The Head Direction Signal: Origins and Sensory-Motor Integration

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The Head Direction Signal: Origins and Sensory-Motor Integration

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Key Words

directional heading, landmark, navigation, path integration, place cells, spatial orientation

Abstract

Navigation first requires accurate perception of one's spatial orientation within the environment, which consists of knowledge about location and directional heading. Cells within several limbic system areas of the mammalian brain discharge allocentrically as a function of the animal's directional heading, independent of the animal's location and ongoing behavior. These cells are referred to as head direction (HD) cells and are believed to encode the animal's perceived directional heading with respect to its environment. Although HD cells are found in several areas, the principal circuit for generating this signal originates in the dorsal tegmental nucleus and projects serially, with some reciprocal connections, to the lateral mammillary nucleus → anterodorsal thalamus → PoS, and terminates in the entorhinal cortex. HD cells receive multimodal information about landmarks and self-generated movements. Vestibular information appears critical for generating the directional signal, but motor/proprioceptive and landmark information are important for updating it.

Contents

INTRODUCTION

One basic cognitive function we often take for granted is the ability to maintain a sense of direction and location while moving about in the environment. This awareness is essential for getting around and functioning normally in the world. Indeed, spatial orientation and its related function, navigation, represent one of the most fundamental cognitive functions that mammals depend on for survival. Mammals rely on spatial cognitive functions for obtaining food and water, avoiding prey, finding mates, and for humans, finding our car in the parking lot at the end of our workday. This chapter reviews some of the neurobiological representations that underlie our abilities of successful spatial orientation and navigation, in particular, our sense of direction.

To navigate between two points successfully, an organism must first have knowledge of its spatial orientation relative to the environment before selecting a route because the planned response will depend on the organism's current spatial orientation. Perception of one's spatial orientation requires knowledge of two types of information: location and directional heading. One without the other provides limited chances of successful navigation. Both types of information are encoded by different groups of neurons within the limbic system. Neurons within the hippocampus encode primarily information about the animal's location and are referred to as place cells (O'Keefe 1976; see Best et al. 2001 and Muller 1996 for reviews). Place cells are also commonly found in the subiculum (Sharp & Green 1994) and in the entorhinal cortex (Quirk et al. 1992, Frank et al. 2000). In contrast, neurons that encode the animal's directional heading in the horizontal (or yaw) plane have been identified in structures primarily within the classic Papez circuit and are referred to as head direction (HD) cells. For example, a particular neuron might discharge whenever the animal points its head northeast, independent of the animal's location. Thus, HD cells are similar to a compass in that their discharge is always tuned to a particular direction and can fire at any location provided the animal's head is facing the correct direction. However, unlike a compass, HD cells are not dependent on the Earth's geomagnetic field. (To view a video of a typical HD cell, follow the Supplemental Material link from the Annual Reviews home page at **http://www.annualreviews.org.**) Cells that share characteristics of encoding both place and head direction have been reported in the presubicular and parasubicular cortices (Cacucci et al. 2004). Finally, recent studies have identified a third type of spatial correlate that may prove useful for determining distance and tracking an animal's route over time. These cells are referred to as grid cells and were found in the dorsocaudal medial entorhinal cortex (Hafting et al. 2005, Sargolini et al. 2006). Grid cells discharge at multiple locations within an environment, and these locations form a regular, repeating pattern, or grid, across the entire environment. This information is intriguing particularly because the entorhinal area receives directional information from the dorsal presubiculum and projects via the perforant pathway to the

Papez circuit: connects the Mammillary nuclei → anterior thalamus → cingulate cortex → hippocampus → mammillary nuclei

HD: head direction

Grid cell: neuron that fires at multiple locations in an environment; locations of high activity form a repeating hexagonal grid-like pattern

hippocampus. It also receives feedback information from the hippocampus primarily via the subiculum. Thus, it is ideally situated to integrate both location and direction information.

This chapter focuses on HD cells. It reviews how the directional signal is generated and presents the major types of information that affect its activity. Two fundamental issues need to be differentiated: (*a*) which types of information are important for generating the directional signal, and (*b*) which cues and brain areas control the signal's preferred orientation? Other recent reviews on HD cells have focused on specific aspects of their activity: relation to behavior (Muir & Taube 2002b), computational properties (Sharp et al. 2001a), persistent activity (Taube & Bassett 2003), and sensory properties (Wiener et al. 2002). The reader should refer to Wiener & Taube (2005) for a comprehensive review of HD cells and the neural mechanisms underlying spatial orientation.

The first section of this chapter describes the general properties of HD cells, including how they respond when the animal locomotes in planes other than Earth horizontal (azimuth), in particular, when the animal is locomoting in the vertical plane or is upside-down. The second section discusses how the preferred firing direction is controlled by different types of landmark cues. The third section reviews the brain areas where HD cells have been identified and lesion experiments that have been conducted to elucidate the signal's origin. The next section reviews the types of information that are integral for generating the directional signal and maintaining its stability over time and movement. In particular, a major distinction is drawn between the mechanisms and types of cues involved in generating the directional signal and the mechanisms and types of cues responsible for controlling the signal's preferred firing direction. In essence, the directional signal is likely derived from the integration of vestibular information, whereas motor and proprioceptive information also play an important role in updating the signal over time during movement. The preferred firing direction can also be updated by landmark cues. The review concludes by discussing where landmark and path integration circuits are located in the brain and where these two information types may converge and be integrated together.

Path integration: the ability to update one's location and directional orientation by monitoring idiothetic cues

Allocentric: use of the external world as the reference frame

GENERAL PROPERTIES

The general properties of HD cells were first described by Taube et al. (1990a,b). Each HD cell can be characterized by a number of parameters on the basis of its tuning curve, which is often plotted on an x-y graph, with firing rate represented on the ordinate axis and the animal's head direction represented on the abscissa (**Figure 1*a***), although HD cells are sometimes depicted using polar plots (e.g., Knierim et al. 1995). Using an x-y graph, each HD cell can be characterized by a number of parameters based on its tuning curve, which are generally triangular or Gaussian in shape (Blair & Sharp 1995, Taube 1995). Each HD cell is tuned to a single allocentric head orientation, and all directional headings are equally represented within a population of HD cells. The direction at which the cell fires maximally is referred to as the cell's preferred firing direction. Each HD cell's firing rate is at or near zero when the animal's head is not pointing in the cell's preferred firing direction, and then it increases approximately linearly as the animal moves its head into the proper orientation. The range of head directions in which the firing rate is above the cell's baseline firing rate is referred to as the cell's directional firing range and averages ~90° for most cells, although it can vary from 60° up to ~150° across cells. The maximal firing rate of the cell at its preferred firing direction is referred to as the peak firing rate. Peak firing rates vary across different HD cells and range from about 5 spikes/s to >120 spikes/s. The determinants of a cell's peak firing rate and the role served by having cells with different characteristic peak firing rates are not known. A recent preliminary study showed that interspike

