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HEAD DIRECTION CELLS AND THE NEUROPHYSIOLOGICAL BASIS FOR A SENSE OF DIRECTION

JEFFREY S. TAUBE*

Department of Psychology, Dartmouth College, 6207 Gerry Hall, Hanover, NH 03755, USA

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Abstract—Animals require two types of fundamental information for accurate navigation: location and directional heading. Current theories hypothesize that animals maintain a neural representation, or cognitive map, of external space in the brain. Whereas cells in the rat hippocampus and parahippocampal regions encode information about location, a second type of allocentric spatial cell encodes information about the animal's directional heading, independent of the animal's on-going behaviors. These head direction (HD) cells are found in several areas of the classic Papez circuit. This review focuses on experimental studies conducted on HD cells and describes their discharge properties, functional significance, role in path integration, and responses to different environmental manipulations. The anterior dorsal thalamic nucleus appears critical for the generation of the directional signal. Both motor and vestibular cues also play important roles in the signal's processing. The neural network models proposed to account for HD cell firing are compared with known empirical findings. Examples from clinical cases of patients with topographical disorientation are also discussed. It is concluded that studying the neural mechanisms underlying the HD signal provides an excellent opportunity for understanding how the mammalian nervous system processes a high level cognitive signal. © 1998 Elsevier Science Ltd. All rights reserved

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* Tel.: 603-646-1306; Fax: 603-646-1419; e-mail: jeffrey.taube@dartmouth.edu.

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ABBREVIATIONS

ADN	anterior dorsal thalamic nucleus	MN	mammillary nuclei
HD	head direction	PoS	postsubiculum
LED	light-emitting diode		

1. NAVIGATION AND CELLS WITH SPATIAL CORRELATES

Navigation represents one of the most fundamental cognitive processes that mammals depend upon for survival. Without accurate navigation, animals would be unable to find food and water resources, their nest or home, and in some cases potential mates for reproduction. To navigate accurately, animals must first be cognizant of their current location and directional heading in the environment. These two types of information appear to be represented by different systems within the brain, and during the past 25 years investigators have tried to unravel their underlying neurobiological mechanisms. Neurons that appear to encode the animal's location in the environment were first reported by John O'Keefe in 1971, and the area where the cell discharged was referred to as the place field of the cell. These "place cells" were primarily found amongst the principal cells in the hippocampus (O'Keefe, 1976; McNaughton *et al.*, 1983; Muller *et al.*, 1987), but they have more recently been identified in other areas of the hippocampal formation, including the subiculum (Barnes *et al.*, 1990; Sharp and Green, 1994), parasubiculum (Taube, 1995b), and medial and lateral entorhinal cortex (Quirk *et al.*, 1992; Fox *et al.*, 1994). The only non-hippocampal area where they have been reported is the striatum (Wiener, 1993). It was the discovery of place cells in the hippocampus that played a large part in O'Keefe and Nadel (1978) postulating that the hippocampus formed the basis for a representation of external space, or cognitive map. Evidence to support the notion that animals contain an overall representation of their environment, that can be manipulated to derive efficient paths to goals, was demonstrated early on in studies showing that animals were capable of taking novel routes, or shortcuts, to get to a goal (Tolman *et al.*, 1946; Gentry *et al.*, 1947; Menzel, 1973; Collett *et al.*, 1986; Chapuis and Varlet, 1987; Chapuis and Scardigli, 1993). A short cut can only be taken if the animal contains an overall spatial representation of the environment. The information encoded by place cells presumably represents the perceived spatial location of the animal in the environment (for a slightly different view of the type of information encoded by place cells, see O'Keefe and Burgess, 1996; Hetherington and Shapiro, 1997). Place cells have undergone many detailed studies and recent reviews have described their properties, their environmental determinants, and their role in navigation (Poucet, 1993; O'Mara, 1995; Muller, 1996; Wiener, 1996).

In an open field, most hippocampal place cells do *not* encode the animal's directional heading within the place field (Muller *et al.*, 1994; Markus *et al.*, 1995). Directional information must therefore be provided by other systems. In 1984 James Ranck, Jr. serendipitously discovered the missing link while attempting to record from neurons in the rat subiculum (Ranck, 1984). In one rat, the recording electrodes had been placed too medially and passed through the dorsal portion of the presubiculum (often referred to as the postsubiculum—PoS). Ranck discovered that many cells in this area discharged as a function of the rat's head direction in the horizontal plane, independent of its location and on-going behavior. For example, one cell might discharge whenever the rat pointed its head northeast; another cell might discharge whenever the rat pointed its head west. These cells were aptly referred to as head direction (HD) cells. Qualitatively, HD cell firing depended neither on the rat's trunk position, nor on whether it was moving or motionless. Pitch or roll of the rat's head a little did not appear to significantly affect HD cell firing. Cell discharge also did not appear to adapt over time when the rat continually pointed its head in the preferred orientation. A common misconception about HD cells is that a cell's preferred firing orientation is directed towards a particular point in the environment. Rather, if vectors are drawn representing the rat's directional heading at the moment of highest activity, one would find that all the vectors are parallel. In this manner cell activity can be viewed as analogous to the response of a compass needle in a local environment, which always points north no matter where one is located.

Since this initial report on HD cells, several studies have focused on understanding how and where this spatial signal is generated in the brain. Other

studies have explored the environmental determinants that effect HD cell firing and how these cells respond when the animal is engaged in spatial tasks. The present article reviews the experimental work that has been conducted on HD cells since their discovery as well as some related studies conducted on human orientation.

2. BRAIN AREAS CONTAINING HD CELLS

Since their initial discovery in the PoS, HD cells have been identified in several other brain areas including the anterior dorsal nucleus (ADN) of the anterior thalamus (Taube, 1995a), the dorsal sector of the caudal lateral dorsal thalamic nucleus (Mizumori and Williams, 1993), both agranular and granular areas of retrosplenial cortex (posterior cingulate) (Chen *et al.*, 1994a), portions of extra-striate cortex (areas Oc2M and Oc2L) (Chen *et al.*, 1994a), lateral mammillary nuclei (MN) (Leonhard *et al.*, 1996) and the dorsal striatum (Wiener, 1993; Mizumori and Cooper, 1995). Note that except for the striatum, all these areas are considered part of the limbic system and many of them are components of the classic Papez circuit. Of these areas, HD cells appear to be most numerous in the ADN, where about 55% of the neurons were classified as HD cells (Taube, 1995a). In contrast, about 25% of the cells in the PoS contained directional-specific discharge (Taube *et al.*, 1990a). However, other studies in the PoS have reported percentages ranging from 11.9% (Golob *et al.*, 1998) to 36.6% (Sharp, 1996); this variability indicates that the percentage of cells associated with HD correlates should, at best, be considered a rough estimate. The percentage of cells showing directional specificity in other brain regions include: lateral MN: 23% (R.W. Stackman and J.S. Taube, unpublished observations), lateral dorsal thalamic nucleus: 30% (Mizumori and Williams, 1993), agranular and granular retrosplenial cortex: 8.4% and 8.5%, respectively (Chen *et al.*, 1994a), medial prestriate cortex: 2.7% (Chen *et al.*, 1994a), dorsal striatum: 10% (Wiener, 1993). These percentages should be considered with caution, as investigators from different laboratories have used different criteria for classifying cells as showing directionality.

