

## **Bridging the models on the localization of hippocampal functions**

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**Abstract:** The hippocampus has been proven to be important for episodic memory and spatial memory. As the structure and connectivity of the hippocampus have been clear, and because of the abundance of the connectivity and cerebral functions regarding hippocampus, multiple models on the localization of hippocampal functions have been proposed. The AT/PM (anterior temporal/posterior medial) model proposed that different parts of hippocampus might process different kinds of information, the computational model proposed that different subfields of hippocampus perform different procedures on information, and the gradient model proposed that different parts of hippocampus would do the latter function. While the models seem diverse from one another, there might be connections that could unify the models. We attempt to explain and rationalize the connections among the models, yet there are still contradictions that would need further research to resolve.

### **1. Introduction**

The hippocampus plays a crucial role in memory, including episodic memory and spatial memory; thus, it has been extensively studied. Starting with the clinical studies of the famous patient H.M., who experienced severe amnesic symptoms resulted from a bilateral lesion of the hippocampus and associated areas, researchers have found the hippocampus's importance in episodic memory. [1] Moreover, results from animal studies show that place cells in hippocampus fire corresponding to the spatial location of the animals, and thus hippocampus is also important in spatial memory. [2] Similar mechanisms regarding special memory have been suspected to exist also in the human hippocampus. In an effort to reconcile the seemingly diverse function of the hippocampus, multiple models have been proposed. While the models are disparate, there seems to be a common underlying mechanism that could bridge those models. The current paper reviews several proposed models and intends to find the connections between those models.

### **2. Structure and connectivity**

The hippocampus rests in the temporal lobe of the human brain. Regions in the human medial temporal lobe (MTL) other than the hippocampus connect extensively to subfields in the hippocampus.

#### **2.1 Structure of Hippocampus**

There are several different ways when dividing regions in the hippocampus. In a cross-sectional view, the hippocampus is composed of several subfields. These subfields run throughout the hippocampus along the longitudinal axis. The subfields include: cornu ammonis (CA) fields CA1 – CA4, dentate gyrus (DG), and subiculum. Their connectivity to different regions differentiates these subfields, which we will discuss in the following sections.

From the anterior extreme to the posterior extreme, the hippocampus can be anatomically divided into head, body, and tail. Even though the physical shapes of these sub-regions are different, they contain similar subfields (CA, DG, and subiculum). Previous literature also proposed that anterior

hippocampus (aHPC) and posterior hippocampus (pHPC) might have different functions. There are several strategies to differentiate this long-axis specialization, yet in general, this segmentation is defined by their location relative to the uncus apex on the longitudinal hippocampal axis. [3]

## **2.2 Connectivity**

Regions in MTL cortex inputs and receive outputs from the hippocampus. With the help of high-resolution MRI, we are now able to identify each sub-region in MTL. [4] These MTL cortex regions include: entorhinal cortex (ERC), perirhinal cortex (PRC), and parahippocampal cortex (PHC).

In the MTL cortex, PRC receives most of its input from the unimodal visual association areas in ventral temporal cortex and information from PHC. The PHC receives input from unimodal association areas such as visual, auditory and somatosensory information, and there are also prominent connections with polymodal association areas. [4] [5] [6] The lateral and medial ERC receives its afferent from PRC and PHC, respectively. Then the perforant pathway connects ERC and the hippocampus. The perforant pathway is composed of two distinct paths, both of which are originated from ERC: one terminating in CA3 and DG subfields, and another terminating in the CA1 and subiculum subfields. DG projects the received signals to CA3 via the mossy fiber pathway. The CA3 subfield has three major sources of input: the mossy fiber pathway and one of the perforant pathway mentioned above, and a recurrent collateral pathway transmitting information from CA3 itself.

Further along the circuit, CA3 provides major input to CA1 subfield through the Schaffer collateral pathway. CA1 then sends the processed information to the subiculum, which is the primary output structure in the hippocampus. The output thus back projects from the hippocampus to ERC. The ERC - DG - CA3 - CA1 circuitry is called the trisynaptic circuit.

