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Dynamic Role of Adult-Born Dentate Granule Cells in Memory Processing

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Abstract

Throughout the adult life of all mammals including humans, new neurons are incorporated to the dentate gyrus of the hippocampus. During a critical window that lasts about two weeks, adult-born immature neurons are more excitable and plastic than mature ones, and they respond to a wider range of inputs. In apparent contradiction, new neurons have been shown to be crucial to solve behavioral tasks that involve the discrimination of very similar situations, which would instead require high input specificity. We propose that immature 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 these novel inputs, favoring discrimination.

Introduction

Among cortical structures, the dentate gyrus (DG) of the hippocampus presents a unique degree of plasticity conferred by the continuous production of new principal neurons, the adult-born dentate granule cells (GCs) [1–3]. Thousands of new GCs are produced every day and develop over several weeks, generating millions of new connections that modify the preexisting circuits [4]. Extensive evidence accumulated over the last decade has demonstrated that adult-born GCs can modify signal processing in the DG and that they are necessary to perform specific tasks requiring discrimination of very similar situations [5,6]. In this review we focus on the hypothesis that the functional role played by adult-born GCs depends on their developmental stage. We propose a mechanism for the involvement of new GCs in novel input discrimination based on recent electrophysiological, behavioral and computational modeling evidence.

Network Remodeling by Adult Neurogenesis

A remarkable and unique process takes place in the subgranular zone of the DG, a thin layer where neural stem cells self-amplify and give rise to new GCs that become integrated to the preexisting circuit. Most of what is known about their functional characteristics comes from

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research in rodents where adult-born GCs develop in living animals and their morpho-functional properties are studied in acute slices (electrophysiology) or fixed tissue sections (microscopy). Recently, the use of transgenic mice and retroviral vectors targeting dividing progenitor cells has allowed the selective expression of fluorescent reporters and light-activated channels into developing GCs to study their function, both *in vitro* and *in vivo*.

The development of adult-born GCs is remarkably slow, lasting about 6 – 7 weeks. Over this time, morphology, intrinsic electrical properties and synaptic connections evolve in parallel towards a mature neuronal phenotype [7–12]. Dendritic GABAergic synaptogenesis occurs during the second week (w2) and it is the earliest event that connects developing GCs with the circuit. The initial combination of a high input resistance and the depolarizing effect of GABA facilitates functional glutamatergic synaptogenesis, which displays a delayed onset in comparison to GABA [13–15]. At this early stage of GC development, activation of GABAergic networks upon brief exploratory behavior in an enriched environment (EE) promotes unsilencing of immature excitatory contacts, which incorporate AMPA-subtype of glutamate receptors into NMDAR-only synapses and become capable of fast transmission [16]. With time, developing GCs undergo a substantial decrease in membrane resistance that is accompanied by a switch that transforms GABA-mediated signaling from excitatory to inhibitory [8]. Around w4, GABAergic transmission is already inhibitory, but GCs continue to be functionally immature due to their membrane resistance (still higher than what is typically found in mature GCs) and lack of perisomatic GABAergic connections, resulting in a high neuronal gain. This peculiar combination of intrinsic and network properties spans from about w4 to w7, during which young (immature) GC activity is characterized by low spiking threshold and poor input specificity [17,18]. Coincidently, GCs at w4 also display enhanced activity-dependent potentiation of glutamatergic synapses that only lasts for about two weeks, suggesting extensive remodeling of input and output connections during this period [19,20]. This remodeling is likely to determine the role of each new GC in information processing. The output of young (w4) and mature (w8) GCs was recently compared using optogenetic stimulation and electrophysiological recordings in the dentate and CA3 areas [21]. While mature GCs can reliably recruit both CA3 networks and feedback inhibition onto the granule cell layer, young GCs can activate CA3 networks but exert poor recruitment of proximal feedback interneurons. Also recently, Bergami and colleagues (2015) showed that the input can be modulated by experience in an EE, producing a dramatic expansion in the number of excitatory and inhibitory neurons that synapse onto developing GCs [22]. Interestingly, sensitivity to EE is highest in GCs within w2 to w6, a window that overlaps with the developmental stages of high excitability, enhanced synaptic plasticity, and poor coupling to inhibitory loops.

Overall, at around w4 GCs undergo a transition, lasting at most until w6 to w8, during which they are very active, poorly coupled to inhibition and highly susceptible to activity-dependent synaptic modification of input and output connections. As maturation proceeds, activation of new GCs becomes input specific and their connections are stabilized.