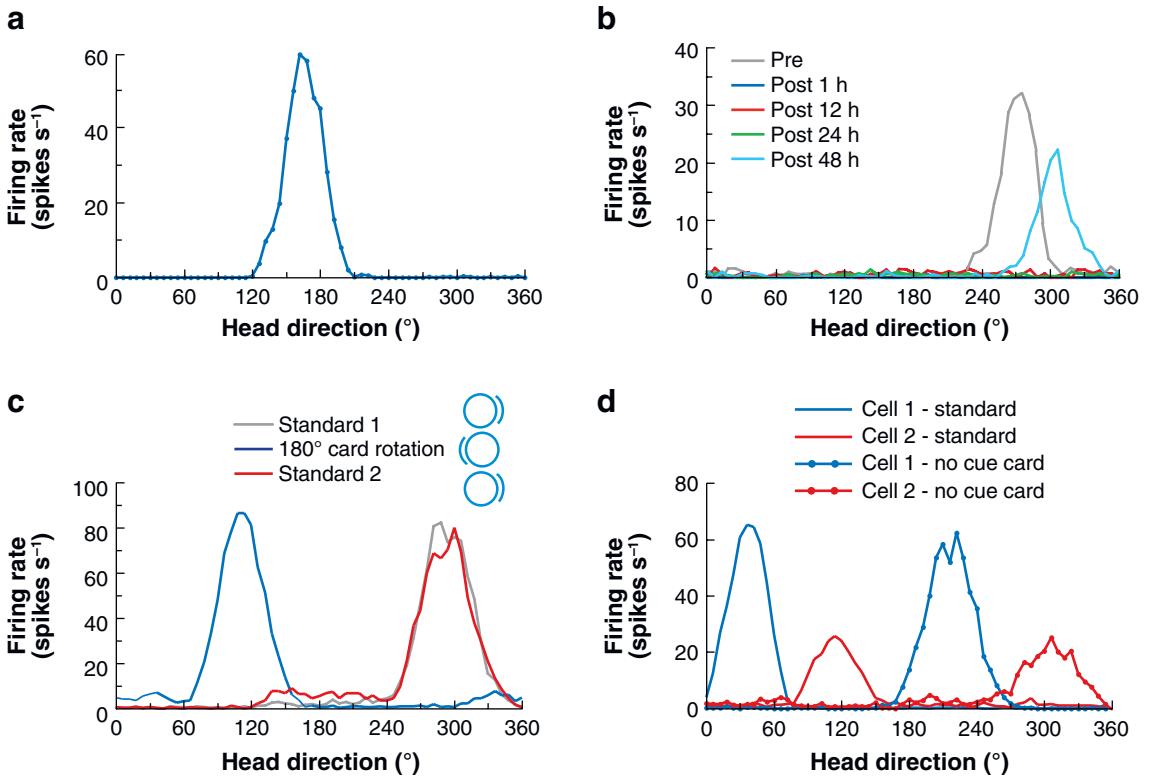

Figure 1

(*a*) Firing rate versus head direction plot for a typical HD cell. Firing rates are shown plotted in 6° bins. (*b*) Responses of an ADN HD cell to TTX. Direction-specific firing was disrupted for 24 h, and when it returned, the preferred firing direction shifted ~30°. (*c*) Responses of an ADN HD cell following an 180° rotation of the visual cue card. The preferred firing direction of the cell shifted a similar amount as the cue rotation (*blue line*) and returned to its original orientation when the cue card was returned to its initial position (*red line*). Initial recording session is shown as gray line. (*d*) Responses of two PoS HD cells recorded simultaneously following removal of the visual cue card. Both cells retained direction-specific firing in the absence of the visual cue, but their preferred firing directions shifted equal amounts and remained in register with one another.

intervals at a cell's preferred firing direction are relatively irregular even under constant environmental conditions (Taube 2004), and in this manner, resemble cortical cells in the visual cortex (Softky & Koch 1993, Shadlen & Newsome 1994).

HD cell firing is largely unaffected by pitch or roll of the animal's head within ~90° of the horizontal plane. As long as the animal's head is in a given cell's directional range, cell firing will continue whether the animal is moving or still and is largely independent of the animal's ongoing behavior. Thus, there is little adaptation of cell firing when the animal is holding its head in the cell's preferred firing direction (Taube & Muller 1998). As discussed further below, HD cells in some brain areas have a secondary correlate with angular head velocity (Taube 1995). For these cells, firing rates are slightly higher when the animal is turning its head rapidly through the cell's preferred firing direction. Nonetheless, even for these cells the firing rate remains high in the cell's preferred direction when the animal turns its head at slow rates or is motionless. Similarly, most HD cells discharge at a slightly higher

rate when the animal is moving faster (high linear speeds) than when it is motionless. For both linear and angular head velocity, firing rate increases are less than 10% of the cell's peak firing rate, and the correlation to angular velocity accounts for only ~1% of the firing rate variance. The firing properties of HD cells in the same environment remain stable across recording sessions that are many days apart.

A few studies have also examined HD cell properties when the animal is locomoting in planes other than the azimuth (Earth horizontal). Stackman et al. (2000) and Kim et al. (2003) reported that HD cells displayed "normal" direction-specific firing when locomoting in the vertical plane. In both cases, directional firing occurred in only one direction within the vertical plane; for instance, a particular cell might fire only when the animal pointed its head upward to the left independent of where it was located on the vertical surface and independent of how the head was oriented relative to its trunk. This finding is consistent with the notion that HD cells may define the horizontal reference frame as the animal's plane of locomotion. Thus, when the animal is locomoting in the vertical plane, it treats this plane as its horizontal plane, and cell firing is similar to that seen when on the ground, and firing remains sensitive to yaw head movements, but independent of head pitch, relative to the new plane of locomotion. These findings in the vertical plane were replicated in a shuttle box task that required rats to climb a vertical wall and then locomote inverted across the ceiling of the apparatus to reach an adjoining vertical wall where they descended into a reward compartment (Calton & Taube 2005). Although directional discharge was normal along the walls—either ascending or descending—it was severely degraded when the rats traversed the ceiling inverted. Directional firing was compromised on the ceiling even in rats that had been trained for months to perform this task. Why the directional signal should be abolished only when an animal is inverted is not known. This finding suggests that otolith organ input is important for normal HD cell discharge, but more work in this area is warranted to delineate the underlying mechanisms for this aberrant cell response.

To understand the types of information processed by HD cells, one should appreciate a major distinction researchers use when describing the cells' properties. Two different strategies are used by animals for navigation: landmark navigation and path integration (Gallistel 1990). Landmark navigation occurs whenever an animal derives its current position and orientation in the environment relative to surrounding landmarks. The sensory information the animal uses can be obtained from any of the sensory modalities (e.g., visual, auditory, olfactory) and are usually referred to as allothetic cues. In contrast, in path integration, the animal knows its starting position and orientation but thereafter estimates its current location and direction by integration of internally available information, such as proprioceptive and vestibular inflow and motor outflow ("efference copy"). The sensory/motor systems involved in path integration are often referred to as idiothetic cues and frequently include optic flow information because this information is also integrated continuously. The process of path integration is analogous to inertial navigation (Darwin 1873, Barlow 1964, Mittelstaedt 1983) and requires the animal to have an internal model of the normal relationship between motor outflow and sensory return; the animal should also maintain an internal cognitive map, which estimates current position and orientation. The brain is normally capable of integrating signals from vestibular/motor (idiothetic) and visual (landmark) systems. Under most circumstances, both processes are used and integrated together simultaneously, but when information from one source of spatial cues is absent, the animal must rely on the other set of cues; thus, for example, animals rely on path integration when in unfamiliar environments where familiar external landmark cues are unavailable. Note that

Allothetic: spatial orientation cues, such as landmarks, that are external to the body

Idiothetic: spatial orientation cues, such as vestibular, proprioceptive, and motor efference copy cues, that are internal to the body

path integration is a continuous process by which the organism must continually monitor its movements to maintain an accurate sense of its orientation. In contrast, landmark navigation need only be an episodic process.

LANDMARK CONTROL OF THE PREFERRED FIRING DIRECTION

The preferred firing direction of a HD cell is controlled by a number of different types of allothetic cues. The most commonly studied cues have been visual. HD cells are often recorded in a 1-m diameter cylinder that contains a prominent visual cue attached to the inside cylinder wall. Rotation of this salient visual landmark leads to a corresponding shift in the preferred firing direction of HD cells, indicating that HD cells can be controlled by landmarks (**Figure 1*c***) (Taube et al. 1990b, Taube 1995). For these experiments, the landmark cue is usually shifted with the animal out of view, and the animal undergoes a disorientation procedure before being returned to the environment. However, a well-established visual cue can control the cell's preferred direction even when it is rotated in view of the rat, although the shift in the preferred firing direction is usually not as accurate as when it is done out of the animal's view (Taube et al. 1990b). Zugaro et al. (2001a) reported that background visual cues were more effective at cue control than foreground visual cues. Goodridge et al. (1998) found that a prominent novel visual cue could gain control over a cell's preferred firing direction within minutes of exposure. Removing the familiar visual cues or turning off the lights, however, does not lead to a change in cell activity, although the preferred firing direction may drift after some time (Taube et al. 1990b, Goodridge et al. 1998). Thus, the preferred firing direction of HD cells can be maintained purely via idiothetic information as the animal moves about its environment in the dark (although one should take care that olfactory or tactile cues do not provide a landmark cue in these conditions). When multiple HD cells are recorded simultaneously, landmark removal leads to an equal angular shift in the preferred direction of all cells by an unpredictable amount (**Figure 1*d***). This finding indicates that afferent input driving one HD cell similarly influences other HD cells, and that HD cells within a particular brain area behave as a network and their preferred directions always remain a fixed angle apart (in register) from one other (also see Yoganarasimha et al. 2006).

