

Study of Pattern Separation in Human being

Jingci Jiang

Department of Psychology, The Ohio State University, Columbus, OH 43210, USA.

Jiang.1857@osu.edu.

Abstract. Pattern separation, the ability to distinguish similar representation of experiences and memories, is crucial to episodic memory. In this review, we summarize different models of memory systems that are important for understanding pattern separation, then introduce the concept and definition of pattern separation, and distinguish it from its counterpart, pattern completion. We evaluate empirical evidences that associate sub-hippocampal brain structures with pattern separation, especially the cinnamons and dentate gyrus, in order to analyze the role each structure plays in this function. We also discuss possible neural mechanisms behind pattern separation that could guide the direction of future studies. Finally, we discuss several ways that are likely to be helpful in improving pattern separation, including exercise and environmental enrichment.

Keywords: *pattern separation, hippocampus, memory, DG/CA3*

1. Introduction

Memory is considered to be one of the most significant part of human cognitions. Without the information memory stored, many cognitive functions would not develop. To some extent, human civilization is based on the existence of memory. Over the years scientists spent on studying memory, different theories have been developed in order to classify and to understand how memory works.

Atkinson and Shiffrin divided memory system into three parts based on the duration memory remain in each memory, which is sensory memory, short-term memory and long-term memory [1]. Long-term memory stores valuable experiences and knowledge from the past and thus is indispensable in human psychological activities. It can be classified as declarative memory, also called explicit memory, and non-declarative, or implicit, memory. Declarative memory can be further divided into semantic memory and episodic memory.

Researchers have found that different types of memories involve different participating brain structures. Overall speaking, prefrontal lobe and medial temporal lobe, including the hippocampus and amygdala, are the regions that play most crucial roles in memory system.

Prefrontal lobe is critical to episodic memory, working memory, spatial information, time-sequence information as well as to the process of memory encoding, storage, and retrieval. Medial temporal lobe is of great importance to declarative memory. In theory, medial temporal cortex is a structure where memories are stored. Under the cortex lies the hippocampus, which is specialize in episodic memory and spatial memory. Close to hippocampus there is an almond shape structure called Amygdala. Amygdala is triggered by strong emotions, especially anger and fear. In memory system, amygdala controls memories associate with strong emotions. Patients with damaged amygdala would have no problem remember things that made them angry or afraid, but they cannot feel such emotions again.

In addition to the traditional memory classification, in recent years, the neurophysiologist put forward a cohort of computational models of the hippocampus, which of most comes from rodent recording. And two concepts -- pattern separation and pattern recognition -- have been derived from those computational models.

2. Definition of Pattern Separation and the Difference from Pattern Completion

Two abilities attributed to hippocampus play critical role in declarative memory—pattern separation and pattern completion. Pattern separation is the ability to distinguish and separate two very similar representations [2]. It is the ability that helps people differentiate two similar and

overlapped memories, such as today's parking spot and yesterday's parking spot in the same parking lot. On the other hand, pattern completion is the ability to relate partial or incomplete inputs with previous experience to form a complete representation. This is the ability that enables people to recognize and categorize a novel, never-seen object as a mug based on their formal knowledge of what mugs look like.

Hippocampus has several sub-regions, with each having different specific functions and features [3]. Entorhinal cortex (EC) is the region through which information from cortical region enters the hippocampus [4]. The cornu ammonis (CA), extending from the parahippocampal gyrus, is divided into sub-regions called CA1 through CA4. Dentate Gyrus (DG) is a sub-hippocampus structure wrapping around the CA [5, 6]. Through perforant pathway (PP), input received by EC is projected to DG and CA field, thus forming the EC-DG-CA3 circuit. This circuit is believed to be involved in pattern separation [7].

Over the years, empirical evidences were provided by a large quantity and variety of studies. The role hippocampus and its subfields play in pattern separation was first supported by rodent studies. Early gene expression [8] and single-cell recordings [9, 10, 11, 12, 13] used the firing patterns of place cells to analyze the relationship between different hippocampal regions and pattern separation/completion. Place cells are neurons in (typically) CA1 and CA3 that fire at a higher rate in a specific location of an environment. When exposed to new stimulus, place cells have either very similar firing pattern or very distinctive one, depends on the degree of change in stimuli. When place cells fire at a different pattern, the new stimulus is stored as a different representation in memory compared to other stimuli, thus pattern separation occurs. Specifically, CA3 area is biased toward pattern separation. A different set of CA3 neurons would be activated when small changes in environment are detected, thus lead to distinctive memory. In comparison, overlap in firing pattern exists in CA1 even under different environment, causing large similarity between memories formed (completion).