Neurogenesis and Pattern Separation

A major challenge in the field is to understand how the network plasticity described above may contribute to information processing in the hippocampus. The structure and sparse activity of the DG suggest its involvement in pattern separation, i.e. the transformation of similar inputs into dissimilar outputs [23,24]. In a way this mechanism acts in the opposite direction of pattern completion, a critical process for the retrieval of memories during which representations are transformed, presumably by the influence of CA3 recurrent collateral connections, to make them similar to a previously stored sample [25,26]. The conflict arises during the acquisition of a new memory due to the fact that any influence from previous stored representations would introduce spurious correlations among memories, compromising their future retrieval. Computational models thus require the prevalence of pattern separation at this stage [27], which is thought to occur due to the strength of detonator mossy synapses targeting CA3 pyramidal cells [28].

In agreement with the pattern separation hypothesis, mice lacking NMDA receptors selectively in GCs show impaired fear-context discrimination for similar but not dissimilar contexts [29]. This manipulation also produces a reduced contextual modulation in the firing rate of CA3 place cells. Accordingly, GCs in rats can exhibit a particular sensitivity to small contextual variations, which is not present in their target CA3 cells [30]. Pattern separation has also been studied in the spatial domain. Lesion studies show that the DG is required to discriminate between two very proximal positions in physical space, and becomes progressively less important with increasing discrimination distance [31,32]. Similar conclusions have been reached through the local manipulation of BDNF [33]. However, the spatial response of GCs has been a somewhat controversial issue. GCs have been reported to be spatially tuned, with response fields as selective as those of CA3 place cells [34], or alternatively as bearers of multiple and unstable fields, suggesting a rather low spatial information content [30]. This difference could be explained by the recent report of two coexisting populations of putative principal cells in the DG, one spatially tuned and one with low spatial information [35,36]. Interestingly, Neunuebel and colleagues (2012) [35] provide indirect evidence pointing to the identification of the low-spatial-information group with immature GCs. This hypothesis agrees with known properties of immature GCs *in vitro* but has not yet been tested *in vivo* by means of age-tagging techniques.

Only in the last decade it has been possible to address the crucial issue of whether or not young GCs are specifically involved in behavioral pattern separation. To achieve this, animals with altered levels of neurogenesis were tested in discrimination tasks with varying levels of similarity. The manipulation of neurogenesis was attained through x-irradiation [37–39], lentiviral expression of dominant-negative Wnt protein [37], expression of proapoptotic Bax protein [38,40], deletion of NR2B-containing NMDA receptors [41] or voluntary exercise [42]. The behavioral paradigms included delayed non-matching to place in a radial arm maze [37,39], two-choice spatial discrimination in a touch-screen system [37,42] and contextual fear-discrimination learning [38– 41]. The convergence of results obtained through this combination of techniques and tests points to a crucial role of young GCs in pattern separation. Animals with ablated neurogenesis were impaired in their capability to discriminate situations with a high degree of similarity, while animals with

increased neurogenesis outperformed controls. In all studies, as the task became easier by making situations more dissimilar, the differences in performance between treated and control animals tended to disappear.

These experiments have been fundamental in describing the importance of newborn GCs in hippocampal processing. However, the question of the precise developmental phase in which young GCs are crucial has remained unaddressed, partly due to the low temporal resolution of the manipulations. In all of the experiments discussed above, alteration of neurogenesis started 6-16 weeks before training and lasted throughout the testing period. For instance, Sahay and colleagues (2011) observed that performance in a contextual fear-discrimination task correlated with the expansion or reduction of the adult-born GC population [38]. The expansion was triggered 8 weeks before training, while the permanent ablation through X-ray irradiation occurred with an anticipation of 4 months. A second element in common in these experiments is that training and testing were almost simultaneous. In such a scheme, it has not been possible to assess the memory stage in which young GCs are important: task *acquisition*, *retrieval* or both. An insight on these time-related issues would be essential to understand mechanistically the proposed role of young GCs in pattern separation.

Computational models

As reviewed in the previous sections, young GCs are:

- **A.** specifically involved in pattern separation,
- **B.** hyper-plastic, excitable and input unspecific,
- **C.** only transiently unique.

The first conceptual challenge for modelers is to solve the apparent contradiction between points **A** and **B**. The separation of very similar patterns of activity would naturally occur if young GCs coded for highly specific details of the input, yet they seem to follow the opposite strategy. Even if these points were reconciled, a second conceptual challenge, posed by point **C**, would remain. Why are these two populations dynamic instead of stable groups with different characteristics? Strategies based on the mere division of labor between different neurons are ubiquitous across the brain, but neurogenesis is a costly extravagance.