Although detailed quantitative analyses with a high resolution of directional heading have only been conducted for cells in PoS, ADN, and lateral MN, the qualitative descriptions of cell firing observed in each of these areas indicate that all these cells share the property that they increase their firing when the rat's head is pointing a particular direction independent of its location. This observation raises the important issue of what function HD cells serve in each of these areas—an issue which awaits elucidation.

3. QUANTITATIVE DISCHARGE PROPERTIES

Following the discovery of HD cells, Taube *et al.* (1990a) designed and built a two-spot video tracking system that allowed them to track two small light-emitting diodes (LEDs) attached above the rat's head along its rostral-caudal axis. A red LED was positioned just above the rat's snout and a green LED was positioned over its back. Because the LEDs were fixed to the implanted headstage and turned with the rat's head, the imaginary line drawn between the two LEDs represented the rat's directional heading. This tracking system was then used to monitor the rat's directional heading, with 6° of resolution, while simultaneously recording HD cell activity. Animals were initially recorded in a 76 cm diameter cylinder while they foraged for small food pellets thrown randomly onto the cylinder's floor. The cylinder was surrounded by a 2 m diameter floor-to-ceiling curtain. Four evenly-spaced lights at the ceiling illuminated the environment. A white card was attached to the inside of the cylinder wall and extended from the floor to the cylinder's rim. The card subtended about 100° of the cylinder's circumference. Cell activity and the rat's directional orientation were monitored at 60 Hz for 8 min. The environment, behavioral task, and recording procedures were identical to those used by Muller *et al.* (1987) when recording from hippocampal place cells and thus facilitated comparisons with these spatial cells.

3.1. Firing Rate vs Head Direction Tuning Curves and Discharge Parameters

From these sessions, tuning curves were constructed that plotted the cell's mean firing rate as a function of the rat's head direction (Figs 1 and 2). Plots showed that the firing rates could be approximated as triangular functions and the firing of each cell could be characterized by several parameters: (1) peak firing rate, (2) preferred firing direction, (3) directional firing range, (4) background firing rate, (5) signal-to-noise ratio (the ratio of the peak firing rate to the background firing rate), and (6) asymmetry ratio. The cell's maximum firing rate (referred to as peak firing rate) occurred at only one directional heading (the preferred direction) and firing rates at head directions on either side of the preferred direction decreased linearly moving away from the cell's preferred direction. This linear decrease in firing rate was relatively symmetrical on both sides of the

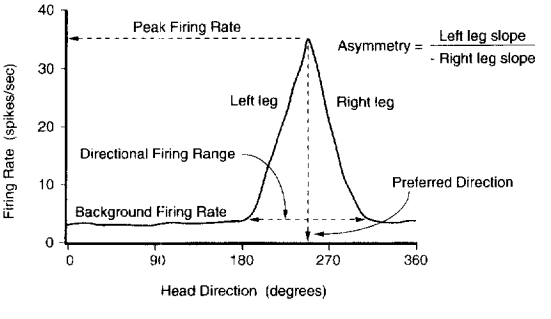

Fig. 1. Firing rate vs head direction tuning curve for a hypothetical HD cell. From this plot five parameters are measured in order to characterize the firing properties of the cell: (1) preferred firing direction, (2) peak firing rate, (3) directional firing range, (4) background firing rate, (5) asymmetry score.

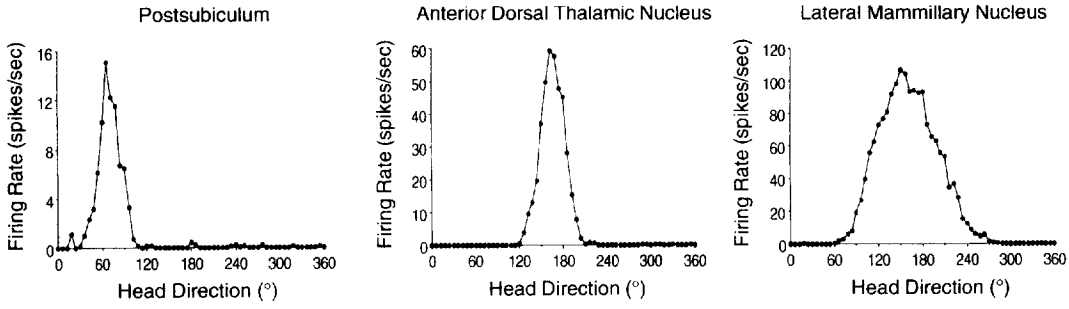

Fig. 2. Firing rate vs head direction tuning curves for three HD cells. The tuning curves represent the mean firing rates recorded across 8 min and are plotted using 6° bins. Each cell is from a different brain area: Postsubiculum, Anterior Dorsal Thalamic Nucleus, and Lateral Mammillary Nucleus. Note the differences in peak firing rates and directional firing ranges among the three cells.

cell's function. Examining HD cells recorded from several animals showed that there was an uniform distribution of preferred directions over a 360° range. There was a considerable range of peak firing rates across different HD cells – from 5 spikes/sec to rates above 100 spikes/sec. The mean peak firing rate across the population of cells was about 35 spikes/sec. The functional significance for different peak firing rates is unknown.

Each HD cell could also be characterized by the range of head directions over which elevated discharge occurred (directional firing range). Again, there was considerable variation found across cells (57–118°); with the mean directional firing range reported to be about 90°. There was little, if any, discharge at head directions outside this angular range. The "background firing rate" of most cells was below 1 spike/sec when the rat's directional heading was outside the cell's preferred direction. Although individual HD cells discharge over a wide range of directional headings, investigators believe that the animal's perception of its directional heading is represented by the summed activity of the cell population within a brain area (i.e., the population vector), in a manner similar to how the animal's perceived location is represented by the population rate vector across place cells (Wilson and McNaughton, 1993). The first row of Table 1 summarizes the discharge properties of PoS HD cells.

To date, most analyses have been conducted on a cell's mean firing rate across several minutes of recording and there has been an absence of a moment-to-moment analysis. Such an analysis may provide useful information concerning variability in cellular firing based on other behavioral factors, such as orientation of the head in the vertical plane (pitch), head turning speed, or attentional factors.

3.2. Stability

HD cell firing is usually stable across recording sessions and across days, as long as the recording environment does not change. Multiple cells monitored over several weeks showed that there was little change in the cell's peak firing rate and preferred direction over that time (Taube *et al.*, 1990a). There were occasions when an HD cell's preferred direction was observed to shift to a new orientation, but these only occurred when the animal was *not* exposed to the recording environment for several weeks. Analyses have also shown that HD cell discharge undergoes little, if any, adaptation when the animal continually points its head in the cell's preferred direction (Taube *et al.*, 1990a; Taube and Muller, 1998).

3.3. Relationship to Location, Angular Rotation, and Translational Movement

Analyses concerning other aspects of spatial orientation, such as angular or translational movement and location, have yielded interesting results. In their initial study, Taube *et al.* (1990a) reported that the animal's *location* had minimal, if any, effect on HD cell firing. This finding was based on observational judgments of firing rate maps that plotted firing rate as a function of both location and directional heading. This finding was also found for ADN HD cells (Taube, 1995a). In contrast, using a multiple-regression analysis Sharp (1996) reported that location had a small but significant influence on firing for most PoS HD cells. However, the mean percent of variance accounted for by location was so small (0.01) that the contribution of location to the directional signal can almost be considered negligible.

