A Biologically Plausible Computational Model of Hippocampal Neurogenesis and Pattern Separation in Memory

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Abstract

Pattern separation, essential for encoding distinct memories of overlapping contexts, relies on dentate gyrus coding shaped by entorhinal input and strong lateral inhibition. Although synaptic plasticity and adult hippocampal neurogenesis have been implicated in this process, their precise contributions remain unclear. The Cbln4-Neo1 complex, which mediates plasticity at entorhinal cortical synapses in the dentate gyrus without affecting basal signal transmission, offers a unique target for investigation. In this study, we selectively deleted Cbln4 from inputs to the mouse dentate gyrus. We found that Cbln4 is required for behavioral pattern separation and suppresses activity-dependent neurogenesis. We then developed a biologically plausible computational model incorporating an entorhinal cortex-dentate gyrus circuit in a reinforcement learning framework. Simulations suggested that either impaired synaptic plasticity or increased neurogenesis alone was sufficient to disrupt behavioral pattern separation by elevating representational similarity in the dentate gyrus. These findings highlight the role of Cbln4 in memory encoding and dissociate the contributions of synaptic plasticity and neurogenesis through computational modeling.

Keywords: pattern separation; neurogenesis; synaptic plasticity; dentate gyrus; entorhinal cortex; fear conditioning

Introduction

Pattern separation, a memory process that enables animals to distinguish similar environments, is essential for adapting to new conditions. Imaging and behavioral studies have shown the necessity of the dentate gyrus (DG) and its inputs from the entorhinal cortex (EC) in this process (Yassa & Stark, 2011). Proposed mechanisms include EC→DG expansion and DG sparse coding via lateral inhibition. However, activity-dependent processes such as neurogenesis and synaptic plasticity have also been implicated, though their precise roles remain unclear (Cayco-Gajic & Silver, 2019). Notably, conflicting evidence suggests that neurogenesis can both enhance and impair hippocampus-dependent learning and memory, including pattern separation (Evans et al., 2022; Sahay et al., 2011). Here, we report that Cbln4, a protein previously identified as a mediator of EC→DG plasticity (Liakath-Ali et al., 2022), promotes behavioral pattern separation while suppressing activity-dependent neurogenesis. To explore the potential contribution of synaptic plasticity and neurogenesis, we developed a biologically plausible computational model of the EC-DG circuit incorporating Hebbian learning and neurogenesis. This model provides a computational framework for each of their distinct contributions to pattern separation.

Methods

Behavioral Experiment

Transgenic mice with conditional knockout of *Cbln4* in presynaptic inputs to the DG were used. On day 0, mice underwent a fear conditioning (FC) task in chamber A with foot shocks. From day 1 to 14, they underwent pattern separation (PS) training, with daily 3-minute exposure to chambers A and B, which differed slightly in sensory cues. Freezing behavior, measured as the percentage of time spent immobile, was recorded in each chamber as an index of contextual discrimination. A 2-second foot shock was delivered in chamber A only, following the 3-minute recording period. Neurogenesis was quantified using EdU and Dcx labeling of hippocampal sections.

Computational Modeling and Simulation

The model, incorporating EC-DG circuit and an actor-critic architecture (Kumar et al., 2022), was based on the neural circuit underlying contextual fear conditioning (**Fig. 1A**; LeDoux, 2000; Pape & Pare, 2010). EC activity in each chamber was modeled as a noisy version of two vectors drawn from a normal distribution, with their cosine similarity controlled by a similarity index (SI) (**Fig. 1B**). DG neurons receive feedforward input from EC and lateral inhibition from other DG neurons, with weights updated via Hebbian rule: $\Delta W_{ik} = \alpha_{EC\to DG}(y_i \cdot x_k - W_{ik})$, $\Delta M_{ij} = \alpha_{lateral}(y_i \cdot y_j - M_{ij})$ (Qin et al., 2023). The ratio of lateral to feedforward learning rates was defined as $r_\alpha = \frac{\alpha_{lateral}}{\alpha_{EC\to DG}}$. Neurogenesis in the DG was modeled by adding new neurons to the DG layer each day.

Results

We first examined the experimental data from the FC + PS task. Mice with Cbln4 deletion showed impaired contextual discriminability between chambers (**Fig. 1C**; $p < 0.05$). In addition to the previously reported impairment of EC→DG synaptic plasticity, we observed increased DG neurogenesis in the Cbln4 deletion group (Edu: Δ892.67, $p < 0.05$; Dcx: Δ610.00, $p < 0.05$). In contrast, basal neurogenesis in the home cage and after FC alone remained unaffected, suggesting that only activity-dependent neurogenesis was disrupted.

Next, we evaluated the pattern separation capability of the EC-DG network. Given overlapping EC input patterns (**Fig. 1B**), the model can produce low-dimensional representations in the DG, with the first principal component (PC) capturing most of the variance in the network dynamics (**Fig. 1D**). These representations became increasingly low-dimensional over the course of training (**Fig. 1D**). When EC input similarity was reduced to counteract noise, the model progressively learned to separate EC inputs by reducing DG similarity (**Fig. 1E**, dark blue curves; $p < 0.01$). Increasing $\alpha_{EC\to DG}$ enhanced pattern separation ($p < 0.001$) and accelerated the reduction in DG similarity over time (**Fig. 1F**). Similarly, increasing r_α, reflecting a stronger sparsity cost within DG, improved pattern separation by reducing DG representational similarity (**Fig. 1G**; $p < 0.001$).

