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Review Paper

Computational Pattern Separation Models of Dentate Gyrus Neural Subpopulation in the Hippocampus

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ABSTRACT

Hippocampus is a part of the brain that has an essential role in memory and learning. It is involved in many cognitive and behavioral phenomena, including the pattern separation process: the ability to distinguish patterns with very high similarity. The present study compared the models of pattern separation in the dentate gyrus of the hippocampus and aimed to investigate the significant cells and factors affecting pattern separation. In this review, we intend to describe the anatomy of the dentate gyrus as a part of the hippocampus, which has an essential role in pattern separation. Other adjacent neural populations are further addressed, too. Models of the dentate gyrus, including neurocomputation and functional, that represent the process of separating patterns in the dentate gyrus are reviewed and analyzed. In this regard, five major models were highlighted and compared from several perspectives. While some models are based on the entorhinal cortex and dentate gyrus regions, others point to the mediation of cornu ammonis (CA3) as well. Models with the lowest cells for pattern separation are addressed first. Finally, inhibition is discussed in the comparison of pattern separation models.

Keywords: Hippocampus, Learning, Memory, Interneurons, Spatial memory

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Highlights

• Hippocampus has an essential role in memory, especially in episodic and spatial memory.

• The capability of distinguishing related episodes, the main feature of episodic memory, is called pattern separation and is attributed to the dentate gyrus in the hippocampus.

• The essential participant cells in pattern separation are granule cells, mossy cells, interneurons, and hilar perforant path-associated cells.

• Inhibition and neurogenesis have significant effects on pattern separation and its facilitation.

Introduction

Hippocampus has a critical role in memory [1] and spatiotemporal cognition [2]. Hippocampus supports cognitive functions such as episodic memory [1-4], thoughtful responses, recalling past experiences, and representing the temporal order of events [1]. Learning and memory processes in the brain are caused by changes in the neuronal representation of stimuli [5]. Episodic learning triggers specific patterns of neural activities in different places of the brain, leading to long-lasting changes in synaptic contact [6]. It is hypothesized that synaptic plasticity, like long-lasting potential (LTP), is the neuronal basis for memory formation [5]. It is suggested that LTP impairment damages subregions in the hippocampus related to learning and memory [6]. Sequence inference in LTP is controlled by the activity of the postsynaptic and presynaptic neurons. This phenomenon is known as metaplasticity [7]. Some studies refer to the hippocampus's role in learning, especially sequential learning [8, 9]. This part of the brain is also involved in diseases such as epilepsy and Alzheimer [10-12].

The hippocampus includes three main subregions: dentate gyrus (DG), cornu ammonis area 3 (CA3), and CA1 [13]. Each subregion is characterized by available information on biomarker expression and electrophysiological features [14]. The structure of the hippocampus and its different regions' connections are represented in Figure 1.

As is evident in Figure 1, inputs of the hippocampus are received from the entorhinal cortex (EC) [15, 16]. DG is the first subregion of the hippocampus that receives incoming information from other parts of the brain [7], mainly from the entorhinal cortex [15, 17, 18] and the projects resulting in CA3 [15, 19, 20]. CA3 can further receive homogenous inputs from the dentate gyrus [21].

The primary role of DG is pattern separation which occurs when fired pattern separation out of the network has much less similarity than fired input patterns [22-24]. It is believed that pattern completion is related to CA3 [25]. Capability of completing incomplete inputs is named pattern completion [22-24, 26]. On the other hand, CA1 performs new signal generation by receiving sensory inputs [27].

As mentioned above, diverse and essential phenomena in the learning and memory process are mediated via different hippocampus regions. The substantial role of the hippocampus in many fields of memory, learning, and its involvement in some brain diseases is a declarative reason for more definitive studies of this part of the brain.

Primary cells of the DG and their connections

The dentate gyrus mediates the mnemonic processing of spatially based information [28] and has a principal role in pattern separation [29, 30]. DG receives its multiple sensory inputs, including vestibular, olfactory, visual, auditory, and somatosensory, from the perirhinal and lateral entorhinal cortex in conjunction with spatially organized grid cells from the medial entorhinal cortex [28, 31].

DG has some essential cells. Several breakdowns of DG cells and their various sections have been represented so far [32]. Figure 2 shows the structure of the primary cells of DG and their connections.

The function of DG in the hippocampus is accomplished via computation, which is called pattern separation [20]. Pattern separation is a process that transforms similar inputs to one without similarity and reports non-overlapping [22, 29].

Pattern separation models of DG

For a precise explanation of pattern separation, much research has been performed, and various models have been presented [3, 7, 33, 34]. Several expositions and comparisons of these DG computational models are presented in this section. All models of DG aim to investigate the pattern separation in the hippocampus of the brain. Another essential purpose is to determine cells and sections of the DG that participate in the pattern separation.