In another analysis HD cells were found to fire a little faster when the animal was moving compared to when it was still (Taube *et al.*, 1990a; Taube, 1995a). Thus, *translational* movement appears to increase the cell's firing rate. The extent to which a rat's *angular* head velocity modulates cell firing depends on which brain area HD cells are recorded from. In general, HD cell firing in the ADN and lateral MN, but not the PoS, is positively correlated (directly proportional to) with the speed of the animal's head turn (Taube, 1995a; Taube and Muller, 1998; R.W. Stackman and J.S. Taube, unpublished observations). Thus, the faster the rat is turning its head, the higher the cell's firing rate will be when the rat's head passes through the preferred direction. Using a different method of analysis, Blair and Sharp (1995) reported similar findings for ADN and PoS cells. These investigators also showed that the firing rate vs. head direction tuning curves for clockwise and counter-clockwise head turns generally overlapped for PoS, but not for ADN, HD cells. Moreover, the amount the ADN curves were separ-

Table 1. HD cell discharge properties

Brain area	Percentage of cells (%)	Peak firing rate (spikes/sec)	Background firing rate (spikes/sec)	Signal/noise ratio	Directional firing range (degrees)	Asymmetry ratio	Information content (bits)	Optimal time shift (msec)	Reference
PoS	25[a]	36	0.9	83.1	83	1.0	1.3	−7	Taube *et al.*, 1990a; Blair *et al.*, 1997; Taube and Muller, 1998
ADN	55	41	2.0	76.1	96	1.1	1.4	+23	Taube, 1995a; Blair *et al.*, 1997; Taube and Muller, 1998
Lateral MN	23	63	5.4	58.3	167	1.2	0.8	+103	Stackman and Taube, unpublished observations
Lateral Dorsal Thalamus	30	22	2.9[b]	7.6					Mizumori and Williams, 1993
Retrosplenial Cortex									
Agranular	8	18[c]	4.0[d]	4.5					Chen *et al.*, 1994a
Granular	8	24[c]	4.9[d]	4.9					Chen *et al.*, 1994a
Medial Prestriate Cortex	3	10[c]	1.3[d]	7.7					Chen *et al.*, 1994a
Striatum	10								Wiener, 1993

[a]Other studies have reported values ranging from 12% (Goloh *et al.*, 1998) to 37% (Sharp, 1995).:
[b]Estimated by dividing the mean peak firing rate by the mean directional selectivity measure;
[c]Estimated from averaging across different types of movements;
[d]Estimated by dividing the mean peak firing rate by the mean directional selectivity measure averaged across different types of movements.

ated from one another increased for faster head turns. However, it's important to note that although ADN HD cell activity is modulated by angular head velocity, these cells continue to discharge even in situations where the rat's head is motionless and pointing in the proper orientation.

There are many variables that may affect HD cell firing which remain to be explored. These variables include the relationship of HD cell firing to the rat's eye position and movement. Although rats have laterally-placed eyes and do not require large eye movements in order to bring an object into view, they nonetheless are capable of making eye movements. While this issue may be of less importance with respect to rats, it becomes more important when considering animals with frontally-placed eyes, such as primates. For example, it remains possible that HD cell firing is more related to attentional mechanisms concerned with the direction of gaze rather than encoding actual directional heading. Another area that remains to be explored is the relationship of HD cell firing to theta rhythm. Many of the brain areas where HD cells are present are also associated with theta activity (PoS: Taube *et al.*, 1990a; ADN: Kirk *et al.*, 1997; also see Bland, 1986). Given the interesting relationship between theta rhythm and place cell discharge in the hippocampus (see O'Keefe and Recce, 1993), this issue warrants further exploration.

3.4. Comparison of HD Cell Firing Properties Across Different Brain Areas

Based on the firing rate/HD tuning curves, the firing properties of HD cells in the ADN and lateral MN are notably similar to HD cells in the PoS (see Fig. 2). Table 1 summarizes the discharge properties of HD cells in the various brain regions. Empty spaces indicate parameters that have not been determined for a particular brain area. In general, most of the parameters for PoS, ADN, and lateral MN HD cells are similar. However, there are some important differences. First, Blair and Sharp (1995) reported that cells in the ADN tend to have higher peak firing rates than cells in the PoS, a difference noted by Taube (1995a), but one that did not reach statistical significance. Second, HD cells in the lateral MN generally have larger peak firing rates and directional firing ranges than HD cells in the PoS and ADN (R.W. Stackman and J.S. Taube, unpublished observations). Third, as discussed above, for HD cells in the ADN and lateral MN, there is a small, but significant positive correlation between the cell's firing rate and the animal's angular head velocity when the animal's head is oriented in the preferred direction (Blair and Sharp, 1995; Taube, 1995a); firing rates are higher at faster angular head velocities compared to slow angular velocities. It is noteworthy that this secondary angular velocity component is *not* present in PoS HD cells, despite the presence of a direct anatomical pathway from the ADN to the PoS (Shibata, 1993; van Groen and Wyss, 1995). The fourth difference amongst these cells involves the extent to which a cell's firing is optimally correlated with the rat's future, current,

or past directional heading and is discussed further below.

There are some other key differences between HD cells reported amongst the different brain areas. First, the signal-to-noise ratios of HD cells in the PoS, ADN, and lateral MN are much higher than the ratios for HD cells in the lateral dorsal thalamus, retrosplenial cortex, and medial prestriate areas (see Table 1). It is possible that these differences are caused by different laboratories using different criteria for classifying a neuron as an HD cell, because using a less strict set of criteria would lead to smaller ratios. Second, many of the tuning curves depicted for HD cells in the retrosplenial and prestriate cortices do not appear similar to the curves reported for HD cells in other parts of the limbic system (e.g., see Fig. 10 in Chen *et al.*, 1994a and Figs 1a, c, and 4 in Chen *et al.*, 1994b). Specifically, many of these cells have low signal-to-noise ratios (<3) or very wide directional firing ranges ($>180°$) compared to PoS and ADN HD cells (see Table 1). Whether these cells are representative of the population within the retrosplenial and prestriate areas remains unclear. In addition, many of these HD cells are modulated by the animal's behavior moving through space (Chen *et al.*, 1994a). For example, some cells had higher firing rates when the rat was turning to the right compared to turning left. Another important difference is that HD cells in the lateral dorsal thalamus appear to depend on visual input for initializing directional firing, because these cells did not show direction-specific discharge when the animals were placed onto a radial arm maze in a darkened room (Mizumori and Williams, 1993); directional firing was only initiated when the room was illuminated. This dependency upon visual input has not been observed in other parts of the HD cell network.

The presence of HD cells in the striatum is interesting, as this area is several synapses removed from nuclei within the Papez circuit where HD cells have been localized. Lavoie and Mizumori (1994) postulated that striatal neurons integrate spatial information with reward-related information which then influences motor output from the striatum. Finally, in addition to addressing where HD cells have been identified, it is also important to note the limbic system areas where HD have *not* been found. These areas include the entire hippocampus (dentate, CA1, CA3), entorhinal cortex, subiculum, anterior ventral and anterior medial thalamic nuclei, and medial MN. Furthermore, most of the cells containing spatial correlates in the parasubiculum were reported to show location-specific, as opposed to direction-specific firing (Taube, 1995b). The types of spatial correlates found amongst cells in the ventral portion of the presubiculum are not known.

