WHAT IS THE MAMMALIAN DENTATE GYRUS GOOD FOR?

Alessandro Treves[1,2], Ayumu Tashiro[1], Menno E Witter[1], and Edvard I Moser[1]

[1]Kavli Institute for System Neuroscience and Centre for the Biology of Memory, NTNU, Trondheim, Norway

[2]SISSA, Cognitive Neuroscience Sector, Trieste, Italy

Short title:

The mammalian dentate gyrus

Editorial correspondence: Edvard Moser, Kavli Institute for System Neuroscience and Centre for the Biology of Memory, NTNU, Trondheim, Norway ; tel. +47 73598278; fax +47 73598294; email: edvard.moser@ntnu.no

Correspondence after publication: Alessandro Treves, SISSA, via Beirut 4, I-34014 Trieste, Italy tel. +39-040-3787623, fax. +39-040-3787615, email: ale@sissa.it

Total number of words in text: ~11,500
Total number of figures: 6, of which 4 in color

Acknowledgements: Alessandro Treves thanks the Institute of Advanced Studies of the Hebrew University for its warm hospitality. The authors gratefully acknowledge discussions with several colleagues, including Bruce McNaughton, Rob Sutherland and Fred (Rusty) Gage. The work is supported by the Kavli Foundation, the McDonnell Foundation, and a Centre of Excellence Grant from the Norwegian Research Council.

Abstract

In the mammalian hippocampus, the dentate gyrus is characterized by sparse and powerful unidirectional projections to CA3 pyramidal cells, the so-called mossy fibers. The mossy fibers 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 dentate gyrus and to CA3. Computational models have hypothesized that the function of the mossy fibers 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 behavioural observations support the notion that the mossy fibers 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 dentate gyrus, leading to new cells that are functionally added to the existing circuitry, and may account for much of its on-going activity. Third, a comparative analysis suggests that only mammals have evolved a dentate gyrus, 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.

WHAT IS THE MAMMALIAN DENTATE GYRUS GOOD FOR?

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, 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* 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 fifty 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., 2008). Why the mammalian hippocampus should need a dentate gyrus is still an open question, despite intense research on this subfield during the past decade (reviewed e.g. in the recent volume edited by H 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 dentate gyrus (Figure 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) mossy fibers, and the huge cerebellar expansion factor from mossy fibers 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 mossy fibers.

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 backpropagation, 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 geometrical sense, which would require entirely separate active units). With recurrent networks, as Marr had envisaged, implemented in the CA3 region, interference problems are more serious, and have to be dealt with already when storing new memories, lest these memories are realized as bad copies of pre-existing ones.

Could it be that the dentate gyrus is there to reduce interference during storage, i.e. to produce a new pattern of firing activity in CA3 that is well separated, or unrelated, to those representing other memories already in storage?

Detonator synapses

With their 1987 review, McNaughton and Morris took the Marr framework closer to the real hippocampus, and brought it to bear on the question of why we have a dentate gyrus. They discussed several 'Hebb-Marr' associative memory model architectures and whether they resembled hippocampal networks. The operation of such models can be more readily analyzed if the memory patterns to be stored are assigned `by hand', rather than self-organized under the influence of on-going inputs. One can imagine that a system of strong one-to-one connections from another area may effectively 'transfer' a pattern of activity from there, where it is determined by some unspecified process, to the associative memory network. McNaughton and Morris (1987) observed that the complex synapses on the mossy-fiber projections from dentate gyrus to CA3, which also by virtue of their proximity to the soma were considered to be individually quite powerful (Blackstad and Kjaerheim, 1961; Andersen and Loyning, 1962), might 'detonate' the postsynaptic cell, borrowing a term from the Eccles (1937) early theory of electrical synaptic transmission. This would offer an approximate implementation in the real brain of such one-to-one connections (Figure 1). The distributions of activity to be stored in memory would be effectively

generated in the dentate gyrus, perhaps by expansion recoding (again, as hypothesized for granule cells in the cerebellum) and then simply transferred to CA3. Correct or not, the detonator proposal selects a subset of hippocampal models – those that envisage a specific role for the dentate gyrus – as potentially explanatory of the organization of the hippocampal formation, as it had been described in mammals; even though other influential system-level neural networks models, much like Marr's original one, may also usefully reproduce certain qualitative aspects of hippocampal memory function, without invoking a similar special role for the dentate gyrus (Schmajuk, 1990; Carpenter and Grossberg, 1993; Burgess et al., 1994; McClelland et al., 1995; Levy, 1996; Gluck and Myers, 2001).

Thus the question that remains open is whether or not the dentate gyrus is essential for hippocampal memory function. Maybe the dentate gyrus is only one of several possible solutions to effective memory storage. Alternatively, function alone, qualitatively characterized ("memory storage"), is insufficient to fully determine structure: the function may be implemented also without a dentate gyrus, and without other solutions, only less well, in quantitative terms. Considering these possibilities is further stimulated by the observation, reviewed below, that the mammalian and avian hippocampi may carry out similar functions with dissimilar structure. By the time the McNaughton and Morris review was published, fortunately, the Hopfield (1982) model had led to the development of much more powerful techniques for the mathematical analysis of neural network models, encouraging a new generation of researchers to take a more quantitative approach than the qualitative simulation typically produced by earlier connectionist models. This approach will be considered again below. First, however, it is useful to ask the basic question, what is "a dentate gyrus"? Which are the essential features of its neural network design?

The Dentate Gyrus

What has been called the dentate gyrus in the mammalian lineage is a strikingly well conserved part of the cortex with a trilaminar structure, considered to be typical of the "primitive" cortex or allocortex (Stephan, 1975; Figure 2). The outermost layer, called the *molecular layer*, is relatively cell free. It comprises the dendrites of the dentate principal cells. In addition, it contains axons that originate in a limited number of sources, the main ones being the perforant path axons arising from the entorhinal cortex and the intrinsic associational and commissural systems which originate in the ipsilateral and contralateral hilar mossy cells, respectively. Additional fibers come from a variety of local interneurons, present in any of the three layers of the dentate gyrus (Houser, 2007; Leranth and Hajszan, 2007).

The second or main *cell layer* is comprised of densely packed so-called granule cells, which have small spherical cell bodies (8-12 μm in diameter). These cells extend dendrites bifurcating very close to the soma and preferentially distributing to the molecular layer. In adult rodents, basal dendrites are largely absent although in young rats of 5-10 days of age such basal dendrites have been described (Seress and Pokorny, 1981; Spigelman et al., 1998; Ribak et al., 2004). In monkeys and in humans, a substantial number of granule cells display basal dendrites, which extend into the hilus (Seress and Mrzljak, 1987). The morphological features of the basal dendrites, such as dendritic branching and spine density, are similar to those of apical dendrites (Seress and Mrzljak, 1987; Frotscher et al., 1991). Basal dendrites, like the apical ones, are involved in the mossy cell mediated excitatory circuitry that is typical for the dentate gyrus (Frotscher et al., 1991).

The third and deepest layer present in the dentate gyrus of mammals is generally referred to as the *hilus*. It is located subjacent to the granule cell layer and extends to the border of the dendritic layer of CA3 that is interposed between the upper (suprapyramidal) and lower (infrapyramidal) blades of the dentate gyrus. Mossy cells are the most numerous cell type in the hilus, although still a factor of 25/30 less abundant than granule cells (Amaral et al, 1990). These excitatory neurons are characterized by their densely spiny dendrites and several thorny excrescences on both the cell body and proximal dendritic shafts and their dendrites are mostly confined to the hilus (Amaral, 1978).

The axons of the DG principal (granule) cells have been called the *mossy fiber* projection. They pass through the hilus on their way to their ultimate target, the CA3 pyramidal cell, and in the hilus they issue collaterals that either synapse onto mossy cells (Claiborne et al., 1986) or form recurrent collaterals into the deepest portion of the molecular layer, where they most likely target basket cells (Ribak and Peterson, 1991). The bundle of axons emerging from the dentate is so conspicuous that it can be seen almost without any additional staining protocols as a translucent area in slices; therefore it has become known as *stratum lucidum* (Ramon y Cajal, 1893; Lorente de Nó 1934). All fibers form giant, spatially complex synaptic terminals onto the dendrites of CA3 pyramidal cells, described as mossy fiber terminals (for reviews, see Henze et al, 2000; Blaabjerg and Zimmer, 2007). Irrespective of species or strain, the complex mossy fiber terminals, in the hilus as well as in CA3, contain high concentrations of Zinc, and this has been used to visualize the mossy fiber system (Timm, 1958; Haug, 1967; Danscher, 1981; see Blaabjerg and Zimmer 2007 for further details). These Zinc-containing complex terminal structures, which are rather sparsely innervating CA3 pyramidal cells (only some 50 synapses per CA3 cell in rodents; Amaral et al., 1990) but appear quite effective at activating their targets (Henze et al, 2002), are the ones considered to be "detonator synapses" by McNaughton and Morris (1987).

The dentate gyrus as an unsupervised CA3 instructor

The vertebrate 'hippocampus' appears to have taken a common evolutionary route, up to the definition of its general functional role. In mammals, it then followed a rather narrow path in further specifying its internal organization. This suggests that in order to understand what the dentate gyrus, in particular, contributes to what the mammalian hippocampus does, we need to ask *how well* it does it, in quantitative terms, because a qualitative account could well work out without a dentate gyrus. To develop a quantitative mathematical analysis was precisely the aim of the Treves and Rolls (1992) network model.

Separate storage and retrieval phases

Apart from the detonator synapse suggestion, early analyses of associative memory networks had focused on characterizing the *retrieval* of patterns already stored, without really considering how those memory patterns could have been *stored*, i.e. embedded in a matrix of synaptic connections. The Hopfield (1982) model, in particular, once analyzed by Amit, Gutfreund and Sompolinsky (1987) with techniques imported from statistical physics, provided a mathematical framework to quantitatively analyze associative retrieval in systems dominated by recurrent connections. The analyses show that a population of N units, representing discrete memories with patterns of firing activity of sparseness a ($0<a<1$ signifying, roughly, that Na units are active in each memory representation), can associatively retrieve up to a well-defined *critical* number p_c of such memories.

The number p_c is proportional to the number of recurrent collateral synapses each unit receives, and it increases as a goes to 0, i.e. the sparser is the representation. Each of the retrieved firing patterns can represent of the order of $Na \ln(1/a)$ bits of information about the content of the memory (Treves and Rolls, 1991). Following Marr, McNaughton and Morris (1987) and Rolls (1989) had pointed out that the extensive system of CA3 recurrent connections could be there to implement such a retrieval operation, through Marr's *collateral effect*. Devoting such extensive resources to retrieval makes sense, however, only if the stored memories actually contain as much information, i.e. roughly $a \ln(1/a)$ bits per unit, as the collaterals are later able to retrieve.

This quantifies, then, to what extent interference from the memory traces already in place should be reduced: the novel pattern to be stored should contain that much *fresh* information. It may be assumed that almost none of it reverberates through recurrent connections, because their presynaptic units largely reflect previously stored patterns (whereas in a feedforward system their activity is determined solely by the new input). As noted by McNaughton and Morris, a system of strong one-to-one projections from a separate population of units, without recurrent connections, i.e. the dentate gyrus, could indeed provide the solution, simply by imposing its own novel pattern of activity onto the postsynaptic units. The one-to-one correspondence is not necessary, however: what matters is that, no matter how sparse the CA3 representation, afferent inputs, which bring novel information, be at least as strong as all recurrent inputs put together, which only reflect previously stored and hence interfering memories (Treves and Rolls, 1992; Figure 3). MF inputs appear strong on their own (Henze et al, 2002; Rollenhagen et al, 2007), and their effective strength may be augmented by concurrent inhibition (Mori et al, 2007) and short-term facilitation (Salin et al, 1996).

Such strong afferent inputs may well be unsupervised, in that they just need to produce patterns uncorrelated with previously stored input patterns. It helps if they convey sparse activity. For effective retrieval, however, recurrent connections should prevail, as they enable reverberatory activity – the collateral effect – to reinstate the original memory pattern, including the components that are not represented in the input cue. In addition, the effective relay of small retrieval cues requires the afferent synapses to relay distributed activity, with weights that have been associatively modified at the time of storage, in order to optimize the cue signal-to-noise ratio (Treves and Rolls, 1992). These conflicting requirements favour, first, separating *in time* a storage phase and a retrieval phase. Temporal separation allows for differential modulation, like the one proposed to be effected by cholinergic inputs, not just in piriform cortex (Hasselmo et al, 1992), but in cortical networks in general (Hasselmo and Bower, 1993). Second, the conflicting requirements favour separating *anatomically* the afferent inputs operating at storage and at retrieval, to optimize the respective parameters separately. Both input systems must report on the same representation, otherwise the retrieval cue cannot be part of the content of a stored memory pattern. The dentate gyrus essentially duplicates, with its mossy fiber projections to CA3, the message that the direct perforant path inputs convey to CA3, about the same patterns of activity in layer II of entorhinal cortex, but it implements the option for anatomical separation. If a new discrete pattern of entorhinal activity has to be stored in CA3, it can first be recoded as a pattern of activity in the dentate gyrus, and then be transformed by the mossy fiber projections into yet another, apparently random, CA3 pattern of activity. If so, it should be possible with appropriate experiments to observe the anatomical separation between the inputs driving CA3 at storage and at retrieval, with only the former coursing through the dentate gyrus side-loop to CA3.