However, hippocampal system does not work as simple as one hippocampal area for one specific function. Activities correlate with pattern separation and pattern completion can both be observed in rodents' CA3. Two studies using electrophysiological recordings first shed the light on this new finding. The first study [9]. created an environment using circular track, with local cues on the track's surface and distal cues surrounding the track. In experimental sessions, relative position of the track and its surroundings was changed to create mismatch between cues. Firing patterns of place cells in CA1 and CA3 were measured when rodents ran on the track. The second study [10] is very similar, except that instead of putting cues on tracks, it created an enclosure with manipulated geometric structure. In this way, the second study made changes in a larger environment, thus led to a larger difference between stimulus. Surprisingly, the measured firing patterns in the two studies contradict each other. While results of the first study show signs of pattern completion, the second study shows pattern separation. This contradiction is reconciled by another study using immediate-early gene (IEG) brain imaging method. This study evaluates the correlation between the degree of environmental difference and firing pattern in CA1 and CA3, and the results indicate that when changes in environment are rather small, CA3 shows signs of pattern completion, and when changes are made larger, neural activities indicate a stronger pattern separation instead [8]. In combination, these studies showed that CA3 is more likely to exhibit pattern separation when larger changes are detected, while more likely to show pattern completion under smaller environmental changes. Such flexible transition also suggests that pattern completion and pattern separation do not stand in two extremity against each other, but rather cooperate with each other to create a better memory system.

While studies in rodents clearly indicate the importance of CA3, studies with human subjects have not yet been able to separate CA3 and DG, due to their spatial proximity [15]. However, many studies with human subjects showed results that are in accordance of rodent studies, especially in finding the significance of CA3/DG areas. One study used Behavioral Pattern Separation Task (now Mnemonic Similarity Task) with functional magnetic resonance (fMRI) technique on human subjects in order to relate MST performance to brain activity. In the experiment, participants are

required to perform the task while their brain activities are being measured. The task shows pictures of daily objects, and the pictures can be either completely new, a repetition of a previous picture, or slightly different from a previous picture. The presentations are also referred to as foils, targets, and lures, respectively. The results show significant difference in CA3/DG activity between a lure representation and a repetition, but similar activity between lure representations and new stimulus. This result indicates that CA3 and DG react to lure images as if they are completely new stimulus, showing a strong bias toward pattern separation [2].

More recently, ultrahigh-resolution fMRI was applied in the hope of better understanding functions of different structures in more detail. In 2016, Berron et al., using fMRI at 7 T, showed that “DG sub-region specifically sustains representations of similar scenes that are less overlapping than in other hippocampal and medial temporal lobe regions”, and that pattern separation in DG is specific to stimulus, suggesting that its participation in overall pattern separation is relatively selective. This is the first study that separately highlights the significance of DG in pattern separation [16].

Altogether, these studies suggest the functional role human DG/CA3 play in pattern separation. Their necessity, however, has to be demonstrated by lesion studies. In an experiment conducted on rats, rats with lesions in DG cannot distinguish two similar yet different environments, evidence of impairment in pattern separation [17]. In the case of patient B.L, who has selective bilateral ischemic lesions in DG, his performance on mnemonic discrimination task is lower than standard, indicating impaired pattern separation ability [18]. The necessity of DG was proved in many different lesion studies. However, the necessary role of CA3 still remain unclear.

3. Possible Mechanisms Behind Pattern Separation

Although pattern separation has been a popular research area for years, the mechanisms behind it still remains elusive. Many possible theories have been put forward, and so far, some of them receive certain degree of support by other studies.

Originally described by David Marr (1969), the sparsification model links the sparseness of granule cells of DG with pattern separation. Although a significantly large amount of granule cells exists in brain, only 1-2% show signs of activity. This property of granule cells leads to suggestion that inputs from EC are sparsely recode in granule cell, so that only a small number of cells are activated, forming different neural pattern from input to input. Most similar models assume that activation of granule cells will further activates local interneurons, which in turn, would inhibit other granule cells. By triggering competition between granule cells, such inhibition serves as regulating mechanism for their activation.