In an eloquent study, Zugaro et al. (2003) showed that a visual cue could reset a cell's preferred firing direction within 80 ms when restoring light to the room after an animal had spent a period of time locomoting in darkness. This short time frame for shifting the preferred direction also suggested that the activity in the continuous attractor networks, which have been used to model HD cell ensembles, may be propagated in abrupt jumps, rather than in a gradual transition that encompasses all intervening head orientations. Finally, a few studies have determined whether nonvisual landmark cues are capable of controlling the cell's preferred firing direction. Goodridge et al. (1998) found that an odor applied to the end of a cotton-tipped swab could shift the cell's preferred firing direction when the swab was rotated 90° within a circular arena. They had less success in controlling a cell's preferred firing direction with an auditory cue, but the nature of the recording environment was not conducive to detecting the spatial source of the sound (also see Rossier et al. 2000, who showed that auditory cues alone were not sufficient to perform a place-learning task in the water maze). Currently, no studies have exclusively examined HD cell responses following manipulation of tactile cues. Information about directional heading can also be derived from optic flow, although this information does not have to involve landmarks per se. To test whether HD cells respond to optic flow, Arleo et al. (2004) projected a pattern of luminous points onto a curtain surrounding a platform and then rotated the pattern slowly at speeds of

4.5°/s for 90 s. They found that in ~50% of sessions the preferred firing directions drifted significantly and that the direction of shift was consistent with the direction of rotation of the points, suggesting that optic flow was capable of influencing a cell's preferred firing direction.

Several studies have explored how HD cells respond when information from landmark sources conflicts with idiothetic (self-motion) information about the animal's movements, and for a comprehensive assessment the reader is referred to a review by Stackman & Zugaro (2005). Most studies have found that when well-established and prominent visual cues are placed in conflict with idiothetic cues, the spatial information derived from visual landmarks usually overrides that of idiothetic information, and HD cells respond by aligning their preferred directions with the spatial information from landmarks (Goodridge & Taube 1995, Blair & Sharp 1996, Zugaro et al. 2000). However, in each of these studies the alignment of the cell's preferred direction was not always perfectly aligned with the landmark information and was clearly less controlled by visual landmarks than in nonconflict situations when only the landmarks were rotated with the animal out of view. These findings indicate that idiothetic cues exert some control over HD cell preferred firing directions even under conditions in which visual cues usually dominate. Moreover, Knierim et al. (1998) reported that idiothetic cues tended to exert more control over HD cell responses when the rotation of the visual cues was large (typically 180°) than when they were small (45°).

BRAIN AREAS THAT CONTAIN HD CELLS

HD cells were originally discovered by Ranck in the dorsal portion of the rat presubiculum [often referred to as the postsubiculum (PoS)] (Ranck 1984), but they have been identified in several other brain areas within the classical Papez circuit. These areas include the anterior dorsal thalamic nucleus (ADN) (Taube 1995), lateral mammillary nuclei (LMN) (Stackman & Taube 1998), retrosplenial cortex (both granular and agranular regions) (Chen et al. 1994, Cho and Sharp 2001), and entorhinal cortex (Sargolini et al. 2006). HD cells have also been identified in significant numbers in other non–Papez circuit areas, including the lateral dorsal thalamus (Mizumori & Williams 1993), the dorsal striatum (Wiener 1993, Mizumori et al. 2000), and the medial precentral cortex (also known as FR2 or AGm cortex) (Mizumori et al. 2005). Other areas in which they have been reported in smaller numbers include the medial prestriate cortex (Chen et al. 1994), CA1 hippocampus (Leutgeb et al. 2000), and the dorsal tegmental nucleus (DTN) (Sharp et al. 2001b). To date, no definitive topographical organization, in terms of cell-preferred firing directions, has been uncovered for any of the areas where HD cells have been identified. The functional utility of HD cells existing in so many brain areas is not well understood. Although an animal's directional heading needs to be monitored for many different aspects of behavior, the purpose of replicating the directional signal in so many different brain areas, as opposed to storing the information in a single brain and then projecting it to other neural circuits that require this information, is difficult to elucidate.

ANATOMICAL NOMENCLATURE: POSTSUBICULUM

Some researchers contend that the dorsal portion of the presubiculum is characterized by cytoarchitectonics and connectivity that differ from the ventral portion of the presubiculum (van Groen & Wyss 1990). These researchers thus prefer to use a different name for the dorsal portion and refer to this area as the postsubiculum. Using this nomenclature, they reserve the term presubiculum for only the ventral portion of this area. Because HD cells have been reported only in the dorsal portion, the term postsubiculum will be used throughout this review. To date, no one has examined whether HD cells are present in the ventral portion of the presubiculum.

PoS: postsubiculum

ADN: anterodorsal thalamic nucleus

LMN: lateral mammillary nuclei

DTN: dorsal tegmental nucleus

Anticipatory time interval (ATI): amount of time the peak firing rate of head direction cells leads (or lags) the animal's instantaneous head direction

Almost all the research on HD cells has used rats as the experimental model, but HD cells have also been identified in the ADN of mice (Khabbaz et al. 2000), chinchillas (Muir & Taube 2002a), and guinea pigs (J. Taube & J. Rilling, unpublished observations), and in the presubiculum of monkeys (Robertson et al. 1999). The latter study with monkeys showed that HD cell activity was not dependent on eye movements or on where the monkey was directing its gaze. Of the quantitative analyses that investigators have conducted on HD cells across different brain areas, the tuning curves are remarkably similar, although there are some notable differences. For example, LMN HD cells tend to have broader directional firing ranges, and ADN HD cells tend to have higher peak firing rates. In addition, many LMN cells are modulated by turn direction, that is, they exhibit higher peak firing rates for head turns that pass through the preferred direction in one turn direction as opposed to the opposite turn direction (Stackman & Taube 1998). In addition, HD cells in the ADN and LMN, but not the PoS, generally show a secondary firing correlate with angular head velocity.

Temporal analyses of HD cell–firing properties in the ADN have revealed that their discharge is optimally correlated with the animal's future directional heading by ~25 ms (Blair & Sharp 1995, Taube & Muller 1998). The peak firing rate is reached just before the head reaches the cell's preferred firing direction. Thus, turning curves show that the preferred firing direction for a cell is slightly different between tuning curves based on clockwise and counterclockwise head turns. The amount of anticipation is referred to as the anticipatory time interval (ATI). Compared with ADN cells, the ATI is greater for LMN HD cells (40 ms, Blair & Sharp 1998; 75 ms, Stackman & Taube 1998), but about the same 25 ms for HD cells in the retrosplenial cortex (Cho & Sharp 2001). In general, HD cells in the PoS neither lag nor anticipate the cell's preferred firing direction. This type of analysis has not been conducted for HD cells in the remaining brain areas where HD cells have been reported. Among the hypotheses proposed to explain this predictive quality is that ADN HD cells are informed of future motor commands that control head movement via corollary discharge (motor efference copy). One prediction of this hypothesis is that when the rat does not actively move its head through the preferred firing direction, the amount of ATI will be reduced or abolished because the motor efference signal is absent. This hypothesis was tested by loosely restraining an animal and passively rotating it back and forth through the cell's preferred direction and then comparing the ATI to sessions during which the animal was engaged in active movements (Bassett et al. 2005). Contrary to predictions, researchers found no reduction in the ATI during the passive sessions and often found a consistent increase in the ATI for each HD cell during the passive sessions. HD cells in the PoS did not show this same effect, suggesting independence between the two sites with respect to anticipatory firing. These results suggest that anticipatory properties of ADN HD cells cannot be accounted for solely by a motor corollary discharge signal.