Towards localizing pattern separation in the dentate gyrus

A generic involvement of the hippocampus in decorrelation of similar experiences is apparent from studies suggesting that animals with complete lesions of the hippocampus are not able to discriminate environments with a number of common features. If an electric shock is given during exposure to one of two similar but not identical chambers, animals with hippocampal lesions are severely impaired in choosing the safe environment on a subsequent preference test (Selden et al., 1991). When reexposed to the training chambers, the lesioned rats exhibit freezing in both environments whereas control animals only freeze in the shock-associated environment (McDonald et al., 1995; Frankland et al., 1998). Similarly, the ability to distinguish overlapping sequences of odour choices is impaired by hippocampal lesions (Agster et al., 2002), as is the ability to distinguish neighbouring food wells in a delayed matching task in a large open arena (Gilbert et al., 1998). Whenever tested, the retrieval deficit correlates with the degree of similarity between the task conditions.

The critical effect of the hippocampus for successful discrimination between similar experiences provides opportunities for testing the specific involvement of the dentate gyrus in pattern separation. Using the same task as in their early study with complete hippocampal lesions, Gilbert and colleagues (2001) showed that animals with colchicine-induced lesions of the dentate gyrus are unable to discriminate correct and incorrect food wells when their locations are close to one another. The deficit decreased with increasing distance between the correct object and the foil. Performance was not impaired by neurotoxic lesions in CA1, suggesting that different subfields of the hippocampus have different functions and that the dentate gyrus may be uniquely associated with spatial pattern separation. Successful separation may depend particularly on the detonator properties of the mossy fiber inputs to CA3 and these properties may be primarily important at the encoding stage (Treves & Rolls, 1992). In support of this idea, mice with a temporary inactivation supposedly selective for the mossy-fiber synapses were impaired in finding the hidden platform if the inactivation occurred just before training in a Morris water maze task, but the animals were unimpaired if they had learnt the platform location one week before (Lassalle et al., 2000). Moreover, rats with colchicine-induced lesions of the dentate gyrus showed impaired within-day acquisition of the most direct trajectory in a ‘Hebb-Williams’ maze, while rats with electrolytic lesions aimed at the perforant path inputs to the apical dendrites of the CA3 cells were reported to show a disproportionate impairment in retrieval, one day after acquisition was completed (Lee and Kesner, 2004). Finally, during learning in a radial-arm maze task, patterns of immediate-early gene expression suggest that the dentate gyrus tends to disengage from hippocampal information flow with increased mastery of the task (Poirier et al, 2008).

While these studies have pointed to a possible role for the dentate gyrus in pattern separation during memory encoding, the treatments are generally too crude to allow the exact mechanisms to be identified. Colchicine has a selective effect on granule cells at low doses but the higher doses required for complete hippocampal lesions may cause significant damage to other neurons and other hippocampal subfields as well. The selectivity of the procedures for lesions of the CA3 component of the perforant path and inactivation of mossy fibers is also uncertain and the exact extent of drug distribution and subregional damage cannot be determined from the reported data. New genetic interventions may allow the outputs from the dentate gyrus to be inactivated more completely and selectively in the near future.

Evidence for network mechanisms of pattern separation

A lot can be learned about the functions of the dentate gyrus by recording neuronal activity from granule cells and targets of granule cells in intact animals. Neuronal recording studies, particularly in the spatial domain, have suggested that the dentate gyrus contributes to pattern separation in at least two ways. First, representations tend to be orthogonalized by sparse firing in what is believed to be the granule cell population. Only a very low proportion of the putative granule cells fire in any given environment (Jung and McNaughton, 1993; Leutgeb et al., 2007). While a typical exploration session may activate between a quarter and a half of the pyramidal cell population in the CA fields, the proportion of active granule cells, as estimated from studies of immediate early gene activation, fluctuates from 2 to 5 per cent of the cell population (Chawla et al., 2005; Ramirez-Amaya et al., 2006; Tashiro et al., 2007). The sparse firing of the granule cells is likely to contribute to approximate orthogonalization of correlated input patterns, much in the same way as the numerous and sparsely active granule cells of the cerebellum (Chadderton et al., 2004) were thought to allow different incoming signals to be dispersed onto largely non-overlapping populations of Purkinje cells (Marr, 1969).

A second mechanism for pattern separation might be based on the recruitment of different populations of hippocampal place cells, enforced by strong 'detonator' inputs from the dentate gyrus during encoding. Place cells are cells that fire in one or sometimes several confined locations ('place fields') through which an animal is moving, but are virtually silent in all other places (O'Keefe and Dostrovsky, 1971; Moser et al., 2008). A well-characterized feature of place cells in the hippocampus is their tendency to switch or 'remap' between multiple uncorrelated representations after only minor changes in the sensory input or the motivational context (Muller and Kubie, 1987; Bostock et al., 1991; Markus et al., 1995). Hippocampal remapping can thus be seen as a special case of pattern separation in which small differences in neuronal activity in the inputs to the hippocampus are transformed to highly differentiated representations.

Where and how does remapping emerge in the hippocampal network? Place-specific firing has been observed in all subfields of the hippocampus. Pyramidal cells in CA3 and CA1 fire at single confined locations; dentate granule cells generally have multiple discrete firing fields (Jung and McNaughton, 1993; Leutgeb et al., 2007; Figure 4). Place-specific firing is abundant also in principal cells of the medial entorhinal cortex (Fyhn et al., 2004) but here the multiple fields of each cell form a periodic triangular array, or a grid, that tiles the entire two-dimensional space available to the animal (Hafting et al., 2005). Transitions between representations can be seen in all entorhinal-hippocampal areas but the nature of the transformation is quite distinct. In the entorhinal cortex, the same cells are active in each environment and the relative offset between the firing fields of the active cells remains constant across environments, suggesting that the entorhinal cortex contains a single map that is used in all environments (Fyhn et al., 2007). In the hippocampus, in contrast, and in particular in the CA3 region, the subsets of active cells in two environments are strongly decorrelated, i.e. they tend to show less than chance overlap even for environments with many common features (Leutgeb et al., 2004). This transformation of spatial representations between entorhinal cortex and hippocampus suggests that a pattern-separating mechanism is located somewhere in the early stages of the hippocampus, possibly in the dentate gyrus.

Experimental evidence suggests that the contribution of the dentate gyrus to remapping in the hippocampus depends on the type of remapping. Two major forms of remapping can be

distinguished in the hippocampal CA areas. When distributions of both place and rate have statistically independent values in two environments, the transition is referred to as 'global remapping' (Leutgeb et al., 2005a). Transitions between such representations are all-or-none, even when the sensory input is changed slowly and incrementally (Wills et al., 2005). Under other conditions, the place fields remain constant and only the rate distribution is changed; this is referred to as 'rate remapping' (Leutgeb et al., 2005a). Rate remapping is gradual and not coherent between different hippocampal neurons (Leutgeb et al., 2005ab).

Global remapping is strongly dependent on ensemble dynamics in the medial entorhinal cortex. During global remapping in the hippocampus, grid cells maintain a constant internal spatial phase relationship but the firing vertices of the grid cells in the two environments are always shifted or rotated relative to each other (Fyhn et al., 2007). Whether the dentate gyrus contributes to the transformation of signals from a single coherent representation in the entorhinal cortex to multiple decorrelated representations in the hippocampus is not known, but global remapping can, in principle, be generated merely by convergence of direct inputs to the hippocampus from modules of grid cells with different alignment to the external landmarks or by translation of the entorhinal representation to a different location on the entorhinal ensemble map (Fyhn et al., 2007, their Supplementary Figure 12). In contrast, direct entorhinal-hippocampal connections are not sufficient for hippocampal rate remapping. When only the rate distribution is changed in CA3, the pattern of coactivity among granule cells in the dentate gyrus is substantially altered after even minimal changes in the shape of the environment (Leutgeb et al., 2007). The lack of simultaneous change in the medial entorhinal cortex under such conditions (Fyhn et al., 2007; Leutgeb et al., 2007) raises the possibility that rate-based pattern separation mechanisms originate in the dentate gyrus. By themselves, these observations are not sufficient to imply that inputs from the dentate gyrus are necessary or indeed sufficient for pattern separation in the hippocampus. However, using a mouse line with NMDA receptors abolished specifically in dentate granule cells, McHugh et al. (2007) found that rate remapping was disrupted in CA3 when the mutant mice were allowed to explore two environments which differed in contextual cues but not location. The impairment in rate remapping was accompanied by a reduced ability to discriminate chambers with different conditioning histories in a fear learning task. The discrimination deficit was only apparent when the difference between the chambers was small, suggesting that synaptic plasticity in the dentate gyrus is necessary for decorrelation and disambiguation of overlapping experiences.

The conclusions from these rodent studies are supported by very recent findings in humans. Bakker et al. (2008) obtained high-resolutions scans from the hippocampus while subjects performed an incidental declarative memory encoding task. Activity in the CA3 and DG regions of the hippocampus differed more across presentations of similar but non-identical pictures than any other subregion that was scanned in the medial temporal lobe. It still needs to be explained why pattern separation should give rise to a change in average regional activity in this study; in the animal studies, representations are separated by recruitment of different populations of active cells but there is apparently no overall change in the total activity of the area. Despite this paradox, the human results suggest that the role of the early stages of the hippocampus in pattern separation is not limited to decorrelation of spatial representations but rather extends to declarative memory processes more broadly.

A need for new models in the spatial domain

The new evidence reviewed above points to some of the main features which future mechanistic models of the dentate gyrus should incorporate, even though important elements are still unclear, and require further experimental work. First, in rats granule cells appear to show place fields qualitatively not too dissimilar from those of their targets, the CA3 pyramidal cells (Jung and McNaughton, 1993; Leutgeb et al., 2007). Second, the quantitative features of those fields appear to require a more complex notion of sparseness than the one that could be used with CA3 place fields. In describing CA3 fields, one could apply the same intuitive notion of sparseness, essentially, that one can apply to discrete, nonspatial representations. For discrete patterns of firing activity, one can loosely refer to the fraction a of 'active cells' – although a more precise definition of sparseness is needed to measure it from experimental data (Treves and Rolls, 1991) – and use the same quantity as the probability that a particular cell will be active in a given pattern. Similarly, with CA3 place cells, although spatial representations are clearly continuous (place fields are graded and not binary) and neighbouring places within an environment are coded by highly correlated firing patterns, one can still use the same intuition, with minimal adjustments. One may measure the typical size f of a place field relative to the size of the environment, say $f \approx 0.1$ in a common recording box, and the probability p that a given cell will be active *somewhere* in the environment, say $p \approx 0.3$ (Leutgeb et al., 2004). Then the probability that a given place cell, recorded e.g. during a sleep session, will be active in a particular location of a particular recording box will be roughly (its coding sparseness) $a=pf$; the probability that it will have *two* place fields in the same box will be roughly p^2, and so on – these are gross estimates, but not completely misleading. They appear to be misleading, instead, in the case of DG granule cells. Why?

Experimental evidence indicates that the probability that a given granule cells be active in a typical environment is quite low, say $p \approx 0.03$ (Chawla et al., 2005; Ramirez-Amaya et al., 2006; Tashiro et al., 2007) but, if active, it is quite likely that it will have more than one place field (Leutgeb et al., 2007). In fact, the number of place fields observed for individual granule cells appears not too different from a Poisson distribution with mean parameter q, say $q \approx 1.7$ (Leutgeb et al., 2007). If f denotes again the typical relative size of their fields, can one again estimate as pf the probability that a given granule cell will be active at a given location of a given environment? Not really. It is more accurate to say that with probability $1-p$ the cell will not be active at all, and with probability p it will be active somewhere, and at a particular location with probability pqf. Two separate mechanisms, which remain to be elucidated, likely determine (i) which (small) subset of granule cells may be active in a particular spatial environment, and (ii) where exactly in the environment they will have their (usually multiple) place fields.

