

## NEWS & VIEWS

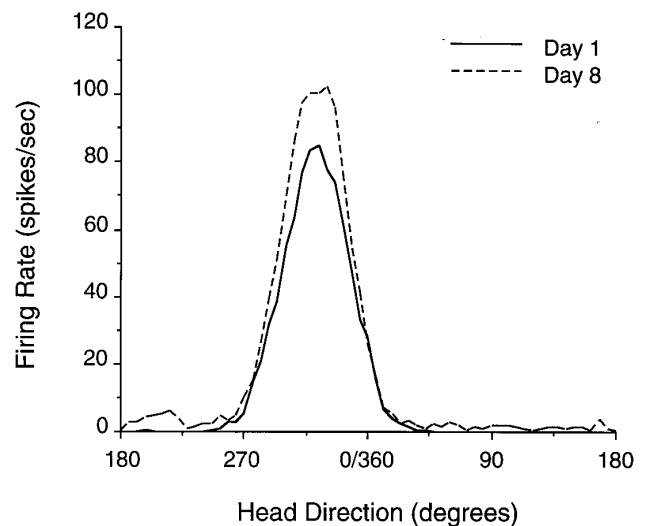
# Computational functions of the hippocampus: does it encode all episodic memories?

**Recent neurophysiological results in animals with hippocampal lesions challenge the notion that the hippocampus is required for encoding all forms of episodic memories.**

In order to maintain accurate spatial orientation, the central nervous system must be able to transform and integrate sensory information from eye, head, and body egocentric coordinate systems into an allocentric coordinate system, so as to maintain a sense of location and direction. This ability is essential for navigation. Many investigators believe that to achieve this egocentric-allocentric transformation, both humans and animals somehow maintain a mental representation (or cognitive map) of the environment, and depend on this map when transforming and interpreting sensory cues and during navigation.<sup>1</sup>

Some of the neural circuitry involved in these processes includes the limbic system and in particular the hippocampus. Although the precise functions of the hippocampus remain unclear, there is little doubt that it is important for spatial information processing, since both animals and humans with damage to the hippocampal region are impaired on a variety of spatial and navigational tasks.<sup>1</sup> Additional evidence comes from studies in rodents showing that two types of spatial cells in the limbic system code allocentric spatial information. One type—place cells—preferentially respond when the animal is located in one *place* in the environment.<sup>2</sup> A second type—head direction (HD) cells—discharge as a function of the animal's *head direction in the horizontal plane*, independent of the animal's place or behavior.<sup>3</sup> This article discusses some of our recent findings concerning HD cells and the hippocampus.

We have quantified the properties of HD cells using an overhead video-based head tracking system to monitor the rat's directional heading.<sup>3</sup> The maximum firing rate of individual cells lies in a fixed direction (preferred direction) and varies from cell to cell. The range of firing is typically about 90°, and decreases away from the preferred direction as shown in Figure 1. Responses are independent of: (1) pitch or roll of the head up to 90°; (2) head location (place); (3) direction of movement; or (4) trunk position relative



**Figure 1** HD cell in the ADN from a hippocampal lesioned animal recorded 8 days apart in a novel environment. The cell's preferred direction was identical in the two recording sessions.

to the head. Response characteristics usually remain stable across weeks, as long as the environmental parameters remain unchanged. HD cell firing is largely movement independent; cells discharge whether the rat is moving or remains still, as long as the animal is pointing its head in the proper direction. Little, if any, adaptation of firing rate is present when the head remains fixed at the preferred direction.

In contrast to place cells which are found in the hippocampus, HD cells were initially identified in the dorsal presubiculum (postsubiculum, PoS),<sup>3</sup> and have since been reported in several brain areas—many of which are in the classical Papez circuit. These areas include the anterior dorsal thalamic nucleus (ADN),<sup>4</sup> lateral mammillary nuclei,<sup>5</sup> retrosplenial cortex,<sup>6</sup> lateral dorsal thalamic nucleus,<sup>7</sup> and the anterodorsal striatum.<sup>8</sup> Many of these areas are anatomically interconnected with one another, and one of the important issues in our field is how the brain generates this directional heading representation. While there are neurons

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in other brain areas that discharge with respect to certain spatial dimensions, the neuronal correlates are based on an egocentric reference frame. Thus, a major coordinate transformation is required to obtain a directional signal based on an allocentric reference frame. It is currently not known how or where in the brain this coordinate transformation occurs.