## **3. Proposed systems regarding localization of hippocampus functions**

In hippocampal studies, even though they might have different criteria while dividing, studies usually anatomically divide the hippocampus into the anterior hippocampus (aHPC) and posterior hippocampus (pHPC). The two parts are claimed to be serving different functions, with the aHPC (ventral or temporal hippocampus in animal studies) primarily accountable for modulating emotional and affective processes, and pHPC (dorsal or septal hippocampus in animal studies) primarily involved in spatial memory and cognition functions. Furthermore, a detailed gene expression study supported the segregation of major hippocampal subfields (CA1, CA3, and DG) into dorsal, intermediate, and ventral zones. Each zone, according to the study, has distinct connectivity patterns from another. These genetic data support the division of aHPC and pHPC. However, as the trisynaptic circuit are preserved in both the anterior and posterior part, the similarity between the two segments should not be overlooked. [7]

Based on several proposals for distinction of functions, aHPC is more predominant in motivational processing, detection for violation of expectations, encoding of episodic memory, vestibular processing, global spatial representation, and schematic gist; while the pHPC is more predominant in retrieval of episodic memory, spatial memory, visual processing, local spatial details, and detailed contextual information. [8]

### **3.1 AT (anterior temporal) /PM (posterior medial) model**

Based on the anatomical and functional differences, Ranganath 2012 divided PRC and PHC into two cortical systems separately. One of the anatomical differences is that the PRC connects primarily to the anterior hippocampus, while the PHC has predominant connections with the posterior hippocampal formation. Moreover, lesion data show that PRC is crucial for familiarity-based item recognition and that it plays a role in learning association between objects, about the affective and motivational significance of objects. Evidence also shows that PRC is important for semantic discriminations and object perception and that PRC might have a crucial role in associating features

across sensory modalities. PHC, on the other hand, is important in episodic memory. Anatomically connected to the default network, the PHC helps to form successful memory under the context. PHC also show importance in spatial memory, scene perception, and spatial navigation. Specifically, place cells in PHC have larger receptive fields and are more sensitive to environmental cue changes than those in the hippocampus. [6]

Due to the differences listed above, Ranganath 2012 proposed two cortical systems for memory-guided behaviors[6]. One of the systems is the anterior temporal system (AT), which is composed of PRC, amygdala, temporopolar, and orbitofrontal cortex. The author proposed that the AT system is essential for semantic and emotional memory, familiarity, and concepts about persons and objects. Another system is the posterior medial system (PM), which is composed of anterior thalamic nuclei, mammillary bodies, and the default network. This system is speculated to be crucial to episodic memory, recollection, and scene perceptions. They also speculated that the hippocampus has a role in modulating activation dynamics within the neocortex in two ways. One of the ways is “sharpening”: the refinement and elaboration representations are coming from direct interactions between the PRC and the PHC and different sectors of the hippocampal formation. More specifically, interactions between the PRC and anterior hippocampal formation (CA1 and subiculum) could be associated with a sharpening of entity representations, whereas interactions between the PHC and posterior hippocampal formation (CA1 and subiculum) could be associated with a sharpening of context representations. Another role of the hippocampus, according to their proposal, is integration, which means the hippocampal formation facilitates the ability to link between representations of entities in the PRC and representations of context in the PHC. This ability was depending on the eventual convergence of the information from the PRC ad PHC to the dentate gyrus and CA3 subfields of the hippocampus.

### **3.2 Computational model for pattern separation and pattern completion**

The ability to discriminate similar experience, called pattern separation, and the opposite process, called pattern completion, which make already overlapping representations even more overlapping, are crucial features of episodic memory. [9]

In order to study pattern separation, researchers often use a paradigm called Mnemonic Similarity Task (MST). The goal of developing the task is to get a measure of pattern separation using behavioral methods. To fulfill the task, participants need to attend two phases. The first phase of the task is a study session, presenting lots of pictures of everyday items, and participants need to categorize the items as either “indoor” or “outdoor”. In the second phase of the task, more pictures would be shown, with one-third of them being previously seen items (targets), one-third being similar items to previous ones (lures), and the remaining being new items (foils). The lures are usually categorized into several lure bins, divided by their mnemonical similarity to the targets. The participants need to respond whether the item shown is “old”, “similar” or “new”. The response time and correctness of each trial would be recorded. Behavioral pattern separation performance (BPS score) was calculated using the difference between the rate of “similar” responses given to lures divided by “similar” responses given to the foils. The BPS is then used as an indicator of the ability of pattern separation. [10]

A related version of MST uses a similar design while with the help of fMRI to record neuroactivities. Research has shown that CA3 and DG, instead of other sub-regions in the hippocampus, are responsible for pattern separation. [11] Using functional imaging and data from lesion studies, Yassa 2011 was able to derive the conclusion that DG is necessary for pattern separation and CA3 is necessary for pattern completion.