Understanding how activity in the dentate gyrus may help establish new spatial representations in CA3, that is, extending the model of an unsupervised instructor to the spatial domain, requires this more articulate notion of sparseness, but it also requires a theoretical framework that remains largely to be developed. A useful start is the Samsonovitch and McNaughton (1997) 'multi-chart' model, which allows for a calculation of storage capacity (Battaglia and Treves, 1998) that smoothly generalizes earlier results applicable to models with discrete memories. While awaiting the refinement of further analytical approaches, useful insight can be obtained with computer simulations. These have shown, for example, that the observed multiple granule cell fields resemble, more than the (usually single) CA3 place fields, those produced by self-organization of feedforward inputs from grid-like-units (Rolls et al., 2006; Franzius et al., 2007), redefining those

feedforward models as relevant for studying granule cell activity and its changes after different manipulations. Convincing simulations remain to be produced, that demonstrate what combination of inputs may be crucial in establishing CA3 fields. It appears increasingly likely, however, that in order to develop a powerful model of the network mechanisms that involve the dentate gyrus, yet another recent finding has to be given proper consideration: adult neurogenesis in the dentate gyrus itself.

The potential value of adult neurogenesis

The dentate gyrus is one of a few regions in the mammalian brain in which neurogenesis continues to occur in adulthood (Gage, 2000). New granule cells are generated from dividing precursor cells located in the subgranular zone, the hilar border of the granule cell layer (Figure 5). Initially, extra numbers of new neurons are generated, and a substantial proportion of them dies before they fully mature (Biebl et al., 2000; Dayer et al., 2003; Kempermann et al., 2003). The survival or death of immature new neurons is affected by experience, including hippocampal-dependent learning (Kempermann et al., 1997; Gould et al., 1999; Dobrossy et al., 2003; Olariu et al., 2005; Dupret et al., 2007; Tashiro et al., 2007; Epp et al., 2007). Although the precise number of newborn cells cannot be accurately assessed using currently available immuno- or genetic-labeling methods, the proportion is thought to be relatively small, e.g., it was estimated as 3-6% of the total number of granule cells per month in some studies using young adult rodents (Cameron and McKay, 2001; Tashiro et al., 2007).

Newly born neurons follow a series of maturational processes similar to neurons born in the developing brain (Esposito et al., 2005; Zhao et al., 2006). Shortly after their birth, new neurons send axons along the mossy fibers down to CA3 and produce dendritic processes into the molecular layer (Hastings and Gould, 1999; Zhao et al., 2006). By two weeks, the new neurons start receiving GABAergic and glutamatergic synaptic inputs (Ge et al., 2006), and then the number of dendritic spines increases rapidly (Zhao et al., 2006). By one month, their gross morphology is indistinguishable from that of pre-existing mature neurons (van Praag et al., 2002; Zhao et al., 2006) while changes in the microstructure of dendritic spines still continue (Zhao et al., 2006; Toni et al., 2007). After full maturation, the electrophysiological properties of new neurons are comparable to those of neurons born in the developing brain (Laplagne et al., 2006) and the responsiveness to behavioral stimulation is also generally similar (Jessberger and Kempermann, 2003; Tashiro et al., 2007; Kee et al., 2007; but see Ramirez-Amaya et al., 2006).

Neurogenesis, learning and memory

Several studies indicate that new neurons, despite their small number, make distinct contributions to learning and memory, although the exact function remains somewhat controversial (Shors et al., 2001, 2002; Bruel-Jungerman et al., 2005; Snyder et al., 2005; Saxe et al., 2006; Winocur et al., 2006). These studies used pharmacology, irradiation and genetic methods to kill dividing cells and block the generation of new neurons in the dentate gyrus. Then they examined the effects of reduced adult neurogenesis on hippocampal-dependent memory tasks. A pioneering study by the Shors and Gould groups used systemic injections of a drug called methylazoxymethanol acetate (MAM), which blocks cell division, and showed that trace eye-blink conditioning, a hippocampal-dependent memory task, was impaired in rats with a substantial reduction in the level of adult neurogenesis. In a follow-up study, these groups showed that another hippocampal-dependent

memory task, trace fear conditioning, was affected by the same manipulation, whereas other forms of learning, such as contextual fear conditioning and spatial learning in the Morris water maze, were not, raising the possibility that new neurons are involved specifically in the association of events separated by time, which is required for establishing trace conditioning. Subsequent studies found impairments in long-term retrieval in object recognition tasks, over days (Bruel-Jungerman et al., 2005), and long-term retrieval in the water maze task, over weeks (Snyder et al., 2005), after blockade of adult neurogenesis by MAM and whole-brain irradiation, respectively. An additional study found instead that contextual fear conditioning, but not acquisition or long-term retrieval of the water maze task, was affected after irradiation or genetic ablation (Saxe et al., 2006) whereas hippocampal-dependent working memory tasks in a radial maze were actually *improved* after those manipulations (Saxe et al., 2007). With such controversial results, it seems premature to conclude that specific functions require adult neurogenesis and others do not. It does appear that hippocampal-dependent memory is in some way dependent on neurogenesis, although the common mechanism underlying the various manipulations leaves the possibility that the observed effects were caused by killing other classes of dividing cells, instead of neuronal precursors. Further quantitative approaches are likely needed to better elucidate such dependence.

Modeling studies have begun to analyze the effect of adult neurogenesis in learning and memory using neural networks with neuronal turnover, where the addition of new neurons with randomly imposed connections is compensated by the death of randomly chosen pre-existing neurons. Under such conditions, slight beneficial effects on new learning accompany the clearance of old memories (Chambers et al., 2004; Deisseroth et al., 2004; Becker, 2005). Predating these models, a behavioral study using forebrain-specific presenilin-1 gene knockout mice had in fact suggested a role of new neurons in memory clearance (Feng et al., 2001). Exposure to an enriched environment increased adult neurogesis and the removal of memories acquired before the exposure, in wild-type mice, while both effects of the enriched environment were impaired in the transgenic mice. It would be important to confirm a role in memory clearance with an interference method more specific to adult neurogenesis in the dentate gyrus. It should be noted, however, that available evidence, based on the number of surviving BrdU-positive new neurons, does not support neuronal turnover in the dentate gyrus, but rather indicates pure addition of new neurons (Kempermann et al., 2003; Leuner et al., 2004; Tashiro et al., 2007). Nonetheless, these studies remind us that adult neurogenesis could have a beneficial effect without requiring any special properties in the new neurons that pre-existing mature neurons do not have. Even the simple addition of new neurons with randomly-assigned connectivity may help the dentate gyrus produce new memory patterns in CA3, uncorrelated with previously stored patterns. With the addition of new neurons the available set of granule cells is changed over time. If a given input pattern to the dentate gyrus activated several newly added granule cells, the output pattern to CA3 would be different from one caused by a similar input pattern before the new granule cells were added, enhancing pattern separation beyond the level which, network models suggest, is already achievable without neurogenesis.

Unique properties of young neurons: a critical period?

Accumulating evidence, however, supports the idea that *young* new neurons do have unique properties, which may be important to consider. Some of the behavioral studies mentioned above suggest that trace eye-blink conditioning and long-term water maze retrieval are impaired by a reduction of young new neurons, less than one month old, but not of older new neurons (Shors et al., 2001; Snyder et al., 2005). Consistent with these observations, two recent studies, using an activity-mapping approach with immediate-early gene expression, indicated that the activity of new

neurons is affected by previous experience (water maze training, or exposure to an enriched environment) at discrete stages of maturation (Kee et al., 2007; Tashiro et al., 2007) - although the specific timing is still controversial - suggesting that new neurons have a sort of *critical period* for representing new information. The critical period may be mediated by two properties of young new neurons. First, they show enhanced synaptic plasticity (Wang et al., 2000; Snyder et al., 2001; Schmidt-Hieber et al., 2004; Ge et al., 2007). Second, it was shown that the survival/death fate of new neurons, which is determined during their immature stages, is input-dependent, through NMDA receptor involvement (Tashiro et al., 2006). The importance of such determination was supported by the finding that performance in a hippocampal-dependent water maze task was impaired when a cell death blocker was infused into the animals (Dupret et al., 2007). Thus, by these two input-dependent mechanisms, new neurons with specific connectivity patterns might be produced, which reflect experience during their critical period.

The existence of a critical period may imply that *time* is an important factor to determine how experience is encoded in the hippocampus. Aimone et al. (2006) assumed that young new neurons respond less specifically to different input patterns than pre-existing neurons and that they have functional synapses onto CA3, and thus proposed that the less specific firing of new neurons may help encode information about unrelated events, which occur close in time, into overlapping subsets of CA3 neurons. Since, at different times, different subsets of new neurons are within their critical period, novel experiences occurring at different times may be encoded into less overlapping subsets of CA3 neurons by those different subsets of new neurons with different birthdates, helping pattern separation. Wiskott et al. (2006) have implicitly modeled the notion of a critical period in which only synapses of new, but not pre-existing neurons can learn, and they have suggested that adult neurogenesis is beneficial to avoid degrading old memories by encoding new ones. Thus, although their contribution is not clear, young neurons during their critical period may help memory encoding in CA3, by virtue of unique properties that mature neurons do not have.

If young new neurons play a role in encoding new information, what would be the role of mature neurons, which have already gone through their critical period? The long-term survival of new neurons over many months suggests that those mature neurons are still useful, perhaps as they may hold on to the information they acquired in their critical period. In agreement with this idea, studies using immediate-early genes, described above, have observed long-term changes, even after months, in the responsiveness of new neurons to events that also occurred earlier, during their critical period (Kee et al., 2007; Tashiro et al., 2007). These findings suggest that time-dependent encoding could occur in the dentate gyrus, in addition to CA3 as proposed by Aimone et al. (2006). Buzzetti et al. (2007) tested the idea that such time-dependent differentiation may help pattern separation, by encoding similar events occurring at different times into different sets of granule cells. Their preliminary results do not show evidence for the recruitment of different sets of granule cells in response to events that initially occurred at different times, weeks apart, although the analysis considered the total granule cell population, not new neurons specifically. Further studies that examine effects specifically implicating new neurons are thus required. The behavioral study showing that long-term, but not short-term, memory retrieval was impaired by blocking adult neurogenesis (Snyder et al., 2005) suggests that information which had been encoded by new neurons during their critical period may still require those (now mature) neurons to be effectively retrieved. This notion brings us back to the unresolved issue whether the dentate gyrus is required only in encoding new memories or both in encoding and retrieval. A possibility, consistent with a role only in encoding, is that new neurons, after their critical period, may help encode in CA3 representations related, somehow, to experience during their critical period. In this perspective, the

critical period can be regarded as a preparatory period, which churns out neurons with a specific inclination to encode (in CA3) certain representations rather than others. For example, if two entorhinal input patterns, coming at different times, reflected important common elements of a sensory scene, they might activate several of the same mature granule cells, which had been predisposed during their critical period to be activated by that scene. The two time-separated input patterns may then be assigned correlated representations in CA3, thereby linking across time specific memories that share substantial components. It had early been proposed, by McNaughton and Morris (1987) and by Rolls (1989), to consider the entorhinal-dentate connections as a competitive network, leading to the representation of relatively stable discrete categories (the 'inclinations' of granule cells) which may then be used to form non-completely random representations in CA3. The new evidence on neurogenesis stimulates now the development of those early ideas, to effectively complement the simple pattern separation/pattern completion distinction with a more refined analysis of the spatio-temporal metric of hippocampal representations.

We have described three possible ways in which new neurons may contribute to memory encoding in CA3. 1) The addition of new neurons (even if random) may enhance pattern separation in CA3 by providing additional available sets of input patterns, uncorrelated with previously-used patterns. 2) Young new neurons may play a special role in memory encoding in CA3 because of their unique properties, that mature neurons do not have. 3) The specific inclinations of new neurons, mediated by experiences during their critical period, may improve CA3 representations established after those new neurons mature. Obviously these are not mutually exclusive, and such multifaceted roles of new neurons along their maturation may help explain why the dentate gyrus needs neurogenesis, instead of simply adding classes of neurons with some specialized functions. Despite the recent expanding interest in adult neurogenesis, exactly how new neurons in the dentate gyrus are involved in learning and memory is still controversial. Further experimental studies to assess their contribution to information storage are essential to develop sharper theoretical concepts.