4. ANTICIPATORY FIRING AND TIME SHIFT ANALYSES

An important property of HD cells was revealed by Blair and Sharp (1995; Blair *et al.*, 1997) who showed that ADN HD cell discharge anticipated the animal's future head direction by about 25 msec. In contrast, PoS HD cell discharge was best correlated with the animal's current, and in some cases, past directional heading. Their analyses were based on the finding that the firing rate vs. HD tuning curves were different for clockwise vs. counter-clockwise head turning directions for ADN cells. For counter-clockwise head turns, the tuning curve was shifted to the left of the tuning curve for clockwise head turns (Fig. 3A). In contrast, the clockwise vs. counter-clockwise tuning curves for PoS HD cells were very similar (Fig. 3B).

Taube and Muller (1998) reported similar findings using a time shift analysis approach applied to different discharge properties. This approach shifts the spike series forwards and backwards in time in 1/60th sec intervals with respect to the animal's head direction. For each shift of the spike series, a new firing rate vs. HD tuning curve is constructed and measurements are obtained of different parameters, such as peak firing rate, firing range width, and information content (a measure of the amount

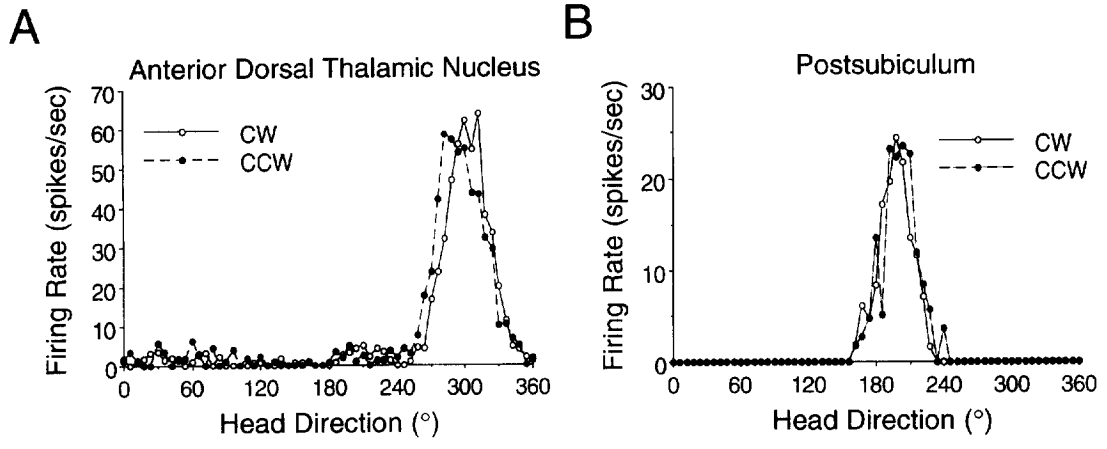

Fig. 3. Firing rate vs head direction tuning curves as a function of the direction the rat is turning its head for a HD cell in the ADN (A) and PoS (B). Note that the CW and CCW functions overlap for the PoS cell, but that the CW function is shifted to the right of the CCW function for the ADN cell.

of directional information encoded by a cell). The optimal time shift for a particular cell is defined as the amount of time the spike series is shifted which yields the maximum peak firing rate and information content and minimum firing range. Their analyses showed that ADN HD cell discharge was optimized when the spike series was shifted forward in time (relative to the animal's directional heading) by about 25 msec. In contrast, PoS HD cell discharge was optimal when the time shift was zero. These results were in agreement with the values reported by Blair and Sharp using the clockwise vs. counter-clockwise functions. It is also noteworthy that this 25 msec value is less than the anticipatory shifts reported for place cells in the hippocampus (120 msec) (Muller and Kubie, 1989) and parasubiculum (75 msec) (Taube, 1995b). Preliminary time shift studies show that HD cell firing in the lateral MN anticipates the animal's directional heading by about 100 msec, an amount that is considerably larger than ADN HD cells (Leonhard *et al.*, 1996).

Interestingly, Taube and Muller (1998) also found that not all cells within the ADN and PoS conformed to this pattern, as some ADN cells showed optimal discharge with the animal's current or past directional heading, and some PoS cells showed optimal discharge with the animal's future directional heading. These results were not attributed to random variability because a second recording session from these same cells showed comparable optimal time shifts. Similar findings were also reported in a second set of analyses by Blair *et al.* (1997). Thus, each HD cell in the ADN and PoS may be "tuned" to a specific time shift, in much the same way that each HD cell can be characterized by its peak firing rate. Blair *et al.* (1997) also reported that ADN cells with larger anticipatory shifts were correlated with cells that had smaller peak firing rates and larger directional firing ranges. However, Taube and Muller (1998) did *not* find any significant correlations between a cell's peak firing rate and its optimal time shift.

What is the significance of these findings? Several explanations have been proposed to account for the anticipatory nature of the ADN HD cell signal. Blair and Sharp (1995) postulated that the 25 msec time shift observed in ADN HD cells occurred because these cells receive information from two sources: (1) a HD cell signal from the PoS encoding the animal's current directional heading, and (2) a signal encoding information about the animal's angular head motions. These two signals combined would yield a signal anticipating where the animal's head would be pointing in 25 msec. However, this scheme is difficult to reconcile with findings showing that lesions of the PoS (the source of the current directional heading signal) do not abolish HD cell discharge in the ADN (see Section 10.2), although it is possible that HD cells in the retrosplenial cortex may provide the current directional heading signal to the ADN. Zhang (1996) showed that the anticipatory quality of the ADN cells can be accounted for by a dynamic shift mechanism inherent in the connections of the HD network. Although the biological implementation of a shift mechanism remains unclear, Zhang suggested that movement information, especially that of the vestibular system, could play a major role in the shift process. How each ADN HD cell becomes tuned to a different anticipatory value is unknown, but this observation has important implications for how HD cells are modeled in neural networks.

Taube and colleagues (1996) pointed out that any sensory inputs derived from landmarks or the vestibular system, would have to arrive at the ADN after the animal had reached each directional heading; thus, sensory inputs can not easily account for the anticipatory nature of the signal. They argued that the anticipatory signal could best be accounted for by the addition of movement-related information, such as a motor efference copy signal, onto ADN HD cells. The importance of a motor signal to HD cell discharge may explain why restraint of the animal frequently disrupts HD cell discharge (see Section 5). Furthermore, preliminary work by Lipscomb *et al.* (1996) showing that ADN cells begin to signal a new directional heading *prior* to the actual initiation of a turn, is consistent with this notion. Taube and Muller (1998) noted that even the PoS HD cells must receive some type of motor input because the PoS's optimal time shift values were too short to be accounted for by solely sensory information, assuming normal conduction velocities and synaptic delays from the visual and/or vestibular systems. Another key finding by Taube and Muller (1998) showed that when each parameter (i.e., peak firing rate, firing range, and information content) was plotted as a function of the amount of time spikes were shifted relative to head orientation, the mean ADN function was shifted to the right of the PoS function only at negative time shifts; at positive time shifts the two functions generally overlapped. This finding may indicate that ADN cells receive primarily a motor input, while PoS cells receive both motor and sensory inputs. Of relevance to these findings was a study showing that human subjects directional headings anticipated the direction they were going to locomote by about 100–200 msec (Grasso *et al.*, 1996).

