1), and he summarily dismissed granule cells as

effectively 'extended dendritic trees' for CA3 cells, which he accordingly labeled as 'collector' cells. It is possible that in this cavalier attitude he was biased by his earlier assessment of the role of the granule cells of the cerebellum, which he thought of as performing expansion recoding (Marr, 1969). In the cerebellum, however, the granule cells are postsynaptic to the axons that are called (there) MF, and the huge cerebellar expansion factor from MF to granule cells is not observed in the hippocampus, where the striking element, instead, is the peculiar type of synapses from the granule cells to CA3 pyramidal cells, those on the hippocampal MF.

Marr was well aware of the interference among distinct memories, in his model, but focused on interference at retrieval, not on the disrupting effect of other memories on the storage of a new one. Moreover, the peculiar firing properties of hippocampal pyramidal cells in rodents had not yet carved their special niche in the collective imagination (the discovery of place cells was nearly simultaneous with his paper; O'Keefe and Dostrovsky, 1971). So Marr did not think in terms of spatial memories, or of the specific interference effects that arise with memory representations that reflect the continuity of space.

Connectionist networks later became widely popular as models of the storage of memories on the synaptic weights between neuron-like units. In such networks, which are typically feed-forward, from input to output, and are trained with artificial mathematical procedures such as back-propagation, controlling interference between memories is simpler. It amounts to ensuring good pattern *separation*, i.e. that two input patterns that should be distinct but are correlated, end up less correlated at the output stage. Sometimes pattern separation is referred to with the more stringent term of *orthogonalization*, which loosely suggests representations 'as different as possible' (even though one does not usually mean strictly orthogonal in the
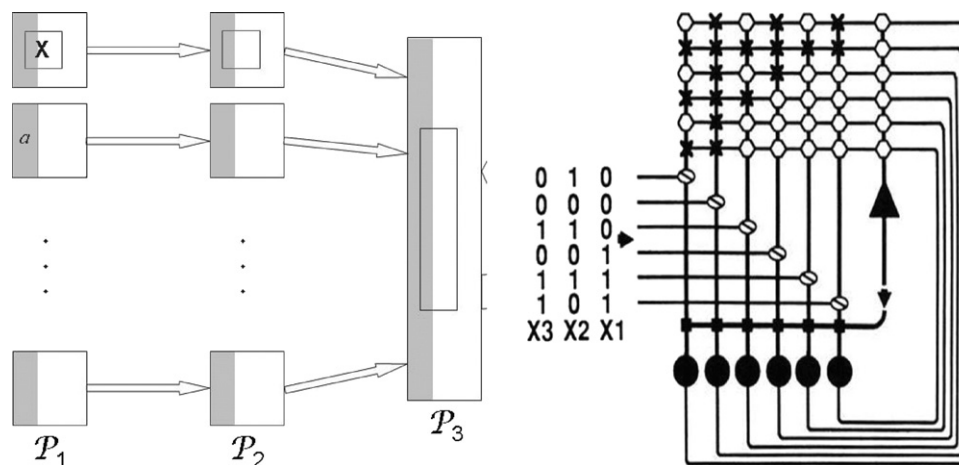
Fig. 1. The model by Marr (1971), like several modern connectionist models, does not ascribe a salient role to the DG, which is not even represented in his block scheme (left); whereas in the 'Hebb-Marr' recurrent network of McNaughton and Morris (1987) the crucial detonator synapses (slashed ovals in the diagram on the right) are taken to represent MF synapses. Note that in the Marr scheme the collaterals in the rightmost population P_3 mix information which had been kept segregated in the earlier feedforward stages P_1 and P_2; a stored event is taken to be represented by a fraction a of active units at each stage, and to be reinstated when a subevent X is given as input even to a single block of P_1. Earlier processing stages are considered also by McNaughton and Morris, but not included in the diagram. Their diagram exemplifies three different patterns X1, X2 and X3 being transferred to the recurrent network for storage.