Hippocampus and memory in non-mammalian vertebrates

Some birds demonstrate exquisite spatial memory, hoarding food at thousands of distinct locations every year and retrieving it after months. An extensive number of studies, reviewed e.g. by Clayton and Krebs (1995) and Clayton (1998), have linked the specific memories associated with food-storing behaviour to the avian homolog of the mammalian hippocampus (see also Healy et al., 2005). Lesion studies, e.g. in pigeons, show that the avian hippocampus is required for navigation, at least when based on a geometrical map of the environment (Bingman and Jones, 1994; Vargas et al., 2004). A most interesting line of evidence suggest that a functional involvement of the hippocampal formation in spatial memory is not limited to mammals and birds, but rather it extends to reptiles and even to ray-finned fish (Rodriguez et al., 2002ab). Analogously to mammals and birds, reptiles and goldfish can use what appears to be a map-like allocentric representation of space to navigate. Moreover, these navigational strategies appear to depend on the homolog of the hippocampal formation (Butler, 2000, Vargas et al., 2006). Such an impressive conservation of the nature of 'hippocampal' functions through hundreds of millions of years of divergent evolution stimulates, with all the prudence that the notion of homology requires (Striedter and Northcutt, 1991), a comparative assessment of the internal circuitry, which might perhaps reveal the magic neural network 'trick' that has allowed us (vertebrates) to draw maps for such a long time.

Divergent patterns of medial forebrain organization

Converging observations from neuronatomical, embryological and genetic approaches support the idea that the mammalian hippocampus is homologous to the mediodorsal cortical domain of reptiles (Stephan, 1975; Lopez-García and Martinez-Guijjaro, 1988; Ulinsky, 1990a,b; ten Donkelaar, 2000) and to the most dorsomedial part of the telencephalon in birds. Whereas in most reptiles the medio-dorsal part of the telencephalic pallium shows a three-layered cortical structure, in birds the medial part of the forebrain looks different since, during development, the medial surface of the pallium merges with more ventrally located pallial structures, resulting in an overall loss of the typical cortical (i.e., layered) appearance.

The cortex in reptiles is generally divided into mediodorsal, dorsal and lateral cortex, which all present a three-layered structure that is strikingly comparable to that seen in the mammalian hippocampus. The mediodorsal cortex is further subdivided into a more medial small celled portion and a mediodorsal large celled one (Cxms and Cxml, respectively; Figure 6, left).

Principal neurons in the small celled portion are pyramidal or spherical neurons, closely packed, extending dendrites into the molecular layer as well as into the deep, polymorph layer. Similar to what is seen in the dentate gyrus in mammals, a majority of the dendrites extend into the molecular layer and the first bifurcation is close to the soma. At least six different cell types have been described within the cell layer, some of which send axons to the adjacent large celled part of the mediodorsal cortex (Wouterlood, 1981) as well as to the dorsal cortex (Olucha et al., 1988; Hoogland, 1993). This projection stains intensely for Zinc with the Timm stain (Timm, 1958), and target neurons in the large celled portion of the mediodorsal cortex. Here, the principal cells mainly have a polygonal or pyramidal cell body with large apical dendrites extending into the molecular layer, as well as basal dendrites extending into the polymorph layer and adjacent white matter (Wouterlood, 1981; ten Donkelaar, 2000). Zinc-positive terminals have further been described on neurons in the polymorph layer of the small-celled portion. The targets are large inverted pyramidal cells and more fusiform cells that show large bulb- or club-like structures with a diameter of up to 2 um, resembling the mossy fiber excrescences described for mammalian mossy cells (Blackstad and Kjaerheim, 1961; Hamlyn, 1962; Amaral, 1978; Wouterlood, 1981; Martinez-Guijarro et al, 1984; Lopez-Garcia et al., 1988; Ulinski, 1990a,b). The axons of these target cells leave the cortex, joining the underlying white matter tracts, but their targets have not been determined.

Using the definition of the dentate gyrus as provided here, and in line with many other authors, it seems thus safe to conclude that the small and large cell portions of the reptilian cortex do correspond to the dentate and CA area, respectively, as seen in mammals, although the reptiles have only a single CA field. In fact, in several mammals, such as the opussum, mice, rat and tenrec, parts of the hippocampus, generally referred to as the anterior tenia tecta and indusium griseum, resemble the lizard medial cortex, where the dentate and CA fields form a continuous sheet of cells with two morphologies, granule and pyramidal (Stephan, 1975; Wyss and Sripanidkulchai, 1983; Shipley and Adamek, 1984; Gloor, 1997; Künzle, 2004). A further piece of information supporting this conclusion is that, similar to what has been reported in the mammalian dentate gyrus, the medial cortex of adult lizards exhibits neurogenesis during the life span and differentiated neurons actually give rise to Zinc-containing projections to other parts of the cortex, thus resulting in a continuous growth of it. In the common lizard *Podarcis hispanica* this results in quadrupling the number of neurons. Even more striking are observations that almost complete lesions of the

mediodorsal cortex, damaging up to 95% of all neurons, stimulate neuroblast formation and subsequent differentiation, such that an almost entirely new cortex, connectionally indistinguishable from the lesioned one, comes into place (Lopez-Garcia et al., 2002). This effect is most likely qualitatively but not quantitatively comparable to the reported increase in neurogenesis as the result of, for example, induction of epileptic seizures in rats (Parent et al., 1997; Nakagawa et al., 2000).

In terms of connectivity, the most salient reptilian-mammalian difference is the lack, in mammals, of projections from the granule cells to either the CA1 field (consistent with the notion that CA1 is differentiated from CA3 in mammals but not in reptiles) or to the dorsal cortex. By forfeiting their longer distance projections the principal cells of the medial reptilian cortex have effectively become, in the mammalian dentate gyrus, local excitatory interneurons.

A different structure in the dorsomedial telencephalon in birds

The avian dorsomedial telencephalon (Figure 6, right) has long been regarded, and referred to, as the hippocampus of birds – or perhaps as their hippocampal complex, including the parahippocampal region (Ariens-Kapper et al., 1936). It has, e.g. in chicken (Molla et al., 1986), the usual three layers, including a middle 'granular' layer of pyramidal cells, similar to reptilian cortex and to paleocortex in mammals, and comparable overall afferent and efferent connectivity (reviewed in Dubbeldam, 1998). It remains unclear, however, whether it is at all possible to go beyond this rather general homology and try to establish a more detailed correspondence between subdivisions of such hippocampal region. In particular with regard to the dentate gyrus, the Timm stain, which in reptiles and mammals clearly identifies the Zinc-rich projections to the pyramidal cells of the large celled region (in reptiles) or to CA3 (in mammals; Figure 2), in birds produces only a weak and diffuse stain (Faber et al., 1989; Montagnese et al., 1993, 1996). In addition, most studies describing the morphology of principal cells have reported an absence of granule cells, such that variously shaped pyramidal cells form the majority of the neuronal population (Montagnese et al 1996; Tömböl et al, 2000; Srivastava et al, 2007). Another approach to try to pinpoint at the avian 'dentate gyrus' would be to make use of connectional criteria, but unfortunately this has lead to contradictory conclusions. In pigeons, Kahn et al. (2003) identify in the most ventro-medial region, which is V-shaped with two blades of neurons and a central area in between, the avian 'CA1', consistent with a correspondence suggested earlier in the zebra finch (Székely and Krebs, 1996). Atoji and Wild (2004), instead, see in the same region the pigeon 'dentate gyrus', a correspondence perhaps more in line with the V shape and the position at the medial extreme of the pallium. Taken together these data have lead several authors to suggest an absence of a dentate gyrus and of the related mossy fiber system in birds, such that only a hippocampus proper would be present (Montagnese et al., 1996; Tömböl et al., 2000; Srivastava et al., 2007).

Whether or not a dentate gyrus in birds is present does not however affect the presence of neurogenesis. It has been reported in a number of avian species that in the ventricular zone associated with the hippocampus, as well as that associated with the so-called hyperstriatum, neurons are born continuously. These neurons migrate into the hippocampal complex, where they become part of functional circuits. The rate of neurogenesis depends on experience, including spatial learning (Patel et al. 1997; Barnea et al., 2006). However, neurogenesis in the avian brain is not restricted to the hippocampal complex but also occurs in a number of other structures, for example those associated with vocalization. In both instances the rate of neurogenesis shows seasonal changes related to behaviour (Barnea and Nottebohm, 1994; Nottebohm, 2004).

Interestingly, in grey squirrels, that show seasonal changes in food caching, similar to those observed in food hoarding birds, no seasonal changes in the proliferation rate in the dentate gyrus have been observed (Lavenex et al., 2000).

Ultimately, it may be safer to resist the temptation to proclaim a trisynaptic circuit in birds, even though various sets of three cell populations with connections from one to the next (not rare in brains) may offer themselves as candidates. While describing the internal organization of the avian hippocampus and understanding how it operates at the network level is a fascinating challenge (Atoji and Wild, 2006), it could well be that our commonalities with birds are more salient at the system level. At the internal, network level, the best preserved original trait appears to be the extensive system of recurrent connections among principal cells, which however in mammals is restricted to the CA3 field. Moreover, our common ancestors may have evolved, for unknown reasons, a subsystem of Zinc-rich connections, which is prominently expressed in reptiles, may have recessed in birds, and which seems to have been perfected in mammals into the very raison d'ētre of the now-intrinsic granule cells.

Can storage and retrieval be separated without the dentate gyrus?

The divergent lines of neuroanatomical evolution reviewed above suggest that the pattern separation function, hypothesized to be enhanced in mammals by the dentate gyrus (Kesner et al., 2000; Acsády and Káli, 2007; Leutgeb and Moser, 2007), may be implemented also in other ways. Perhaps, the competition between the afferent projections, forcing a novel ensemble to represent a new memory, and the recurrent connections, reinstating fragments of previously stored ones, can be simply modulated in time, without a duplication of inputs, by potentiating afferent inputs at storage and recurrent inputs at retrieval. A temporal separation between distinct operating modes is itself a recurrent idea, although it has been articulated differently in disparate contexts. Sleep/wake algorithms, studied in machine learning, separate a wake phase in which activity reflects inputs from the sensory world and is propagated forward, and a sleep phase in which it reflects internal "models of the world' and is propagated backward (Hinton et al, 1995). Closer to the hippocampus, the rich rhythm phenomenology presented in particular by rodents has encouraged theories which allocate distinct network operations to temporal segments characterized by different rhythmic activity (Buzsaki, 1989, 2007). Over much of the past few years, several laboratories have investigated the notion that patterns encoded in the hippocampus at times of robust theta activity, during exploratory behaviour, may be retrieved in temporally compressed form in the sharp waves that accompany slow-wave sleep or rest (e.g., Wilson and McNaughton, 1994; Nádasdy et al, 1999; Lee and Wilson, 2002; Foster and Wilson, 2006; Euston et al., 2007). A more recent idea is that different phases within individual theta periods might be differentiated along the storage/retrieval axis (Hasselmo et al., 2002; Kunec et al., 2005; Zilli and Hasselmo, 2006).

A selective modulation of the activity (and plasticity) of specific synaptic systems may also be obtained at arbitrary times, irrespective of rhythmic activity, by neuromodulators such as acetylcholine (ACh). Even if spreading to all neighbouring synapses, neuromodulators can exploit the orderly arrangement of pyramidal cell dendrites in the cortex, which allows for differential action on the synapses distributed in distinct layers, as well as receptor specificity (Hasselmo and Schnell, 1994). Acetylcholine is one of several very ancient neuromodulating systems (Wessler et al., 1999), well conserved across vertebrates, and it may have operated in this way already in the early reptilian cortex, throughout its subdivisions. Although clearly relevant to the hippocampus

and to the CA3 subfield in particular, with its own complement in the dentate gyrus (Hasselmo et al., 1995, Hasselmo and Wyble, 1997; Kremin and Hasselmo, 2007), ACh action does not seem specific to it, and it has been studied in detail, for example also in piriform cortex, or in abstract networks which could be taken as models of different structures (Hasselmo et al., 1995). In neuromodulators, and indeed in other mechanisms that might modulate storage and retrieval based on different types of rhythmic activity, evolution may have found partial solutions to accomodate the conflicting drives towards optimizing storage and optimizing retrieval. One drawback of relying on ACh modulation alone is that it requires an active process that distinguishes storage from retrieval periods, and regulates ACh-release accordingly. Combining ACh modulation with rhythmic activity may dispense from such a process. In general, however, it appears that such qualitative arguments are insufficient to appreciate what can and cannot be done with neuromodulation and temporal parsing, and it remains an exciting challenge for future work to develop further quantitative analyses of these memory mechanisms.

