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A putative role for neurogenesis in neurocomputational terms: Inferences from a hippocampal model

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ABSTRACT

New neurons are generated daily in the hippocampus during adult life. They are integrated into the existing neuronal circuits according to several factors such as age, physical exercise and hormonal status. At present, the role of these new neurons is debated. Computational simulations of hippocampal function allow the effects of neurogenesis to be explored, at least from a computational perspective. The present work implements a model of neurogenesis in the hippocampus with artificial neural networks, based on a standard theoretical model of biologically plausible hippocampal circuits. The performance of the model in retrieval of a variable number of patterns or memories was evaluated (episodic memory evaluation). The model increased, in a phase subsequent to initial learning, the number of granular cells by 30% relative to their initial number. In contrast to a model without neurogenesis, the retrieval of recent memories was very significantly improved, although remotes memories were only slightly affected by neurogenesis. This increase in the quality of retrieval of new memories represents a clear advantage that we attribute to the neurogenesis process. This advantage becomes more significant for higher storage loads. The model presented here suggests an important functional role of neurogenesis on learning and memory.

1. Introduction

The role of the hippocampus and other structures of the medial temporal lobe in episodic memory formation have been discussed extensively in the literature (Eichenbaum, 2000, 2004; Maguire, 2001). Their function enables event codification and event retrieval by conjugating information coming from distinct association cortices in the temporal, parietal and occipital lobes (Eichenbaum, 2000). In the dentate gyrus of hippocampal formation, proliferation of neuronal precursors has been reported as an important characteristic (specifically in the subgranular zone). Some of these precursors then differentiate into granular cells, which are functionally integrated into already established circuits (Gould & Gross, 2002; van Praag et al., 2002) (for a complete review, see Ming and Song (2005)). However, the true physiological relevance of adult neurogenesis and its clinical potential remains unclear in some cases (Scharfman & Hen, 2007).

Two mutually exclusive hypotheses can be proposed regarding hippocampal neurogenesis:

1. Neurogenesis is a vestigial process without functional relevance.
2. Neurogenesis has a specific role in hippocampal function.

Among other methods, mathematical models provide a method for generating experimental and verifiable hypotheses in order to elucidate biological functions. The hippocampus is eminently amenable to such mathematical modeling. It has a structure which has been relatively preserved across the phylogenetic scale and a network

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architecture which is relatively easy to simulate through a neurocomputational approach. The present work is based on the computational theory of the hippocampus and its simulation as proposed by (Rolls, 1995; Rolls & Treves, 1998; Treves & Rolls, 1994), and introduces neurogenesis into a hippocampal model. This model, comprised of biologically plausible artificial neural networks (e.g., simulating anatomical structures), is intended to generate hypotheses concerning the role that new neurons could have in hippocampal function.

An exhaustive review of hippocampal function, computational modeling of the hippocampus, or adult neurogenesis, is beyond the remit of this paper; see recent work by Becker (2005), Rolls and Kesner (2006), and Wiskott, Rasch, and Kempermann (2006). The simulation we present here models the generation of new neurons in the adult hippocampus as physiological event, so as to infer the effects of neurogenesis on hippocampal function in relation to episodic memory. The question we addressed was how the network's retrieval capacity, understood as the number of retrievable patterns representing unique events and contexts, could vary with these new neurons. Our hypothesis, in line with the view that new neurons are implicated in new learning, is that new neurons would help the hippocampal network to increase its efficiency in codifying and storing episodic memory. Specifically, the process of neurogenesis would increase the number of recent episodic memories capable of being retrieved, with relatively few neurons and sensitive to environmental requirements. Exactly how this is achieved is something we return to below, after detailing our simulations. For our analyses, the pattern separation function we assumed for the dentate gyrus was tested with and without neurogenesis.

2. Materials and methods

2.1. Generalities

The artificial neural network that models the episodic memory formation in the hippocampus was based on its main excitatory circuits (Fig. 1). The model includes the entorhinal cortex (EC), the dentate gyrus (DG) and the hippocampal subfields CA3 and CA1. These areas are integrated in a non-reciprocal, unidirectional pathway (Fig. 2). The subiculum was not modeled because we consider it simply to be a route through which the memories pass on their way back to the entorhinal cortex. It is not, therefore, essential given the aims of the model.

The values used in the simulation were mainly taken from Rolls (1995), with some modifications (see below). We constructed a model which does not exhibit neurogenesis and which served as a control for evaluating the results of a model which does exhibit neurogenesis in a subsequent stage. The code implementing the algorithms and simulations presented here were developed on DELPHI 6.0 (using Object Pascal), running on a Pentium D 3.40 GHz computer.

2.2. The hippocampal formation model

The model comprises 4 sub-networks reflecting the different regions modeled (EC, DG, CA3 and CA1). Its biologi-

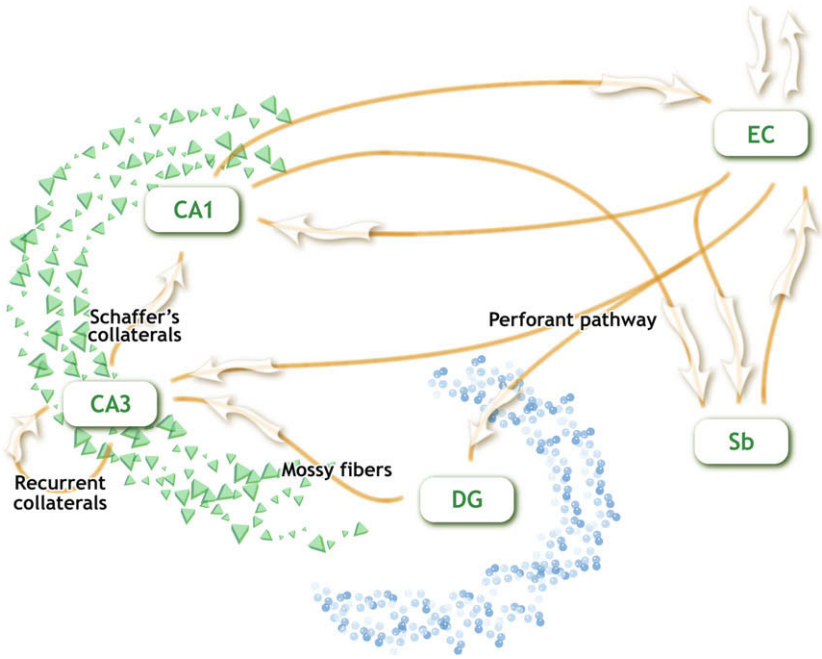

Fig. 1. Hippocampal connections. The main entrance to the hippocampus is made through the entorhinal cortex (EC). The neurons in EC project to the dentate gyrus (DG) and to the CA3 subfield through the perforant pathway. With a different pathway, they also project to the CA1 subfield and to the subiculum. The axons from the dentate gyrus constitute the so-called mossy fibers that project to CA3. CA3 emits two ramifications: recurrent collaterals and Schaffer's collaterals, the former projecting to CA3 and the latter to CA1. From CA1 and from the subiculum, the projections go back to EC, forming a loop (Amaral, 1993; Milner et al., 1998).