5. RESTRAINT

Previous studies have shown that hippocampal place cells cease discharging when an animal is wrapped up in a towel and securely restrained, even when the rat was in the cell's place field (Foster *et al.*, 1989). Initial studies on PoS HD cells reported that cell firing continued when the animal was handheld and passively turned through the cell's preferred direction, although many cells had reduced firing rates (Taube *et al.*, 1990b). Later studies on ADN and PoS cells found that if the animals were restrained as securely as in the study with hippocampal place cells, then many, but not all, HD cells ceased discharging (Knierim *et al.*, 1995; Taube, 1995a; Golob *et al.*, 1998). Indeed, there may be a continuum across cells, where some cells are unaffected by restraint, some cells show reduced firing, and other cells cease discharging completely. These results suggest that some type of proprioceptive or motor input is necessary to drive many of the HD

cells. In contrast to these findings, Mizumori and Williams (1993) reported that all HD cells in the lateral dorsal thalamus maintained directional firing when the animals were hand-held and pointed in the cell's preferred direction.

6. ENVIRONMENTAL DETERMINANTS

6.1. Visual Landmarks

To determine the sensory features of the environment which affect cell firing, several studies have monitored HD cell firing following the manipulation of salient landmarks. To keep the environment simple and to maintain uniform behavior across all areas in the environment, several investigators have used a 50 cm high, 76 cm diameter cylindrical enclosure (Muller *et al.*, 1987; Taube *et al.*, 1990a). To prevent the animal from using other visual features of the room, the cylinder is surrounded by a floor-to-ceiling black curtain and the animal is usually transported into the curtained area inside a cardboard box after undergoing a disorientation procedure (where the experimenter walks around the apparatus while slowly turning the box back-and-forth). The primary cue that can be used for spatial orientation is a large white sheet of cardboard taped to the inside wall of the gray-colored cylinder.

6.1.1. *Cue Card Rotation*

To investigate the control exerted by the white cue card on HD cells, Taube *et al.* (1990b) rotated the card to various positions in the cylinder and monitored the response of HD cells. For these card rotation sessions, the animal was removed from the cylinder in between recording sessions and thus did not see the card being repositioned. Under these conditions, the preferred directions of HD cells usually shifted a near-equal amount as the cue card rotation, and thus maintained the same relationship with the cue card as in the original recording session. Similarly, when the cue card was returned to its initial position, the cell's preferred direction shifted back to its original position. Rotation of the cue card had no effect on the cell's peak firing rate or directional firing range. Similar results have been obtained for HD cells in all brain areas where this manipulation, or similar ones, have been conducted (ADN: Taube, 1995a; lateral MN: Leonhard *et al.*, 1996; retrosplenial cortex: Chen *et al.*, 1994a,b). These findings indicated that a prominent visual landmark could exert control over a cell's preferred direction. Furthermore, the visual spatial information obtained from the cue card overrode any potential information obtained from either static background cues within the recording room or the Earth's geomagnetic cues, which, in theory, could also provide allocentric directional information about the animal's orientation.

Although a cell's preferred direction usually shifted with the cue card, the shift in the preferred direction was generally less than the amount of card rotation (under-rotation). The mean under-rotation reported for PoS and ADN cells was about 15° (Taube *et al.*, 1990a; Taube, 1995a). This value is considerably larger than the variability in a cell's preferred direction between two control recording sessions, which is about 5°. This result suggests that other cues within the recording environment can influence a cell's preferred direction even in the presence of the salient visual cue. A few experiments have also been conducted where the cue card was rotated in the presence of the rat (see Section 9).

6.1.2. *Landmark Removal*

Removal of the cue card with the rat out of view had no effect on the cell's peak firing rate or range of firing, but in the majority of cells the preferred direction rotated more than 30° (Taube *et al.*, 1990b). When the cue card was returned to the cylinder *in the presence of the rat*, the cell's preferred direction usually shifted to return to its previously established relationship with the cue card (Goodridge and Taube, 1995a). Knierim *et al.* (1997), however, only reported this finding when the disparity between the cell's current preferred direction, and its preferred direction when the cue card was present, was smaller than 50° (see Section 9 below). HD cells in the retrosplenial cortex also maintained their direction-specific discharge following cue removal (Chen *et al.*, 1994b).

6.2. HD Cell Responses in the Dark and to Blindfolding

Taube (unpublished observations) found that turning off the lights in the recording room had no effect on HD cell discharge in the PoS. Cells maintained their peak firing rates and directional firing ranges and the preferred directions did not shift over a 4 min recording period. Similarly, when the rat was introduced into the cylinder in the dark, HD cells maintained direction-specific firing over an 8 min recording period. Goodridge *et al.* (1998) extended these findings by showing that directional-specific discharge was not disrupted in either the ADN or PoS when the animals were blindfolded and placed in the cylinder in a darkened room, although the preferred direction of most cells shifted compared to the initial non-blindfolded recording session. For many cells, however, the cell's preferred direction shifted 20–30° between the initial and final 2 min periods of an 8 min recording session.

Chen *et al.* (1994a) found that HD cells in the retrosplenial and Oc2 areas maintained their directional firing when the room light was turned off. In contrast, Mizumori and Williams (1993) reported that lateral dorsal thalamic HD cells did *not* discharge in a directional manner when the animal was initially placed on the apparatus in the dark. Once directional firing was established with the lights on, when they were turned off again, the preferred direction of lateral dorsal thalamic cells started to rotate systematically in one direction after 2–3 min. These results suggest that lateral dorsal thalamic cells may be fundamentally different than PoS and ADN HD cells in that they require visual inputs. In theory, idiothetic sensory information from internal sources (see Section 8 below) should be able to sustain HD cell firing in the absence of visual cues. While this

finding appears to be true for HD cells in most brain areas, it does not appear to be true for lateral dorsal thalamic HD cells and suggests that these cells do not receive updated spatial information from other brain regions.

6.3. Auditory Landmarks

In another series of experiments Goodridge *et al.* (1998) tested the response of HD cells to rotation of an auditory click of one/sec which emanated from one of four audio speakers spaced uniformly around the inside cylinder wall. For these experiments, there was no cue card in the cylinder. Although previous studies have shown that rats can discriminate the localization of a click from a second click spaced 24° apart (Kelly and Glazier, 1978), rotation of the auditory cue did not lead to a corresponding shift in the cell's preferred direction. Thus, despite the fact that the animal was given extensive experience with the auditory click, it was not able to exert stimulus control over the preferred direction of HD cells in the same manner as the cue card. It is possible, however, that if the auditory cue was made more salient, for example, by having the animal perform a task where it had to utilize the spatial information about the cue to obtain a reward, then maybe the cells would have shifted their preferred direction when the click was rotated.

