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Impaired neurogenesis of the dentate gyrus is associated with pattern separation deficits: A computational study

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The separation of input patterns received from the entorhinal cortex (EC) by the dentate gyrus (DG) is a well-known critical step of information processing in the hippocampus. Although the role of interneurons in separation pattern efficiency of the DG has been theoretically known, the balance of neurogenesis of excitatory neurons and interneurons as well as its potential role in information processing in the DG is not fully understood. In this work, we study separation efficiency of the DG for different rates of neurogenesis of interneurons and excitatory neurons using a novel computational model in which we assume an increase in the synaptic efficacy between excitatory neurons and interneurons and then its decay over time. Information processing in the EC and DG was simulated as information flow in a two layer feed-forward neural network. The neurogenesis rate was modeled as the percentage of new born neurons added to the neuronal population in each time bin. The results show an important role of an optimal neurogenesis rate of interneurons and excitatory neurons in the DG in efficient separation of inputs from the EC in pattern separation tasks. The model predicts that any deviation of the optimal values of neurogenesis rates leads to different decreased levels of the separation deficits of the DG which influences its function to encode memory.

Keywords: Entorhinal cortex; dentate gyrus; neurogenesis; Alzheimer's disease; pattern separation; interneurons; granule cells.

1. Introduction

The dentate gyrus (DG) receives information from the entorhinal cortex (EC) and transfers it into other parts of the hippocampus [Fig. 1(a)]. Pattern separation is a well-known function of the DG that plays an important role in information processing in the hippocampus (Bakker *et al.*, 2008; Leal *et al.*, 2014; Schmidt *et al.*, 2012). In pattern separation, input patterns of activated neurons in the EC with different levels of similarity (overlap in activated neurons) are represented as highly separated

sets of neurons in the DG [Fig. 1(a)]. The population of activated excitatory neurons in the DG for each input pattern is estimated to be about 1–2% of the total neuronal population (Piatti *et al.*, 2013). Low activity levels of excitatory neurons result from GABAergic circuits that generate powerful feedback and feedforward inhibitory input into excitatory neurons (Ewell & Jones, 2010; Wiskott *et al.*, 2006). The interaction of excitatory neurons and interneurons in the DG mediates the maintenance of the sparse coding that is associated with efficient pattern separation by the DG (Sahay *et al.*, 2011a; Faghini & Moustafa, 2015a). These characteristics of the DG make it network that demonstrates sparse spiking over time. It has been indicated that mossy cell excitation results in feedback inhibition of granule cell activity and enables DG pattern separation (Jinde *et al.*, 2012).

The DG is a region in the hippocampus of the mammalian brain in which neurogenesis occurs throughout life as new immature neurons are incorporated into preexisting networks (Eriksson *et al.*, 1998). The main question that we address here is why a predominantly sparse spiking network needs to continually incorporate more neurons. Immature excitatory neurons of the DG show very important characteristics: (a) increased excitability and plasticity while older cell populations are less plastic and more silent (Espósito *et al.*, 2005; Ge *et al.*, 2007a,b), (b) higher intrinsic excitability and less synaptic inhibition than mature granule cells (Marín-Burgin & Schinder, 2012; Neunuebel & Knierim, 2012), and (c) recruitment of inhibition that could promote sparse neural activity (Piatti *et al.*, 2013). The newborn neurons are crucial for tasks involving the discrimination of very similar situations. Adult-born neurons may enhance sparse coding in the DG to influence pattern separation. It has been shown that developing granule cells transit from weak to strong coupling to feedback inhibition, which in turn contributes to sparse coding (Temprana *et al.*, 2015). During a time of about two weeks, adult-born immature neurons are more excitable than mature neurons, and they respond to a wider range of inputs. It has been proposed that new-born neurons are initially unspecific because their task is to identify novel elements inside a high dimensional input space. With maturation, they would specialize to represent details of the inputs, favoring discrimination (Kropff *et al.*, 2015). As new excitatory neurons transit toward maturity, they reliably recruit GABAergic feedback loops that restrict spiking of neighboring granule cells, a mechanism that would promote sparse coding (Temprana *et al.*, 2015).

Adult-born dentate excitatory neurons integrate into existing hippocampal circuitry and may provide network plasticity necessary for certain forms of hippocampus-dependent learning and memory (Snyder *et al.*, 2001). Hence, activity patterns entering the DG can undergo differential encoding by a heterogeneous population of excitatory neurons originated at different times. As a fraction of newborn neurons become GABAergic interneurons, the hippocampal-dependent learning and memory deficits could be linked at least partially to the declined neurogenesis of one or both excitatory or inhibitory neurons (Hattiangady *et al.*, 2004). An excitation–inhibition imbalance may underlie aberrant functional integration of newborn neurons that is associated with psychiatric disorders (Saaltink & Vreugdenhil, 2014). In order to

reveal the role of normal and abnormal neurogenesis in the DG functions, we chose to simulate the information flow from the EC into the DG and the related structural and physiological parameters using computational modeling. Prior experimental and theoretical studies have mainly focused on neurogenesis in the DG without discrimination of inhibitory and excitatory neurons. However, interneurons have demonstrated high variation in their morphology and electrophysiological features but lower population size compared with excitatory neurons. Therefore, interneurons and their neurogenesis may play a role in balancing excitation–inhibition inputs into the DG such that any abnormality in normal neurogenesis may be associated with some cognitive disorders such as Alzheimer's disease.