Model 1

Four primary cells, i.e., granule cell, mossy cell, hilar perforant path associated (HIPP), and inhibition interneurons, such as basket cells, are components of this model. The Model cycle is represented as entorhinal cortex-dentate gyrus (EC-DG) by the perspective of competing parts. Briefly, the following operations were performed. The inputs to DG from the perforant path exhibit the granule cells ordered in multiple layers. Then inhibition interneurons employ their inhibition on granule cells. The most robust granule cells make other cells silent. This competitive model is called a winner-take-all. Granule cells project their effect on mossy cells, and in turn, mossy cells excite granule cells. HIPP cells receiving their input from the perforant path have an inhibition influence on granule cells. In the implementation phase of the model, 500 granule cells (1/2000 out of one million granule cells in rats) were classified into 25 clusters. There is one interneuron in each cluster that is activated by granule cells in the same cluster, and in turn, it creates inhibition for granule cells.

According to the winner-take-all policy, there is one winner in any cluster, and in total, 25 cells of 500 cells remain active. There are 1200 HIPP cells in the model. Inputs come from 100 afferents and have a ratio of 1:5 in granule cells. Simplicity and a small number of free parameters are benefits of the model. Although this model does not contain the physiological and anatomical complexity, it allows us to test the theory that there are a few essential keys in the DG network for gathering some aspects of empirical data [13].

Model 2

This model [35] includes the CA3 region. The cycle of the model is EC-DG-CA3. In this model, CA3 has a back projection to DG, which is the same as Model 1. Still, a simple automatic associative memory is constructed from CA3, which is capable of providing and saving the pattern, then recalling and allowing it to have a treat with DG. The implementation of the model contains 1000 granule cells in 10 layers. Inhibition of interneuron baskets and axo-axonic cells influence each layer. The current model includes 30 mossy cells, which gives a projection from granule cells as in Model 1 and sends the excitatory effect back. The number of HIPP hilar cells in this model is 12, which gives inputs from the Perforant Path (PP) and creates an inhibitory influence on granule cells. There are 200 inputs from PP in this model.

The critical point is that in Model 1, the output is assumed to be depolarized, but here, DG's output is verified as the firing granule cells. Each granule cell is silent or produces potential action [35].

Model 3

The structure of this model [26] resembles previous models in the case of a functional role in each region. The current model's cycle is EC-DG-CA3, as in Model 2. In this model, in addition to granule cells and interneurons in DG, CA3 includes interneurons and pyramidal cells.

Since pattern separation needs pairing sparse connections in the DG-CA3 path that provides an index for CA3's population, in this model, relationships among sections are produced so that sparse activity of CA3 cells is resumed via the mossy fiber system of DG-CA3.

For implementing this model, the number of cells estimated by the adult rat brain is reduced by a factor of 1000. Two different types of inhibitory neurons were included. Six inhibitory cells in DG received excitatory input. An inhibitory cell in CA3 received input from the local pyramidal cell.

The model contains two inhibition neuron types: six neurons in DG and one inhibition CA3 cell, which give input from local pyramidal cells and operate to repress CA3 network activity. There are two reasons for the inhibition of CA3 in the model. First, it ensures that the low diversity in DG activity does not result in extreme variety in CA3 activity. Second, it acts as a quantity threshold. If an adequate amount of CA3 cells respond to patterns directly, the CA3 inhibition cell signals it as a known one.

In this model, unlike the previous one, which attempts to balance learning against recalling, each represented pattern gets learned or remembered (denoting its novelty) [26].