Making space for the dentate gyrus

Emboldened by the recent discoveries, and exploiting the rather unconstrained nature of speculations about neural systems in the past, we may attempt a simplified sketch of the evolution of the structures subserving the formation of complex memories. Even though their complexity was then quite limited, we can hypothesize that already half a billion years ago these memories emerged as the culmination of sensory processing in the vertebrate pallium. In amniotes, some three hundred million years ago, memory formation occurred, foremost, in the newly organized orderly arrangement of paleocortex (where recurrent connections would dominate on the basal dendrites of pyramidal cells, leaving to afferent inputs the synaptic territory closer to the surface) with the relatively more complex, relational and spatial types of memories arising after lateral and dorsal processing, in the medial portion, rich in Zinc. One may reckon that a tentative distinction between storage and retrieval modes, to help pattern separation, was operated by neuromodulators, chiefly ACh, possibly assisted by rhythmic activity, and that the Zinc may have been there for unrelated reasons. In cold-blooded reptiles, whose inability to sustain protracted efforts, including long food searching explorations, limits the utility of spatial memory, the existing arrangements for memory formation were “deemed satisfactory”, and the dynamics of evolutionary change concentrated elsewhere – e.g., in sharpening the teeth of *T. Rex*. In birds and in mammals, instead, the possibility of long-term planned behaviour afforded by endothermy stimulated the refinement of the network mechanisms for establishing new spatial memories, with reduced interference and enhanced capacity (Carroll, 1988). Birds, at least some birds, conceived a way to achieve such refinement. They have not told us, and we still have no clue what it is (Smulders, 2006). We mammals, some two hundred million years ago, thought of using all that Zinc to set up powerful and sparse synaptic connections (the complicated way Zinc may help is just beginning to be unraveled, Vogt et al, 2000; Bischofberger et al, 2006; Mott et al, 2008), and we asked our medialmost cortex to please curl up and absolve the new instructor function. This new arrangement works fine, and we all have retained it ever since.

The above scenario might seem satisfying, but at a closer look it opens up more questions than it answers. Assuming that indeed both birds and mammals have devised separate mechanisms for memory formation, which augment rather than replace the earlier ones based on neuromodulation, what is the avian mechanism like? Is it just a different answer to the same question, as it were, or is the question that evolution had to answer a bit different in the case of birds, for example because

they fly? Do the different statistical properties of space, as perceived in flight, place different constraints on the formation of spatial memories?

And, if the dentate gyrus is indeed the mammalian 'answer', is it an answer determined by their spatial environment being essentially two-dimensional? Is it a solution that comes in the same package, so to speak, with place cells? It is interesting to note that bats, mammals that can fly, have recently been shown to have hippocampal cells with place fields similar to those observed in rodents - at least when they walk (Ulanovsky and Moss, 2007). Convincing place cells have not yet been demonstrated in monkeys, which present instead with a small proportion of hippocampal "spatial view" cells (Rolls et al., 1997); but they have been reported in humans (Ekstrom et al., 2003); and it is unclear to what extent parallel spatial correlates determine the activity of cells in various subdivisions of the avian hippocampus (Bingman and Sharp, 2007). And if the 2D topology of typical mammalian space indeed favours the dentate solution, with or without place cells, what about mammals that went back to the sea, like dolphins and whales? Are they equally well serviced by their mammalian dentate gyrus, or are they stuck in an evolutionary *cul-de-sac*, as perhaps suggested by the regressive scaling (relatively limited size) of their overall hippocampi (Morgane et al., 1982; Hof and van der Gucht, 2007)?

Scaling relations, in general, provide a body of quantitative data across mammalian species (Finlay and Darlington, 1995; Reep et al., 2007). Can we hope to understand them with quantitative mechanistic models, thus predicting the number of granule cells, for example, in a species in which it has not been measured yet, and how many new ones are produced per month? Further, with the possible advent of techniques for stimulating neurogenesis in the human dentate gyrus, is there just a potential for functional repair, or also for the outright enhancement of memory processes?

Fortunately, some of these questions seem far from being answered anytime soon, providing the prospect of many years of exciting research.

References

Acsády L, Káli S (2007) Models, structure, function: the transformation of cortical signals in the dentate gyrus. Prog Brain Res 163:577-599.

Agster KL, Fortin NJ, Eichenbaum H (2002) The hippocampus and disambiguation of overlapping sequences. J Neurosci 22:5760-5768.

Aimone JB, Wiles J, Gage FH (2006) Potential role for adult neurogenesis in the encoding of time in new memories. Nat Neurosci 9:723-727.

Amaral DG (1978) A Golgi study of cell types in the hilar region of the hippocampus in the rat. J Comp Neurol 182:851-914.

Amaral DG, Ishizuka N, Claiborne B (1990) Neurons, numbers and the hippocampal network. Prog Brain Res 83:1-11.

Amit DJ, Gutfreund H, Sompolinsky H (1987) Statistical mechanics of neural networks near saturation. Ann Phys (N.Y.) 173:30-67.

Andersen, P, Bliss, TVP, Skrede, KK (1971) Lamellar organization of hippocampal excitatory pathways. Exp Brain Res 13:222-238.

Andersen P, Loyning Y (1962) Interaction of various afferents on CA1 neurons and dentate granule cells. Colloq Int CNRS 107:23-45.

Ariens-Kapper CU, Huber GC, Crosby EC (1936) The comparative anatomy of the nervous system of vertebrates, including man. New York: Hafner Publishing.

Atoji Y, Wild JM (2004) Fiber connections of the hippocampal formation and septum and subdivisions of the hippocampal formation in the pigeon as revealed by tract tracing and kainic acid lesions. J Comp Neurol 475:426-461.

Atoji Y, Wild JM (2006) Anatomy of the avian hippocampal formation. Rev Neurosci 17:3-15.

Bakker A, Kirwan CB, Miller M, Stark, CEL (2008) Pattern separation in the human hippocampal CA3 and dentate gyrus. Science 319:1640-2.

Barnea A, Mishal A, Nottebohm F (2006) Social and spatial changes induce multiple survival regimes for new neurons in two regions of the adult brain: an anatomical representation of time? Behav Brain Res 167:63-74.

Barnea A, Nottebohm F (1994). Seasonal recruitement of hippocampal neurons in adult free-ranging black-capped chikadees. Proc Natl Acad Sci USA 85: 11217-11221.

Battaglia FP, Treves A (1998) Attractor neural networks storing multiple space representations: a model for hippocampal place fields. Phys Rev E 58:7738-7753.

Becker S (2005) A computational principle for hippocampal learning and neurogenesis. Hippocampus 15:722-738.

Biebl M, Cooper C.M, Winkler J, Kuhn H.G (2000). Analysis of neurogenesis and programmed cell death reveals a self-renewing capacity in the adult rat brain. Neurosci Lett 291:17-20.

Bingman VP, Jones TJ (1994) Sun-compass based spatial learning impaired in homing pigeons with hippocampal lesions. J Neurosci 14:6687-6694.

Bingman VP, Sharp PE (2006) Neuronal implementation of hippocampal-mediated spatial behavior: a comparative evolutionary perspective. Behav Cogn Neurosci Rev 5:80-91.

Bischofberger J, Engel D, Frotscher M, P Jonas P (2006) Timing and efficacy of transmitter release at mossy fiber synapses in the hippocampal network. Pflugers Arch - Eur J Physiol 453:361–372

Blaabjerg M, Zimmer J. (2007) The dentate mossy fibers: structural organization, development and plasticity. Prog Brain Res163:85-107.

Blackstad TW, Kjaerheim A (1961) Special axo-dendritic synapses in the hippocampal cortex: electron and light microscopic studies on the layer of mossy fibers. J Comp Neurol. 117:133-159.

Bostock E, Muller RU, Kubie JL (1991) Experience-dependent modifications of hippocampal place cell firing. Hippocampus 1:193-205.

Bruel-Jungerman E, Laroche S, Rampon C (2005) New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. Eur J Neurosci 21:513-521.

Burgess N, Recce M, O'Keefe J (1994) A model of hippocampal function. Neural Networks 7:1065-1081.

Burgess N, O'Keefe J (1996) Neuronal computations underlying the firing of place cells and their role in navigation. Hippocampus 6:749-762.

Butler AB (2000) Topography and topology of the teleost telencephalon: A paradox resolved. Neurosci Lett 293:95-98.

Buzsaki G (1989) Two-stage model of memory trace formation: a role for" noisy" brain states. Neurosci 31:551-570.

Buzsaki G (2007) Rhythms of the Brain. New York: Oxford Univ Press.

Buzzetti RA, Marrone DF, Schaner MJ, Chawla MK, Bohanick JD, Khoboko T, Seymor AW, Leutgeb JK, Leutgeb S, Moser EI, Moser M-B, McNaughton BL, Barnes CA (2007) Do dentate gyrus granule cells tag time-specific experiences? Soc Neurosci Abstr 744.16.

Cameron H A, McKay RD (2001) Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 435:406-417.

Carpenter GA, Grossberg S (1993) Normal and amnesic learning, recognition and memory by a neural model of cortico-hippocampal interactions. Trends Neurosci 16:131-137.

Carroll RL (1988) Vertebrate Paleontology and Evolution. New York: W H Freeman & Co.

Chadderton P, Margrie TW, Häusser M (2004) Integration of quanta in cerebellar granule cells during sensory processing. Nature 428:856-860.

Chambers RA, Potenza MN, Hoffman RE, Miranker W (2004) Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. Neuropsychopharmacol 29:747-758.

Chawla MK, Guzowski JF, Ramirez-Amaya V, Lipa P, Hoffman KL, Marriott LK, Worley PF, McNaughton BL, Barnes CA (2005) Sparse, environmentally selective expression of *Arc* RNA in the upper blade of the rodent fascia dentate by brief spatial experience. Hippocampus 15:579-586.

Claiborne BJ, Amaral DG, Cowan WM (1986) A light and electron microscopic analysis of the mossy fibers of the rat dentate gyrus. J Comp Neurol 246:435-458.

Clayton NS (1998) Memory and the hippocampus in food-storing birds: a comparative approach. Neuropharmacol 7:441-452.

Clayton NS, Krebs JR (1995) Memory in food-storing birds: from behaviour to brain. Curr Opin Neurobiol 5:149-154.

Danscher G (1981) Histochemical demonstration of heavy metals. A revised version of the sulphide silver method suitable for both light and electronmicroscopy. Histochemistry 71:1-16.

Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA (2003) Short-term and long-term survival of new neurons in the rat dentate gyrus. J Comp Neurol 460:563-572.

Deisseroth K, Singla S, Toda H, Monje M, Palmer TD, Malenka RC (2004). Excitation-neurogenesis coupling in adult neural stem/progenitor cells. Neuron 42:535-552.

Dobrossy MD, Drapeau E, Aurousseau , Le Moal M, Piazza PV, Abrous DN (2003) Differential effects of learning on neurogenesis: learning increases or decreases the number of newly born cells depending on their birth date. Mol Psychiatry 8:974-982.

Dubbeldam JL (1998) The neural substrate for 'learned' and 'nonlearned' activities in birds: a discussion of the organization of bulbar reticular premotor systems with side-lights on the mammalian situation. Acta Anat (Basel) 163:157-172.

Dupret D, Fabre A, Dobrossy MD, Panatier A, Rodriguez JJ, Lamarque S, Lemaire V, Oliet SH, Piazza PV, Abrous DN (2007) Spatial learning depends on both the addition and removal of new hippocampal neurons. PLoS Biol 5:e214.

Eccles JC (1937) Synaptic and neuro-muscular transmission. Physiol. Rev. 17:538-55.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I (2003) Cellular networks underlying human spatial navigation. Nature 425:184-188.

Epp JR, Spritzer MD, Galea LAM (2007) Hippocampus-dependent learning promotes survival of new neurons in the dentate gyrus at a specific time during cell maturation. Neuroscience 149:273-85.

Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, Schinder AF (2005) Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci 25:10074-10086.

Euston DR, Tatsuno M, McNaughton BL (2007) Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. Science 318:1147-1150.

Faber H, Braun K, Zuschratter W, Scheich H (1989). System-specific distribution of Zinc in the chick brain. A light- and electron-microscopic study using the Timm method. Cell Tissue Res 258:247-257.

Feng R, Rampon C, Tang YP, Shrom D, Jin J, Kyin M, Sopher B, Miller MW, Ware CB, Martin GM, Kim SH, Langdon RB, Sisodia SS, Tsien JZ (2001) Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. Neuron 32:911-926.

Finlay BL, Darlington RB (1995) Linked regularities in the development and evolution of mammalian brains. *Science* 268:1578-1584.

Foster DJ, Wilson MA (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature 440:680-683.

Frankland PW, Cestari V, Filipkowski RK, McDonald RJ, Silva AJ (1998) The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. Behav Neurosci 112:863-874.

Franzius M, Vollgraf R, Wiskott L (2007) From grids to places. J Comput Neurosci 22:297-299.