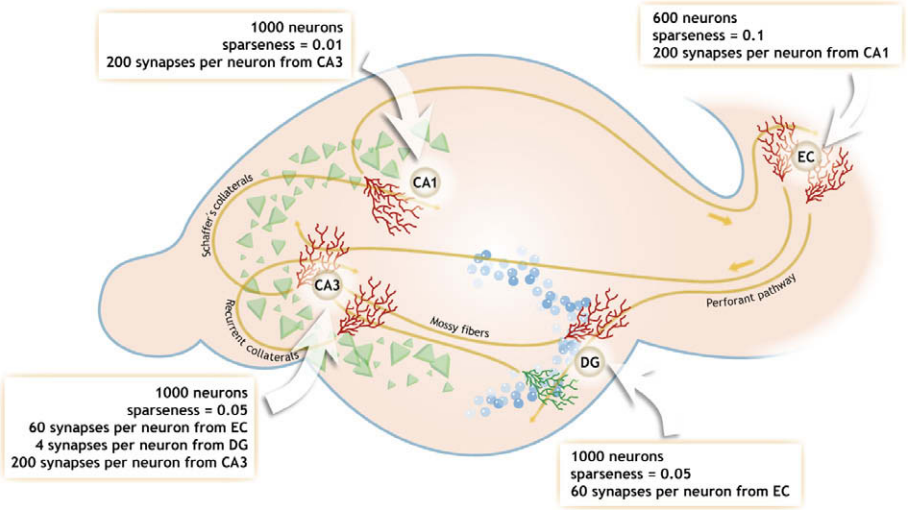

Fig. 2. Hippocampal model. The entorhinal cortex (EC), the dentate gyrus (DG), and the hippocampal subfields CA3 and CA1 are represented here. The cell number, the connectivity and the sparseness of each region are shown in the figure (adapted from Rolls (1995)). In green, new granular cells (born in adult life) are shown in DG. These new neurons will be introduced into the circuitry when modeling neurogenesis.

cal plausibility rests in part on this reflection of the actual architecture of the hippocampus. We assume different functional roles for each region, as proposed by Treves and Rolls. The network corresponding to a specific region was designed to account for the specific, hypothesized function of that region.

Thus, while the EC is the neural group for presenting inputs to, and outputs from, the hippocampus, the principal region which presumably "stores" the different patterns or memories is CA3, due to its remarkable recurrence (it is the only region presenting this characteristic) which enables it to function as an autoassociative network. This kind of network enables the storage of single events (as distinct single patterns) as well as the pattern completion function that is required to restore a complete pattern when only a small part of it is available as a cue. The theory also suggests that the two input pathways to CA3 should have different functions: the patterns to be stored would be presented through the mossy fibers (coming from DG), while the cue initiating memory retrieval would enter through the perforant pathway (coming from EC) (Treves & Rolls, 1992).

Since an autoassociative network has a limited capacity for storing patterns, it is desirable in order to maximize this capacity that the patterns are as dissimilar as possible (being stored as highly separated patterns), thereby avoiding interference between them. This can be done in our neurocomputational model by using a competitive network implemented by the dentate gyrus (Rolls & Treves, 1998). The sparse coding in DG, mainly due to the highly divergent input stream from EC to DG (Amaral, Ishizuka, & Claiborne, 1990) has been assumed to support a pattern separation function (Chawla et al., 2005; Treves & Rolls, 1992).

We chose a competitive network for CA1, given its putative categorization function that enables remapping and to reorganization of the patterns. Finally, the last sub-network performs pattern association between the outputs of CA1 and the original inputs in EC.

The number of units in each region, the sparseness and the connectivity between them, was adjusted to match in prior experimental work (Amaral et al., 1990; Barnes, McNaughton, Mizumori, Leonard, & Lin, 1990). We started from the model of Rolls (1995), which was first tested with these values and then scaled, to produce the same results, to fit into a smaller final network. We made few changes to that model in order to capture the main characteristics of the regions being modeled. Specifically, we changed the sparseness value in EC (in our model, the representation in EC is now denser than that of DG), and the connectivity of the CA1→EC pathway (our model does not have complete connectivity). For the values used in the simulation, see Fig. 2.

Memories were represented as random binary patterns (each neuron firing with its minimal or maximal firing rate). As mentioned above, an important parameter to bear in mind when representing the firing patterns of the different neural groups is their sparseness. In a sparse representation with binary neurons, less than half of the neurons are active for any one stimulus or event. For binary neurons, as in this model, we can use the proportion of neurons in the active state as a measure of sparseness (Rolls & Treves, 1998). For low sparseness, this measure is large.

2.2.1. The entorhinal cortex

The entorhinal cortex was simulated with 600 neurons. The sparseness employed by the model for this neural group was 0.1, i.e., each pattern was represented with 60 active neurons. The initial patterns (or memories to codify) created in this region (created by setting the activity of each neuron randomly to zero or one) constituted the input to the first sub-network.

2.2.2. The dentate gyrus

The dentate gyrus was represented with 1000 neurons. The sparseness was set to 0.05 (50 active neurons *per* pattern). The connectivity between these neurons and those of the entorhinal cortex was 60 synapses *per* neuron, i.e., each neuron of the dentate gyrus received afferent input from 60 neurons in the entorhinal cortex. The selection of these connections was randomly made. Here, the perforant pathway→dentate granule cells system acted as a competitive learning network. Competitive learning removes redundancy, so the output from the DG system will be less correlated and more categorized than the inputs to it from the perforant pathway. Thus overlapping signals on the perforant pathway will be separated before they reach CA3.

Initially, the synaptic weights (w_{ij}) between EC and DG were random (a random function between 0 and 1) and scaled in such a way that they had a maximum value of 7 (an arbitrary scaling value that was constant across all the weights). This scaling tends to prevent winning neurons from being always the same and it can be thought as responding to homeostatic mechanisms of synaptic scaling (Meltzer, Yabaluri, & Deisseroth 2005). This normalization was effected by Eq. (1):

$$w_{ij}^{\mathrm{EC-DG}} = \frac{w_{ij}^{\mathrm{EC-DG}}}{n\sqrt{\sum_{j=1}^{n}\left(w_{ij}^{\mathrm{EC-DG}}\right)^2}} \tag{1}$$

Here, the first subscript (i) refers to the receiving neuron in DG and the second subscript (j) to a particular input to that neuron via a synapse of weight w_{ij} in EC; n is the number of neurons in EC. For the output pattern generation, the activation of each neuron i in DG (denoted h_i^{DG}) was evaluated following the Eq. (2):

$$h_i^{\mathrm{DG}} = \sum_{j=1}^{n} r_j^{\mathrm{EC}} w_{ij}^{\mathrm{EC-DG}} \tag{2}$$

where r_j^{EC} is the firing rate of the jth input in EC to that neuron. The letter r is used to indicate that the inputs and outputs of real neurons are firing rates.

The activation function in DG was a binary threshold. The winning neurons for each input pattern were those exceeding the threshold set by the sparseness of the region (i.e., the 50 neurons having the highest activation). The neurons not exceeding this threshold were set to 0 (representing inactive neurons). Finally, the outputs were normalized. The interneurons of the region would be in charge of carrying out this competition and of maintaining the firing rates within the established limits (Freund & Buzsáki, 1996; Moser, 2003).

During learning, the synaptic weights were modified according to the modified Hebb's rule (3), a biologically plausible rule which includes weight normalization, necessary in competitive networks to ensure that one or a few neurons do not always win the competition:

$$\delta w_{ij}^{\mathrm{EC-DG}} = k \cdot r_i^{\mathrm{DG}} \cdot \left(r_j^{\mathrm{EC}} - w_{ij}^{\mathrm{EC-DG}}\right); \quad k = 0.5 \tag{3}$$

where r_j^{EC} is the presynaptic term, r_i^{DG} the postsynaptic term and k the learning rate. Such a modification in synaptic strength is termed heterosynaptic long-term depression (LTD) in the neurophysiological literature (Rolls & Treves, 1998).