Understanding neurogenesis as a key component of pattern separation (Clelland *et al.*, 2009; Sahay *et al.*, 2011b) is important for understanding the role of DG function in health and disease (Aimone *et al.*, 2010; Alme *et al.*, 2010). Theoretical studies can help understand fundamentals of information processing in the DG using different rates of neurogenesis of both inhibitory and excitatory neurons and allow us to present some hypotheses on conditions that may lead to cognitive disorders.

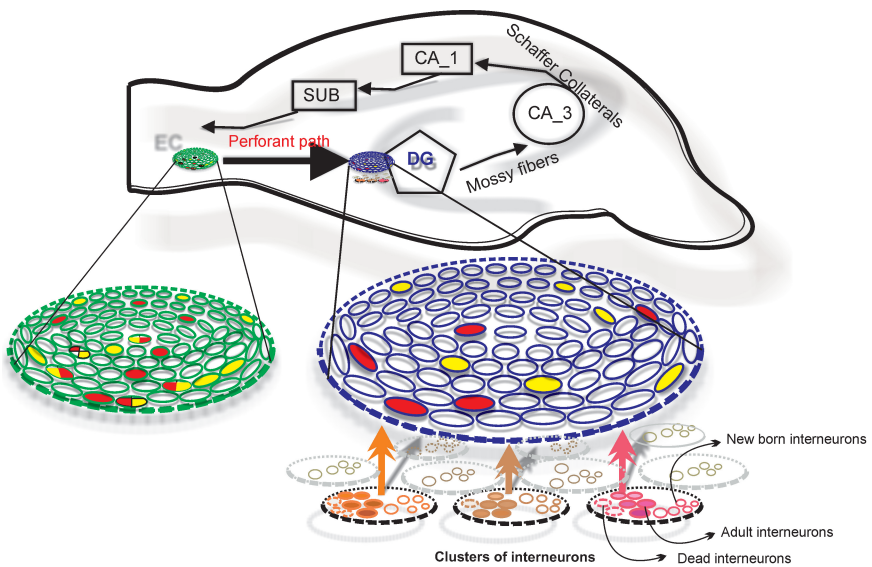
Although psychological theories have postulated the existence of decay processes for declarative memory, the corresponding neurobiological mechanisms are unknown. Here we hypothesize that ongoing hippocampal neurogenesis represents a decay process that continually clears memories from the hippocampus. As newborn granule cells integrate into established DG circuits, they form new input and output connections over the course of several weeks. Because successful memory retrieval relies on reinvoking patterns of activity that occurred at the time of encoding (pattern completion), neurogenesis-induced remodeling of DG circuits incrementally reduces the likelihood that a given retrieval cue will reinvoke a previously stored pattern (Frankland *et al.*, 2013). Neurogenesis of excitatory and interneurons is essential for maintaining the excitation and inhibition balance, the lack of which underlies various brain diseases. Although a large proportion of inhibitory interneurons are preserved in the epileptic human DG, their distribution, morphology and synaptic connections differ from controls (Maglóczky *et al.*, 2005). These functional alterations of inhibitory circuits in the DG are likely to be compensatory changes with a role to balance the enhanced excitatory input in the region. How their dysfunction may lead to a variety of brain disorders has been studied, suggesting new therapeutic strategies based on balancing the excitation and inhibition (Ko *et al.*, 2015).

The questions we are addressing in this study are as follows: why a normally silent neural network like DG needs neurogenesis and how abnormal neurogenesis is associated with memory disorders. For this purpose, we present a computational model of separation efficiency (SE) in the simulated EC-DG network and neural activity using electrophysiological and structural information. The role of balance between excitatory and inhibitory inputs is also simulated in the model. Moreover, a theory on the relationship between abnormal neurogenesis in DG and cognitive disorders related to pattern separation in the hippocampus is presented.

2. Method

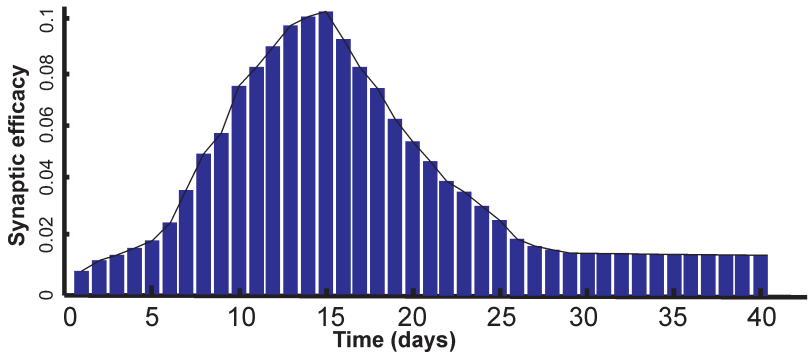
2.1. *Model structure*

In order to simulate the first stage of information processing in the hippocampus, information flow from the EC to the DG was modeled as follows. A feed-forward two-layer neural network was constructed with 500 neurons in the first layer as the EC and 2500 neurons in the second layer as the DG [Fig. 1(a)]. The change of synaptic efficacy between interneurons and excitatory neurons in the DG over time was simulated and shown in Fig. 1(b). It demonstrates the basic assumption about gradual increase in the synaptic efficacy of a single interneuron and excitatory neurons and the decay over time. This assumption has been used in all simulations when a new neuron is generated with a defined rate and added to the pre-existing population. The neurogenesis rate of interneurons is exerted as a mechanism to compensate for the gradual decrease in the synaptic efficacy between interneurons and