Frotscher M, Seress L, Schwerdtfeger WK, Buhl E (1991) The mossy cells of the fascia dentata: a comparative study of their fine structure and synaptic connections in rodents and primates. J Comp Neurol 312:145-163.

Fyhn M, Molden S, Witter MP, Moser EI, Moser M-B (2004) Spatial representation in the entorhinal cortex. Science 305:1258-1264.

Fyhn M, Hafting T, Treves A, Moser M-B, Moser EI (2007) Hippocampal remapping and grid realignment in entorhinal cortex. Nature 446:190-194.

Gage FH (2000) Mammalian neural stem cells. Science 287:1433-1438.

Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439:589-593.

Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559-566.

Gilbert PE, Kesner RP, DeCoteau WE (1998) Memory for spatial location: role of the hippocampus in mediating spatial pattern separation. J Neurosci 18:804-810.

Gilbert PE, Kesner RP, Lee I (2001) Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus 11:626-636.

Gloor P (1997) The Temporal Lobe and Limbic System. New York: Oxford Univ Press.

Gluck M, Myers C (2001) Gateway to Memory: an introduction to neural network modeling of the hippocampus and learning. Cambridge MA: MIT Press.

Gould E, Beylin A, Tanapat P, Reeves A, Shors T J (1999) Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 2:260-265.

Hafting T, Fyhn M, Molden S, Moser M-B, Moser EI (2005) Microstructure of a spatial map in the entorhinal cortex. Nature 436:801-806.

Hamlyn LH (1962) The fine structure of the mossy fibre endings in the hippocampus of the rabbit. J Anat 96:112-120.

Hasselmo ME, Anderson BP, Bower JM (1992) Cholinergic modulation of cortical associative memory function J Neurophysiol 67: 1230-46.

Hasselmo ME, Bodelón C, Wyble BP (2002) A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. Neural Comput 14:793-817.

Hasselmo ME, Bower JM (1993) Acetylcholine and memory. Trends Neurosci. 16:218-22.

Hasselmo ME, Schnell E (1994) Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: Computational modeling and brain slice physiology. J Neurosci 14:3898-3914.

Hasselmo ME, Schnell E, Barkai E (1995) Dynamics of learning and recall at excitatory recurrent synapses and cholinergic modulation in rat hippocampal region CA3. J Neurosci 15:5249-5262.

Hasselmo ME, Wyble BP (1997) Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. Behav Brain Research 89:1–34

Hastings NB, Gould E (1999) Rapid extension of axons into the CA3 region by adult-generated granule cells. J Comp Neurol 413:146-154.

Haug FM (1967) Electron microscopical localization of the Zinc in hippocampal mossy fibre synapses by a modified sulfide silver procedure. Histochemie 8:355-368.

Healy SD, de Kort SR, Clayton NS (2005) The hippocampus, spatial memory and food hoarding: a puzzle revisited. Trends Ecol Evol 20:17-22.

Henze DA, Wittner L, Buzsaki G (2002) Single granule cells reliably discharge targets in the hippocampal CA3 network in vivo. Nat Neurosci, 5:790-5

Henze DA, Urban NN, Barrionuevo G (2000) The multifarious hippocampal mossy fiber pathway: a review. Neuroscience 98:407-27.

Hinton GE, Dayan P, Frey BJ, Neal RM (1995) The "wake-sleep" algorithm for unsupervised neural networks. Science 268:1158-1161.

Hof PR, Van der Gucht E (2007) Structure of the cerebral cortex of the humpback whale, Megaptera novaeangliae (Cetacea, Mysticeti, Balaenopteridae). Anat Rec (Hoboken) 290:1-31.

Hoogland PV, Vermeulen-VanderZee E (1993) Medial cortex of the lizard Gekko gecko: a hodological study with emphasis on regional specialization. J Comp Neurol 331:326-338.

Hopfield JJ (1982) Neural networks and physical systems with emergent collective computational abilities. Proc Natl Acad Sci USA 79:2554-2558.

Houser CR (2007) Interneurons of the dentate gyrus: an overview of cell types, terminal fields and neurochemical identity.Prog Brain Res 163:217-232.

Jessberger S, Kempermann G (2003) Adult-born hippocampal neurons mature into activity-dependent responsiveness. Eur J Neurosci 18:2707-2712.

Jung MW, McNaughton BL (1993) Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus 3:165–182.

Kahn MC, Hough GE, ten Eyck GR, Bingman VP (2003) Internal connectivity of the homing pigeon (*Columba livia*) hippocampal formation: an anterograde and retrograde tracer study. J Comp Neurol 459:127-141.

Kee N, Teixeira CM, Wang AH, Frankland PW (2007) Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. Nat Neurosci 10:355-362.

Kempermann G, Gast D, Kronenberg G, Yamaguchi M, Gage FH (2003) Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. Development 130:391-399.

Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. Nature 386:493-495.

Kesner RP, Gilbert PE, Wallenstein GV (2000) Testing neural network models of memory with behavioral experiments. Curr Opin Neurobiol 10:260-265.

Kremin T, Hasselmo ME (2007) Cholinergic suppression of glutamatergic synaptic transmission in hippocampal region CA3 exhibits laminar selectivity: Implication for hippocampal network dynamics. Neurosci 149:760-767.

Kunec S, Hasselmo ME, Kopell N (2005) Encoding and retrieval in the CA3 region of the hippocampus: a model of theta-phase separation. J Neurophysiol 94:70-82.

Künzle H (2004) The hippocampal continuation (indusium griseum): its connectivity in the hedgehog tenrec and its status within the hippocampal formation of higher vertebrates. Anat Embryol 208:183-213.

Lassalle J-M, Bataille T, Halley H (2000) Reversible inactivation of the hippocampal mossy fiber synapses in mice impairs spatial learning, but neither consolidation nor memory retrieval, in the Morris navigation task. Neurobiol Learn Mem 73:243-257.

Lavenex P, Steele MA, Jacobs LF (2000) The seasonal pattern of cell proliferation and neuron number in the dentate gyrus of wild adult eastern grey squirrels. Eur J Neruosci 12:643-648.

Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36:1183-1194.

Lee I, Kesner RP (2004) Encoding versus retrieval of spatial memory: Double dissociation between the dentate gyrus and the perforant path inputs into CA3 in the dorsal hippocampus. Hippocampus 14:66–76.

Leuner B, Mendolia-Loffredo S, Kozorovitskiy Y, Samburg D, Gould E, Shors TJ (2004) Learning enhances the survival of new neurons beyond the time when the hippocampus is required for memory. J Neurosci 24:7477-7481.

Leranth C, Hajszan T (2007) Extrinsic afferent systems to the dentate gyrus. Prog Brain Res 163:63-84.

Leutgeb S, Leutgeb JK, Treves A, Moser M-B, Moser EI (2004) Distinct ensemble codes in hippocampal areas CA3 and CA1. Science 305:1295-1298.

Leutgeb S, Leutgeb JK, Barnes CA, Moser EI, McNaughton BL, Moser M-B (2005a) Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. Science 309:619-623.

Leutgeb, JK, Leutgeb S, Treves A, Meyer R, Barnes CA, McNaughton BL, Moser M-B, Moser EI (2005b) Progressive transformation of hippocampal neuronal representations in "morphed" environments. Neuron 48:345-358.

Leutgeb JK, Leutgeb S, Moser M-B, Moser EI (2007) Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science 315:961-966.

Leutgeb JK, Moser EI (2007) Enigmas of the dentate gyrus. Neuron 55:176-178.

Levy WB (1996) A sequence predicting CA3 is a flexible associator that learns and uses context to solve hippocampal-like tasks. Hippocampus 6:579-590.

Lopez-Garcia C, Martinez-Guijjaro FJ (1988) Neurons in the medial cortex give rise to TIMM-positive boutons in the cerebral-cortex of lizards. Brain Res 463:205-217.

Lorente de Nó R(1934) Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. J Psychol Neurol 46:113-177.

Markus EJ, Qin YL, Leonard B, Skaggs WE, McNaughton BL, Barnes CA (1995) Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J Neurosci15:7079-7094.

Marr D (1969) A theory of cerebellar cortex J Physiol (London) 202:437–470.

Marr D (1971) Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci 262:23-81.

Martinez-Guijarro FJ, Berbel PJ, Molowny A, López García C (1984) Apical dendritic spines and axonic terminals in the bipyramidal neurons of the dorsomedial cortex of lizards (Lacerta). Anat Embryol (Berl) 170:321-326.

McClelland, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review 102:419-457.

McDonald RJ, Koerner A, Sutherland RJ (1995) Contextual fear conditioning and hippocampus. Soc Neurosci Abstr 21:1218.

McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S (2007) Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. Science 317:94-99.

McNaughton BL, Morris RGM (1987) Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci 10:408-415.

Molla R, Rodriguez J, Calvet S, Garcia-Verdugo JM (1986) Neuronal types of the cerebral-cortex of the adult chicken (Gallus gallus) – A golgi study. J Hirnforsch 27:381-390.

Montagnese CM, Geneser FA, Krebs JR (1993) Histochemical distribution of Zinc in the brain of the zebra finch (Taenopygia guttata). Anat Embryol (Berl) 188:173-187.

Montagnese, CM, Krebs JR, Meyer G (1996) The dorsomedial and dorsolateral forebrain of the zebra finch, Taeniopygia guttata: a Golgi study. Cell Tissue Res 283:263-282.

Morgane PJ, McFarland WL, Jacobs MS (1982) The limbic lobe of the dolphin brain: a quantitative cytoarchitectonic study. J Hirnforsch 23:465-552.

Mori M, Gähwiler BH, Gerber U (2007) Recruitment of an inhibitory hippocampal network after bursting in a single granule cell Proc Natl Acad Sci U S A., 104: 7640-5.

Moser EI, Kropff E, Moser M-B (2008) Place cells, grid cells and the brain's spatial representation system. Annu Rev Neurosci, in press.

Mott DD, Benveniste M, Dingledine RJ (2008) pH-dependent inhibition of kainate receptors by zinc. J Neurosci. 28:1659-71.

Muller RU, Kubie JL (1987) The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci 7:1951-1968.

Nádasdy Z, Hirase H, Czurkó A, Csicsvari J, Buzsáki G (1999) Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 19:9497-9507.

Nakagawa E, Aimi Y, Yasuhara O, Tooyama I, Shimada M, McGeer PL, Kimura H (2000) Enhancement of progenitor cell division in the dentate gyrus triggered by initial limbic seizures in rat models of epilepsy. Epilepsia 41:10-18.

Nottebohm F (2004) The road we travelled: discovery, choreography, and significance of brain replaceable neurons. Ann NY Acad Sci 1016: 628-658.

O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map: preliminary evidence from unit activity in the freely moving rat. Brain Res 34:171-175.

O'Keefe J, Nadel (1978). The Hippocampus as a Cognitive Map. Oxford: Clarendon Press.

Olariu A, Cleaver KM, Shore LE, Brewer MD, Cameron HA (2005) A natural form of learning can increase and decrease the survival of new neurons in the dentate gyrus. Hippocampus 15:750-762.

Olucha F, Martinez-Garcia F, Poch L, Schwerdtfeger WK, Lopez-Garcia C (1988) Projections from the medial cortex in the brain of lizards: correlation of anterograde and retrograde transport of horseradish peroxidase with Timm staining. J Comp Neurol 276:469-480.

Papp G, Treves A (2007) Network analysis of the significance of hippocampal subfields. In: Hippocampal place-fields: Relevance to Learning and Memory (ed S. Mizumori). Oxford University Press.

Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH (1997) Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. J Neurosci 17: 3727-3738.

Patel SN, Clayton NS, Krebs JR (1997) Spatial learning induces neurogenesis in the avian brain. Behav Brain Res 89:115-128.

Poirier GL, Amin E, Aggleton JP (2008) Qualitatively different hippocampal subfield engagement emerges with mastery of a spatial memory task by rats. J Neurosci. 28:1034-45.

Ramon y Cajal S (1893) Estructura del asta de Ammon y fascia dentate. Ann Soc Esp Hist Nat 22:53-114.

Ramirez-Amaya V, Marrone DF, Gage FH, Worley PF, Barnes CA (2006) Integration of new neurons into functional neural networks. J Neurosci 26:12237-12241.

Reep RL, Finlay BL, Darlington RB (2007) The limbic system in mammalian brain evolution. Brain Behav Evol 70:57-70.

Ribak CE, Peterson GM (1991) Intragranular mossy fibers in rats and gerbils form synapses with the somata and proximal dendrites of basket cells in the dentate gyrus. Hippocampus 1:355-364.

Ribak CE, Korn MJ, Shan Z, Obenaus A (2004) Dendritic growth cones and recurrent basal dendrites are typical features of newly generated dentate granule cells in the adult hippocampus. Brain Res 1000:195-199.