2.2.3. The CA3 subfield

This second sub-network, which implemented the autoassociation of the inputs coming from the dentate gyrus, specifically constituted the codifying site. The region was represented with 1000 neurons and a sparseness of 0.05. Three kinds of inputs were distinguished here: those coming from the dentate gyrus (via the mossy fibers), those coming from the entorhinal cortex (via the perforant pathway), and those coming from CA3 (via its self-connections). The number of synapses *per* neuron from each kind of input was 4, 60, and 200, respectively.

According to Rolls' theory these inputs would have different functions (Rolls & Kesner, 2006; Treves & Rolls, 1992), considered in the following way: During learning, the memories to be codified and stored in CA3 were presented by the mossy fibers. The connection weights between the dentate gyrus and CA3 were fixed ($w_{ij}^{\mathrm{DG-CA3}}$ =1), since it was empirically found that these synapses are modifiable, but not in an associative or Hebbian way (Bliss & Collingridge, 1993; Milner, Squire, & Kandel, 1998). On the other hand, the weights $w_{ij}^{CA3-CA3}$ in CA3 (the synaptic efficiencies of the recurrent connections) were calculated by the covariance rule (4), a Hebbian-type associative learning rule:

$$w_{ij}^{CA3-CA3} = \begin{cases} \sum_{p=1}^{N} k \cdot (r_i^p - \bar{r}_i) \cdot (r_j^p - \bar{r}_j) & 1 \leqslant i,j \leqslant neurons_{CA3}; i \neq j \\ 0 & 1 \leqslant i,j \leqslant neurons_{CA3}; i = j \end{cases} \tag{4}$$

where r_i^p: Firing rate of the ith neuron in the pth pattern that the network has to learn (total input from DG), $\bar{r}$: Mean firing rate of a single neuron in CA3 along the complete set of patterns, $\mathrm{neurons}_{CA3}$: Number of neurons in CA3, N: Number of patterns to learn.

The synapses originating in the entorhinal cortex constituted the presentation pathway for the cues that initiated the retrieval. Their synaptic weights $w_{ij}^{\mathrm{EC-CA3}}$ were modified during the learning phase according to the covariance rule (5), which compared the patterns stored in CA3 with those original patterns in the entorhinal cortex:

$$\delta w_{ij}^{\mathrm{EC-CA3}} = k \cdot (r_i^{CA3} - \bar{r}_i^{CA3}) \cdot (r_j^{\mathrm{EC}} - \bar{r}_j^{\mathrm{EC}}); \quad k = 6.7 \tag{5}$$

Again, $\bar{r}$ is the mean firing rate of a single neuron along the complete set of patterns. Neuron activations in CA3 were calculated according to:

$$h_i^{CA3} = k_{\mathrm{DG-CA3}} \cdot \sum_{j=1}^{x} r_j^{\mathrm{DG}} w_{ij}^{\mathrm{DG-CA3}} + k_{\mathrm{EC-CA3}} \cdot \sum_{j=1}^{y} r_j^{\mathrm{EC}} w_{ij}^{\mathrm{EC-CA3}} + k_{CA3-CA3} \cdot \sum_{j=1}^{z} r_j^{CA3} w_{ij}^{CA3-CA3} \tag{6}$$

The three components here correspond to the three input pathways (mossy fibers, perforant pathway and recurrent collaterals with *x*, *y*, and *z* connections, respectively). During the learning phase, only the input from the dentate gyrus was considered ($k_{DG-CA3} = 1, k_{EC-CA3} = 0, k_{CA3-CA3} = 0$). During the retrieval phase, the two other pathways were considered ($k_{DG-CA3} = 0, k_{EC-CA3} = 1, k_{CA3-CA3} = 1$). The activation function of the neurons in CA3, which determined their firing rates or outputs *r*, was a binary threshold. The threshold was fixed by the sparseness, as it was in the dentate gyrus.

Once the cues that initiate retrieval were presented, the recurrent synapses were the only synapses modified during the retrieval phase. The learning rule governing the weight change was the covariance rule (7):

$$\delta w_{ij}^{CA3-CA3} = k \cdot (r_i^{CA3} - \bar{r}_i^{CA3}) \cdot (r_j^{CA3} - \bar{r}_j^{CA3}); \quad k = 2 \tag{7}$$

We made this choice because of the need for a rule which included LTP and LTD (Rolls & Treves, 1998). This network was allowed to repeat this recurrent collateral loop 15 times. Each time the loop operated, the output firing pattern became more like the originally stored pattern. After the iterations, this progressive recall was usually complete.

2.2.4. The CA1 subfield

The third sub-network was composed of the neurons of CA1. The inputs to these neurons came from CA3 (Schaffer collateral synapses). The CA1 subfield was represented with 1000 neurons, a sparseness of 0.05 (50 active neurons *per* pattern) and a randomly selected connectivity to CA3 of 200 synapses *per* neuron. This network carried out competitive learning, as suggested by its anatomical and physiological characteristics, implemented in the same way as in the dentate gyrus (random and normalized weights, a binary threshold activation function with threshold set by the sparseness in CA1, and a modified Hebb's rule). The learning rate was set to 0.5. Here, competitive learning might result in neurons that represent conjunctions of "whole scenes" or episodic memories in CA3, resulting in a more effective representation that facilitates retrieval to the neocortex (Treves & Rolls, 1994).

Regarding this subfield, we can state that although the model does not take into account the contribution of the direct perforant pathway into CA1 (it is not taken account in most published models (see discussion) nor in Rolls' simulation), we consider that such a contribution would not interfere with the effects of neurogenesis. However, most likely it could be taken into account in future studies to improve the hippocampal model.

2.2.5. Pattern association between CA1 and the entorhinal cortex

In this last stage, the outputs from CA1 were associated with the patterns stored in EC (the former as conditioned stimuli and the latter as unconditioned stimuli). For this to occur, the weights of these connections were calculated during the learning phase. They were originally set to zero and were modified as the different patterns were presented, according to the modified Hebb rule already introduced:

$$\delta w_{ij}^{CA1-EC} = k \cdot r_i^{EC} \cdot (r_j^{CA1} - w_{ij}^{CA1-EC}); \quad k = 1 \tag{8}$$

The connectivity between CA1 and EC was set to 200 synapses *per* neuron. Again, the activation function employed was the binary threshold, where the threshold was given by the sparseness in EC.

2.2.6. Pattern separation in the dentate gyrus

In order to verify the hypothesis that the dentate gyrus does produce pattern separation, the output of the dentate gyrus was analysed in the simulation once the complete set of input patterns was presented in the entorhinal cortex. This pattern separation function would consist in transforming the memories to make them more dissimilar, facilitating their storage as distinct representations.

The more dissimilar the patterns are, the more separated they are. The similarity between patterns in the entorhinal cortex and in the dentate gyrus was estimated by building a similarity matrix *S* for each group. Each similarity matrix gives us an idea of how separated or similar the patterns are in that region. Then, the infinity norm *Norm(S)* was calculated as a way of establishing a unique magnitude with which to estimate the size of the matrices (similar to the norms for vectors) for comparative purposes. Ideally, for dissimilar patterns *Norm(S)* should be small.