(a)

Fig. 1. (Color online) Model architecture. (a) Information is transferred from the EC into the DG, and then to other parts of the hippocampus. Information flow from the EC to the DG is modeled as a two layer feed-forward neural network composed of 500 neurons in the EC and 2500 neurons in the DG. Neurons in the EC are connected to neurons in the DG according to probability between 0.1 and 0.4. The number of neurons of the EC and the DG are dynamically determined by birth and death rates. The number of interneurons organized as clusters in the DG is changed over time according to death and birth rate too. The DG separates input patterns in the EC in intact hippocampus such that overlapped patterns in the EC (neurons in the EC activated by both stimulus shown as red-yellow neurons) are presented as fully or well-separated sets of neurons (shown as red and yellow neurons in the DG). (b) Change of the synaptic efficacy between the interneurons and excitatory neurons in the DG over time. In this modeling framework, it is assumed that synaptic efficacy between interneurons and DG excitatory neurons is changed over time such that it is increased gradually after birth and gets its maximum value after 15 days then it is decreased gradually to a low level.



(b)

Fig. 1. (*Continued*)

excitatory neurons by adding new interneurons which after a short time can effectively impact inhibition of excitatory neurons.

The activity of neurons in the first layer was modeled as a different probability of firing in a series of time bins represented as trains of ones and zeros. This firing rate is used to present stimuli with different intensities. The DG layer receives signals from the EC and may spike with different frequencies according to an integrate and fire neuron model constrained by electrophysiological characteristics of the granule cells.

$$C\frac{dV}{dt} = -g_{\text{leak}}(V - V_{\text{rest}}) + I_{\text{exc}}(t) - I_{\text{inh}}(t), \tag{1}$$

$$I(t) = \omega\frac{t}{\tau}e^{\frac{-t}{\tau}}\sum_{tp}(t - tp), \tag{2}$$

where $\tau = 0.2\ s$ and ω is the synaptic weight between pre and post synaptic sites. tp is the time it takes the action potential to reach the axonal terminal and consequently induces current flow into post synaptic site.

The actual connectivity patterns of the EC and the DG are not known. Theoretical studies have shown that the system benefits of low connectivity rates (Faghini & Moustafa, 2015a). Therefore, the connectivity rate of neurons in the EC and the DG in the model was assumed as random values between 0.1 and 0.4. The connectivity rate of neurons in the DG and the EC was updated in each run of simulations to allow new born neurons in the DG connecting to neurons in the EC. Here connectivity rate is the probability of physical connection of each neuron in the EC to the neurons in the DG. In order to model interneurons and their interaction with excitatory neurons, we divided the interneurons into 20 clusters each composed initially of 20 neurons which is changed over time according to birth and death rates [Fig. 1(a)].

Neuronal population at time $(t) : N_t^i$,
Neuronal population at time $(t+1) : N_{t+1}^i$,

where i represents cluster numbers of interneurons or total excitatory neurons. The dynamics of change in neurons' number are presented as Eq. (3).

$$N_{t+1}^{i} = N_{t}^{i} + N_{t+1}' - D_{t+1}', \tag{3}$$

where N' is the number of added neurons and is determined by β and γ as neurogenesis rate of excitatory and inhibitory neurons, respectively. D' is the number of deleted neurons in the populations at a given time and is determined by δ [Eqs. (4)–(6)].

$$N_{t+1}' = \beta * N_{t}^{i}, \tag{4}$$

$$N_{t+1}' = \gamma * N_{t}^{i}, \tag{5}$$

$$D_{t+1}' = \delta * N_{t}^{i}. \tag{6}$$

The death rate (δ) acts as a model parameter but for all simulations to study the role of different neurogenesis rates in SE of the DG it was set to a fixed value. The low death rate is defined as the probability of deleting 2% of current neurons per day. The probability of deletion was set to 0.02. The interneurons of each cluster are fully connected to 50% of neurons (here 1250 neurons) in the DG while they also have connection to other excitatory neurons with probability equal to 0.25. This results in a variety of inhibitory input numbers into excitatory neurons. This assumption allows modeling of different inhibitory inputs to the DG neurons. The activity of interneurons was modeled by an integrate and fire model constrained by electrophysiological characteristics of DG basket cells (see: *www.Hippocampome.org*).

3. Neurogenesis Modeling

For both interneurons and excitatory neurons the initial number of neurons is changed over time according to the neurogenesis rate and the death rate of neurons. Different neurogenesis rates were selected to study their effect on the SE of DG. The synaptic efficacy between interneurons and excitatory neurons as a function of time was modeled as a relationship shown in Fig. 2(b). The synaptic efficacy is enhanced gradually and is decayed after 15 days. The time window of the study was 40 days. As we assume a rapid decay in synaptic efficacy, a short time window was sufficient to measure average SE of the DG.

4. SE and Simulations

At each time bin, for each pair of neurogenesis rate of excitatory neurons and interneurons, SE was measured as follows: Two kinds of pattern separation tasks were simulated: (1) presenting different input patterns (80% similarity) as activated sets of the EC neurons into the DG network, (2) presenting a given input pattern with different firing rates of neurons (80% similarity in the firing rates of input pairs).