The percentage of cells classified as HD cells varies among different brain areas. No brain area contains solely HD cells. They are most abundant in the ADN, where ~60% of the cells exhibit directional firing (Taube 1995). Taube & Bassett (2003) estimated that for each anterodorsal thalamic nucleus there were ~20,000 neurons, which translates to ~12,000 HD cells. Although this number should be viewed as a rough estimate, it nonetheless provides a starting point for constructing realistic network models concerning HD cell discharge. The percentage of HD cells in other brain areas has been estimated as follows: PoS, 25% (Taube et al. 1990a); LMN, 25% (Stackman & Taube 1998); retrosplenial cortex, 10% (Cho & Sharp 2001); lateral dorsal thalamus, 30% (Mizumori & Williams 1993); and striatum, 6% (Mizumori et al. 2000). Sharp et al. (2001b) classified 6 out

of 48 cells (12.5%) in the DTN as classic HD cells. Bassett & Taube (2001), however, were unable to identify any classic HD cells in the DTN out of 44 recorded cells, although they reported that some cells, which were sensitive primarily to angular head velocity (see below), were also sensitive to the animal's directional heading. Sargolini et al. (2006) classified as HD cells nearly half of all cells recorded in the dorsocaudal medial entorhinal cortex, but their criteria for classification using a Watson's U^2 test was considerably less strict than other studies.

GENERATION OF THE HD SIGNAL: LESION STUDIES

HD cells were originally identified within the PoS, a structure closely associated with the hippocampus. The PoS is synonymous with the dorsal portion of the presubiculum, one of the three nuclei forming the subicular complex. It sends major projections to the superficial layers of the entorhinal cortex, the same layers that project to the hippocampal dentate gyrus. It receives projections from several structures including ADN, anterior ventral thalamic nuclei, lateral dorsal thalamic nuclei, retrosplenial cortex, and subiculum (for a review of anatomical connections of the PoS and other brain areas contained in the HD cell circuit, see **Table 1**). The PoS is thus positioned at a major crossroad of information transfer to and from the hippocampus, where place cells are present. Thus, early studies traced the origins of the directional signal from the PoS and examined afferent structures. **Figure 2** shows a block diagram indicating major areas where HD cells have been identified (*shaded blue*) and the major connections between these areas. Many of these areas are interconnected, which complicates understanding how the signal is generated. Moreover, several "side" pathways add to the complexity of the circuit. For example, as shown in **Figure 2**, there is (*a*) a pathway from ADN → retrosplenial cortex → PoS, (*b*) a return pathway from the PoS → LMN, and (*c*) reciprocal connections between the DTN and interpeduncular nucleus.

Combined lesion and recording studies, however, have begun to elucidate how the directional signal is processed. Initial studies showed that lesions of the PoS (Goodridge & Taube 1997), lateral dorsal thalamic nuclei (Golob et al. 1998), hippocampus (Golob & Taube 1997), or posterior parietal cortex (J. Calton, C. Turner, D. Cyrenne, B. Lee, J. Taube, unpublished observations) did not disrupt the presence of HD cells in the ADN. In contrast, lesions of the ADN disrupted HD cell activity in the PoS (Goodridge & Taube 1997). Later studies showed that bilateral lesions of the LMN or DTN disrupted HD cell firing in the ADN (Blair & Sharp 1998, Bassett et al. 2006) or in the PoS (Sharp & Koeste 2006). Unilateral lesions of the LMN, however, did not lead to impaired HD cell discharge in the ADN (Blair et al. 1999).

Preliminary studies that lesioned the retrosplenial cortex indicated that ADN HD cells could still maintain direction-specific firing (Bassett & Taube 1999). These lesions spared the most posterior portions of the retrosplenial cortex, which contains a substantial portion of the dysgranular region (area 29d, now termed area 30 to be consistent with the primate literature; Vogt et al. 2004). Further studies, however, have shown that when this most caudal area was lesioned, direction-specific firing was still intact, but the preferred firing direction was often unstable and drifted considerably over the course of several minutes (S. Wang & J. Taube, unpublished observations). These data would be consistent with recent behavioral findings, which found that lesions of the dysgranular retrosplenial cortex impaired animals on a working memory version of the radial arm task, during which they had to rely on distal visual cues (Vann & Aggleton 2005). The task was run under two configurations. In the first version, all 8 arms were baited and there was no delay in traveling between different arms. In the second version, the animal initially chose 4 arms followed by a 1-min delay where all the arms were

TABLE 1 Anatomical connections of the HD cell circuit

Principal hierarchical pathways	
Vestibular nuclei → nucleus prepositus	McCrea & Baker 1985
Nucleus prepositus → DTN	Liu et al. 1984, Graf et al. 2002
DTN → LMN	Groenewegen & van Dijk 1984, Hayakawa & Zyo 1984, Shibata 1987, Allen & Hopkins 1989, Wirtshafter & Stratford 1993
LMN → ADN	Hayakawa & Zyo 1989
ADN → postsubiculum	Thompson & Robertson 1987a, van Groen & Wyss 1990b, 1995; Shibata 1993a
Postsubiculum → entorhinal cortex	Shipley 1975, van Groen & Wyss 1990b, Caballero-Bleda & Witter 1993
Reciprocal connections and side pathways	
LMN → DTN	Hayakawa & Zyo 1989, 1990
Postsubiculum → ADN	van Groen & Wyss 1990b, Shibata 1992
Postsubiculum → LMN	Allen & Hopkins 1989, Shibata 1989, van Groen & Wyss 1990b
Postsubiculum → retrosplenial cortex	van Groen & Wyss 1990b, 1992a
Lateral dorsal thalamic nucleus → postsubiculum	Thompson & Robertson 1987a, van Groen & Wyss 1992b
Retrosplenial cortex → lateral dorsal thalamic nucleus	Thompson & Robertson 1987b; van Groen & Wyss 1990a, 2003
Postsubiculum → lateral dorsal thalamic nucleus	Thompson & Robertson 1987b
ADN → retrosplenial cortex	Sripanidkulchai Wyss 1986; Thompson & Robertson 1987a; van Groen & Wyss 1990a, 1995; Shibata 1993b
Retrosplenial cortex → ADN	van Groen & Wyss 2003
Retrosplenial cortex → postsubiculum	Sripanidkulchai Wyss 1987, van Groen & Wyss 1990a, Shibata 1994
Interpeduncular nucleus → DTN	Contestabile & Flumerfelt 1981, Liu et al. 1984, Groenewegen et al. 1986
DTN → interpeduncular nucleus	Contestabile & Flumerfelt 1981, Groenewegen & van Dijk 1984, Hayakawa & Zyo 1990
DTN → nucleus prepositus	Groenewegen & van Dijk 1984, Brown et al. 2005
Vestibular nuclei → supragenual nucleus	Biazoli et al. 2006
Nucleus prepositus → supragenual nucleus	Biazoli et al. 2006
DTN → supragenual nucleus (contralateral)	Biazoli et al. 2006
Supragenual nucleus → DTN (contralateral)	Liu et al. 1984, Hayakawa & Zho 1985, Biazoli et al. 2006
Lateral habenula → DTN	Liu et al. 1984, Hayakawa & Zho 1985
Lateral habenula → interpeduncular nucleus	Contestabile & Flumerfelt 1981
Medial habenula → Interpeduncular nucleus	Groenewegen et al. 1986
Entopeduncular nucleus → lateral habenula	van der Kooy & Carter 1981

rotated 45°, after which the animal had to complete the task. Although lesioned animals were unimpaired in the first version, they were impaired in the second version in a way that suggested their choices were based on a motor-response strategy. Because visual information from areas 17 and 18b and the lateral dorsal thalamus project to this dysgranular area, the authors attributed the impairment to the loss of visual spatial information and to animals changing their response bias to a motor turn strategy. Thus, this caudal dysgranular area may be important for processing visual information and contributes visual information to the HD cell circuitry.