The similarity matrix *S* that estimates the similarity between patterns in a single layer or neural group was built as follows:

$$S = \begin{bmatrix} \langle p_1, p_1 \rangle & \langle p_1, p_2 \rangle & \langle p_1, p_3 \rangle & \cdots & \langle p_1, p_N \rangle \\ \langle p_2, p_1 \rangle & \langle p_2, p_2 \rangle & \langle p_2, p_3 \rangle & \cdots & \langle p_2, p_N \rangle \\ \langle p_3, p_1 \rangle & \langle p_3, p_2 \rangle & \langle p_3, p_3 \rangle & \cdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \langle p_{N-1}, p_N \rangle \\ \langle p_N, p_1 \rangle & \langle p_N, p_2 \rangle & \cdots & \langle p_N, p_{N-1} \rangle & \langle p_N, p_N \rangle \end{bmatrix} \tag{9}$$

where $\langle p_x, p_y \rangle$ is the dot product between p_x and p_y (representing their distance), and where p_1, p_2, p_3 …, p_N are the representations of the *N* patterns for that group (here, EC or DG).

For each matrix S_{EC} and S_{DG} (similarity matrixes in EC and in DG, respectively) the infinity norm, mathematically defined by:

$$Norm(S) = \max_i \left\{ \sum_j |s_{ij}| \right\} \tag{10}$$

was calculated. By this definition, this norm is the maximum of the sums obtained by adding the absolute values of the elements in each row. Finally, $Norm(S_{EC})$ and $Norm(S_{DG})$ were compared.

2.3. The neurogenesis model

Starting from the hippocampal model presented above, the network's learning proceeded with a given number of patterns or memories (pre-neurogenesis stage). The neurogenesis phase was then implemented by incorporating 30% of the initial number of neurons in the dentate gyrus, i.e.,

300 new neurons, while maintaining the preset sparseness level of the dentate gyrus. This percentage, representing the neurogenesis rate in rats accumulated along an individual's life, was chosen to take into account the following: (1) different studies have suggested different rates, ranging from 10% to 40%, as referred by Wiskott et al. (2006); (2) rates are extremely variable, by animal strain and living conditions (i.e., lab-kept vs. living in the wild); (3) depending on how you define neurogenesis (e.g., proliferation or survival), the rates will differ. This study requires survival rates; nevertheless the main reported ones are based on proliferation rates. In our model, the neurogenesis phase was modeled with a net increment in the number of cells; this is distinct from studies where neuronal turnover was considered to be what really occurs and where the final number of cells does not change. This issue remains controversial, with no established consensus so far (Meltzer et al., 2005; Wiskott et al., 2006).

In the second stage (post-neurogenesis), the network was trained again with new patterns (new episodic memories) which were created using the same methodology used in the pre-neurogenesis stage. Learning new patterns implied the adaptation of synaptic strengths with different forces depending on whether the synapses were old or new. This implementation was chosen because the new synapses appear to be more plastic in biological hippocampus, where they present an LTP induction threshold lower than the one of mature neurons (Schmidt-Hieber, Jonas, & Bischofberger, 2004; Snyder, Kee, & Wojtowicz, 2001; Wang, Scott, & Wojtowicz, 2000), though the older dentate granule cells still exhibit LTP. As we shall see later, this distinction also allowed the new neurons to become more active for new patterns than for the old ones, as reported in recent work (Bischofberger, 2007; Kee, Teixeira, Wang, & Frankland, 2007).

In the model, the new neurons established connections with the entorhinal cortex and with CA3, using the same connectivity values employed in the pre-neurogenesis stage (Fig. 2, in green). Since each neuron in the dentate gyrus is connected with approximately 15 neurons in CA3 in the real hippocampus (Amaral et al., 1990), each unit in CA3 received only 5 connections from the new neural group in DG $[(300 \times 15) \div 1000]$ in the model. Also, as in the first stage, each new neuron in DG in the model received 60 synapses from EC. The precise way by means of which the new neurons are integrated into the existing circuits has not been studied yet. An exhaustive physiological and anatomical analysis is still required.

After creating new, random patterns in the EC, the activity in each region was computed and propagated in the same way and with the same formulae as used in the pre-neurogenesis stage (implementing competition in DG, autoassociation in CA3, competition in CA1, and pattern association in CA1-EC). Weight modifications, due to the learning of the new patterns, were also implemented using the same formulae as used in the first stage. The main point here was that the synapses from DG to CA3 were updated with different learning rates, depending on the kind of synapse (old: $k = 0.25$; new: $k = 0.5$), thereby taking account of biological constraints. Moreover, the weight matrices where the new associations were added or stored were no longer null or random; they were the weight matrices calculated from the patterns stored in the previous stage.

3. Results

The entire network was trained with different numbers of patterns[1] (N) or learning exemplars that enabled us to assess the retrieval quality of the model vs. the network storage load, i.e., as a function of the number of patterns that were stored in the hippocampus. To evaluate retrieval, cues composed of 5%, 10%, 15%, etc., up to 100% of the original patterns that had been presented in EC were, again, presented in EC as inputs.

The cue's remainder was completed with zeros (like a mask) to permit its biological plausibility, representing the missing aspects of the context. To analyse how similar the cue was to the original pattern presented in EC, the linear correlation coefficient between the cue and its original pattern was calculated for each network input (input correlation). The retrieved pattern in EC constituted the network output, for which its linear correlation with the stored pattern was calculated again (output correlation). This last value, indicating how similar the output is to the original memory, measured the retrieval quality. The correlation value will range from 0 for absolutely different patterns to 1 for identical patterns.

Because each memory was presented just once and in sequence, the output correlation shown in the figures was the averaged for the ten first (remote), or the ten last (recent), memories presented to the network; this allowed us to distinguish between remote and recent memories.

3.1. The hippocampal formation model

3.1.1. Pattern retrieval and system variability

Fig. 3A shows a representative curve of pattern retrieval with the network storing $N = 50$ patterns (mean and standard deviation, $n = 20$ trials). The curve represents the retrieval in EC as a function of the cue quality (output correlation vs. input correlation), once the complete network has fully operated. An output larger than an input (above the diagonal line) indicates effective retrieval, meaning that the network was able to restore part of the missing context. The variation among trials (creating multiple individualized networks from a generic one) was due to the fact that initial weights in the networks (representing synaptic efficacy) were random, as were the generated patterns. These differences among initial weights represent intersubject variability.

Fig. 3B shows that the retrieval quality (here estimated with the mean output correlation) decreased as the network was exposed to a larger number of patterns. The figure also shows that the network was effective in retrieving patterns until a specific number of them were stored (we will name this specific number the 'critical limit', here $Nc \approx 100$). Beyond this point, the information added to the

[1] By a pattern we mean a binary code representing a unique, single event.

cues was null (mean output correlation ⩽ mean input correlation).

3.1.2. Pattern separation in the dentate gyrus

Fig. 4 shows the values for *Norm(S)* both in EC and in DG for a representative case ($N = 50$ patterns). After the passage from EC to DG, a significant decrease in the similarity between patterns is seen between these two groups, confirming the pattern separation function in DG.