One line of models addresses these issues by focusing on the idea that hyper-plasticity would make young GCs code for all events occurring during their critical time window, so that all associated representations in DG and CA3 would share a common piece of code, i.e. a temporal tag [43]. This tag would help discriminating situations that were not experienced during the same period of life but would bring together memories of contemporaneous events, encoded by the same cohorts of new GCs [44]. Interestingly, simulations predict that the contribution of young GCs to the discrimination of similar contexts would be negative [45]. This prediction could be tested by recording specifically young GCs while animals face a task involving small contextual variations, such as carried out by Leutgeb and colleagues (2007) [30].

A different line of models assigns to young GCs the task of representing novel experiences, characterized by surprising inputs with different statistics than expected from the individual history of the animal. As opposed to the temporal tagging idea, distinct features of the novel phenomena would be represented by different neurons, so no common piece of code would be present in CA3 representations. Simulations show that if input statistics change over time, a strategy based on a growing internal chart obtains a better input representation than other strategies such as fixed populations of plastic neurons or partial neural turnover [46,47]. Young GCs may be unique in their firing properties because they are ready to expand the code in any necessary direction, which only becomes specific after a critical time window that involves learning and maturation (Fig. 1) [21,48,49]. Thus, although young GCs would be essential to learn a novel task, it is only in their mature stage that they would perform actual pattern separation, enabled by high input specificity and strong coupling to feedback inhibitory networks.

Conclusions

Recent years have witnessed great advances in the description of the course of new GCs incorporated to the DG. Important behavioral correlates of the deficit or surplus of young GCs were found, allowing us to construct computational models that aim to explain their role and importance inside the hippocampal machinery. Models suggest that a new generation of experiments should take into account the developmental timing and the different stages of memory processing. In an idealized experiment, a specific cohort of new GCs could be tagged to express opto- or chemogenetically activated channels, allowing for reversible and temporally-restricted silencing. The model by Wiskott and colleagues (2006) [46], further developed by Temprana and colleagues (2015) [21], predicts that not all silencing of young GCs would result in a pattern separation deficit. Instead, four different scenarios arise (Fig. 2). First, coincident training and silencing during the critical window would result in a learning deficit (i), affecting all future performance even without further silencing. The experiments discussed in the Neurogenesis and Pattern Separation section fit into this scenario. Second, if learning took place normally without silencing (ii), a performance deficit would only appear at a later stage when silencing this particular cohort of (mature) GCs. Finally, training outside the critical window of the tagged GCs (iii-iv) would result in no deficit, independently of whether silencing is applied or not.

The confirmation or refutation of these predictions would increase our knowledge on the functional role of young GCs in mechanistic terms. However, other questions would remain open, such as the nature of the mechanism that recruits young GCs in a task-specific manner, perhaps following similarity criteria. Only the combined effort of computational and experimental research will allow us to further understand this information-processing aspect of neurogenesis.

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Highlights

- New immature neurons are incorporated to pre-existing networks of the dentate gyrus
- They are hyper-plastic, excitable, uncoupled from inhibition and input unspecific
- They are crucial for tasks involving the discrimination of very similar situations
- While immature they could detect novel input features in a high dimensional space
- Only in their mature stage they would engage in input discrimination

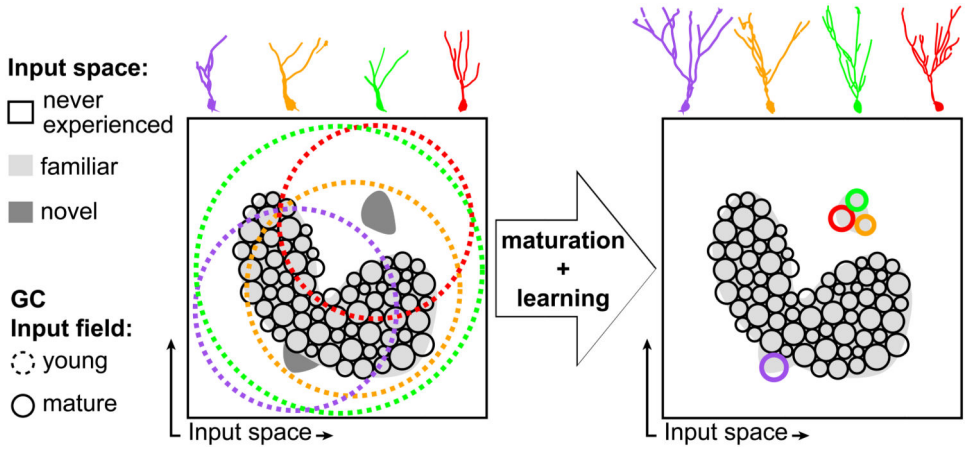

Figure 1. A conceptual model of the functional role of GCs in pattern separation across maturation