Taken together, these lesion studies are consistent with the view that the LMN is critical for directional sensitivity in the PoS

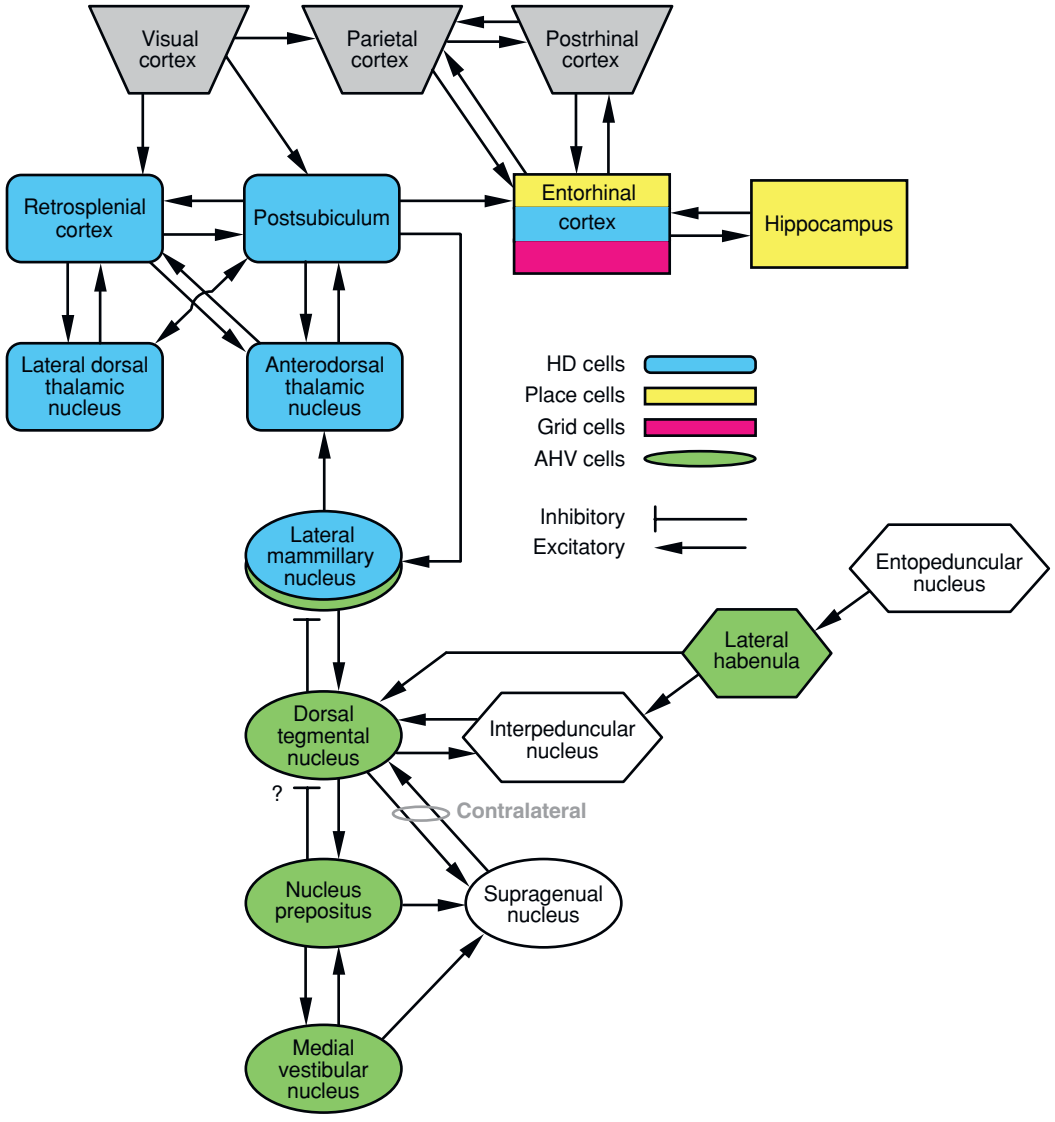

Figure 2

Circuit diagram showing principle connections of areas containing HD, place, grid, and angular head velocity (AHV) cells. Color key indicates the types of neuronal correlates identified for cells in that brain area. Note that LMN contains both HD and AHV cell types, and entorhinal cortex contains HD, place, and grid cell types.

and ADN and that the DTN is necessary for directional activity in the ADN. Although not yet confirmed experimentally, most researchers believe that the directional signal in brain areas outside the Papez circuit (e.g., dorsal striatum, medial precentral cortex) is derived from connections within the DTN→LMN→ADN→PoS circuit.

Although some areas within the HD cell circuit could be lesioned without disrupting HD cell firing per se, lesions of these areas had other effects on HD cell responses.

The most interesting was the finding that lesions of the PoS lead to poor cue control in ADN HD cell activity (Goodridge & Taube 1997). Thus, whereas rotation of a prominent visual landmark leads to a similar shift in the preferred firing direction of HD cells in control animals, the preferred firing direction does not shift a corresponding amount in PoS lesioned animals. Similar effects were observed in hippocampal place cells following lesions of the PoS (Calton et al. 2003). This inability to follow the landmark cue was not observed following lesions of the parietal cortex, lateral dorsal thalamus, or hippocampus, which suggests that the PoS plays a critical role in processing information concerning landmarks. Vogt & Miller (1983) reported the presence of direct connections between areas 17/18b of the visual cortex and PoS in rats. Thus, at least for rats, the visual information concerning landmarks could be projected directly to the PoS and bypass the dorsal visual stream in the parietal cortex, which is thought to be important for processing visual spatial information in primates. Coupled with the behavioral and recording studies in retrosplenial cortex discussed above, available evidence suggests that the connections between the PoS and retrosplenial cortex are critically involved in processing information concerned with spatial landmarks.

SUBCORTICAL ROLE IN SIGNAL GENERATION

Both McNaughton et al. (1991) and Taube et al. (1990b) early on postulated that the vestibular system may play an important role in updating the directional signal. When investigating the differing contributions of motor versus vestibular cues in HD cell responses, Stackman & Taube (1997) reported that neurotoxic lesions of the vestibular labyrinth abolished the HD cell signal in the ADN for up to three months postlesion. Whether the nervous system could compensate for this loss and the directional signal could return after this time are not known. Consistent with this finding, Stackman et al. (2002) inactivated the vestibular hair cells with intratympanic injections of tetrodotoxin and found similar effects on HD cells in the PoS (**Figure 1*b***). This inactivation also disrupted location-specific firing in hippocampal place cells. In both cases, normal HD and place cell firing returned once the effects of the tetrodotoxin had worn off after 24–48 h. With both types of lesions, the background activity of HD cells increased compared with prelesion controls. The absence of directional firing in vestibular-impaired animals is surprising when considering two points: (*a*) the presence of familiar landmark cues, intact motor/proprioceptive cues, and intact optic flow is insufficient to generate directional activity, even though HD cells are known to be responsive to these cues; and (*b*) tonic firing returns to secondary vestibular neurons in the vestibular nuclei, reaching 50% of normal rates within 24 h and recovering to prelesion rates within one week following the labyrinthectomies (Ris & Godaux 1998). Although it is not clear which mechanisms contribute to the return of the resting discharge rate in vestibular neurons, these observations clearly indicate that the generation of the directional activity is not due to the tonic firing of vestibular neurons.

More recently, in a preliminary study using chinchillas, Muir et al. (2004) occluded all three semicircular canals bilaterally and found again that direction-specific activity in the ADN was abolished, although an interesting pattern of activity emerged. Some ADN cells displayed periodic bursts of firing that appeared to be randomly generated. These high firing-rate bursts typically lasted about 1 s but could last longer and were not correlated to any specific HD or place within the apparatus. The burst could be initiated when the animal was motionless or when it spun around in circles, a behavioral consequence of the canal occlusions. We postulate that this activity represents HD cells that are disconnected from their inputs and thus the preferred firing directions continuously drift. Alternatively,

because of an imbalance between the two hemispheres (because one side may be more occluded than the other side), there could be a continuous sensation of rotation in one direction (i.e., vertigo), and if this happened, one would expect periodic firing from HD cells. On several occasions we have simultaneously recorded from two cells that showed this burst activity. During these occasions, when one cell burst, the other cell remained silent. But as the first cell's burst ended, the second cell underwent a burst. This temporal sequence of activity was preserved despite changes in the cells' burst duration. Furthermore, the temporal order in which the pair of cells fired during a rotation by the animal was contingent on the rotation direction. The duration of the cell's burst was also likely related to the animal's rotation velocity. Researchers have modeled HD cell firing using a ring attractor network (e.g., Skaggs et al. 1995, Redish et al. 1996, Zhang 1996, Song & Wang 2005). This activity pattern would be consistent with an attractor network in which the activity hill was not stabilized. In this case, activity would circulate around the ring, perhaps at varying rates, and cells that were encoding different head directions would fire in a fixed temporal relationship one after the other. The absence of a normal directional signal in the ADN following canal occlusions indicates the important role the vestibular system plays in generating the HD cell signal in rostral brain areas.