Given that the PoS receives a major projection from the subiculum, the primary output target of the hippocampus, and that the hippocampus appears important for normal spatial learning, it was possible that the hippocampus in general, or place cells in particular, influenced or contributed to the HD cell signal, either through its spatial processing or mnemonic functions. We were thus interested in how HD cells would function in an animal without a hippocampus. After neurotoxically lesioning the hippocampus bilaterally, we found that HD cells in the PoS and ADN maintained their normal stable firing properties, indicating that the HD cell signal must be generated by structures external to the hippocampus.<sup>9</sup> Interestingly, recent lesion studies have indicated that the ADN, but not the lateral dorsal thalamus, is critical for the directional sensitivity of PoS HD cells.<sup>10,11</sup>

How else could the hippocampus influence HD cell activity? To examine this issue, it is first important to understand how sensory and motor systems affect HD cell discharge. Several studies have shown that HD cells receive multisensory convergence from different sensory and motor systems. For example, the preferred direction of HD cells was maintained when the animal moved about, even in darkness, but was simultaneously rotated about an earth vertical axis by rotation of surrounding visual landmarks.<sup>12</sup> Repositioning a large white cue card mounted on the wall of a cylindrical test chamber by 90, 180, or 270° around the animal produced a corresponding shift in a cell's preferred direction. However, removing the cue card and then returning the animal to the cylinder did not lead to cessation in firing, but only an unpredictable shift in the preferred direction. These results indicate that salient visual cues can exert control over the HD cell's preferred firing direction. They also suggest that HD cell firing is *not* simply a sensory response to a visual cue, but rather represents more abstract information concerning the animal's directional heading. Furthermore, this representation must, in part, be based on idiothetic information (vestibular, proprioceptive, motor efference copy cues) since, without an orienting landmark, the only ongoing indication of directional heading is presumably based on the animal's own angular and linear motion. On occasions when multiple HD cells were monitored simultaneously, the effects of an environmental manipulation on one cell's preferred direction were similar to the effects observed in the second cell. This finding indicates that afferent input driving one HD cell similarly influences other HD cells, and suggests that HD cells within a particular brain area behave as a network, with their preferred directions always remaining a fixed angle apart from one other. Importantly, we

have recently shown that lesions of the PoS,<sup>11</sup> but not the hippocampus,<sup>9</sup> can disrupt the ability of the cue card to exert control over a HD cell's preferred direction.

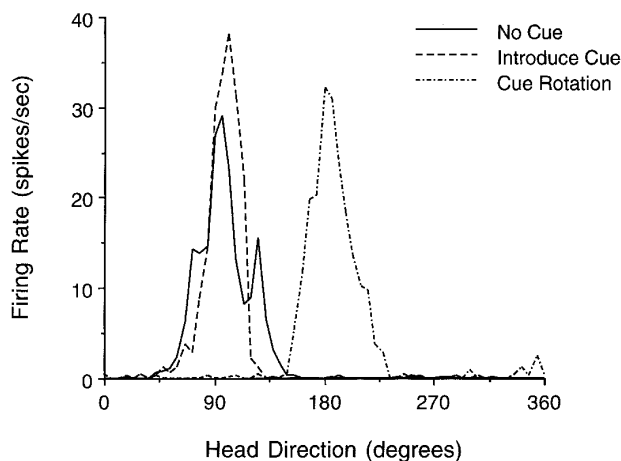
If the animal was restrained and passively rotated, HD cell firing either ceased or was attenuated, even when the animal's head was in the preferred direction.<sup>4,10</sup> HD cells in the ADN, but not PoS, actually anticipate the animal's future directional heading by about 25 msec.<sup>13</sup> These findings suggest that HD cells receive motor outflow information. Lesions of the hippocampus did not effect the anticipatory quality of the ADN directional signal. It is also clear that HD cells require vestibular input, as neurotoxic lesions of the vestibular apparatus abolish the directional firing properties of ADN HD cells.<sup>14</sup> This disruption was quite evident despite the continued presence of all the visual cues within the room. These data suggest that the neural code for directional bearing is critically dependent upon vestibular information and that the loss of HD cell information may account for the orientation and navigational deficits observed following vestibular dysfunction.<sup>15</sup> Recent studies in our lab have also demonstrated that hippocampal place cell firing is disrupted following inactivation of the vestibular apparatus.<sup>16</sup>

In addition to landmarks, animals also rely upon path integration for navigation.<sup>17</sup> Path integration is defined as the process whereby an animal's orientation and location are updated continuously based on how fast, how long, and in what direction it is moving through the environment. Several component processes are thought to be involved in path integration. First, the animal must define a reference point and its orientation to it. The reference point can be the animal's place of origin or some other point in the environment. Furthermore, the animal must remain cognizant of its reference point and store this information 'on-line' in a working memory fashion. Second, the animal must continually keep track of its angular and linear movements through space. This process can be accomplished by monitoring its idiothetic cues and possibly optic flow. Third, a computational process must be performed whereby the animal computes its current position (including both location and direction) from its previous position and its subsequent movements.