This theory, nevertheless, raise question as to how such a simple model can support the fast learning process episodic memory has. As a result, researchers argue that sparsification is necessary but not sufficient to support pattern separation. There should be other mechanisms that work interactively with sparsification in order to produce functional pattern separation. The granule cell-mossy cell- granule cell circuit is considered one of the possibilities. This circuit, supported by a pattern of connectivity produced by granule cell axons, the mossy fibers, mossy cells and GABAergic neurons, as well as the plasticity of synapses between mossy cells and granule cells, may serve as a surface for second level of information processing. Hilar circuit is another candidate, where hilar cells are thought to bias competition between granule cells and regulate the pattern separation [20, 21].

4. Improvement of Pattern Separation

More and more studies have shown evidences indicating that regular, moderate-level exercise is beneficial to brain function, in both animal models and human. In animal studies, regular exercise has been observed to improve memory and learning in rodents, due to its influence on neural plasticity, especially in DG area [22, 23, 24]. In human studies, older adults who finish one year of

moderate exercise program show increase in hippocampal volume as well as improvement in spatial memory [25]. Similarly, young adults who went through 12 weeks of moderate exercise have increase in DG cerebral blood volume, indirectly indicating neurogenesis [26]. The improved brain function correlated with exercise led to the suggestion that exercise may play a similar role in pattern separation as well. In 2013, the study conducted by Déry et al. [27] linked increase in aerobic fitness level to improved task performance in pattern separation, which built the foundation stone for understanding the role exercise play in pattern separation. While chronical effects of exercise on pattern separation have been observed and studied, the study done by Soya et al. (2007) [28] showing that one single session of moderate exercise can improve pattern separation. Suwabe et al. (2017) [29] conducted participants either complete 10 minutes of moderate exercise (experiment group) or rest (control group) 15 minute, 5 minutes after exercise or rest, participants started the mnemonic discrimination task (MST) to evaluate their pattern separation ability. The overall result suggest that one single session of moderate exercise can improve pattern separation.

In addition to exercise, exploration of enriched environment is also believed to contribute to improved pattern separation. In 2000, van Praag et al. [30] show that adding sensory stimulation in rodents' living environment can not only promote hippocampal function and neuroplasticity, but also ease cognitive deficit symptoms due to degenerative disease and aging. In order to study how such enrichment acts on human, Gregory Clemenson and his colleagues developed experiments that use video games as a form of environmental manipulation. Clemenson and Stark (2015) conducted experiments to explore how the enriched environment contributes to pattern separation in human being. This experiment evaluates the correlation between gaming experience and performance in MST task. The results indicating a better pattern separation in video gamers. Additionally, that gamers who played more complicated, 3D games tend to have better performance in pattern separation. They also conducted an intervention study, 69 participants were all non-video gamers, and were divided into three subgroups: NC control group, which had no contact of any game; 2D active control group, which played Angry Birds; and 3D experimental group, which played Super Mario 3D World. Pattern separation was improved after 3D game training, but no significant improvement was found in control group and 2-D video game group. Importantly, no significant difference on enumeration task is found in any of the experiment, which further suggests that the effect of 3D video game is specifically on hippocampal-dependent memory, instead of general memory [31].

Clemenson et al. (2019) [32] conducted another intervention study using Minecraft. This experiment is another effort in understanding how environmental enrichment interacting with human hippocampal memory, especially in pattern separation. 82 non-active game players with no previous Minecraft experience were recruited. They were further divided into four subgroups: Free Building, Directed Building, Free Exploration, and Explore and Build. Both building groups focused more on building, but while Free Building group received no specific direction, Directed Building group were asked to follow instruction and potentially to build more complex structures. The Free Exploration group were free to explore the game on their own, but they were provided a list of objects and places which they were encouraged to search for. The Explore and Build group spent their first week as the Free Exploration group, but spent their second week like the Directed Building group, except they were asked to find building materials on their own. Before and after training, participants were asked to complete MST. In addition, using the data from the game, researchers calculated the roaming entropy (RE) of each participant to quantify their level of spatial exploration. The higher the RE, the more they explore in the game. The amount of building is calculated as the number of blocks changed in the game. The overall result indicates that pattern separation improved in all four groups, but the degree of exploration, rather than travel distance, is more important in improving pattern separation. This experiment provides clearer evidences that spatial exploration plays an important role in improving hippocampal memory.

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