6.4. Olfactory Cues

The responses of PoS and ADN HD cells following the rotation of a salient olfactory cue (a cotton Q-tip soaked with peppermint extract) were also assessed in rats recorded in the cylinder without a cue card (Goodridge *et al.*, 1998). Four Q-tips were spaced uniformly on the floor around the cylinder's perimeter. Only one of the Q-tips was soaked in peppermint. Following an initial recording session, the Q-tip containing the peppermint odor was rotated to a new position with the animal out of view. A second recording session showed that in about half the cases, the cell's preferred direction shifted a similar amount. There were, however, several sizable under-rotations, as well as a higher incidence of them, compared to cue card rotations. These results indicate that HD cells can be responsive to olfactory information, but not as well as to visual information.

Consistent with these results was the finding that when the floor paper of the apparatus was rotated, the preferred directions of HD cells in *blindfolded* rats frequently shifted in the same direction, although there were significant under-rotations in all cases (Goodridge *et al.*, 1998). Because the floor paper was not changed in between recording sessions, this result suggests that the rats were using olfactory cues laid down on the floor paper to help keep track of their directional orientation, although the results do not exclude the possibility that the rats were using tactile features from the urine and boli markings they left on the floor.

6.5. Enclosure Shape

When the shape of the animal's environment is changed, for example, from a cylinder to a rectangle, a cell's preferred direction frequently shifts to a new direction without effecting its peak firing rate or directional firing range (Taube *et al.*, 1990b). Sometimes a cell's preferred direction will be unaffected by a change in the shape of one enclosure (e.g., going from a cylinder to a square), but will be affected when going to another shaped enclosure (e.g., rectangle).

6.6. Multiple HD Cell Recordings and Environmental Manipulations

On some occasions, two or more HD cells were monitored simultaneously in the same animal. In all cases, the effects of an environmental manipulation on the preferred direction for one cell were similar to the effects observed in other cells (Taube *et al.*, 1990b; Taube, 1995a). This finding provides a strong demonstration that afferent input driving one HD cell similarly influences other HD cells within the same brain area, and indicates 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.

These findings can be compared with the effects of environmental manipulations on place cells. Kubie and Ranck (1983) showed that place cell firing, that was established in one apparatus, was abolished in some cells when an animal was placed in a different enclosure, even though the second enclosure was in an identical place in the room as the first enclosure. Muller and Kubie (1987) showed similar findings when recording place cells in cylindrical versus rectangular-shaped apparatuses. In contrast, HD cells were never observed to cease firing under any environmental condition. These findings suggest that the location-specific firing observed for place cells can be dissociated from the directional-specific firing of HD cells and have implications for how the HD cell network represents the external environment.

A central issue with regard to both HD and place cells is how the external environment is mapped onto a set of neurons in a specific brain area. For the hippocampus, investigators agree that most cells within the hippocampus are silent in any given environment and that only a fraction of the neurons within a brain area (~30%) will discharge in a given environment (Thompson and Best, 1989). If the animal is moved to a different environment then a different set of neurons will discharge (Kubie and Ranck, 1983). This second set, however, will contain some neurons that belonged to the first set; these neurons thus fired in both environments. In contrast, every HD cell appears to discharge in all environments. This finding suggests that the animal's directional heading in any environment maps onto the entire neuronal network within a brain area. Thus, all the HD cells within a network are used for encoding directional headings in any given environment.

7. HD CELL RESPONSES IN THREE DIMENSIONS

To understand how HD cells respond in an Earth vertical plane and how an animal defines its horizontal reference frame, Stackman *et al.* (1997) monitored HD cell activity as a rat locomoted into a vertical plane—one that was 90° orthogonal to the floor of the recording cylinder. This study also explored whether HD cell activity was affected when the rat was in a second horizontal plane that was significantly separated from, but still in sight of, the first horizontal plane. HD cell activity in the ADN and PoS was recorded in a tall cylinder that contained a wide rim (annulus) around the top with 4 equally spaced food wells. A vertical wire mesh "ladder" placed onto the inside cylinder wall allowed the rat to access the annulus. HD cells were monitored as rats climbed up and down the wire mesh to retrieve food pellets on the floor and annulus. The wire mesh was positioned at 0, 90, 180 and 270° relative to the cell's preferred direction. HD cell discharge properties were similar when the rat locomoted in either horizontal plane (floor or annulus). When the wire mesh position corresponded with the cell's preferred direction, HD cells continued to fire at peak rates as the rat climbed up the wire mesh, but not when the rat climbed down. If the rat turned its head left or right when it was climbing the mesh, cell firing was reduced. With the mesh positioned 180° opposite the cell's preferred direction, cell firing continued when the rat ran down the mesh, but not when it ran up. Background firing rates were exhibited when the rat ran up or down the ladder when it was positioned 90° clockwise or counter-clockwise from the cell's preferred direction.

These findings are consistent with the notion that the horizontal reference frame can be translated with the animal into an earth vertical plane. If HD cell firing is represented in three dimensional polar coordinates, then the cell's responses can be characterized as the surface of a hemi-torus (Fig. 4) (C.M. Oman, personal communication). In this figure, the positive y axis represents the preferred direction of a HD cell response in two dimensions in polar coordinates. The z axis is aligned with the gravitational vertical, and the x–y plane is horizontal. The length of the vector from the origin to the hemi-torus surface defines the magnitude of the HD cell response, and the vector direction indicates the directional heading of the rat when the cell fires. This model can account for the findings reported above. For example, consider an HD cell that responds maximally when the animal's head faces in the positive y axis direction. Because HD cell responses are independent of head pitch and roll up to 90°, the model predicts that the cell will discharge at its peak rate when the rat's head is oriented anywhere along the y–z plane, as long as the animal's head orientation contains a positive y-axis component. Thus, the cell will continue to fire if the animal climbs the wall located in the direction of the cell's preferred direction (defined as the wall in the x–z plane by the positive y axis), but not on the wall opposite the cell's preferred direction. It also predicts that if an animal is climbing up a vertical wall in the cell's preferred direction, the cell will shut off abruptly as the animal locomotes onto the ceiling from the vertical wall.

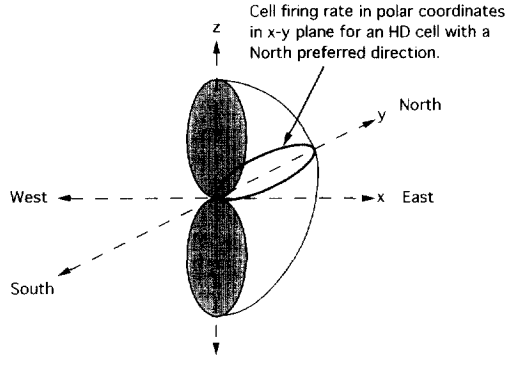

Fig. 4. Three-dimensional model of HD cell firing. The surface of the hemi-torus-shaped figure represents the maximum firing rate of the cell as a function of azimuth and height. Note that there are abrupt transitions from high firing rates to directions where the cell ceases responding.