All possible patterns of inputs to the dentate gyrus are projected into a two-dimensional space for visualization purposes. Inputs are divided into familiar (light grey), novel (dark grey) and a vast majority of never experienced input combinations (white). Every GC has an *input field*, a region of the input to which it is responsive, represented by solid (mature) or dashed (immature) circles. Left: The familiar input space is covered by small and non-overlapping mature input fields, so that close-by inputs are represented by different neurons, reflecting pattern separation. In contrast, immature GCs present wide and overlapping fields due to high excitability and low inhibition. Right: Through maturation, learning, and coupling to feedback inhibitory networks these GCs acquire mature input fields. This strategy allows the coverage of vast regions of unexperienced but potentially novel input by a few young GCs, which identify the small novel input regions and learn to represent their details in a highly specific way. Upper panels represent developing GCs at immature (left) and mature (right) developmental phases. Diagram adapted with permission from ref. [21]. GC, granule cell.

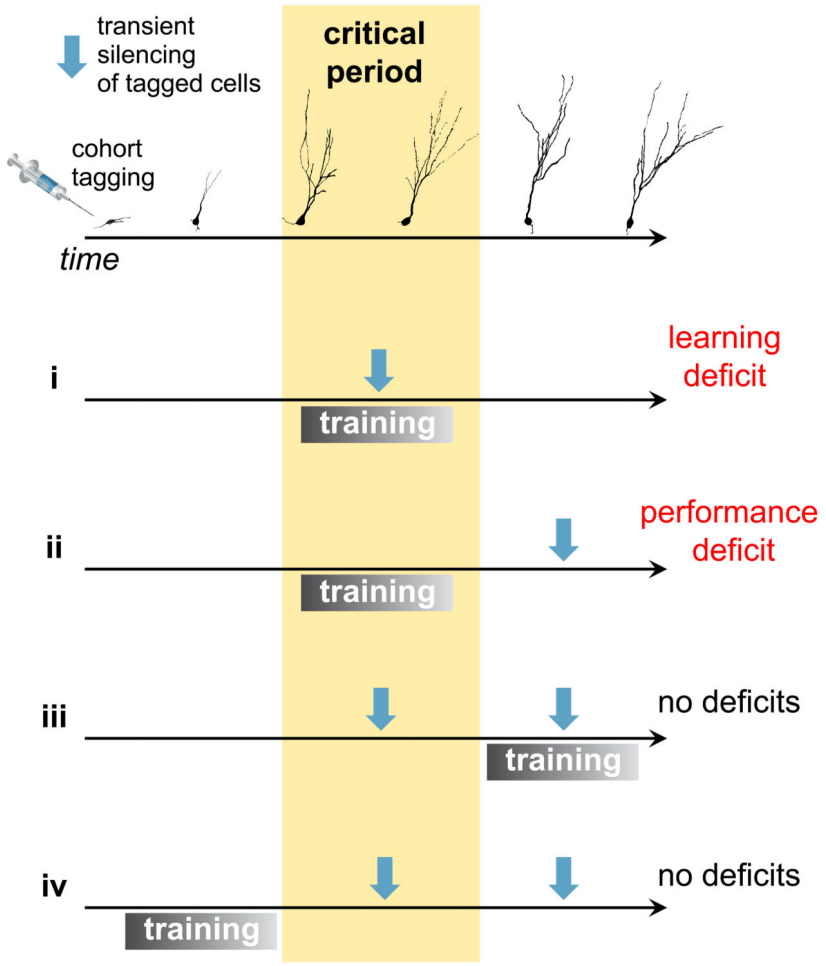

Figure 2. Experimental testing and predictions for the conceptual model presented in Fig. 1

In an idealized experiment, a cohort of young GCs is tagged with opto- or chemogenetically activated channels, allowing for a precise control of their silencing. A novel task requiring pattern separation is introduced. If training occurs while tagged GCs undergo their critical period, silencing these cells during training will generate a learning deficit, compromising future performance even without further silencing (i). If no silencing occurs during the training stage, future deficits in performance will appear transiently when silencing these GCs, even if fully mature (ii). If training occurs outside the critical window, no effect of silencing on performance is expected (iii and iv). The upper panel depicts the maturation process of a tagged cohort of developing GCs. GC, granule cell.