

Spatial responses, immediate experience, and memory in the monkey hippocampus

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Debate about the function of the hippocampus often pits theories advocating for spatial mapping against those that argue for a central role in memory. This review addresses whether research in the monkey supports the view that processing spatial information is fundamental to the function of the hippocampus. In support of spatial processing theories, neurons in the monkey hippocampal formation have striking spatial tuning, and an intact hippocampus is necessary to effectively utilize allocentric spatial relationships. However, the hippocampus also supports non-spatial processes, as its neurons acutely respond to distinct task events and hippocampal damage disrupts both expedient task acquisition and the monitoring of ongoing events in non-spatial paradigms. The features that are shared between spatial and non-spatial hippocampal-dependent tasks point toward a common mechanism underlying hippocampal function that is independent of processing spatial information. We suggest that spatial information is only one facet of immediate experience represented by the hippocampus. The current data support the idea that the hippocampus tracks many aspects of ongoing experience and the primary role of the hippocampus may be in linking experienced events into unitary episodes.

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Introduction

The function of the hippocampus is a topic of spirited debate, and recent studies in non-human primates offer insight into this ongoing controversy. Theories of hippocampal function have been primarily informed by behavioral impairments following hippocampal lesions as well as electrophysiological characterization of its neural activity, but results from these two approaches often yield

divergent interpretations that are difficult to reconcile. One view is rooted in the tradition of human neuropsychology, casting the hippocampus as the critical mediator of memory — especially autobiographical, conscious recollection [1,2]. In contrast, rodent physiology research has led to a prominent interest in spatial processing and navigation, owing to the remarkable specificity of place and grid cells that fire in discrete locations as the animal moves through an environment [3,4]. These striking patterns of activity bring to light how robustly immediate experience is represented in the hippocampus, and necessitate that a complete description of hippocampal function must account for the instantaneous activity that is present as the animal interacts with the environment. The spatial processing theories of the hippocampus offer an intuitive interpretation of this ongoing activity, and consequently they have increasingly gained traction across all species in recent years [5–10]. In this article, we summarize the behavioral and electrophysiological evidence for spatial processing within the monkey hippocampus, and we explore the commonalities of findings in spatial and non-spatial tasks. In the course of this review, we will evaluate the hypothesis that processing spatial information is a fundamental constituent of hippocampal function. We will also consider an alternative hypothesis that spatial information is a non-essential contributor to a broader hippocampal function, that of linking experienced events into a unitary structure.

Hippocampal dependence in spatial tasks

To assess whether processing spatial information is an essential component of hippocampal function in the monkey, it is informative to evaluate the deficits seen in spatial tasks after lesions of the hippocampus. Though hippocampal involvement in navigation or path integration has not been explicitly tested, some studies suggest the monkey hippocampus is important for other forms of spatial cognition. Monkeys with lesions of the hippocampus show deficits in returning to the location of a hidden reward within a large open room, especially when there is a delay after sampling the target [11]. This deficit principally manifests when the target is only identifiable by its position relative to distal landmarks and the monkey approaches the arena from different entry points [12]. Along similar lines, damage to the monkey hippocampus also interferes with the ability to recognize an array of familiar objects in an unfamiliar spatial arrangement after a long delay has elapsed [13,14]. More recently, transient inactivation of the anterior hippocampus was shown to impair the ability to keep an ongoing record of which

locations had been sampled from an array of boxes. Importantly, short delays do not interfere with the ability of the monkey to efficiently self-order responses, but long delays reveal a significant impairment [15^{*}]. Similar results have been observed when monkeys with hippocampal lesions are required to monitor the accumulation of spatial targets in the delayed-recognition-span task [16]; but see [17]. Together the evidence from these studies suggests that the hippocampus may be important for recognizing the relative positions of objects, especially after delays. However, it is critical to note that these studies mark the few examples of hippocampal-dependent spatial cognition. Importantly, processing positional information alone does not seem to rely on the hippocampus [14,18–20] particularly when it can be egocentrically defined from the perspective of the stationary monkey [21]. Instead, the hippocampus seems to be required when spatial relationships between objects in allocentric space must be formed, and when spatially distinct objects must be linked across time. Though the hippocampus is not necessary for all aspects of spatial cognition, the studies summarized here suggest that the hippocampus is important for (1) forming allocentric spatial relationships, (2) bridging spatial information across a delay period, and/or (3) accumulating a history of spatial relationships.