Investigators have also shown that another vestibular-related phenomenon, known as velocity storage, may be involved in HD cell activity. In response to a head turn, neural signals in the vestibular nuclei, nucleus prepositus, and other brainstem areas are known to outlast the generated vestibular signal by two to three times its length in the vestibular nerve. This prolongation in the time constant of decay is referred to as velocity storage. In a preliminary report, Taube & Bassett (2005) sectioned the midline fibers between the two medial vestibular nuclei; this transection severs the commissural connections between the two vestibular nuclei and disrupts the velocity storage effect, thereby undersignaling head velocity at lower frequencies of head turns (Raphan et al. 1979). The consequence for HD cells was predicted to be an underrotation of the HD signal relative to actual displacement, which would be evident as shifts in the preferred firing direction in the head turn direction. Results to date have confirmed this prediction, especially when animals were passively rotated on a turntable. When the animals self-locomoted, the preferred firing directions were relatively stable for short intervals, particularly when the rat moved its head while stationary, but when the animals walked around foraging for food, the preferred firing directions were highly unstable and could shift suddenly. These results indicate that HD cell stability requires intact commissural connections between the vestibular nuclei and suggests that, as with oculomotor behaviors, the HD signal benefits from the lengthened vestibular time constant produced by the velocity storage integrator. Interestingly, mice are thought to lack a velocity storage system (van Alphen et al. 2001), yet HD cells are present in mice, although the degree of stability in the preferred firing direction of mouse HD cells over time remains to be determined.

In addition to the role played by the semicircular canals, the otolith organs may also contribute to the directional signal. As described above, HD cells lost all semblance of a directional response when rats locomoted

ATTRACTOR NETWORKS

Continuous attractor networks have been the primary approach for computationally modeling HD cell activity. These networks contain interconnected neurons, which involve recurrent excitation onto HD cells of similar preferred directions and inhibition onto cells with different preferred firing directions. Once initiated, the network can sustain activity without outside excitation. The local area of activity (referred to as the activity hill) is moved around the ring to different directional headings following inputs from idiothetic or allothetic sources.

Velocity storage: prolongation of the vestibular time constant within the central nervous system compared with that in the vestibular VIIIth nerve

inverted on the ceiling (Calton & Taube 2005). In these experiments, direction-specific firing went from being "on" when the animals were on the wall (vertical plane) to "off" when on the ceiling. The experiment was conducted in a cue-rich environment, and the only readily apparent difference between locomotion on the wall and the ceiling was the altered otolith signals the animal would receive in the two conditions. Taken together, these studies emphasize the important role the vestibular system contributes to the directional signal.

VESTIBULAR PATHWAYS TO THE HD CELL CIRCUIT

Given that the LMN is critical for directional firing in other limbic areas, how might vestibular information be projected to the LMN? The primary projections to LMN originate in the DTN and are thought to be inhibitory because they use primarily GABA as a neurotransmitter (Allen & Hopkins 1989, Wirtshafter & Stratford 1993). In turn, the DTN receives inputs from three main sources: (*a*) the nucleus prepositus, a known recipient of projections from the vestibular nuclei (McCrea & Baker 1985); (*b*) the interpeduncular nucleus and lateral habenula, areas whose functions are not well delineated but are reciprocally connected with one another and contain prominent connections with the striatum (Contestabile & Flumerfelt 1981, Groenewegen & van Dijk 1984, Liu et al. 1984); and (*c*) the supragenual nucleus, a little-known nucleus that resides adjacent to the vestibular nucleus and rostral to the nucleus prepositus and also receives inputs from the vestibular nuclei (Biazoli et al. 2006). Injections of a transneuronal retrograde tracer (pseudorabies virus) into the LMN labeled each of these areas (Brown et al. 2005; see also Graf et al. 2002). Before proceeding to a discussion of these pathways, we first consider the types of neural responses found in the DTN.

Two studies have demonstrated that the majority of DTN cells (~75%) discharge in relation to the animal's angular head velocity (Bassett & Taube 2001, Sharp et al. 2001b). Bassett & Taube (2001) reported that DTN cells exhibited one of two types of firing patterns: (*a*) symmetric, in which firing rate was positively correlated with angular head velocity during head turns in both directions (**Figure 3*a***), or (*b*) asymmetric, in which firing rate was positively correlated with head turns

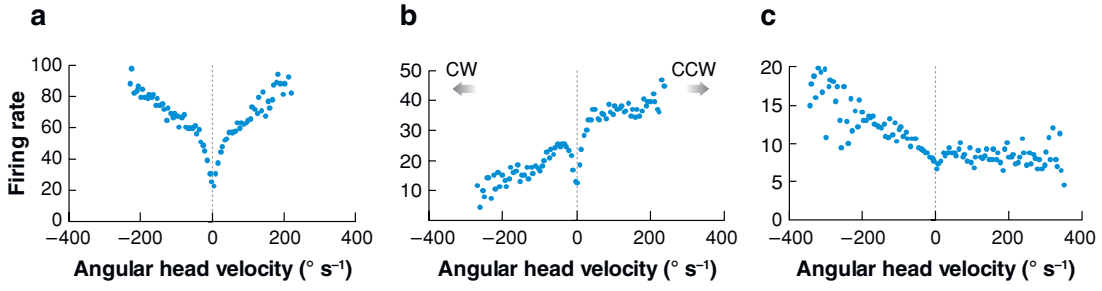

Figure 3

Firing rate versus angular head velocity for three different types of AHV cells in the DTN. (*a*) Symmetric AHV cell. Note that firing rate increases linearly as a function of angular speed for both CW and CCW head turns. (*b*) Asymmetric AHV cell. Note that except for very slow angular head velocities (<12° s^{-1}) firing rate is proportional to head turning speed for both CW and CCW directions but that firing rate increases for faster head turns in only one direction (CCW) and decreases for faster head turns in the opposite direction (CW). (*c*) Asymmetric AHV. For this cell the firing rate is proportional to head turning speed in only one direction (CW) and is not influenced by head turning speed in the opposite direction (CCW). CW and CCW directions for *a* and *c* are as noted in *b*. Reproduced with permission from Bassett & Taube 2001, copyright 2001 by the Society for Neuroscience.

in one direction and either correlated negatively **(Figure 3*b*)** or not at all in the opposite direction (**Figure 3*c***). Most, but not all, asymmetric cells were localized to the hemisphere opposite the preferred turning direction. In addition to modulation by angular head velocity, some of the angular head velocity (AHV) cells (~40%) were weakly modulated by the rat's linear velocity and a smaller number by HD (~10%) or head pitch (~15%). Autocorrelation analyses indicated that with the head stationary, AHV cells displayed irregular discharge patterns. Sharp et al. (2001b) reported somewhat similar findings in their DTN recordings. However, they identified only cells with asymmetric tuning curves and did not find any cells with symmetric tuning curves. They also found that ~10% of the neurons within the DTN could be classified as "classical" HD cells, meaning their tuning curves resembled those found elsewhere in the limbic system. Because afferents from the DTN are the major source of information projecting to the LMN, these results suggest that angular head velocity information from the DTN plays a significant role in generating the HD signal in LMN.

AHV neurons are also found in the LMN, where they constitute nearly 50% of the cells (Stackman & Taube 1998). Both symmetric and asymmetric cells are found within the LMN (termed fast AHV cells), and these cells comprised about half of the AHV cells. The remaining half of the AHV cells in LMN contained tuning curves where the firing rate was negatively correlated with the speed of head turn for both clockwise and counterclockwise turn directions (referred to as slow AHV cells). Slow AHV cells were not observed in the DTN. In general, the properties of fast LMN AHV cells are similar to those in the DTN, although the correlation to angular head velocity is not as strong in the LMN compared with the DTN. Furthermore, the slope of the relationship between firing rate and angular head velocity is steeper for DTN than LMN cells. Finally, the firing of ~10% of recorded cells in PoS was correlated to angular head velocity; all these cells were classified as the asymmetric type (Sharp 1996).

Angular head velocity information could originate from several sources. The most obvious source is the vestibular system. The vestibular nuclei project to the nucleus prepositus, which is thought to be the site of the neural integrator for the vestibulo-ocular reflex (Robinson 1989). Although many prepositus neurons carry information concerning eye position, some neurons convey signals independent of eye position (McFarland & Fuchs 1992). Most of the studies conducted on prepositus neurons have used monkeys, and little is known about the types of neural correlates in this area in freely moving rats.