Inhibitory inputs into the DG excitatory neurons depend on both the number of active interneurons and synaptic efficacy between interneurons and the excitatory

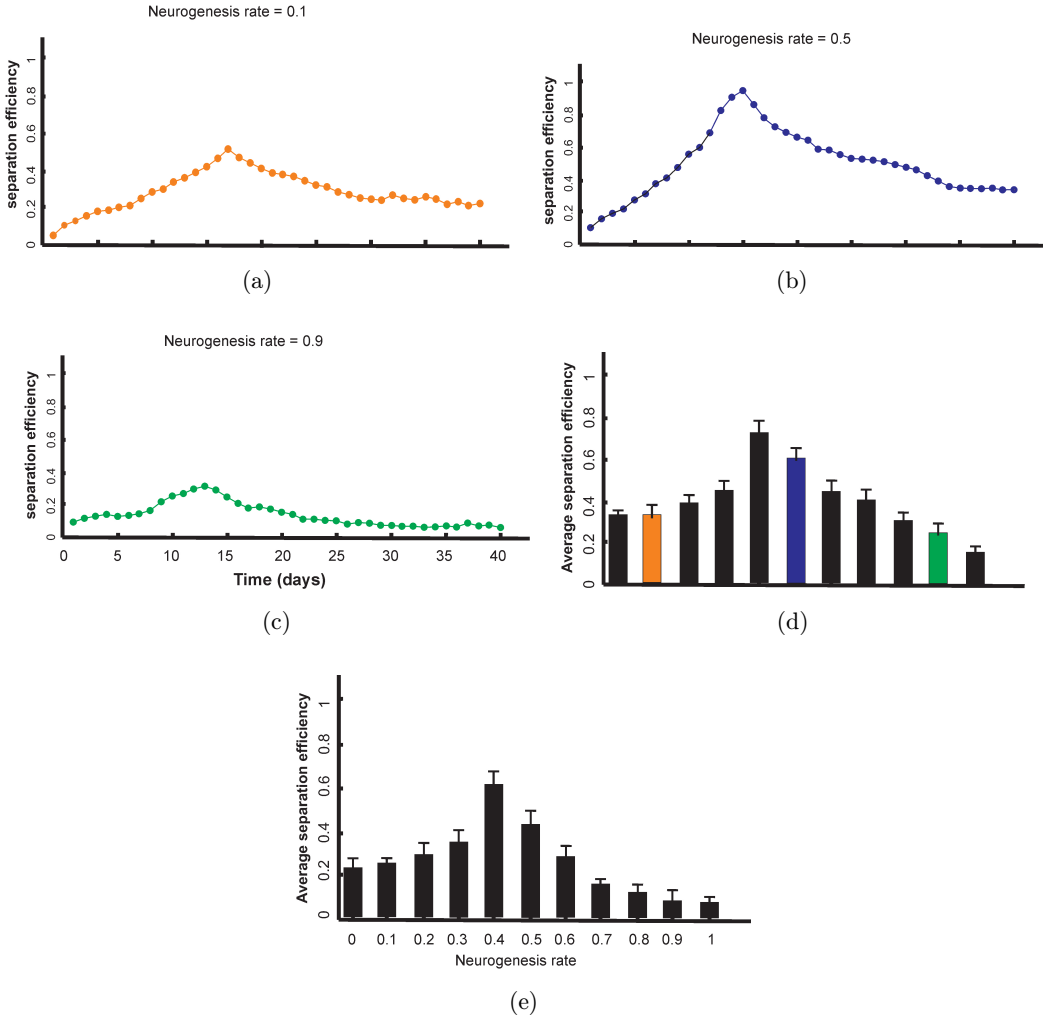


Fig. 2. SE of the DG over time for different neurogenesis rates of interneurons. The SE of the DG was measured for different neurogenesis rates as a function of time of interneurons in the absence of neurogenesis in excitatory neurons. (a) For a low neurogenesis rate equal to 0.1, maximum efficiency was obtained after 17 days. The efficiency is decreased gradually and gets low levels of efficiency. (b) For a neurogenesis rate equal to 0.5 the maximum efficiency was obtained after 15 days and then simulations show a low effect on the SE. (c) For a high neurogenesis rate the maximum SE was obtained after 13 days but it was lower than SE for a neurogenesis rate equal to 0.1. (d) Average SE of the DG for similar input patterns over time for different neurogenesis rates. Average SE of the DG over 40 days for different interneurons' neurogenesis rate was measured by presenting input patterns to the EC with 80% similarity. Maximum average efficiency was obtained at neurogenesis rate equal to 0.4. For higher rates it is decreased to lower levels. (e) Average SE of the DG for input patterns with different intensities for different neurogenesis rates. Maximum average SE was obtained at a neurogenesis rate equal to 0.4. Increase in neurogenesis rate leads to remarkable decrease in the efficiency especially for rates higher than the 0.6.

neurons. One expects that high interneurons' neurogenesis rate and low excitatory neurogenesis rate would lead to a very low activity of excitatory neurons in the DG. The SE of the DG output is measured by the normalized Euclidian distance (d) between the activation patterns of different DG neurons where activated DG neurons

are represented as ones. For high neurogenesis rates, high inhibitory inputs cause a decrease in the number of activated neurons in the DG. Therefore, SE is calculated as Eq. (7).

$$\mathrm{SE} = \frac{d * p}{P}, \tag{7}$$

where p is the average number of activated excitatory neurons in a given inhibitory input and P is the average number of activated excitatory neurons for inhibitory input equal to zero.