3.2. The neurogenesis model

3.2.1. Pattern retrieval

Once the neurogenesis process had been modeled (and the network trained with N_1 patterns in the pre-neurogen-

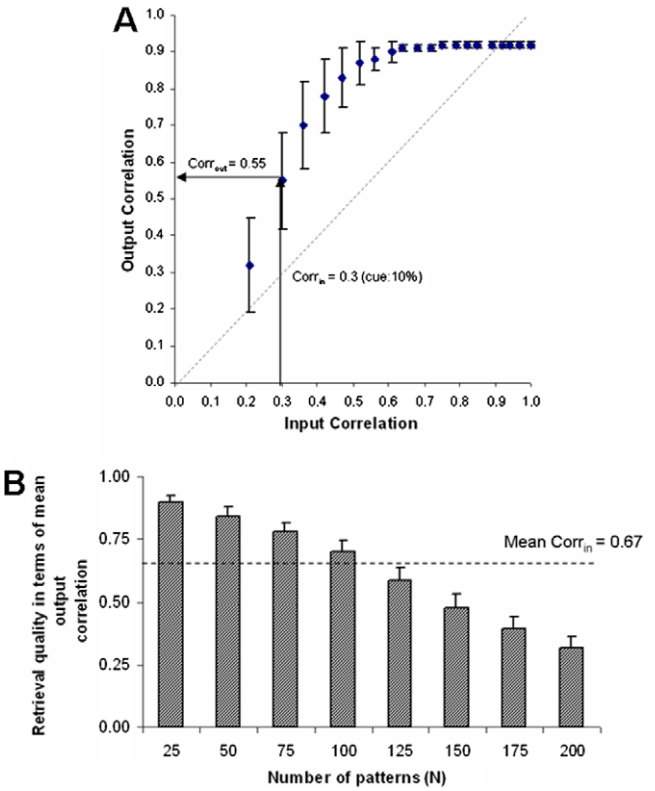

Fig. 3. Hippocampal model: pattern retrieval in the entorhinal cortex. (A) Representative curve for pattern retrieval with $N = 50$ patterns (mean and standard deviation, $n = 20$ trials). The retrieval in EC is shown as a function of the cue quality (output correlation vs. input correlation) once the network has fully operated. For each cue (ranging from 5% to 100% of the complete pattern) the output correlation (here measuring the retrieval quality) was plotted against the input correlation (output correlation: correlation between the output and the original pattern; input correlation: correlation between the cue and the original pattern). An output larger than an input (above the diagonal) indicates effective pattern retrieval. (B) Mean output correlation vs. storage load.

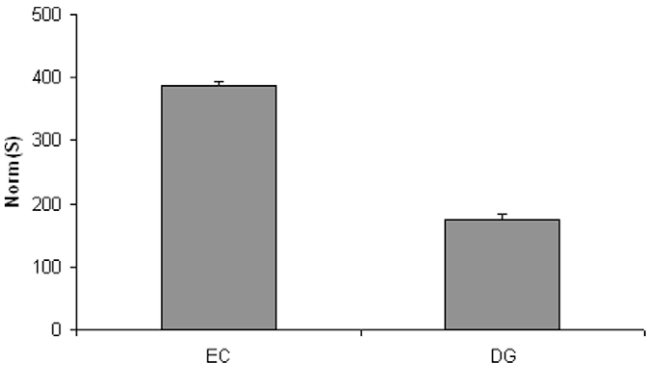

Fig. 4. Pattern separation in the dentate gyrus. To show how the pattern separation degree varies from EC to DG, the measure used to estimate the similarity between patterns *Norm*(*S*) is shown for both regions.

esis stage and N_2 patterns in the post-neurogenesis stage), the results of this model were compared with those of the previous hippocampal model (lacking neurogenesis). In order to do this, we set the same total number of stored patterns in each case ($N = N_1 + N_2$; where N_1 equals the number of stored patterns in the pre-neurogenesis stage, N_2 equals the number of stored patterns in the post-neurogenesis stage and N equals the total number of stored patterns). Also, the proportion $N_1 = N_2 = N/2$ held constant as the number of patterns increased.

Fig. 5 shows how neurogenesis increased significantly the retrieval of recent memories (the last ten memories). On the other hand, although neurogenesis affected the retrieval of remote memories (the first ten memories), its impact was smaller. Again, as we increased the storage load in the model with neurogenesis, we arrived at a new critical limit (Nc≈250), beyond which retrieval was no longer efficient, as previously stated.

3.2.2. Effect of the initial size of the dentate gyrus in pattern retrieval. Comparison with the effects of neurogenesis

The observed increase in retrieval might be due to the fact that the number of neurons in the dentate gyrus increased. We hypothesize that these new neurons, incorporated into the circuitry during adult life and presenting characteristics which make them different from the pre-existing neurons, present some advantages beyond the mere presence of more neurons from the beginning. To test this hypothesis, the model was ran with an initial size of 1300 neurons in DG (the same number as the final value with neurogenesis) and these results were compared with those shown in Fig. 5. The 3 conditions (no-neurogenesis, DG = 1300 neurons; no-neurogenesis, DG = 1000 neurons; neurogenesis, DG = 1000 + 300 neurons) were merged in Fig. 6. We see there that an *initial* increase in the number of units does not change significantly the pattern retrieval. This fact demonstrates that the neurogenic process in DG is more efficient (when evaluating retrieval) that the simple addition of new neurons from the very beginning.

3.2.3. New granule cells and pattern separation

Our hypothesis at the outset of this work was that new neurons improve retrieval by separating patterns in the dentate gyrus to a greater extent than would be possible on the basis of the old granule cells alone. In order to test this hypothesis, we built the similarity matrixes S_{EC} and S_{DG} again (post-neurogenesis) and calculated *Norm(S)* for each. The results are shown in Fig. 7. Surprisingly, the new neurons did *not* increase the distance between patterns. The analysis and implications of this are discussed in the next section.

If we look at the activity patterns for old and new neurons in the dentate gyrus when representing remote and recent memories, we can see that the new neurons were statistically more active for the new patterns than for the old ones. This can be quantified by averaging the number of new neurons which are activated for new memories. If all granule cells in DG have the same probability of being

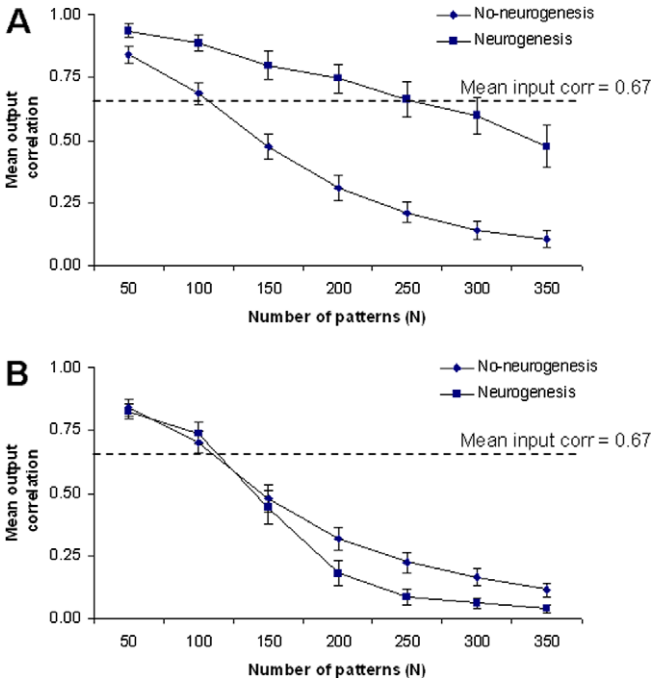

Fig. 5. Effects of neurogenesis on pattern retrieval. The retrieval quality was estimated by the mean output correlation for each storage load (mean and standard deviation, $n = 20$ trials). The same curves as in Fig. 3B are plotted for recent memories (mean for the ten last stored) (A) and for remote ones (mean for the ten first stored) (B), and then compared with the control cases (without neurogenesis, recent and remote memories). When testing the neurogenesis case, the number of stored memories in the pre- (N_1) and post-neurogenesis stages (N_2) were the same ($N_1 = N_2 = N/2$) for each value of N (total number of patterns).