In order to understand how animals use HD cells for navigation, we have monitored HD cell activity as an animal enters a novel environment. For cell firing to continue in the same preferred direction when the animal moves into a novel environment, the animal must use path integration and rely on idiothetic cues, since there are no familiar azimuth cues for orientation. We found that when animals locomoted into the novel environment, HD cells continued to discharge in a similar direction as they did in the familiar environment.<sup>18</sup> In contrast, cells from animals with hippocampal lesions did *not* maintain the same preferred direction,<sup>19</sup> suggesting that the hippocampus (or possibly the overlying damaged cortex) is essential for at least

one of the component processes involved in path integration. It will be important for future experiments to identify which of the component processes the hippocampus is critical for.

The more traditional view of hippocampal function posits that the hippocampus is important for encoding episodic (declarative) memory.<sup>20</sup> According to this view, both humans and animals with hippocampal lesions are impaired at performing tasks which require them to recall information concerning the learned relationships amongst items across time and space. Fear-conditioning experiments in animals have shown that hippocampal lesions specifically abolish fear to the contextual aspects of the environment without interfering with fear displayed to a single sensory cue (a tone).<sup>21</sup> These results demonstrate that the hippocampus is particularly important in encoding the contextual aspects of a task. One of the primary components of context is the spatial features of the environment—for example, a room's spatial configuration, where salient stimuli are located, or how an animal is oriented with respect to that environment. This type of material can be considered spatial episodic information because it involves the formation of associations among various items in the environment. These associations not only define the shape of an environment, but also enable one to determine their orientation with respect to those stimuli. Additionally, most episodic memories contain a spatial element to them—such as where I was and how I was oriented when a particular incident occurred, or that my keys were located next to the umbrella. Finally, the encoding of



**Figure 2** HD cell responses to a novel cue. This hippocampal lesioned animal was initially trained and recorded without the cue card (No Cue). Introducing the cue card for 8 min did not change the cell's preferred direction (Introduce Cue). After a delay of 4 h, the animal was brought back into the environment with the cue card in a 90° rotated position. Under these conditions, the cell's preferred direction shifted a similar amount (84°) (Cue Rotation). Returning the cue to its original position reinstated the cell's initial preferred direction (data not shown). These results show that the hippocampus is not required for a novel cue to gain control over a cell's preferred direction.

new information, particularly of an episodic nature, has been shown to activate the hippocampus in a PET study.<sup>22</sup>

Given these considerations, one would expect that animals without a hippocampus would have difficulty recalling their spatial experiences in an environment if their only experiences in that environment were after they were lesioned. For this reason we were surprised to find that the preferred directions of our HD cells recorded from hippocampal-lesioned animals were stable across days in a novel environment (Figure 1).<sup>9</sup> Although this stability appeared to weaken in a couple of cases over several days when the animal was not exposed to the environment during the intervening period, it initially spanned a length of time which usually results in memory impairments in animals with hippocampal lesions. This stability reflects the encoding and retrieval of new spatial information about the environment by these cells, and suggests that selective episodic information can be stored and maintained over time without a hippocampus.

To further determine whether the hippocampus is required for the storage of episodic spatial information, we directly assessed the ability of a novel cue to gain stimulus control over the HD cell's preferred direction. Animals with hippocampal lesions were trained to forage for food pellets in an apparatus without a prominent polarizing cue. When a HD cell was identified, a salient novel cue was introduced into the apparatus for 8 min, after which the animal was removed and returned to its home cage. Following a 4-h delay, the cue was rotated by 90° and the HD cell was monitored again. We found that the preferred direction of most cells shifted by an amount that corresponded with the cue's angular rotation, and that all cells shifted their preferred direction after a second set of test sessions (Figure 2). These results show that the hippocampus is *not* required for the establishment of stimulus control by a novel cue in ADN HD cells.<sup>23</sup> These findings also demonstrate that the shift in preferred direction when the lesioned animals locomote into a novel environment cannot be attributed to a general impairment in establishing stimulus control by the cues contained within the novel environment.

Taken together, our results suggest that extra-hippocampal structures are capable of creating and maintaining a novel representation of the animal's spatial context. This representation shares features in common with mnemonic processes involving episodic memory which until now were thought to require an intact hippocampus.

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