5. Results

The inhibition into excitatory neurons play an important role in sparse coding in the DG. Therefore, the SE of the DG for different neurogenesis rates of interneurons and absence of excitatory neurons' neurogenesis were measured (Fig. 2). Figures 2(a)–2(c) show the change of the DG SE for three different interneurons' neurogenesis rates over time. These simulations show an increase in SE by increase in neurogenesis rate while high levels of neurogenesis rates may lead to a decrease in the DG separation tasks. Therefore, one expects to find optimal interneurons' neurogenesis rate which corresponds to maximum SE of the DG when different input patterns from the EC are presented [Fig. 2(d)] or inputs with different intensities (different firing rate of the activated EC neurons) are presented into the DG [Fig. 2(e)]. In both cases, the maximum SE was obtained for interneurons' neurogenesis rate equal to 0.4. The optimal rate obtained by these simulations corresponds to an increase in the number of interneurons that can be used to estimate expected neuronal population sizes' increase that can be checked by experiments.

As the increase in the number of interneurons leads to higher levels of inhibition into the excitatory neurons, higher interneurons' neurogenesis rates can lead to a decrease in the number of activated neurons in the DG by any input from the EC. This effect depends on synaptic efficacy between interneurons and excitatory neurons. Figure 3(a) left panel shows the decrease in the average number of activated neurons in the DG as a consequence of increasing the neurogenesis rate of interneurons at early stage of the simulation. Figures 3(b) and 3(c) left panels demonstrate the effect of neurogenesis rate at middle stage and late stage of simulations consequently. Moreover, such high levels of inhibition induced by interneurons' neurogenesis can cause low firing rate of excitatory neurons in the DG (sparse spiking) [Figs. 3(a)–3(c), right panels]. The maximum effect of neurogenesis rate of interneurons on the number of activated neurons in the DG and their firing rate over time was observed in middle time (15 days) as the synaptic efficacy between interneurons and excitatory neurons gets maximum values.

In order to study the impact of excitatory neurons' neurogenesis on the overall SE of the DG, different neurogenesis rates of excitatory neurons were investigated in the simulations while the optimal interneurons' neurogenesis rate was used (equal to 0.4).

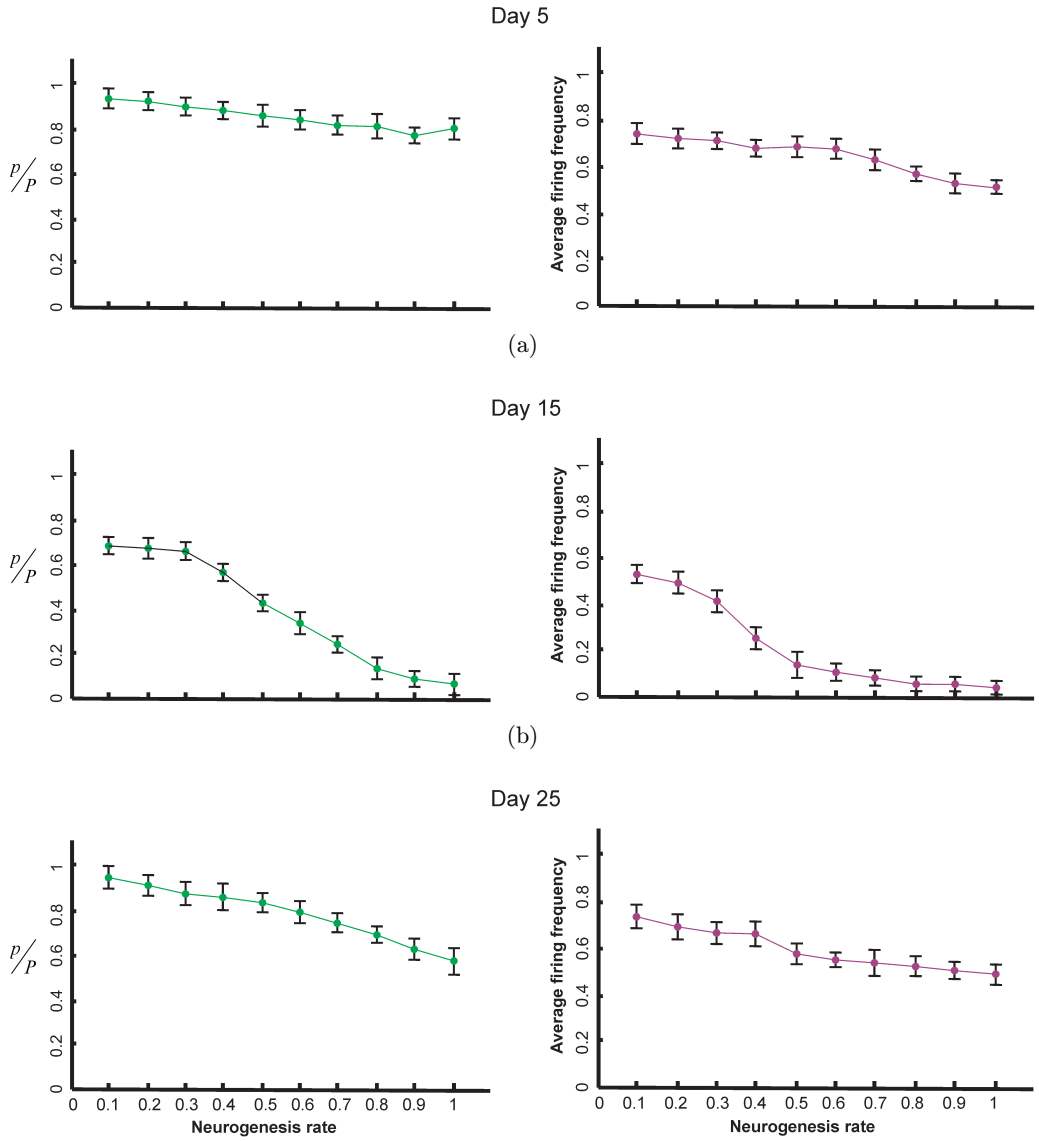
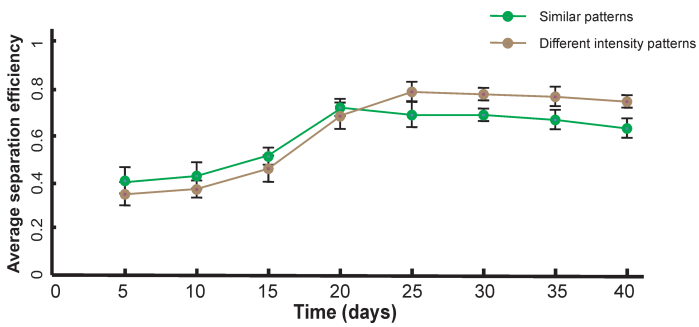
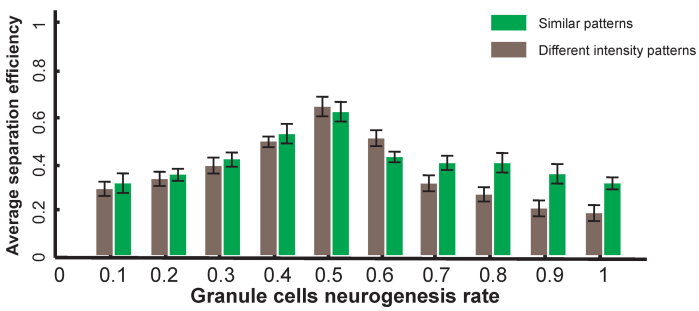