### **3.3 Gradient model of hippocampal long axis specialization**

Even though hippocampal subfields expand along the longitudinal axis of the hippocampus, the proportion if each subfield along the axis is not even. A lower proportion of DG (~25%) and a higher proportion of CA1-3(~50%) were found in aHPC, while a higher proportion of DG (~38%) and a lower proportion of CA1-3 (~40%) are found in the pHPC. (Malykhin, Lebel, Coupland,

Wilman, & Carter, 2010) The computational model proposes that DG is necessary for pattern separation, and CA3 is necessary for pattern completion. Therefore, because of the low DG to CA ratio in aHPC and the high ratio in pHPC, the anterior and posterior parts of the hippocampus are likely to bias toward pattern completion and pattern separation, respectively. This difference thus might contribute to the low match specificity (corresponding to pattern completion) in aHPC and the high match specificity (corresponding to pattern separation) in pHPC. In rodent studies, the finding of a dorsal-to-ventral gradient (posterior to anterior in human) of increasing receptive field sizes supports the account. This account also concords with the connectivity to ERC, which is composed of grid cells with a corresponding gradient pattern of receptive fields. These features could contribute to the diverse aHPC and pHPC functions: the aHPC codes information in terms of global spatial relations regardless of its form or origin; the pHPC codes information in terms of precise positions. [3]

#### **4. Bridging the hippocampal models**

Even though the different models seem to be different steps for memory, it is possible to unify those speculations. For the AT (anterior temporal) / PM (posterior medial) model and the computational model, the function of pattern completion is roughly contained in that of the AT system, and so do pattern separation and the PM system. These relationships might indicate that there are underlying connections between these mechanisms.

In the cortical regions of the hippocampal circuit, the information is sent in parallel pathways from PRC to lateral ERC and from PHC to medial ERC. The input from ERC converges to DG and CA3, which might distinguish the function of these hippocampal subfields from cortical regions. DG and CA3 might function as a place to combine inputs from PRC and PHC, playing a domain-general role in episodic memory. [4] In the AT/PM model, the role of the hippocampus was also speculated by the author. One of the proposed functions was that the hippocampal formation facilitates the ability to link between information from PRC and PHC, which accords with the previous speculation. [6] The sharpening was more correlated with CA1 and subiculum, no matter anterior or posterior, and integration was more correlated with DG and CA3. The AT/PM model emphasizes more on how PHC and PRC correlated with other neocortex and process information as a network, with the hippocampus functioning as a hub in the model. In this model, the function of the anterior hippocampus is mainly dealing with entity representations, and the posterior hippocampus was responsible for the context representations. For the subregions, the model speculated that CA1 and subiculum are mainly responsible for sharpening the information, but the DG and CA3 are more responsible for the integration of information. However, this view is not supported by direct evidence. In fact, the computational model of the hippocampus put forward a clearer, more elaborated and more solid theory about the specific function of the subregions in the hippocampus.

As previously mentioned, the computational model concluded that DG is necessary for pattern separation, which further induces that DG is more responsible for “sharpening” and CA3 is necessary for pattern completion. Moreover, in the gradient model, aHPC contains more CA areas, and are more responsible for low match specificity. Meanwhile, pHPC contains more DG areas, and are more responsible for making the high matched representation more distinct. Therefore, anterior and posterior hippocampus are proposed to have different functions, with anterior hippocampus specializing in global and general information, while posterior hippocampus specializing in local and detail information. [8]

These theories might confirm each other, because the entity representations in the AT/PM model, the global information processing in the gradient model and the pattern completion in the computational model, to some extent, may all express the same meaning, which is correlated with the anterior hippocampus. Similarly, the context representation, the detail information processing, and the pattern separation might also mean the same thing, which is correlated with the posterior hippocampus. Even so, there is still contradictory within these theories. The AT/PM model, for instance, has more emphasis on the different kinds of information the anterior and posterior

hippocampus are dealing with; meanwhile, the computational model and the gradient model focus more on the different forms of processing while handling information in the hippocampus. Moreover, AT/PM model supported that DG is responsible for the integration, while the other two models tend to consider DG as being responsible for highlighting detail information. At this point, no confirmative conclusion regarding unifying the proposed models can be drawn without further empirical data. To integrate those models, more researches are needed to resolve the above contradictions.

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