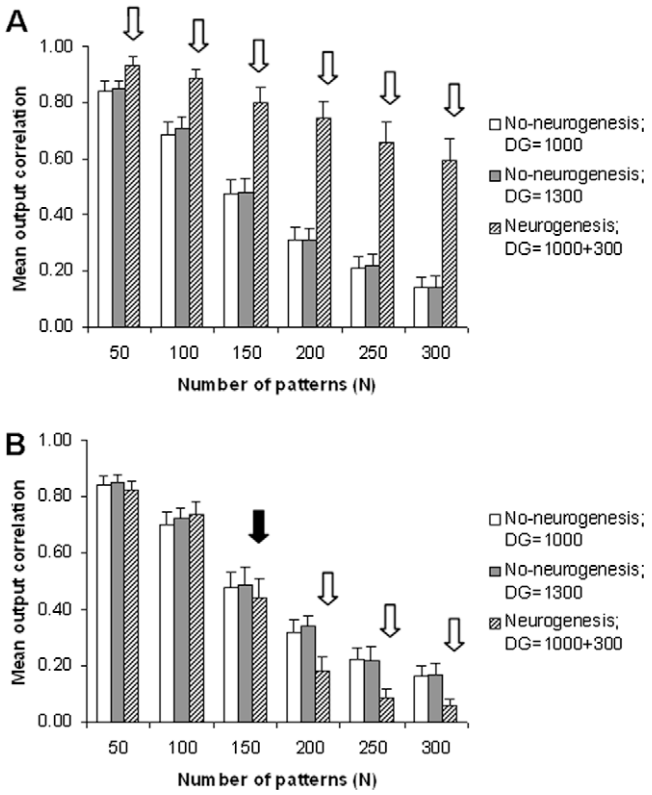

Fig. 6. Adding more neurons after the initial storing is more efficient on recent memories than starting with the same number of neurons with no new additions. The efficiency of 300 more neurons added after storing was compared: (a) control case (1000 neurons in DG. Fifty patterns stored); (b) more initial neurons (1300 neurons in DG. Fifty patterns stored) (non-neurogenic condition); (c) more neurons by neurogenesis (initial number of neurons in DG = 1000. Once the first 25 patterns were stored, 300 neurons were added. Finally, the remaining 25 patterns were stored) (neurogenic condition). The efficiency of new neurons can be assessed by the increase in retrieval (difference between mean output correlations) for the neurogenic and non-neurogenic conditions when compared with the control case. (A) Recent memories. (B) Remote memories. (Open arrows indicated an statistical difference; $p < 0.001$) (Filled arrows indicated an statistical difference of $p < 0.05$) ANOVA test, $n = 20$ trials.

activated (this probability is given by the sparseness of the representation in DG), then this average number would be:

$$\text{Number of activated new neurons} = \textit{Number of new neurons} \times \textit{Sparseness}_{\text{DG}} = 300 \times 0.05 = 15 \quad (11)$$

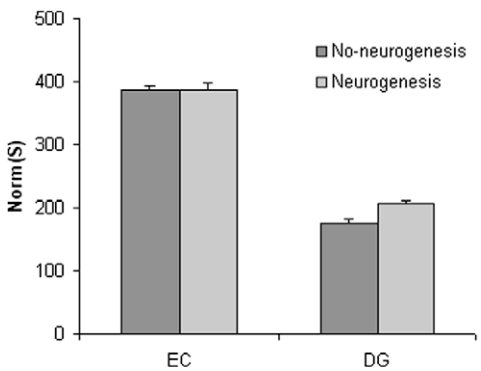

Fig. 7. Effects of new granule cells on the pattern separation function performed in the dentate gyrus. The estimate of similarity among patterns *Norm*(*S*) in the entorhinal cortex (EC) ($p > 0.05$, "*t*" test) and the dentate gyrus (DG) ($p < 0.05$, "*t*" test) is shown for the neurogenesis and no-neurogenesis conditions.

For $n = 20$ trials and using a representative case ($N = 25 + 25$, i.e., 25 patterns in the pre-neurogenesis stage and 25 patterns in the post-neurogenesis stage), this value was:

$$\text{Number of activated new neurons} = 20.93 \pm 0.55 \quad (\text{Mean} \pm \text{SD}),$$

i.e., a higher number than shown in (11). As we have already seen, a higher activation of new neurons was an important condition of the model from the perspective of its biological plausibility.

4. Discussion

It has long been recognized that the hippocampus participates in cognitive processes such as learning and memory. Equally, some studies suggest that it is possible that the addition of new neurons (adult neurogenesis) in this region could serve as a mechanism towards brain plasticity (Shors et al., 2001). New neurons are known to have special characteristics through which they are thought to have an important role in dentate gyrus plasticity (Snyder et al., 2001). Specifically, the new granular cells seem to have a smaller LTP and LTD induction threshold, leading to a bi-

directional improvement of plasticity (Ge, Yang, Hsu, Ming, & Song, 2007; Schmidt-Hieber et al., 2004; Song et al., 2005; Wang et al., 2000). However, current data are insufficient to determine the precise functional role of neurogenesis and the relationship between the generation of new neurons, synaptic plasticity and memory. Beyond the obvious necessity of biological experiments, it is widely recognized that in order to model some forms of memory, biologically plausible neural networks are a useful tool.

4.1. Modeling neurogenesis in the dentate gyrus

Our analyses in this study have focused on a specific moment in the adult life of the subject being modeled. At this specific moment, the subject has a large number of mature neurons and a lesser number of new neurons that are being incorporated into the circuitry, and, critically, are being incorporated after previous learning has taken place. The model is applied to this time window when the new neurons present their characteristic hyperplasticity while the mature neurons remain normo-plastic. Of course, outside this time window these conditions change. As time goes by, these new neurons mature and other new neurons arise, recreating at this later time, the situation we have modeled. Beyond our chosen time window, we hypothesize that the impact of new neurons on learning would be qualitatively the same as that we have observed here, albeit with higher or lesser strength.

With respect to the actual process of neurogenesis, and contrary to our implementation in the model, we do not wish to imply a sudden one-off lifetime "dose" of neurogenesis. Our implementation as such was intended purely as an approximation on which basis to test our hypotheses.

The neurogenesis phase was implemented in the dentate gyrus but in no other hippocampal subfields, because although it is known that neurogenesis does occur here, the comparison with a network that does not present neurogenesis in this region has been neither predictable nor quantifiable. In contrast, for an autoassociative network, which is the hypothetical case for CA3, it has been shown that the number of different patterns that the network can store and recall correctly depends more on the sparseness of the representation and on the number of connections to each neuron devoted to the recurrent collaterals than on the network's effective nodes (Rolls & Treves, 1998).

Briefly, our results indicate that:

1. Neurogenesis enables an important increase in the capacity of the hippocampus to retrieve recent memories. It also decreases the retrieval of remote memories, but to a lesser extent. These data seems to indicate that neurogenesis increases network capacity for new information, while increasing the forgetting of old information. However, this hypothesis would need to be confirmed in future *in silico* and *in vivo* experimentation.
2. The effect of neurogenesis on recent memories is not merely an additional effect due to the presence of more processing units. Neurogenesis represents a successive, dynamic adaptation to environment.
3. The above mentioned effects of neurogenesis are likely to be more significant for higher storage loads (i.e., with a larger number of patterns to be stored).

It is important to note that simply starting with a larger number of neurons or indiscriminately adding others does not have the same consequences. The question is how and with which unique properties the new neurons added through neurogenesis (which are only a few and which become fewer with time) can make a difference to the network's performance without interfering with the information it had previously stored. We explored this issue by using different learning rates (standing for different levels of plasticity) for old vs. new neurons. The values finally chosen in the model were in accordance with empirical findings regarding greater plasticity and greater general activation for new neurons (Bischofberger, 2007; Ge et al., 2007; Kee et al., 2007).