8. ROLE OF IDIOTHETIC CUES IN NAVIGATION

Two different strategies can used by animals for navigation—piloting and path integration. Piloting, or landmark navigation, involves the use of landmarks, while path integration, sometimes referred to as dead-reckoning, entails the continuous monitoring of self-generated movements (Gallistel, 1990; McNaughton *et al.*, 1991). 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. 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 from efferent copies. The sensory systems involved in path integration are often referred to as idiothetic cues. Path integration is analogous to inertial navigation (Barlow, 1964; Mittelstaedt, 1983), and requires that the animal have an internal "model" that integrates both motor outflow and sensory return in order to maintain an accurate estimate of its current position and orientation. The internal model is likened to a cognitive map and represents the animal's spatial relationship to the external world. This map is normally capable of integrating information from idiothetic and landmark cues. However, the animal must rely solely on path integration when external landmark cues are unavailable. When they are available, both internal and external position and orientation cues must be integrated. Otherwise, the information from idiothetic and landmark signals are in conflict with one another, and the organism would experience the

condition known as motion sickness (Reason, 1978; Oman, 1990). Note that landmark navigation, as opposed to path integration, is an episodic, exteroceptive process. In addition, optic flow and haptic flow, which both rely on continuous information from external sense receptors, could in theory also provide information about the animal's orientation with respect to its surroundings. In sum, animals can use a combination of different types of sensory and motor cues, either episodically or continuously, to provide an accurate estimate of their directional heading.

8.1. HD Cell Responses in Novel Environments

Many behavioral studies have emphasized the importance of idiothetic cues for spatial orientation and navigation (e.g., Beritoff, 1965; Potegal *et al.*, 1977; Mittelstaedt and Mittelstaedt, 1980; Miller *et al.*, 1983; Etienne *et al.*, 1985; Traverse and Latto, 1986; Matthews *et al.*, 1988, 1989; Zoladek and Roberts, 1980). The card rotation experiments described above demonstrate that HD cells are capable of utilizing landmark information. But what is the evidence that HD cells also respond to and utilize idiothetic cues? Taube and Burton (1995) took advantage of the finding that a HD cell usually fired in different directions in two different shaped environments placed in the same recording room (i.e., cylinder vs. rectangle) (see Section 6.5). These investigators monitored HD cell activity in the ADN or PoS as an animal locomoted from a familiar cylinder environment to a novel rectangular enclosure via an U-shaped passageway. Under these conditions, the preferred direction for most cells remained relatively constant between the familiar and novel environments, although some cells showed a small (6–18°) shift in their preferred firing direction in the novel environment. For cell firing to continue in the same preferred direction when the animal moves into the novel environment, the animal must use a path integration approach, since there are no familiar azimuth cues for orientation.

8.2. Contributions of Different Idiothetic Cues

While these results infer the involvement of idiothetic cues in HD cell discharge, they do not distinguish which types of idiothetic cues the cells rely on for path integration. To assess whether vestibular cues alone could support accurate directional firing in HD cells Taube *et al.* (1996b) monitored HD cells as the rat was passively transported from a familiar to a novel environment on a wheeled-cart. Note that under passive transport conditions, the animal is deprived of the normal motor, proprioceptive, and kinesthetic cues that accompany self-locomotion. Under these conditions, the HD cells were not able to maintain a stable preferred direction between familiar and novel environments. Thus, while the vestibular system may play a crucial role in supporting the HD cell signal (see Section 10.7), these findings suggest that vestibular cues alone are *not* sufficient to allow maintenance of a stable preferred direction, and point to the importance of actively generated motor and kinesthetic cues. Similarly, behavioral studies have shown that hamsters are more accurate on spatial tests when they have access to active movement cues than when they are passively transported (Etienne *et al.*, 1988).

The contributions of different idiothetic cues to HD cell activity have also been assessed by monitoring ADN HD cells in a cylinder mounted on a turntable (Blair and Sharp, 1996). The walls of the cylinder contained four identical visual cues spaced equally apart. Turning of the cylinder with the floor in place or rotating the turntable with the walls remaining fixed provided visual motion cues (optic flow), while rotation of the turntable provided vestibular stimulation. The authors conducted a series of manipulations that involved combinations of either the floor or walls moving at fast or slow speeds, and with the room lights either on or off. Normally, in the absence of motor feedback cues an organism determines whether it is moving with respect to the world, or the world is moving with respect to it, by interpreting sensory cues from optic flow and vestibular information simultaneously. Optic flow in the absence of vestibular sensations indicates the world is moving about the organism, while vestibular activation with the appropriate optic flow indicates the organism is moving with respect to its environment. Thus, how a rat perceives these types of sensory information when on the turntable would predict how HD cells might respond. Blair and Sharp (1996) reported that whether or not a cell's preferred direction shifted following a manipulation depended upon the combination of stimuli presented. The most consistent results were obtained when the vestibular cues and optic flow provided the same spatial information. When the information from the two cues differed, a cell's preferred direction was sometimes linked to the information provided by vestibular cues and other times it was bound to the optic flow information. Furthermore, there were frequent occasions when a cell's preferred direction shifted partially, and the cell's response was a mixture of the information from the two cues. In sum, Blair and Sharp concluded that HD cells were capable of integrating sensory information from both optic flow and the vestibular system.

Several results discussed above also indicate the involvement of idiothetic cues in the ADN and lateral MN HD signal. First, the anticipatory nature of the signals in these areas (see Section 4) is best accounted for by a motor efferent copy signal. Second, the importance of the vestibular system is exemplified by the finding that removing vestibular input through labyrinthectomies abolished direction-specific firing in ADN cells (Stackman and Taube, 1997).

The role of idiothetic cues on HD cell discharge has also been examined for cells in the striatum and retrosplenial cortex. Wiener (1993) monitored three HD cells in the striatum as animals were rotated 90° in a large darkened, cueless box. Following the rotation, the cells' preferred directions usually shifted 90° with respect to the room. Thus, despite the absence of salient visual cues within the box, the cells' preferred directions remained in alignment with the reference frame of the box. These results in-

dicate that either the cells were *not* monitoring the animal's idiothetic cues and compensated for the box's rotation, or there were unintended landmark cues that rotated with the box (e.g., olfactory cues) that the rat relied on for its orientation. In another study, Chen *et al.* (1994b) passively rotated rats on a turntable while monitoring HD cells in the retrosplenial cortex. They found that many cells did *not* maintain directional firing under these conditions and suggested that active movement plays an important role in supporting direction-specific firing for these cells.

These experiments can also be compared to studies exploring similar issues in humans. Path integration abilities were found to be similar in sighted and congenitally blind subjects (Loomis *et al.*, 1993; also see Klatzky *et al.*, 1990), suggesting that accurate path integration can occur without input from optic flow. Glasauer *et al.* (1994) reported that labyrinthine-defective humans showed accurate performances in a task requiring linear locomotion toward a remembered target. The authors concluded that the vestibular system was not necessary for *linear* path integration. In another study, Telford *et al.* (1995) tested the contributions of different systems to a subject's perceived directional heading following various combinations of locomotor, vestibular, or optic flow stimulation. The authors found that subjects had smaller errors when locomotion was combined with optic flow than when vestibular stimulation alone, or in combination with optic flow, were presented. These results show the importance of motor cues in controlling the judgment of directional heading. Similar conclusions were reached by Rieser *et al.* (1995), who reported that subjects experienced turning sensations when they held onto a brake bar in the dark and had to maintain their position while a turntable they were standing on rotated at speeds above the vestibular threshold. In contrast, other studies have shown that subjects can estimate very accurately both their velocity profile, and the distance they traveled, even when passively transported (Berthoz *et al.*, 1995; Israël *et al.*, 1997). Berthoz and colleagues concluded that these abilities were mediated by information from vestibular, and possibly somatosensory, cues. Based on studies with normal and vestibular-deficient subjects Mergner and colleagues reported that neck proprioception plays an integral role in the perception of directional heading (Heimbrand *et al.*, 1991; Mergner *et al.*, 1991, 1993). These authors proposed that a head in space signal is computed from the summation of two signals: (1) a head on trunk signal based on neck proprioceptors and (2) a trunk in space signal that is based on a complex interaction between the vestibular system and leg proprioception; the latter signal provides information on feet versus trunk position (Mergner *et al.*, 1993). For a detailed review of earlier studies concerning human perception of the body in space, the reader is referred to Young (1984).