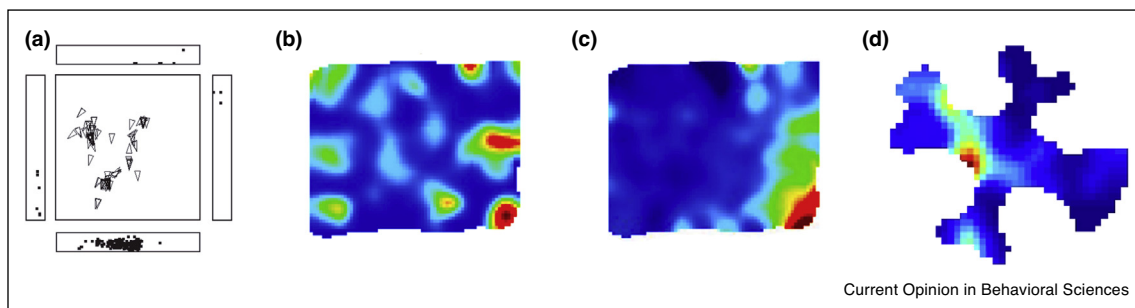
Spatial activity in neurons of the hippocampal formation

Further insight into the role of the monkey hippocampus in spatial cognition comes from electrophysiological studies, which offer an important comparison to the rodent literature [5,8]. Just as rodent neurons instantaneously respond as the animal moves through space, monkey hippocampal neurons change their activity as the animal explores the environment. However unlike rodent place

cells that respond when the animal enters a specific position in the room [3], monkey hippocampal neurons fire when monkeys *look at* a particular location. These *spatial view cells* respond irrespective of the orientation of the monkey's body or position within a room as long the preferred location is in view (Figure 1a). The mapping of spatial view cells is sustained even after multiple seconds in the dark [22] or occlusion of the items viewed [23], indicating that the neurons are not directly driven by visual features of a foveated object. Furthermore, the allocentric specificity of spatial view cells can be relative either to distal landmarks [24–26], or to a locally defined subset of space, for example the position of the gaze on a computer monitor irrespective of the monitor's position in the room [27]. Thus, the activity characterizing spatial view cells demonstrates that the monkey hippocampus has access to robust spatial information, and can track spatial relationships as the animal explores meaningful portions of the environment.

Research within our laboratory confirms the availability of spatial information to the primate hippocampus in its direct afferent, the entorhinal cortex. In this structure, we have identified spatially selective neurons that are active as monkeys freely view pictures: *grid cells* that fire in a repeating hexagonal pattern that spans the space (Figure 1b), and *border cells* that fire along a vector parallel to an environmental boundary (Figure 1c) [28^{**}]. These spatially selective neurons are notably different from their counterparts in the rat which respond as the animal translocates through space [4,29]; instead the spiking we observe is anchored to viewed locations and manifests as the gaze of the monkey moves over the monitor. In more recent research, we have elaborated our description of spatially selective neurons in the entorhinal cortex to

Figure 1



Spatially tuned neurons in the monkey hippocampal formation. (a) Spatial view cell in the hippocampus which responds when looking at a particular location in the environment. For each time this neuron fired, a triangle indicates the location of the monkey and a dot on the wall indicates the visual position of the gaze (modified with permission from Georges Francois et al., 1999). (b) Visual grid cell in the entorhinal cortex that fires in a hexagonal pattern that spans the field of view. (c) Visual border cell in the entorhinal cortex that responds in viewed locations that are parallel to an environmental boundary. (b,c) Reproduced with permission from Killian et al., 2012). (d) Allocentric 'place cell'-like neuron in the hippocampus that fires when the monkey occupies a particular location during virtual navigation (modified with permission from Furuya et al., 2014). Colors range from blue to red to indicate low to high firing rates at each location in the field of view (b,c) or location in the virtual environment (d).

include cells with irregular, but reliable, spatial fields. We find that the spatial tuning of grid cells and non-grid cells can be locked to different reference frames in a manner similar to spatial view cells [27], being anchored either to the subregion of the screen where the image appears or to the broader allocentric space defined by landmarks within the room [30]. Together, the neural activity within the hippocampus and entorhinal cortex seems to utilize an elaborate spatial organization, which may be essential for binding discontinuous visual percepts into a mosaic of objects within a three-dimensional world.

Glimpses of the mechanisms that provide spatial structure may be seen in the entorhinal activity that is modulated by the path of saccadic eye movements. As a monkey scans a visual scene, a subset of entorhinal neurons fire in a directionally specific manner either just before or just after the gaze moves from one part of the screen to the next [31^{**}], registering either where the gaze was or where it is going. Considered in the aggregate, the entorhinal population is capable of continuously tracking the trajectories of the gaze through visual space. This suggests that the entorhinal network benefits from an accumulated history of scan paths, providing a means of spatiotemporally linking objects seen across fixations through time. Binding percepts across time into an organized structure would be key to creating a cogent representation of the experienced environment, and suggests that the entorhinal cortex may mediate the specificity of visuospatial responses in the hippocampus.