Some important conclusions can be drawn from these results, in line with the predictions derived from a theoretical analysis of the effect of adding new units in the manner we adopted for our model: First, neurogenesis is not performing a sparse coding here; this is the general function of dentate gyrus, with or without neurogenesis (in the model, the sparseness before and after neurogenesis was the same). Second, the new neurons are not performing pattern separation in general; they are only implicated in the representation of new patterns, and there will thus be less overlap between remote and recent memories – their higher general activation for new patterns will in fact cause increased overlap among new patterns.

In conclusion, it would seem that the new granule cells engage in the representation of events that occur during the time window when they are still immature, presenting the special characteristics described above, enabling thereby the establishment of associations between memories close in time. Moreover, neurogenesis increases the number of retrievable codes, especially those for memories formed during the given time window.

4.2. Compatibility of the model with empirical data

Several experimental studies have demonstrated that neurogenesis is specifically affected by, and potentially involved in, associative memory formation, a fact that supports our results (Gould, Beylin, Tanapat, Reeves, & Shors, 1999). Interestingly, empirical evidence of improved memory retrieval scores when inducing neurogenesis in an animal model has recently been reported (Pourié et al., 2006). Furthermore, several authors have also reported that decreasing neurogenesis in young rats is correlated in time with a deficit in retention of hippocampus-dependent memories (Rola et al., 2004; Snyder, Hong, McDonald, & Wojtowicz, 2005). Regarding our hypothesis, this decrease would correspond to a failure in the adaptation mechanism provided by neurogenesis for new environmental requirements.

It is important to bear in mind that in our model, the benefits would be more noticeable in the long-term, when the number of stored memories is larger, a fact already observed in experimental reports (Pourié et al., 2006). In this respect, the role recently attributed to neurogenesis by Snyder et al.

in the long-term spatial memory formation (Snyder et al., 2005) is consistent with our hypothesis. This fact might also justify the discrepancies among empirical results on the relationship between neurogenesis and learning. The advantages attributed to neurogenesis in hippocampal-dependent learning tasks have not been observed in all studies (Doetsch & Hen, 2005; Feng et al., 2001; Shors, Townsend, Zhao, Kozorovitskiy, & Gould, 2002). In our model, for low storage load, the cases with and without neurogenesis gave similar results in terms of memory retrieval, probably indicating that the required volume of information is adequately supported by the pre-existing neurons.

4.3. Compatibility of the model with clinical data

Aging and depressive disorders target the hippocampal formation and are often accompanied by impairments in forming new memories (Suzuki, 2007; Wilson, Gallagher, Eichenbaum, & Tanila, 2006). Moreover, the capacity to generate new neurons decreases dramatically with aging (Heine, Maslam, Joels, & Lucassen, 2004; Kuhn, Dickinson-Anson, & Gage, 1996). How this decrease occurs is not fully understood, but we hypothesize that the results generated by our model could explain the physiological role of neurogenesis in aging. The association between declining hippocampal neurogenesis and cognitive dysfunctions in normal aging has also been assumed in at least one recent study (Montaron et al., 2006).

Regarding depression, antidepressant treatments increase adult hippocampal neurogenesis, and there is some evidence that the inhibition of neurogenesis blocks behavioural responses to antidepressants (Santarelli et al., 2003). Coping with a novel environment needs both the effects of antidepressants and an intact capacity to produce new neurons in the DG of the hippocampus. Finally, there is some evidence that indicates that the functional disorganization in the hippocampus in schizophrenic patients could be related to major difficulties when coping with new events (Boyer, Phillips, Rousseau, & Ilivitsky, 2007). The relationship between neurogenesis and schizophrenia is supported to some degree by clinical diagnostic imaging techniques, as well as by animal models such as reelin and NPAS3 knockout mice. It has been suggested that altered neurogenesis may lead to erroneous temporal encoding of new memory traces, thereby contributing to the cognitive deficits observed in schizophrenia (Reif, Schmitt, Fritzen, & Lesch, 2007). Interestingly, it has recently been suggested that neurogenesis plays a role in the encoding of time in new memories (Aimone, Wiles, & Gage, 2006).

4.4. Other computational approaches. Future directions

Several computational models have attempted to hypothesize the function of adult-born neurons. Most of them share the view, as do we, that new neurons could be necessary for the hippocampus to adapt to new environmental requests, allowing it to cope in the face of novelty and a growing volume of information (Becker, 2005; Chambers & Conroy, 2007; Chambers, Potenza, Hoffman, & Miranker, 2004; Deisseroth et al., 2004; Meltzer et al., 2005; Wiskott et al., 2006). A recent study, which does not deny the cited effects of neurogenesis on memory, focused on a different hypothesis (albeit in the absence of an explicit computational model): As described earlier, Aimone et al. (2006) proposed that adult neurogenesis could be a mechanism to encode time in memories, and suggested that the physiological properties of immature neurons would enable the establishment of close associations between the memories formed in the recurrent CA3 network.

The work we presented here extends the analysis of preceding models in several ways. First of all, we assumed a broad biological plausibility criterion for our model, combining old structural and relatively new functional (neurophysiological) information. This issue has received less attention in previous models. This biological plausibility criterion determined, roughly, the different hippocampal regions to model (and the different pathways), the number of cells in each region, the connectivity between the neuronal groups, the learning rules employed, the sparseness of the representation in the entire hippocampus, as well as the different levels of plasticity and activity for old and new neurons. Second, we believe our hypothesis reconciles the two perspectives mentioned above in respect of the functional significance of neurogenesis – increase of memory capacity and time encoding, placing greater emphasis on the former. From a very general point of view we can combine these two perspectives without major contradictions. Third, our results are broadly compatible with the empirical data. Finally, it takes account of the crucial control case, ignored in many other studies, of a dentate gyrus that *starts off* with more units rather than acquiring them through neurogenesis.

Some experimental predictions can be made from this work, an important point for using theoretical models. If adult neurogenesis can increase the retrieval of recent memories, this effect can be measured in animals by means of behavioural tests (testing episodic memory) after inducing neurogenesis, no matter what strategy we employ (running-wheel, enriched environment, etc.). An issue we are already working on.

4.5. Final comments

In conclusion, several physiological, morphological and behavioural experiments suggest that neurogenesis has an important role to play in hippocampal functions such as learning and memory. The evidence is not conclusive and new experimental models and perhaps new hypotheses need to be designed. Neurocomputational models will continue to be an indispensable tool in the generation of new, more advanced, accounts of the functional significance of neurogenesis. In this sense, the model presented here supports the idea that hippocampus-dependent memory involves the integration of newly generated neurons into the existing circuits of the dentate gyrus. Neurogenesis may play a central role in some forms of episodic memory, and predominantly in respect of the retrieval of new, recent memories.

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References

Aimone, J. B., Wiles, J., & Gage, F. H. (2006). Potential role for adult neurogenesis in the encoding of time in new memories. *Nature Neuroscience, 9*, 723–727.

Amaral, D. G. (1993). Emerging principles of intrinsic hippocampal organization. *Current Opinion in Neurobiology, 3*, 225–229.

Amaral, D. G., Ishizuka, N., & Claiborne, B. (1990). Neurons, numbers and the hippocampal network. *Progress in Brain Research, 83*, 1–11.

Barnes, C. A., McNaughton, B. L., Mizumori, S. J. Y., Leonard, B. W., & Lin, L. H. (1990). Comparison of spatial and temporal characteristics of neuronal activity in sequential stages of hippocampal processing. *Progress in Brain Research, 83*, 287–300.

Becker, S. (2005). A computational principle for hippocampal learning and neurogenesis. *Hippocampus, 15*, 722–738.

Bischofberger, J. (2007). Young and excitable: New neurons in memory networks. *Nature Neuroscience, 10*, 273–275.