Fig. 3. The effect of interneurons' neurogenesis rate on the DG neurons activity for inputs with different intensities for early stage (a), Middle stage (b) and late stage (c) of interneurons' lifetime in the simulations. Left panels: The percentage of activated neurons in the DG for different neurogenesis rates when low intensity inputs were presented to the EC. Compared to zero neurogenesis rate, an increase in neurogenesis rate causes an increase in inhibitory current into the DG neurons, which in turn leads to a decrease in activated neurons in the EC. The maximum effect is observed for middle stage of interneurons' time in the simulations (b). Right panels: Average firing frequency of the DG neurons for different neurogenesis rates. An increase in the neurogenesis rate results in a decrease in the firing rate of the DG neurons especially in middle stage of interneurons' lifetime in the simulations (b). This decrease in the firing rate leads to low information transfer to other parts of the hippocampus.



(a)



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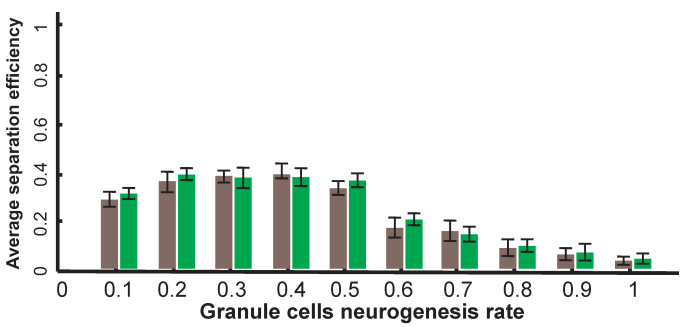
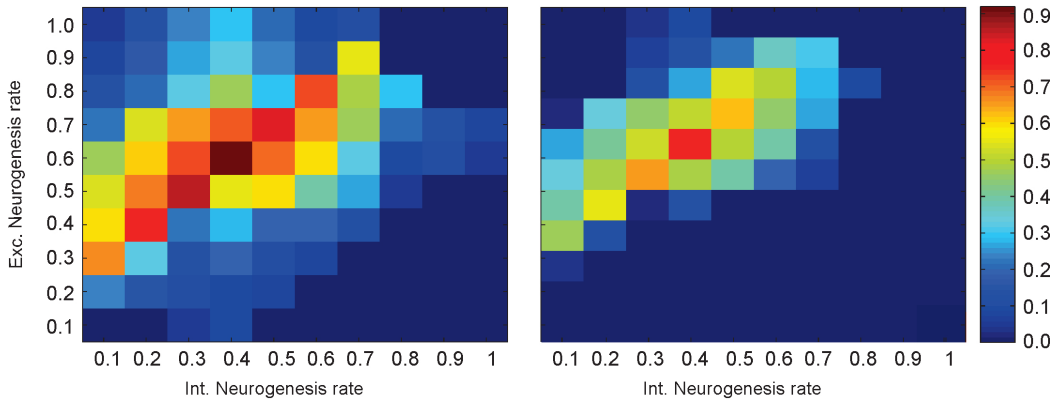


(c)

Fig. 4. Average SE of the DG with and without the combination of excitatory and inhibitory neurons neurogenesis. (a) Average SE of the DG for different pattern separation tasks for excitatory neurons' neurogenesis rate equal to 0.5 and interneurons' neurogenesis rate equal to 0.4. (b) Average SE for different excitatory neurons' neurogenesis rate with combination with inhibitory neurogenesis rate equal to 0.4 leads to a maximum efficiency at 0.5 for both kinds of separation tasks. (c) Average SE for different granule cell neurogenesis rate in the absence of inhibitory neurogenesis. These simulations demonstrate the critical role of balanced neurogenesis of interneurons and excitatory neuron rates.