The breadth of hippocampal spatial activity also extends past the locations that are viewed to include allocentric representations based on translocation of the monkey's body through space, as is the case with rodent place cells. Recordings from head-fixed monkeys that maneuver around a room in a motorized cab have identified neurons in the hippocampus that differentially fire as the monkeys traverse space [32–34]. Similar results were obtained from freely moving squirrel monkeys foraging in a large, open cage [35]. Notably, these neurons fire more diffusely than rat place cells, so it is uncertain whether allocentric space is the best predictor of the neural activity. Experiments utilizing virtual navigation have yielded hippocampal activity with tighter correlates to allocentric location (Figure 1d) [36,37^{*}]. Changing the distance between the maze cues and the virtual arena cause these neurons to alter their firing pattern, indicating a sensitivity to the allocentric arrangement of distal landmarks. Recent work extends these findings by demonstrating that the position of the monkey and the location of the gaze conjunctively drive the activity of individual hippocampal neurons [38^{**}]. In addition, the authors show that neurons that respond to specific landmarks are also contingent on current position, and that encountering upcoming landmarks can be anticipated in the hippocampal activity. Although a true counterpart to the rodent place cell has

yet to be found in the monkey, it is nonetheless apparent that neurons within the hippocampus have enough information to disambiguate between the monkey's locations within an environment.

The function of the hippocampus outside the spatial domain

In considering the impressive breadth of spatial responses manifest in the monkey hippocampus, it is clear that the hippocampal network continuously tracks location information as the animal explores the environment. However, the mere presence of spatial responses does not confirm that hippocampal activity is dominated by spatial processing. Indeed, the most recent virtual reality work demonstrates that space alone is not a sufficient predictor of hippocampal activity [38^{**}]. Instead, hippocampal neurons conjunctively code immediate experience based on the present position of the animal and the expectation of encountering a targeted object — revealing that the monkey hippocampus is processing multiple types of information in relation to the task at hand.

The prominence of task-relevant responses has been consistently shown in paradigms that do not involve spatial exploration. In these experiments, hippocampal neurons acutely respond to the distinct events in cued response tasks, despite the monkey being situated in a fixed location in front of a monitor. Neurons that respond during the cues differentiate their activity based on the cue identity [39–42] or the associated response to the cue [39,42–44] indicating that the hippocampus registers non-spatial events as they occur and the neural response is also contingent on the rules of the task. More recently, it has been shown that cue-specific activity can span the delay period before a response, creating a bridge between the events of the task [45,46]. These task-specific responses develop around the time that the animal learns the contingencies of the experimental paradigm [43,47,48], suggesting that the activity of hippocampal neurons may be the direct result of abstracting conditional relationships across task events. In this way, the hippocampal network may be extracting a schematic representation of the task [49], incrementally building a circuit that recognizes the progression of upcoming events. This interpretation of the neural activity is supported by the finding that hippocampal lesions disrupt performance in paradigms that require the monkey to maintain an ongoing record of recent responses [15^{*},16,50^{*}]. Furthermore, linking events through hippocampal circuitry is congruent with the consistent finding that hippocampal lesions greatly impede the acquisition of new tasks [16,19,50^{*},51,52], and suggests that learning new tasks may be mediated by sculpting the hippocampus to track ongoing events. It is notable that the features of non-navigational hippocampal-dependent tasks, i.e. (1) forming task relationships, (2) bridging task delays, and (3) accumulating a history of task events, are also the critical

features of hippocampal-dependent spatial tasks. This suggests there is nothing exceptionally important about the modality of space, and that the more generalized function of the hippocampus may be to impart structure that shapes an ongoing record of experience.

Conclusion

The research reviewed here illustrates that the hippocampus prominently exhibits activity reflecting the immediate experiences of the animal. This phenomenon has been robustly captured in the spatial domain within monkey hippocampal neurons, just as it has been often demonstrated in rodents. The exquisite spatial resolution of positional information is certainly remarkable, and undoubtedly motivates the rich interest in spatial processing theories of the hippocampus. However, the hippocampus is not limited to a specific modality of information, because other task features also elicit clear neural responses. Instead, spatial information seems to be just one of many features utilized by the hippocampus to disambiguate the events experienced by the animal. By registering each event as it occurs, the hippocampal network continuously tracks the progression of events within an experience. This interpretation of the ongoing neural activity complements research showing that hippocampal lesions impair the ability to monitor recent choices [15^o,16,50^o] and to track events across time [11,13,14,20].

By highlighting the importance of representing immediate experience with ongoing activity, we gain insight into the means by which the hippocampus may support memory. As described above, neurons within the hippocampus can sustain task-contingent activity across different events and delay periods. While individual hippocampal neurons are only transiently active, the population in the aggregate collectively spans task events. By tracking the elements of experience with a continuous sequence of activity, the hippocampus is positioned to link the passing events into a unitary entity — creating an episode from individual percepts. In this way, the hippocampus may be critical for linking events as they initially occur, and would therefore be a prerequisite for the memory of an episode to be formed. Without the hippocampus tracking passing events, the animal would be unable to form traces of recent experiences, displaying anterograde amnesia — a hallmark of hippocampal dysfunction. In this light, the sequential activity of the hippocampus mediates a continuous record of experience, which monitors the progression of important events that can later be remembered as continuous episodes.

Conflict of interest statement

Nothing declared.

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