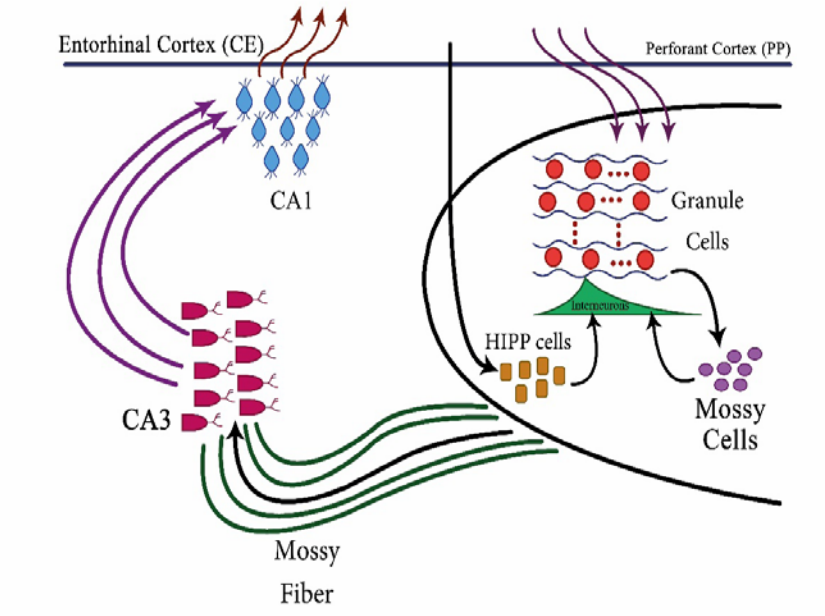

Figure 1. Hippocampus parts and their connections

Abbreviation: CA, cornu ammonis; HIPP, hilar perforant path

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Model 4

This model represented the exploration of hilar in which the ectopic granule cells affect the pattern separation as in the DG-CA3 cycle. In this model, the influences of CA3 are also mediated and illustrate that the anatomical and physiological structures of DG and CA3 are compatible with pattern separation and pattern completion. In complex DG and CA3 cells, the pyramidal cells in CA3 containing back-projection, play a significant role in the sparse firing of granule cells. As mentioned above, this model is based on models 1 and 2, to which the influence of ectopic hilar is added exclusively [36].

The implementation of this model is based on the model [37], including ten layers, each one with 100 granule cells, one interneuron, three fiber cells, and one HIPP cell. In CA3, each layer includes 30 pyramidal cells and

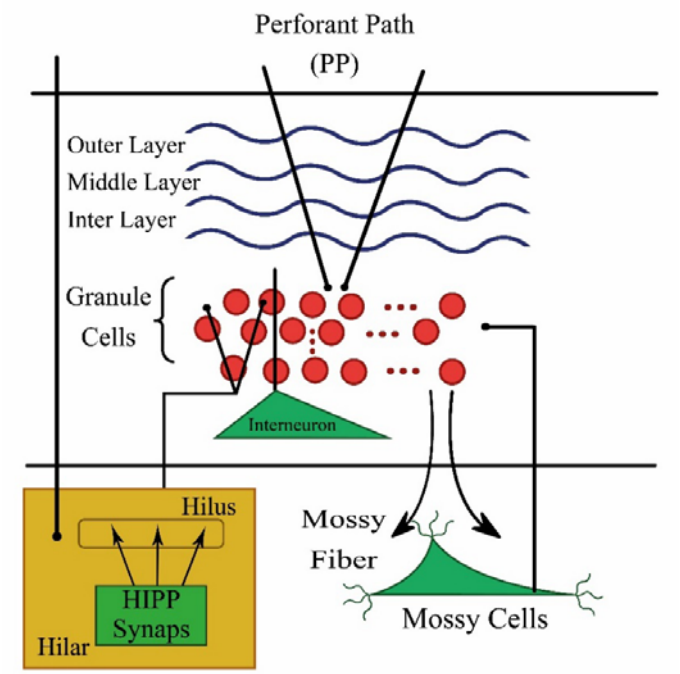

Figure 2. Main dentate gyrus cells and their connections

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Table 1. Broad overview of the main DG models

Models	Cycle	Participated Cells	Inhibitors Cells
Model 1 [13]	EC-DG	GC, interneuron, HIPP, mossy fiber	Interneuron, HIPP
Model 2 [35]	EC-DG-CA3	GC, interneuron, HIPP, mossy fiber	Interneuron, HIPP
Model 3 [26]	EC-DG-CA3	DG: interneurons, HIPP CA3: interneurons, pyramidal	DG: interneuron CA3: interneuron
Model 4 [36]	EC-DG-CA3	DG: interneurons, HIPP, mossy fiber CA3: interneurons, pyramidal	DG: interneuron, HIPP CA3: interneuron
Model 5 [29]	EC-DG	GC, mossy fiber, HIPP	HIPP

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Abbreviation: EC: entorhinal cortex; DG: dentate gyrus; GC, granule cell; HIPP, hilar perforant path associated, CA, cornu ammonis.

one interneuron. Inputs of PP are simulated with a vector of 200 axons; each can be 1 (activated or fired) or 0 (inactivated or unfired). The trail starts with the activation of one subset of these inputs and a representation of them to DG and CA3. The trail terminated with the reading of DG and CA3's outputs. Outputs can be supra-threshold or sub-threshold-two output patterns exit. One of them represents the outputs of DG, a vector of zero or one that implicates produced action potentials in granule cells. The other one is the output of CA3, a similarity vector that produces pyramidal cell actions [36].

Model 5

This model was offered for evaluation if dendrites participate in pattern separation and how this participation is. This model [29] has been developed based on Model 1 and has four substantial cells: granule cells, mossy cells, basket cells, and HIPP. The number of granule cells' dendrites affects pattern separation; two approaches are used for assessment: pruning and growth of dendrites.