Figure 4(a) shows the average SE over time for two defined pattern separation tasks when excitatory neurons neurogenesis rate equal to 0.5. Figure 4(b) shows the average SE of the DG for interneurons' neurogenesis rate equal to 0.4 and different excitatory neurogenesis rates. Maximum SE was obtained for excitatory neurons' neurogenesis rate equal to 0.5 for both kinds of pattern separation tasks. In the



(a) (b)

Fig. 5. Average SE of the DG for different neurogenesis rates of interneurons and excitatory neurons. (a) Different input patterns were presented to the neural system. The maximum efficiency is obtained for neurogenesis rate of interneurons equal to 0.4 and neurogenesis rate of excitatory neurons equal to 0.6. (b) Patterns with different intensities were presented to the neural system. The SE of the DG was measured for different neurogenesis rate of excitatory neurons and interneurons. The maximum efficiency is obtained for neurogenesis rate of interneurons equal to 0.4 and neurogenesis rate of excitatory neurons equal to 0.5.

absence of interneurons' neurogenesis, for both separation tasks the obtained SE shows low levels especially for high levels of excitatory neurons' neurogenesis [Fig. 4(c)]. Figure 4(c) shows that observed neurogenesis of the excitatory neurons in the absence of interneurons' neurogenesis cannot help obtain efficient separation capability.

Therefore, we examined all pairs of neurogenesis rates of interneurons and excitatory neurons to find global optimal conditions which leads to maximum SE when different inputs patterns [Fig. 5(a)] or inputs with different intensities are presented in the DG [Fig. 5(b)]. The optimal neurogenesis rate of interneurons obtained for both tasks are neurogenesis rate of interneurons equal to 0.4 and neurogenesis rate of excitatory neurons equal to 0.6. Moreover, it shows that high or low levels of either neurogenesis rates of excitatory neurons or interneurons result in low efficiency of pattern separation of the DG.

6. Discussion

Our modeling results have shown that different neurogenesis rates (which are related to adding newborn interneurons) into pre-existing DG neural population can help separation efficiency. This is due to an increase in inhibition flow into excitatory neurons. However, the accumulated interneurons may decrease the separation efficiency over time because their low death rate leads to imbalance in inhibition-excitation in the DG. We also incorporated changes in the number of excitatory neurons in the DG network by different neurogenesis rates. In the model each added excitatory neuron is immediately connected into multiple interneurons but the synaptic

efficacy of these connections changes over time. In biological neural systems, generation of new connections may be a slow process that occurs in parallel with changes in strength. These newly born excitatory neurons that are not held under inhibition from interneurons can initially increase separation efficiency of the DG to encode inputs but are not involved in retrieving previously encoded inputs. Because memory retrieval relies on reinvoking patterns of activity that occurred at the time of encoding (pattern completion), neurogenesis in hippocampal circuits incrementally decreases the likelihood that a given retrieval cue will reinvoke a previously stored pattern (Frankland *et al.*, 2013). Therefore, in order to gain a full understanding of the encoding process in the hippocampus, modeling pattern separation in the DG and pattern completion in the CA3 is required.

Furthermore, newly added excitatory neurons gradually make strong connections with interneurons that lead in turn to an increase in inhibitory input onto excitatory neurons. Such inhibition may increase or decrease separation efficiency depending on the balanced neurogenesis rates of inhibition–excitation in the DG network. GABAergic interneurons in the DG show variation in their morphological and electrophysiological characteristics. But the local connectivity patterns between different types of interneurons and between interneurons and excitatory neurons have not been fully determined. However, their role in DG pattern separation function is known. Computational studies have demonstrated that strong inhibition input from local interneurons onto excitatory neurons are required to obtain high levels of separation efficiency in the DG while keep their firing rate at low levels (Faghini & Moustafa, 2015a). The role of balanced inhibition–excitation in normal encoding of the neural systems has been shown by a recent modeling study (Faghini & Moustafa, 2015b). In addition, cognitive deficits in *Down* syndrome (DS) have been linked to increased synaptic inhibition, leading to an imbalance of excitation–inhibition. Overexpression of some genes affects pathways involved in synaptogenesis and synaptic plasticity and influences excitation–inhibition balance (Souchet *et al.*, 2014).

The balanced flow of inhibitory and excitatory inputs is governed by both synaptic efficacies between neurons that determine current into post-synaptic neurons and the number of functionally active interneurons and excitatory neurons in the DG. The connectivity of layers is also involved in the process of stimulation from interneurons onto excitatory neurons. Synaptic efficacy can be affected by aging such that it is decreased over time. The number of active neurons is determined by both birth and death rate of neurons. The study of adult neurogenesis in different neurogenic regions from a systems neuroscience perspective will pave the way to understanding why its dysfunction correlates with some brain disorders (Lepousez *et al.*, 2015). Neurogenesis in the DG as a silent neural network has fascinated and also puzzled neuroscientists, as it is not clear what role it plays in information processing in the hippocampus.