Rodríguez F, López JC, Vargas JP, Gómez Y, Broglio C, Salas C (2002a) Conservation of spatial memory function in the pallial forebrain of reptiles and ray-finned fishes. J Neurosci 22:2894-2903.

Rodríguez F, López JC, Vargas JP, Broglio C, Gómez Y, Salas C (2002b) Spatial memory and hippocampal pallium through vertebrate evolution: insights from reptiles and teleost fish. Brain Res Bull 57:499-503.

Rollenhagen A, Sätzler K, Rodriguez EP, Jonas P, Frotscher M, Lübke JHR (2007) Structural determinants of transmission at large hippocampal mossy fiber synapses. J Neurosci 27:10434-44.

Rolls ET (1989) Functions of neuronal networks in the hippocampus and cerebral cortex in memory. In: Models of Brain Function (ed Cotterill R) pp 15-33. Cambridge UK: Cambridge Univ Press.

Rolls ET, Robertson RG, Georges-Francois P (1997) Spatial view cells in the primate hippocampus. Eur J Neurosci 9:1789-1794.

Rolls, ET, Stringer SM, Elliot T (2006) Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning. Network 17:447-465.

Salin PA, Scanziani M, Malenka RC, Nicoll RA (1996) Distinct short-term plasticity at two excitatory synapses in the hippocampus. Proc Natl Acad Sci U S A. 93:13304-9.

Samsonovich A, McNaughton BL (1997) Path integration and cognitive mapping in a continuous attractor neural network model. J Neurosci 17:5900-5920.

Saxe MD, Battaglia F, Wang JW, Malleret G, David DJ, Monckton JE, Garcia AD, Sofroniew MV, Kandel ER, Santarelli L, Hen R, Drew MR (2006) Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc Natl Acad Sci USA 103:17501-17506.

Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, Kandel ER, Hen R (2007) Paradoxical influence of hippocampal neurogenesis on working memory. Proc Natl Acad Sci USA 104:4642-4646.

Scharfman H (2007) (ed.) The Dentate Gyrus: A Comprehensive Guide to Structure, Function, and Clinical Implications. Prog Brain Research 163:1-840

Schmajuk NA (1990) Role of the hippocampus in temporal and spatial navigation: an adaptive neural network. Behavioural Brain Research 39:205-229.

Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429:184-187.

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiat 20:11-21.

Selden NRW, Everitt BJ, Jarrard LE, Robbins TW (1991) Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. Neurosci 42:335-350.

Seress L, Mrzljak L (1987) Basal dendrites of granule cells are normal features of the fetal and adult dentate gyrus of both monkey and human hippocampal formations. Brain Res 405:169-174.

Seress L, Pokorny J (1981) Structure of the granular layer of the rat dentate gyrus. A light microscopic and Golgi study. J Anat 133:181-195.

Shipley MT, Adamek GD (1984) The connections of the mouse olfactory bulb: a study using orthograde and retrograde transport of wheat germ agglutinin conjugated to horseradish peroxidase. Brain Res Bull 12:669-688.

Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E (2002) Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 12:578-584.

Smeets WJ, Hoogland PV, Lohman AH (1986) A forebrain atlas of the lizard Gekko gecko. J Comp Neurol 254:1-19.

Smulders TV (2006) A multi-disciplinary approach to understanding hippocampal function in food-hoarding birds. Rev Neurosci 17:53-69.

Snyder JS, Hong NS, McDonald RJ, Wojtowicz JM (2005) A role for adult neurogenesis in spatial long-term memory. Neuroscience 130:843-852.

Snyder JS, Kee N, Wojtowicz JM (2001) Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol 85:2423-2431.

Spigelman I, Yan XX, Obenaus A, Lee EY, Wasterlain CG, Ribak CE (1998) Dentate granule cells form novel basal dendrites in a rat model of temporal lobe epilepsy. Neurosci 86:109-120.

Squire LR (1991) Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psychol Rev 99:195-231.

Srivastava UC, Chand P, Maurya RC (2007) Cytoarchitectonic organization and morphology of the cells of hippocampal complex in strawberry finch, *Estrilda amandava*. Cell Mol Biol (Noisy-le-grand) 53:103-120.

Stephan H (1975) Allocortex. In: Handbuch der mikr. Anatomie des Menschen (ed. Bargmann W) Vol. 4, Teil 9, p998. Berlin, Heidelberg, New York: Springer.

Striedter GF,Northcutt RG (1991) Biological hierarchies and the concept of homology. Brain Behav Evol 38:177-189.

Székely AD, Krebs JR (1996) Efferent connectivity of the hippocampal formation of the zebra finch (*Taeniopygia guttata*): an anterograde pathway tracing study using *Phaseolus vulgaris* leucoagglutinin. J Comp Neurol 368:198-214.

Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH (2006) NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. Nature 442:929-933.

Tashiro A, Makino H, Gage FH (2007) Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 27:3252-3259.

ten Donkelaar HJ (2000). Major events in the development of the forebrain. Eur J Morphol 38:301-308.

Timm F (1958) Zur Histochemie der Schwermetalle, das Sulfid-Silber-Verfahre. Deutsch Z Gerichtl Med 46:706-711.

Tömböl T, Davies DC, Németh A, Alpár A, Sebestény T (2000) AGolgi and a combined Golgi/GABA immunogold study of local circuit neurons in the homing pigeon hippocampus. Anat Embryol (Berl) 201:181-196.

Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH (2007). Synapse formation on neurons born in the adult hippocampus. Nat Neurosci 10:727-734.

Treves A, Rolls ET (1991) What determines the capacity of autoassociative memories in the brain? Network 2:371-397.

Treves A, Rolls ET (1992) Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 2:189-199.

Ulanovsky N, Moss CF (2007) Hippocampal cellular and network activity in freely moving echolocating bats. Nat Neurosci 10:224-233.

Ulinski PS (1990a) The cerebral cortex of reptiles. In: Cerebral Cortex Vol 8A: Comparative Structure and Evolution of Cerebral Cortex (eds Jones EG, Peters A) pp139-215. New York: Plenum Press.

Ulinsky, PS (1990b) Nodal events in the forebrain evolution. Neth J Zool 40:215-240.

van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH (2002) Functional neurogenesis in the adult hippocampus. Nature 415:1030-1034.

Vargas JP, Petruso EJ, Bingman VP (2004) Hippocampal formation is required for geometric navigation in pigeons. Eur J Neurosci 20:1937-1944.

Vargas JP, Bingman VP, Portavella M, López JC (2006) Telencephalon and geometric space in goldfish. Eur J Neurosci. 24:2870-2878.

Vogt K, Mellor J, Tong G, Nicoll R (2000) The actions of synaptically released Zinc at hippocampal mossy fiber synapses. Neuron. 26:187-96

Wang S, Scott BW, Wojtowicz JM (2000) Heterogenous properties of dentate granule neurons in the adult rat. J Neurobiol 42:248-257.

Wessler I, Kirkpatrick CJ, Racké K (1999) The cholinergic 'pitfall': acetylcholine, a universal cell molecule in biological systems, including humans. Clin Exp Pharmacol Physiol 26:198-205.

Wills TJ, Lever C, Cacucci F, Burgess N, O'Keefe J (2005) Attractor dynamics in the hippocampal representation of the local environment. Science 308:873-876.

Willshaw D, Buckingham J (1990) An assessment of Marr's theory of the hippocampus as a temporary memory store. Philos Trans R Soc Lond B Biol Sci 329:205-215.

Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676-679.

Winocur G, Wojtowicz JM, Sekeres M, Snyder JS, Wang S (2006) Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 16:296-304.

Wiskott L, Rasch MJ, Kempermann G (2006) A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. Hippocampus 16:329-343.

Wouterlood FG (1981) The structure of the mediodorsal cerebral cortex in the lizard Agama agama: a Golgi study. J Comp Neurol 196:443-458.

Wyss JM, Sripanidkulchai K (1983) The indusium griseum and anterior hippocampal continuation in the rat. J Comp Neurol 219:251-271.

Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 26:3-11.

Zilli EA, Hasselmo ME (2006) An analysis of the mean theta phase of population activity in a model of hippocampal region CA1. Network 17:277-297.

Figure legends

Figure 1. The model by Marr (1971), like several modern connectionist models, does not ascribe a salient role to the dentate gyrus, 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.

Figure 2. What is the dentate gyrus? Left: The dentate gyrus of mammals is a three-layered cortex, with an outer molecular layer, a central granule cell layer and a deep polymorph layer, also called hilus. The principal cells of the dentate gyrus issue axons, the mossy fiber system, to area CA3. Pseudo-colored horizontal section stained for the neuronal marker NeuN in blue and for the presence of Calbindin D-28 in red. Antibodies against Calbindin not only clearly stain the three layers of the dentate gyrus, and the Zinc-containing mossy fiber projection superficial to the CA3 pyramidal cells, but also a large proportion of CA1 pyramidal cells and their dendrites, as well as parts of presubiculum and entorhinal cortex. Right: The dentate gyrus receives its main input from a single higher order cortical association area, entorhinal cortex, and the same input axons go on to make contact on the principal cells of the directly adjacent area CA3, which is massively recurrent. The mossy fibers apparently duplicate entorhinal input: they terminate with "en passant" three-dimensionally complex presynatic terminals, rich in Zinc, onto very complex spines, the thorny excrescences, of CA3 pyramidal cells, as well as of neurons in the hilus. Hilar neurons, also called mossy cells, are the major origin of the intrinsic associational system of the dentate gyrus.

Figure 3. The amount of new information, in bits per unit (*y*-axis) at storage and at retrieval, as a function of the sparseness of the CA3 representation (*x*-axis), The shaded area is the amount of information that can be retrieved by the collateral effect; hence efficient storage has to result in *more* information (i.e., in the non-shaded region). The three broken curves show the information in a memory pattern driven by afferent inputs (mossy fibers) 5 times stronger than recurrent connections, for three different sparseness values of the inputs they relay, a_{DG}=0.004, 0.02 or 0.1. All three curves are in the 'efficient' storage white region, indicating that mossy fiber strength is more important than exactly how sparse is activity on the input lines (provided it is sparse). The lower curve shows the amount that would result from direct cortical (perforant path) projections 4 times weaker than the collaterals. This curve is invariant with respect to input sparseness, and its remaining in the shaded area shows that efficient storage is not possible with inputs distributed over many synapses, collectively weaker than recurrent connections. From Treves and Rolls (1992).

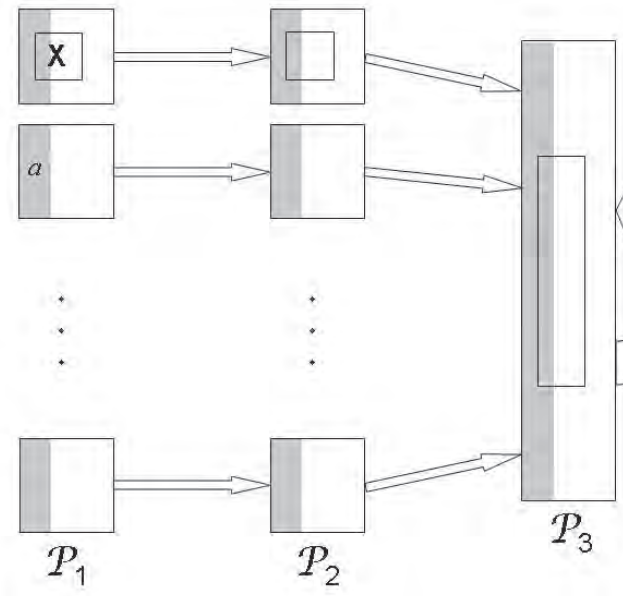
Figure 4. Examples of place fields in CA3, dentate gyrus (DG) and perforant-path axons presumably originating in medial entorhinal cortex (MEC). The animal was running in a square box (left) or a cylinder (right). Three different cells are shown for each subregion. Adapted from Leutgeb et al. (2007).

Figure 5. Newly born granule cells incorporated in the dentate gyrus of adult mice. (Top) New granule cells (green) were transduced by GFP-expressing retroviral vectors 4 weeks before the time of section preparation. All neuronal cell bodies are immunolabeled with anti-NeuN antibody (red). (Bottom) Young granule cells are immunostained with anti-doublecortin antibody (light blue). Doublecortin is a commonly used marker for immature neurons. Images were taken by A. Tashiro and F. H. Gage.