Finally, we used an actor-critic algorithm to associate DG representations of environments with foot shock punishment, generating freezing ratio as a measure of behavioral pattern separation. When the number of neurons added to the

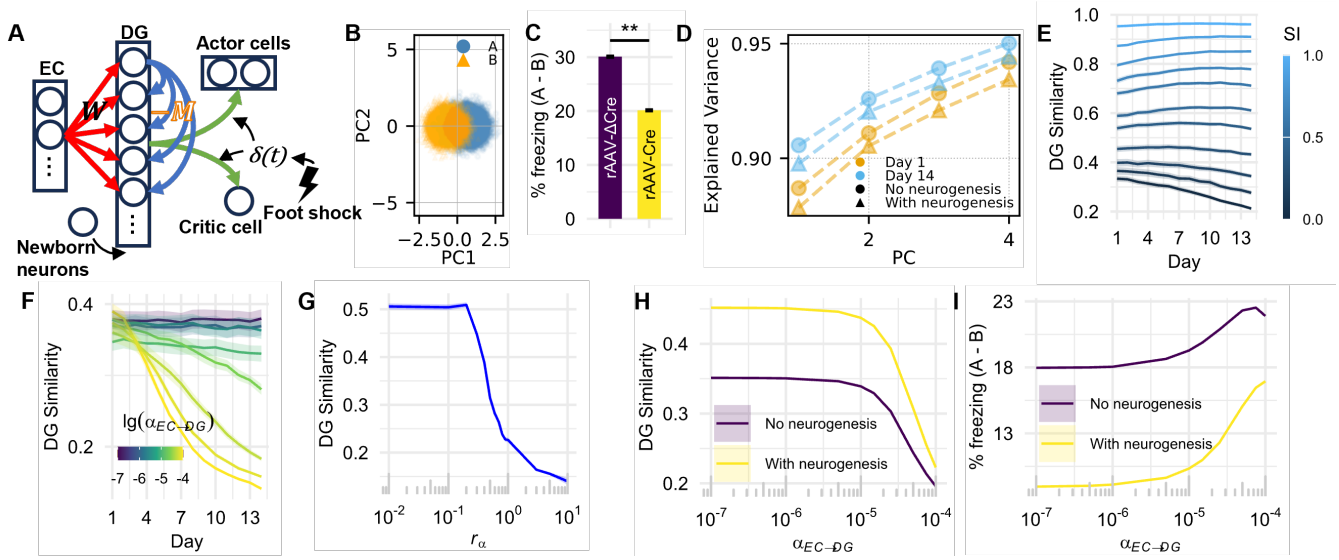

Figure 1: **(A)** Model architecture. Feedforward (W, red arrows) and lateral ($-M$, blue arrows) weights were updated via Hebbian learning. DG→actor-critic weights (green arrows) were updated via temporal difference learning. **(B)** First two principal components of a representative pair of EC input vectors. **(C)** Difference in freezing ratios between chambers A and B in behavioral experiments, grouped by Cbln4 deletion (purple: control; yellow: mutant). **(D)** Cumulative variance explained by the first four principal components at early (orange) and late (blue) stages of learning in models with (circles) or without (triangles) neurogenesis. **(E-G)** Global cosine similarity of DG activity across time steps in PS-only simulations, varying **(E)** EC cosine similarity (SI), **(F)** $\alpha_{EC\to DG}$, **(G)** r_α. **(H-I)** Simulated **(H)** DG similarity and **(I)** freezing ratio differences in the FC + PS task, modulated by $\alpha_{EC\to DG}$ and neurogenesis. Abbreviations: EC: entorhinal cortex. DG: dentate gyrus. $\delta(t)$: temporal difference error. PC: principal component. SI: similarity index. lg: common logarithm.

network each day was set to match biological scales, both neurogenesis and reduced synaptic plasticity $\alpha_{EC\to DG}$ impaired pattern separation by elevating DG similarity (**Fig. 1H**; $\alpha_{EC\to DG}$: $p < 0.001$; neurogenesis: $p < 0.001$). Concurrently, contextual discrimination behavior was impaired, as indicated by a decreased difference in the freezing ratio between chambers A and B (**Fig. 1I**; $\alpha_{EC\to DG}$: $p < 0.001$; neurogenesis: $p < 0.001$). Compared with the model without neurogenesis, the neurogenic model required more PCs to represent EC inputs, further indicating interference with pattern separation (**Fig. 1D**).

Discussion

Based on our experimental results, we identified Cbln4 as a significant regulator of pattern separation and a suppressor of activity-dependent hippocampal neurogenesis. To help further dissect the underlying mechanisms, we developed a biologically plausible model incorporating EC→DG synaptic plasticity, lateral inhibition, and DG neurogenesis, which not only reproduces key aspects of pattern separation but also extends beyond existing theories centered on EC→DG expansion and sparse coding via inhibition. Both the experimental deletion of Cbln4 and model-based impairment of EC→DG plasticity or DG neurogenesis led to deficits in pattern separation, highlighting their potentially individually sufficient and converging contributions.

Previous studies have suggested a causal relationship between dopamine signals and fear conditioning (Fadok, Dickerson, & Palmiter, 2009; Tsai et al., 2009). While the amygdala's role in reinforcement learning (RL) is well recognized, its neurocomputational basis in associative memory remains underexplored (Niv, 2009). By implementing the actor-critic algorithm, we propose a potential computational model for RL in the amygdala. However, further research is required to validate and refine their connection.

Acknowledgments

This research was supported by the Healthy Longevity Translational Research Programme Pilot Studies Grant, NUS Artificial Intelligence Institute Seed Funding, and Singapore Ministry of Education Academic Research Fund Tier 2 (MOE-T2EP30122-0016).

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