Simulation and modeling studies can effectively provide plausible hypotheses by modifying some parameters that are often difficult to assess by experimental techniques. Although some theories have been proposed to model the dynamics of the neurogenesis of excitatory neurons, these models have not incorporated the

balanced neurogenesis of interneurons and excitatory neurons and their possible role in pattern separation tasks as well as impairment of such processes in cognitive disorders.

Neurogenesis has been studied using computational neurosciences methods (Aimone & Gage, 2011). Some works have modeled neurogenesis as a multi-compartmental system of ordinary differential equations based on experimental data (Ziebell *et al.*, 2014). Systems of partial differential equations have been used to model the migration of immature neurons (Ashbourn *et al.*, 2012; Aimone *et al.*, 2009) and have been used to simulate the functional integration of new neurons to the hippocampus as artificial neural networks. Therefore, the question addressed here is how neurogenesis rates affect separation efficiency of the DG. Unlike prior models, we also simulate neurogenesis rates of interneurons in pattern separation independently of excitatory neurons' neurogenesis. Experimental techniques such as optogenetics can be used to test rates of neurogenesis of excitatory neurons and interneurons as well as their function and permit acquisition of data for comparison with the modeling results.

Although psychological theories have postulated the existence of decay processes for declarative memory, the corresponding neurobiological mechanisms are unknown. Here we developed the hypothesis that synaptic efficacy between excitatory and inhibitory neurons induces a decay process that continually clears memories from the hippocampus. The rapid decay in synaptic efficacy between interneurons and excitatory neurons is an assumption that was used in order to simulate the effect of aging on the DG function. However, in the biological network it may take longer time to influence the hippocampus function.

As mentioned, linking impaired pattern separation function of the DG to cognitive abnormalities is a challenge. The imbalanced neurogenesis may take place over long times. But such abnormal neurogenesis rates may have other causes like mutation of genes involved in the cellular events underlying the process of adding newly born neurons in the DG. In this modeling work, we have also used low death rates of the neurons. Therefore, an increase in the death rate of each kind of neuron may have an impact on the separation efficiency of the DG. In general, adding new interneurons into the neuronal population of the DG can compensate for the decrease in the synaptic efficacy between excitatory and inhibitory neurons for a short time. However, the added interneurons can gradually suppress excitatory neurons' activity due to low death rate. On the other hand, an increase in the number of excitatory neurons as a consequence of some levels of neurogenesis rates leads to an increase in the active excitatory neurons that are able to encode input flow from the EC. Likewise, higher neurogenesis rates or low death rates of the excitatory neurons result in high number of newborn excitatory neurons which may decrease separation efficiency due to overlap of the pattern of activated neurons in the DG. The current knowledge on neurogenesis in the DG is mainly limited to excitatory neurons. However, interneurons may show dynamics in their numbers according to the birth and death rates. Moreover, interneurons which have variation in their morphology

and electrophysiological features but are present in lower numbers are essential in the sparse activity of the DG. These features can assign importance to the involvement of interneurons in information processing in the DG.

Our simulations suggest a theory about the necessity of neurogenesis in the DG as a low activity network that shows sparse coding (low number of activated neurons in response to its input from the EC) and low firing rate of neurons. Both these features are believed to be caused mainly by inhibitory inputs from GABAergic interneurons. In this theory, optimal inhibitory input into excitatory neurons is required for efficient encoding of the inputs from the EC. For this purpose, excitatory neurons' neurogenesis is essential to balance inhibition into the DG. Any change in the optimal inhibitory inputs can lead to different levels of deficiency of pattern separation capability of the DG. The changes in the inhibitory activity in the DG may be caused by different deviation from optimal conditions like low or high rates of neuronal birth and death. In addition, imbalanced neurogenesis rates of interneurons and excitatory neurons lead to deficiency of encoding low intensity inputs from the EC or separation of different input patterns from the EC. Advances in our understanding of adult neurogenesis will not only shed light on the basic principles of adult plasticity, but may also lead to strategies for cell replacement therapy after injury or degenerative neurological diseases.

In this computational study, the balance between excitatory and inhibitory neurons in the DG was studied; interestingly, experimental studies (Isaacson & Scanziani, 2011; Xue *et al.*, 2014) as well as theoretical studies (Henry *et al.*, 2013; Rangan & Young, 2013) have suggested a role for feedback inhibition and the balance between excitatory and inhibitory neurons in information processing in cortical circuits. Such balance is established by synaptic plasticity at inhibitory synapses and can provide an explanation for sparse firing pattern in the cortex (Vogels *et al.*, 2011). In addition, synaptic plasticity can play critical role to enhance excitatory/inhibitory balance in perception (Froemke, 2015). Imbalanced excitatory/inhibitory neuronal activity contributes to symptoms of some mental disorders, for example, focal dystonia and epilepsy (Ridding *et al.*, 1995).

Several changes to cortical neural population in AD patients have been reported (Arendt *et al.*, 2015; Braak & Del Tredici, 2015). Moreover, a decrease of axonal transport in temporal cortex neurons has been shown in AD patients (Dai *et al.*, 2002; Romito-DiGiacomo *et al.*, 2007). Although neurogenesis has not been reported in cortical layers, it is highly important to study the impact of changes in neuron numbers on balanced activity of excitatory and inhibitory neurons that could be achieved by changes in synaptic plasticity (Esiri & Chance, 2012) or connectivity of excitatory and inhibitory neurons in cortex (Ferreri *et al.*, 2016; Teipel *et al.*, 2016). Therefore, theoretical and computational explorations may help experimental studies by developing clinical strategies to identify and eventually prevent disorders like AD.

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