Figure 6. Neither the reptilian (left) nor avian hippocampus (right) include a subdivision with all the features of the mammalian dentate gyrus. The mammalian dentate gyrus is considered to be homolog to the medial, small celled cortex of reptiles (Cxms; left, photograph adapted from Smeets et al., 1986), whereas no clear correspondence has been established with the subdivisions of the avian hippocampus (right, picture courtesy of Henrik Lange and Tom Smulders; nomenclature according to Atoji and Wild, 2004). Other abbr: Cxd, dorsal cortex. DVR, dorso-ventricular ridge. Nsd, dorsal septal nucleus. Nsm, medial septal nucleus. Tr, triangular part between V-shaped layer of hippocampal formation. DM, dorsomedial region of hippocampal formation.

Figure 1
Click here to download Figure: NSC-08-159R_Fig1.pdf

Figure 1



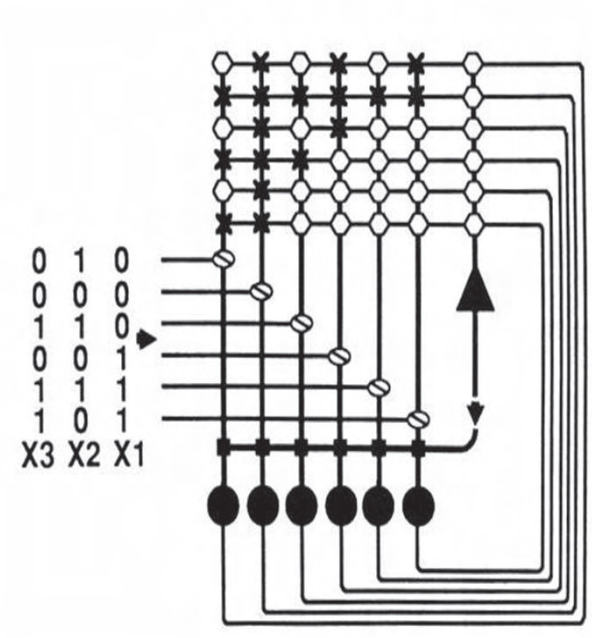


Figure 2

Click here to download Figure: NSC-08-159R_Fig2.pdf

Figure 2

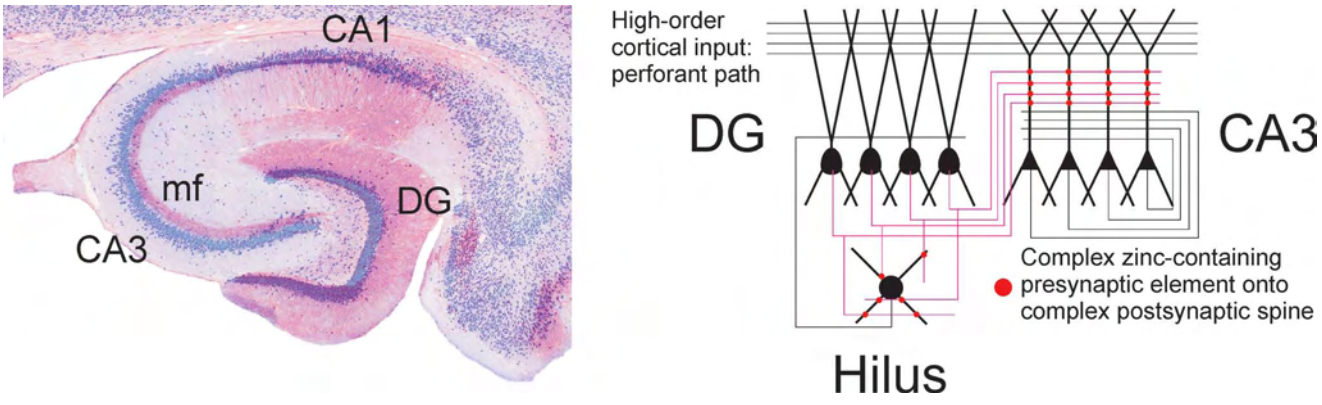


Figure 3
Click here to download Figure: NSC-08-159R_Fig3.pdf

Figure 3

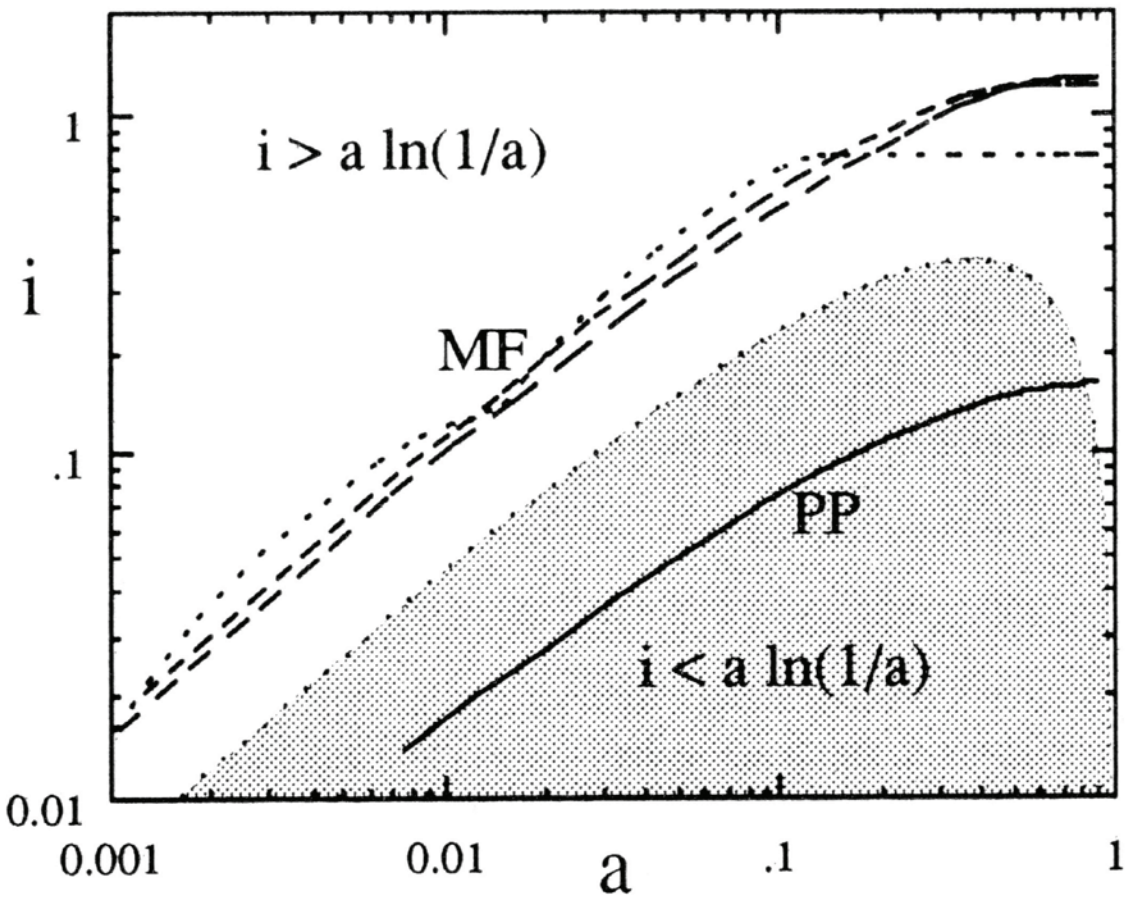


Figure 4

Click here to download Figure: NSC-08-159R_Fig4.pdf

Figure 4

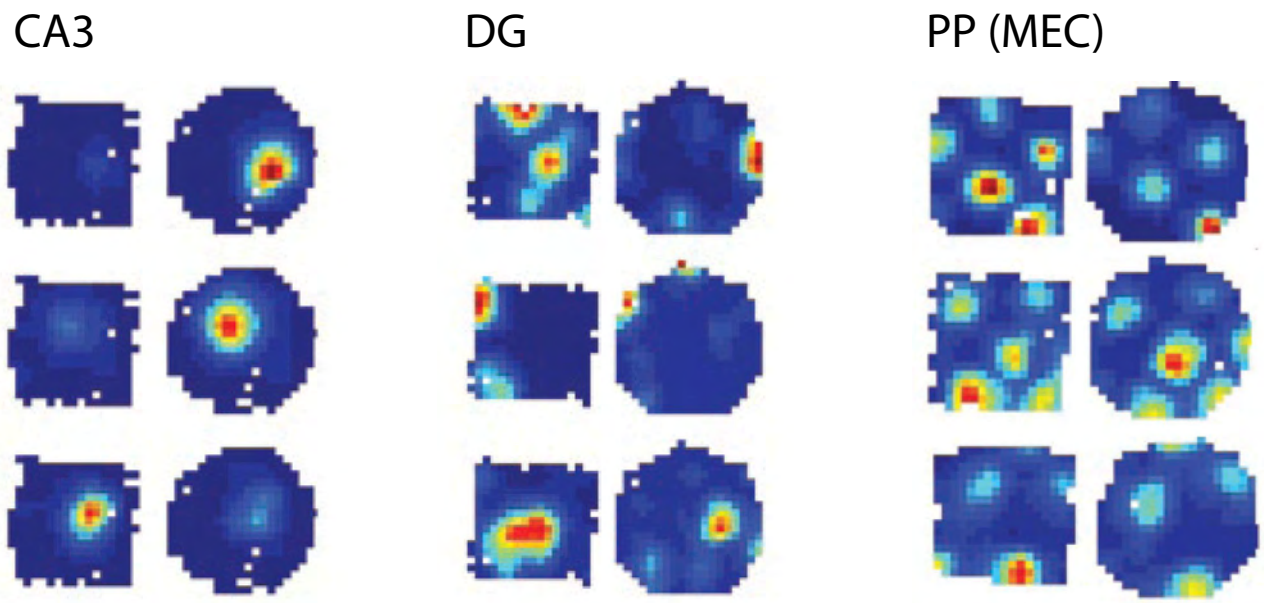


Figure 5

Click here to download Figure: NSC-08-159R_Fig5.pdf

Figure 5

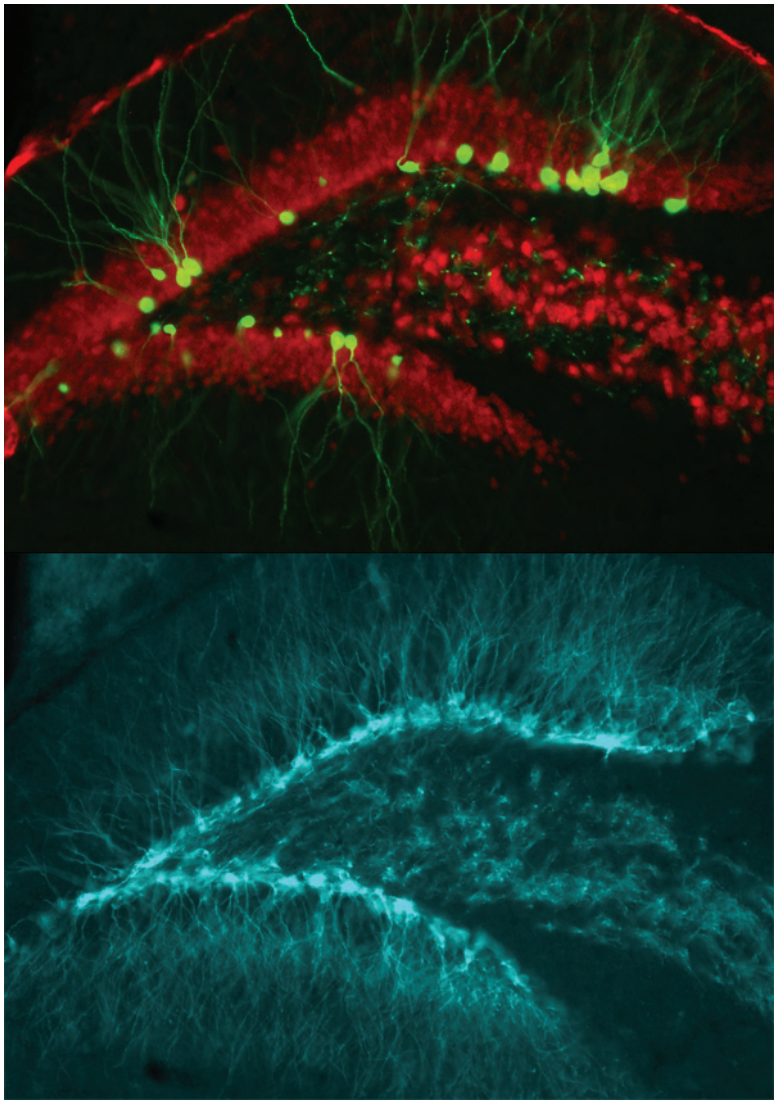


Figure 6

Click here to download Figure: NSC-08-159R_Fig6.pdf

Figure 6