The interpeduncular nucleus is reciprocally connected with the DTN. Hayakawa & Zyo (1984, 1988) divided the DTN into two subdivisions along the dorsal-ventral dimension and suggested that interneurons interconnected the two areas. The ventral subdivision projects primarily to LMN, whereas the dorsal subdivision projects to the interpeduncular nucleus; thus, there is likely some segregation of information as it is parsed to these two areas. A recent study by Sharp et al. (2006) recorded from interpeduncular neurons in freely moving rats, and they did not find any cells that contained direction-specific firing. In a preliminary report, Taube et al. (2006) found that interpeduncular lesions did not disrupt directional firing in ADN but led to instability in the cells' preferred firing directions. The lateral habenula also projects to both the DTN and the interpeduncular nucleus (Contestabile & Flumerfelt 1981, Liu et al. 1984, Groenewegen et al. 1986; note, the medial habenula has an even stronger projection to the interpeduncular nucleus than does the lateral habenula), but its functional role in this circuit is not known. Sharp et al. (2006) found that a small percentage of lateral habenular neurons (7.5%) discharged in relation to the animal's angular head velocity, and activity from another small percentage of cells (10%) correlated with the animal's linear

AHV: angular head velocity

AHV cell: fires on the basis of the speed and direction when an animal turns its head

running speed. The lateral habenula receives projections from the entopeduncular nucleus, the rat equivalent of the human globus pallidus, an area believed to be involved in motor functions. Rats with habenula lesions are impaired in spatial tasks, such as the water maze task (Lecourtier et al. 2004). Thus, this circuit may convey motor information about head movements to the HD cell circuit along the DTN-LMN-ADN axis.

The other major source of information to the DTN is from the supragenual nucleus, which projects only to the contralateral DTN but does contain ipsilateral connections to the LMN (Biazoli et al. 2006). Although these projections are quite prominent, the functional role served by the supragenual nucleus in contributing to the HD cell signal is unknown, and future work involving this area is particularly warranted. Nonetheless, because this nucleus resides adjacent to both the nucleus prepositus and the vestibular nuclei, and is connected with both areas, it is likely important for aiding in the processing of vestibular information about head movements.

ROLE OF MOTOR SYSTEMS IN DIRECTIONAL FIRING

Although vestibular inputs appear critical for generating direction-specific firing, the directional signal appears more complex than purely a simple integration of vestibular information. Several findings support this view. First, the directional signal is about as robust when the animal is not moving as when it is, and under nonmovement conditions, the vestibular signals would be providing only a tonic resting level of activity to efferent structures. Furthermore, this tonic activity alone is not likely sufficient to generate the directional signal because, as mentioned above, tonic activity returns in a few days after labyrinthectomies. Second, if vestibular information was critical solely for HD cell functions, then animals should be able to rely on this system for orientation in the absence of familiar landmarks such as when moving from a familiar to a novel environment. Taube & Burton (1995) showed that the preferred firing directions of HD cells were relatively stable (mean shift = 18°) as the animal locomoted from a familiar environment to a new one. Similar findings were demonstrated when animals were deprived of optic flow cues and locomoted between the two environments in the dark, although there was a little more shift in the preferred firing direction compared with lit conditions (mean shift = 29°). However, if the animals were passively transported between the two environments on a wheeled cart, the preferred firing directions of HD cells usually shifted substantial amounts between the two environments (mean shift = 68°; 20 out of 21 cells shifted ≥36°), despite the availability of vestibular information (Stackman et al. 2003). Furthermore, this result occurred whether the animals were transported under light or dark conditions. These findings suggest that vestibular information may be important for generating the directional signal, but it is insufficient for maintaining a stable preferred firing direction under conditions when the animal is passively moved. In this case, signals from motor efference copy or proprioceptive systems appear critical for updating the preferred firing direction over time.

The involvement of motor systems in updating the directional signal was suggested in the initial HD cell studies on PoS cells because passive rotation of the animal through a cell's preferred firing direction often led to a reduced firing rate (Taube et al. 1990b). Later studies with HD cells in ADN further showed that directional firing was often severely disrupted when the animal was tightly restrained with a towel wrapped around its body and then passively rotated through the cell's preferred firing direction (Taube 1995, Knierim et al. 1995). The tight restraint may have been stressful to the animal to the point that it did not place sufficient attention to its perceived directional heading. However, these animals usually received several days of pretraining in the restraint conditions. In theory, this

procedure should have acclimated the rats to these conditions and reduced the level of stress they were exposed to during restraint. More recently, Zugaro et al. (2001b) confirmed many of these findings by reporting that active displacement of the animal increased the peak firing rates of ADN HD cells compared with passive rotations in a task where the animals were trained to remain stationary at the center of a rotatable platform while the turntable was rotated back and forth in a lit room with stable background visual cues. Peak firing rates were reduced 27% on average during the passive rotations. The different responses observed to loose versus tight restraint may also be due to the fact that during loose restraint it may be possible for the rat to make compensatory neck movements for balance. Thus, during loose, but not tight, restraint there may be a small active head movement component that enables directional firing.

Of course, HD cells maintain their directional firing properties even when the animal is not restrained and not moving, and Taube & Muller (1998) reported little, if any, adaptation in cell firing when the animal pointed its head continuously in a particular cell's preferred firing direction. Thus, although motor/proprioceptive feedback systems can influence HD cell firing, normal directional activity can continue in the absence of movement. The problem of what sustains directional firing in the absence of movement is usually solved computationally by applying the principles of continuous ring attractor networks. These networks, which involve recurrent excitation onto HD cells of similar preferred directions and inhibition of cells with different preferred firing directions, can sustain activity without outside excitation. The hill of activity is moved around the ring to different directional headings following inputs from idiothetic or allothetic sources.

In recent years, a number of studies have begun to compare how central vestibular neurons discharge during active versus passive rotations in behaving monkeys that are free to move their heads (for review, see Cullen & Roy 2004). These studies have shown an important property: Responses in many vestibular neurons are substantially depressed when the monkey makes an active head turn. Passive rotation of the head elicits classic vestibular responses in secondary vestibular neurons. But responses from these same neurons are diminished when the monkey makes an active head turn (McCrea et al. 1999, Roy & Cullen 2001). Position-vestibular-pause neurons showed suppression of vestibular modulation during gaze redirection (i.e., combined head and eye movement) that ended once the eye-in-space position was stable, showing angular head velocity modulation only while the head was still turning to bring the head in line with the eyes. Vestibular-only neurons showed suppression of vestibular modulation through the entire head movement regardless of eye movement. Both types were velocity modulated during passive rotations in the dark. Furthermore, the suppression of modulation occurred only when the monkey turned its head relative to its trunk, thereby activating neck motoneurons and not when the monkey "steered" an apparatus to turn the head and body together (Roy & Cullen 2001). The authors concluded that an efference copy of the neck motor command, rather than higher-order motor commands planning head-in-space position, was responsible for influencing vestibular firing patterns. These findings demonstrate the important contribution that motor and proprioceptive signals must make in driving secondary vestibular neurons.

If firing of second-order vestibular neurons is attenuated during active motion then these vestibular signals would be diminished, or "off," when the animal is in the freely moving condition, and one might expect less influence from these neurons than from other types of inputs, such as motor or visual cues, during active motion. However, a paradox arises from the finding that vestibular input is essential for establishing the directional signal. How these seemingly conflicting findings will be resolved is presently unclear. The AHV

signals in DTN may represent integrated motor, proprioceptive, and vestibular information rather than solely processed vestibular signals. For these reasons it would be interesting to know how AHV signals in the DTN or LMN respond to passive rotations. Would their firing remain robust as in the second-order vestibular neurons, or would their firing be attenuated similar to HD cells? The one study that addressed this issue examined passive rotations for 12 AHV cells in the DTN and obtained mixed results (Sharp et al. 2001b). Most cells became quiescent or lost their angular head velocity correlate during the passive rotations, whereas only a few cells maintained their angular velocity correlates. These results emphasize the importance of motor cues for many of the DTN cells and provide further support for the notion that motor cues play an integral role in HD cell firing.