Firstly, two granule cell models were implemented that differ only in the number of dendrites, but their path length is identical. Then, two granule cell models were performed, which vary in quantity and the length of the dendrite's path. For this implementation, the 2000 granule cells were simulated. This population perch in clusters without any overlapping. Each cluster contains 20 granule cells. There are 80 mossy cells, and 40 HIPP were considered in the model. Network inputs were received from 400 afferents [29].

Comparing pattern separation models

As seen from the comparison of the models of DG, only Model 1 and Model 2 agree with a cycle of EC-DG for pattern separation in the hippocampus. The other models consider that CA3 participated in the pattern separation process.

The comparison of essential features of these models is displayed in Table 1. Model 5 represented the lowest and Model 4 the largest number of cells for pattern separation. In Model 5, only granule cells, mossy fiber, and HIPP cells were provided. Interneurons of DG, interneurons, and pyramidal of CA3 are added for pattern separation in Model 4.

These models of pattern separation can be implemented in various fields, such as modeling networks for pattern recognition [38]. In research [38], an artificial neural network has been proposed based on Model 1 [13], which is used for handwritten recognition. The proposed network was evaluated with six datasets of digits and characters from five languages. Experiments on all of the used datasets showed promising results. Therefore, modeling the functionality of dentate gyrus pattern separation can be considered a research field in various categories.Neurogenesis Role in the Pattern Separation

Hippocampal neurogenesis is a process in which primary neurons are produced in DG and functionally snuggle and integrate into hippocampal circuits in the adult mammal brain [39]. Granules are the cells that undergo neurogenesis in the adult brain [40]. These granule cells are produced in mammal brains during life. This phenomenon is called postal neurogenesis [41-43].

Some findings show that adult-born DGs are hyperexcitable between weeks 2 and 6 of their age, meaning that these granule cells are especially adequate for pattern separation [44-46]. Granule cells are generated from precursors in the subgranular zone and normally migrate a short distance to the adjacent granule cells layer [37]. Adult-born granule cells (abGC) are categorized in

two parts: mature abGCs and immature ones [47, 48]. Adult-born GCs migrate via the mature process in several weeks [49], in which immature GCs get to develop the properties of GC [22]. During the activity of these abGCs, mature abGC's populations will be more active than mature GCs [50]. Also, neurogenesis migrated to hilus in the opposite path [41]. Adding a small population of hEGCs (5% of all GSs) with observable empirical features is adequate for discounting pattern separation and pattern completion. Results show that hEGCs effects are essentially due to the back-projection of axons of CA3 pyramidal cells to hilus [41]. Nevertheless, do adult-born neurons have an inhibition feature? huHong Liu et al. (2003) showed that some adult-born neurons have inhibitory effects [51]. Bettina Seri et al. (2005) showed that no inhibitory adult-born cells had been observed in DG. Despite all research in this field, there is a question: Is neurogenesis directly mediated in pattern separation? [52]. Based on the model of Aimone et al., neurogenesis increases the pattern separation for events that occur at a distinct time (pattern separation), but learned patterns have a gradation of similarity (pattern integration). This model is represented based on the biological model of EC-DG [53]. This model predicts that mature DGCs construct a distinct intersection for DG's separation features.

Conclusion

Many studies reported the role of DG as one of the essential sections of the hippocampus. This study has especially focused on pattern separation research. The represented models of pattern separation in the DG of the hippocampus are delineated and compared.

The comparison was performed from several perspectives. While some models were based on EC and DG regions, others believe in the mediation of CA3 as well. Models with the lowest cells for pattern separation were based on granule, mossy, and HIPP cells. In the other models, interneurons of DG, interneurons, and pyramidal cells of CA3 were added for pattern separation. In one model, only HIPP cells are represented for inhibition. Some models also added interneurons for the inhibition of pattern separation. One model performed the inhibition with interneurons of the DG and interneurons of the CA3 without HIPP cells, and one model suggested DG's interneurons, HIPP's DG, and interneurons of CA3 for inhibition. This model suggested the largest number of cells for inhibition.

Sparse connections in mossy fiber facilitate the pattern separation process. Sparse coding is performed in different fired places of mossy cells, which is performed by GCs. On the other hand, inhibition is critical for pattern separation. As can be seen, inhibition generally improves pattern separation. Neurogenesis has a significant effect on DG's pattern separation.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were conducted following the ethical guidelines of the Declaration of Helsinki 2013.

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Authors contributions

All authors contributed to conceptualization and supervision, methodology, investigation, original draft writing, review, and editing, funding acquisition, and resources.

Conflict of interest

The authors declared no conflict of interest.

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