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature, 361*, 31–39.

Boyer, P., Phillips, J. L., Rousseau, F. L., & Ilivitsky, S. (2007). Hippocampal abnormalities and memory deficits: New evidence of a strong pathophysiological link in schizophrenia. *Brain Research Reviews, 54*, 92–112.

Chambers, R. A., & Conroy, S. A. (2007). Network modeling of adult neurogenesis: Shifting rates of neuronal turnover optimally gears network learning according to novelty gradient. *Journal of Cognition Neuroscience, 19*, 1–12.

Chambers, R. A., Potenza, M. N., Hoffman, R. E., & Miranker, W. (2004). Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. *Neuropsychopharmacology, 29*, 747–758.

Chawla, M. K., Guzowski, J. F., Ramirez-Amaya, V., Lipa, P., Hoffman, K. L., Marriot, L. K., Worley, P. F., McNaughton, B. L., & Barnes, C. A. (2005). Sparse, environmentally selective expression of Arc RNA in the upper blade of the rodent fascia dentata by brief spatial experience. *Hippocampus, 15*, 579–5786.

Deisseroth, K., Singla, S., Toda, H., Monje, M., Palmer, T. D., & Malenka, R. C. (2004). Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron, 42*, 535–552.

Doetsch, F., & Hen, R. (2005). Young and excitable: The function of new neurons in the adult mammalian brain. *Current Opinion in Neurobiology, 15*, 121–128.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience, 1*, 41–50.

Eichenbaum, H. (2004). Hippocampus: Cognitive processes and neural representations that underlie declarative memory. *Neuron, 44*, 109–120.

Feng, R., Rampon, C., Tang, Y., Shrom, D., Jin, J., Kyin, M., Sopher, B., Martin, G. M., Kim, S., Langdon, R. B., Sisodia, S. S., & Tsien, J. Z. (2001). Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. *Neuron, 32*, 911–926.

Freund, T. F., & Buzsáki, G. (1996). Interneurons of the hippocampus. *Hippocampus, 6*, 347–470.

Ge, S., Yang, C., Hsu, K., Ming, G., & Song, H. (2007). A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron, 54*, 559–566.

Gould, E., Beylin, A., Tanapat, P., Reeves, A., & Shors, T. J. (1999). Learning enhances adult neurogenesis in the hippocampal formation. *Nature Neuroscience, 2*, 260–265.

Gould, E., & Gross, C. G. (2002). Neurogenesis in adult mammals: Some progress and problems. *Journal of Neuroscience, 22*, 619–623.

Heine, V. N., Maslam, S., Joels, M., & Lucassen, P. J. (2004). Prominent decline of newborn cell proliferation, differentiation and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus–pituitary–adrenal axis activation. *Neurobiology of Aging, 25*, 361–375.

Kee, N., Teixeira, C. M., Wang, A. H., & Frankland, P. W. (2007). Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nature Neuroscience, 10*, 355–362.

Kuhn, H. G., Dickinson-Anson, H., & Gage, F. H. (1996). Neurogenesis on the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. *Journal of Neuroscience, 16*, 2027–2033.

Maguire, E. A. (2001). Neuroimaging studies of autobiographical event memory. *Philosophical Transactions of the Royal Society of London, Series B, 356*, 145–441.

Meltzer, L. A., Yabaluri, R., & Deisseroth, K. (2005). A role for circuit homeostasis in adult neurogenesis. *Trends in Neurosciences, 28*, 653–659.

Milner, B., Squire, L. R., & Kandel, E. R. (1998). Cognitive neuroscience and the study of memory. *Neuron, 20*, 445–468.

Ming, G., & Song, H. (2005). Adult neurogenesis in the mammalian central nervous system. *Annual Review of Neuroscience, 28*, 223–250.

Montaron, M. F., Drapeau, E., Dupret, D., Kitchener, P., Aurousseau, C., Le Moal, M., Piazza, P. V., & Abrous, D. N. (2006). Lifelong corticosterone level determines age-related decline in neurogenesis and memory. *Neurobiology of Aging, 27*, 645–654.

Moser, E. I. (2003). Interneurons take charge. *Nature, 421*, 797–799.

Pourié, G., Blaise, S., Trabalon, M., Nédélec, E., Guéant, J.-L., & Daval, J.-L. (2006). Mild, non-lesioning transient hypoxia in the newborn rat induces delayed brain neurogenesis associated with improved memory scores. *Neuroscience, 140*, 1369–1379.

Reif, A., Schmitt, A., Fritzen, S., Lesch, K.P. (2007). Neurogenesis and schizophrenia: Dividing neurons in a divided mind? European Archives of Psychiatry and Clinical Neuroscience. (Epub ahead of print).

Rola, R., Raber, J., Rizk, A., Otsuka, S., VandenBerg, S. R., Morhardt, D. R., & Fike, J. R. (2004). Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Experimental Neurology, 188*, 316–330.

Rolls, E. T. (1995). A model of the operation of the hippocampus and entorhinal cortex in memory. *International Journal of Neural Systems, 6*, 51–70.

Rolls, E. T., & Kesner, R. P. (2006). A computational theory of hippocampal function, and empirical tests of the theory. *Progress in Neurobiology, 79*, 1–48.

Rolls, E. T., & Treves, A. (1998). *Neural networks and brain function*. New York: Oxford University Press.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., & Hen, R. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Physics, 301*, 805–809.

Scharfman, H. E., & Hen, R. (2007). Is more neurogenesis always better? *Science, 315*, 336–338.

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

Shors, T. J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., & Gould, E. (2001). Neurogenesis in the adult is involved in the formation of trace memories. *Nature, 410*, 372–376.

Shors, T. J., Townsend, D. A., Zhao, M., Kozorovitskiy, Y., & Gould, E. (2002). Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus, 12*, 578–584.

Snyder, J. S., Hong, N. S., McDonald, R. J., & Wojtowicz, J. M. (2005). A role for adult neurogenesis in spatial long-term memory. *Neuroscience, 130*, 843–852.

Snyder, J. S., Kee, N., & Wojtowicz, J. M. (2001). Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. *Journal of Neurophysiology, 85*, 2423–2431.

Song, H., Kempermann, G., Overstreet Wadiche, L., Zhao, C., Schinder, A. F., & Bischofberger, J. (2005). New neurons in the adult mammalian brain: Synaptogenesis and functional integration. *Journal of Neuroscience, 9*, 10366–10368.

Suzuki, W. A. (2007). Making new memories: The role of the hippocampus in new associative learning. *Annals of the New York Academy of Sciences, 1097*, 1–11.

Treves, A., & Rolls, E. T. (1992). Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus, 2*, 189–199.

Treves, A., & Rolls, E. T. (1994). Computational analysis of the role of the hippocampus in memory. *Hippocampus, 4*, 374–391.

van Praag, H., Schinder, A. F., Christie, B. R., Toni, N., Palmer, T. D., & Gage, F. H. (2002). Functional neurogenesis in the adult hippocampus. *Nature, 415*, 1030–1034.

Wang, S., Scott, B. W., & Wojtowicz, J. M. (2000). Heterogenous properties of dentate granule neurons in the adult rat. *Journal of Neurobiology, 42*, 248–257.

Wilson, I. A., Gallagher, M., Eichenbaum, H., & Tanila, H. (2006). Neurocognitive aging: Prior memories hinder new hippocampal encoding. *Trends in Neuroscience, 29*, 662–670.

Wiskott, L., Rasch, M. J., & Kempermann, G. (2006). A functional hypothesis for adult hippocampal neurogenesis: Avoidance of catastrophic interference in the dentate gyrus. *Hippocampus, 16*, 329–343.