Where are motor/proprioceptive cues integrated into the HD cell circuit? Some evidence stemming from studies with monkeys shows that neck proprioceptive inputs are integrated as early as the vestibular nuclei (Roy & Cullen 2004). These authors postulated that during a self-generated head turn sensory feedback from neck muscle receptors was subtracted from angular head velocity information derived from primary vestibular afferents. The resultant information from the two circuits cancelled each other and accounted for the finding that active head turns led to a diminished signal in central vestibular neurons. However, as discussed above, it is difficult to reconcile how this nulled vestibular nucleus signal is projected onto the DTN where an AHV signal is observed during head turns. Thus, it may be important to consider other routes for which motor information may impact DTN cell activity. Another possibility is through the interpeduncular/habenula circuit. Both the interpeduncular nucleus and the lateral habenula project to the DTN, and the lateral habenula in rats receives major projections from the entopeduncular nucleus (van der Kooy & Carter 1981), which is homologous to the internal subdivision of the globus pallidus in primates and considered a major motor output pathway of the basal ganglia. As mentioned above, Sharp et al. (2006) reported a small number of cells in the lateral habenula whose activity correlated with the animal's angular head velocity or its running speed. Thus, there appears to be some information about the animal's self-generated movements within this circuit.

PATH INTEGRATION

Because organisms low on the phylogenetic scale can navigate using path integration (Barlow 1964), navigational systems based on idiothetic cues and path integration may have evolved before more complex navigational systems utilizing landmarks developed. Furthermore, because navigation based on path integration may have evolved early on during evolution, the navigational systems that use idiothetic sensory cues may be processed in brainstem and diencephalic structures, whereas cortical areas are more involved in processing landmark information. Indeed, in terms of landmark navigation, the amount of information processing required for understanding the spatial relationships among a set of landmark cues is probably considerable because it requires several cognitive processes. For example, the subject must first perceive and identify the object. Second, a subject must interpret the object as a useful item to use for a landmark (i.e., the subject would not want to use as a landmark an object that moves around all the time). Finally, an analysis of the spatial relationships of the object in the context of the current environment must occur. Thus, the neural machinery required for these multiple cognitive processes is more suited and consistent with a cortical locus for processing than for brainstem sites.

Path integration probably involves several processes, including (*a*) the establishment of an initial reference point (often, but not necessarily the animal's starting location), (*b*) monitoring the appropriate self-motion cues,

(*c*) computation of the animal's new position and orientation based on its initial position and subsequent movements, and (*d*) a mnemonic component that stores "online" the distance and direction of the initial reference point relative to the animal's current position. A disruption in any one of these processes would interfere with accurate path integration. There is no evidence nor a priori reason to suggest that the path integration processes are executed in a single brain area, and they, as well as the possible attractor networks underlying them, may well occur over multiple brain areas. Nonetheless, one might expect that damage to one of several brain areas could affect path integration abilities. Because each of the above processes requires different computational demands, it is more plausible that multiple brain regions, rather than a single structure, will prove to be participating in path integration.

The precise areas of the brain involved in path integration are not well understood. Although a good argument could be made for a subcortical locus for path integration, most studies have investigated cortical sites. For example, several studies have used a homing task that requires path integration and investigated performance following lesions in a particular brain area. In this task, a blindfolded rat leaves a home refuge to forage for a food pellet that is too large to consume quickly. The rat's path during foraging is circuitous and appears random, with no consistent exploration pattern. Because the rat probably feels less safe in the open field, once it finds the food pellet it returns directly to the refuge to consume it. Lesions of the parietal cortex (Save et al. 2001, Parron and Save 2004), the retrosplenial cortex (Whishaw et al. 2001), or hippocampus (Maaswinkel et al. 1999; compare Alyan & McNaughton 1999) disrupt behavioral performance in this task. Using a similar task Frohardt et al. (2006) reported that ADN lesions led only to mild performance deficits, whereas lesions of the DTN led to significant impairments; the DTN lesions also disrupted performance in a nonblindfolded version of this task during which the animals could view their environment. These findings, of course, point to a subcortical locus for path integration. Moreover, the finding that these animals were equally impaired even in the presence of landmarks would suggest that the functional contribution of the DTN goes beyond its role in path integration and may be critical for fundamental processes of spatial orientation and navigation.

The recent excitement of finding grid cells in the entorhinal cortex demonstrates this area's potential importance for path integration (McNaughton et al. 2006), and recent models have shown how these cells may play a role in path integration (Fuhs & Touretzky 2006; compare Burak & Fiete 2006). Given the nature of the grid cell correlate, however, it may be more parsimonious that cells that monitor grid cell activity are more likely to perform functions of path integration. Although other cells within the entorhinal cortex that are interconnected with grid cells could perform this function, the area containing grid cells projects to all areas of the hippocampus proper (dentate, CA1, CA3) via the perforant and alvear pathways, making a more compelling case that the hippocampus may be involved in the computations of path integration. Studies with hippocampal place cells have also supported a role for hippocampal involvement in path integration (for review, see McNaughton et al. 1996). In terms of HD cells, it is noteworthy that lesions of the hippocampus (Golob & Taube 1999) impaired the ability of ADN HD cells to maintain a stable preferred firing direction when the animal locomoted from a familiar to a novel environment, a task that requires path integration. Whereas the preferred firing directions of HD cells in control animals showed only a mean shift of $\sim 18^\circ$ between the two environments ($n = 24$), cells from animals with hippocampal lesions had mean shifts of $\sim 95^\circ$ ($n = 12$). Lesions of parietal cortex led only to a small shift in the preferred direction of ADN cells (mean: 38°, $n = 11$) (J. Calton, C. Turner,

D. Cyrenne, B. Lee, & J. Taube, unpublished observations), a finding that is not consistent with the results from parietal lesioned animals in the path integration studies mentioned above. Lesions of the PoS also led to only mild impairments in ADN HD cells in this task (mean: 45°, $n = 6$) (Goodridge & Taube 1997).

In sum, as might be expected with such a complex process, path integration may be processed over multiple brain areas. Therefore, lesions to various structures could impair path integration mechanisms. As reviewed above, much of the evidence to date is consistent with this view. Finally, another issue of interest is where might idiothetic and landmark information be integrated? Given the anatomical observations that the ADN is centrally located within the brain to receive both cortical (retrosplenial, PoS) and subcortical inputs (mammillary nuclei), perhaps the landmark and idiothetic information streams for the HD system converge at the ADN and/or LMN (see **Figure 2**). In this scheme, HD information reaching the hippocampus via the PoS and entorhinal cortex would already be highly processed and thereby ready for integration with other types of information, such as associating places with goals or computing trajectories to them.

SUMMARY POINTS

1. This article reviewed the general properties of HD cells and how this signal is generated and updated over time. HD cells discharge as a function of the animal's head direction in the horizontal plane, independent of the animal's location and ongoing behavior.
2. HD cells are found in many brain regions but are most abundant throughout the classic Papez circuit and in particular in the anterodorsal thalamic nucleus. HD cells are multimodal in that they receive and integrate sensory and motor information from several sources.
3. Vestibular information concerning angular head velocity is projected rostrally to the nucleus prepositus and supragenual nucleus and then to the DTN. From the DTN the information is conveyed to the LMN → ADN → PoS → entorhinal cortex, at which point it can be integrated with place and grid cell information in the hippocampal formation.
4. Whereas vestibular information is essential for generating the directional signal, information from visual landmarks and motor/proprioceptive systems are important for updating the signal.

FUTURE ISSUES

1. HD cell activity has been identified in many brain areas. What role does it serve in each of these areas?
2. A wide range of peak firing rates can be found within a population of HD cells. What functional role do these varying rates serve?
3. What do the supragenual nucleus and the interpeduncular/lateral habenula circuit contribute to HD cell processing?

4. Where mechanisms of path integration occur in the brain is unclear. The evidence suggests that several areas are important, but further experiments are warranted to clarify this issue.
5. Although only reviewed briefly here, most computational models of HD cell firing use attractor network dynamics. However, the known connectivity within and across brain areas containing HD cells is not readily conducive to the types of connections thought necessary for an attractor-type network. A finer understanding of the microanatomy within regions will be necessary to either support or refute these computational models.
6. What are the neural correlates of disorientation? Is an animal disoriented when HD cell activity becomes disrupted? Alternatively, does an animal become disoriented first, and then the resulting perception leads to degradation of HD cell activity?

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