9. SENSORY CONFLICT EXPERIMENTS

Several studies have examined the response of HD cells when the animal is confronted with conflicting spatial information from different sensory cues. As discussed above Blair and Sharp (1996) monitored ADN HD cells under conditions where vestibular cues conflicted with optic flow. In the majority of the cases, cells were bound to the vestibular information, although there were instances where influence from optical flow was readily evident.

In a second phase of their dual-chamber apparatus experiment Taube and Burton (1995) monitored HD cells in either the ADN or PoS when visual landmark spatial information conflicted with idiothetic cues. After the rat became familiar with the novel passageway and rectangle, it was removed from the apparatus and the cue card in the cylinder was rotated 90°. The rat was returned to the cylinder with the doorway closed and, as expected, the cell's preferred direction shifted along with the cue card's rotation. The door was then opened and the animal was permitted to walk back via the passageway into the now-familiar rectangle. Immediately upon entering the passageway, the preferred direction spontaneously reverted back to its original orientation and maintained this same orientation in the rectangle. When the animal was allowed to walk back into the cylinder, the results varied between animals depending on the specific trial and animal analyzed. One of three outcomes occurred. First, sometimes the preferred direction would remain the same as in the rectangle (i.e., the animal failed to use the rotated cue card in the cylinder for orientation). Second, for other animals, the preferred direction appeared linked with the orientation cue for the corresponding environment because the preferred direction would shift back to the appropriate orientation for the rotated cylinder session. Third, in some animals, the preferred direction shifted to a new position that lay between the preferred directions for the rotated cylinder condition and rectangle.

In another cue conflict experiment, HD cell activity was initially monitored in a cylinder containing a single orientation cue card (Goodridge and Taube, 1995). The animal was then removed and put into a closed box. The cue card was removed and the floor paper changed. The animal was returned to the chamber and monitored again. As in previous experiments, the cell's preferred direction shifted to an unpredictable orientation (see Section 6.1.2). Then, without removing the animal from the cylinder and in full view of it, the cue card was returned to its initial position in the cylinder. In this case, since the animal had already established its directional orientation, the cell's preferred firing direction may have remained bound to the animal's idiothetic cues and not change when the card was returned. However, if the cell was responding strictly to landmark information, the preferred direction should rotate in order to maintain the previously established relationship with the card. The authors found that for HD cells in both the ADN and PoS, the preferred direction usually shifted to the originally established relationship with the cue card.

This finding indicated that inputs onto HD cells from the landmark navigational system were capable of overriding spatial signals derived from idiothetic cues. These results are similar to findings reported in behavioral studies in hamsters (Etienne *et al.*, 1990) and mice (Alyan and Jander, 1994). Interestingly, a later study by Etienne *et al.* (1993) showed that when distal visual cues were pitted against idiothetic cues and path integration in a task that rewarded the animals for using the idiothetic cues, hamsters initially used the distal visual cues, but later switched and chose paths that were indicative that they were using information from idiothetic cues. These findings indicate that the hamster's behavior was sufficiently flexible such that it could adopt a different strategy for performing the task when its strategy of first choice proved incorrect.

Two studies have also rotated the salient visual cue while the rat remained in the apparatus. Taube *et al.* (1990b) rotated the cue card in 90° increments in four stages. The preferred direction of PoS HD cells shifted with the card's rotation, but the shifts were not as accurate as when the card was rotated with the rat out of view (see Section 6.1.1). Knierim *et al.* (1994, 1997), using a similar cylinder and cue card, rotated both items under lit conditions. When the rotations were small (e.g., 45°) the cells also shifted their preferred directions. When the rotations were large (e.g., 180°) over half the cells did *not* shift their preferred direction; some cells shifted their preferred direction an intermediate amount. Similarly, a behavioral study by Etienne *et al.* (1996) found that when landmark and idiothetic information conflicted, animals relied on the landmark information when the conflict between the two sources was small (i.e., ≤90°), but when the conflict was large (e.g., 180°), animals relied on idiothetic cues.

Two other studies have monitored HD cells in other brain areas under conflict conditions. After initially monitoring a retrosplenial HD cell under lit conditions, Chen *et al.* (1994b) rotated the salient visual cue while the rat was in the dark. Upon turning the light back on, the HD cell did *not* shift its preferred direction. In another experiment, Wiener (1993) rotated a rat in darkness in an enclosed box. After rotation, the cue light was turned back on in the same position it had been before the box rotation. The preferred directions of striatal HD cells shifted with the box's rotation, thus ignoring both the salient visual cue and its vestibular information. Although both these studies suggest that idiothetic cues can override spatial information from landmark cues, unfortunately, neither study showed that the visual cue initially exerted control over the cell's preferred direction. It is critical to demonstrate this control before conducting the conflict manipulation in order to confirm that the cell's preferred direction under non-conflict conditions is normally controlled by the visual cue.

Taken together, these studies show that under conditions where salient familiar visual landmarks are present, HD cells are usually bound to these cues as long as they are not too incongruent with idiothetic information. However, in situations where the landmarks are not familiar to the animal, or when the landmark information is incongruent with the spatial information provided by idiothetic cues by a large amount, then HD cells may rely more on the idiothetic cues (for further discussion, see Section 14).

10. GENERATION OF THE HEAD DIRECTION SIGNAL

10.1. Anatomy and Connectivity of Areas Involved in the HD Cell Circuitry

Because HD cells were initially identified in the PoS, attention has focused on this area, or areas connected with it, for understanding how the HD signal is processed. The anatomical review that follows is confined to studies in the rat, since HD cells have only been reported in this species thus far. The PoS together with the subiculum, presubiculum, and parasubiculum comprise the subicular complex. Based on cytoarchitectonics and anatomical connectivity, some investigators have considered the PoS to be a separate, distinct area from the presubiculum (Rose and Woolsey, 1948; Swanson and Cowan, 1977; Vogt and Miller, 1983; van Groen and Wyss, 1990a,b). In contrast, other investigators have not recognized this distinction and therefore, have not used the term "postsubiculum" (Blackstad, 1956; Shipley, 1975; Amaral and Witter, 1995). The two areas have very similar connectivity, but one of the important differences is that the presubiculum does not project to the ADN (van Groen and Wyss, 1990a) and is therefore unlikely to contribute significantly to the directional signal in the ADN.

The major inputs into the PoS are from the subiculum, the anterior dorsal nucleus (ADN) and anterior ventral nucleus (AVN) of the anterior thalamic nuclei, and the lateral dorsal thalamic nuclei (Sorenson and Shipley, 1979; Wyss *et al.*, 1979; Thompson and Robertson, 1987a; van Groen and Wyss, 1990a,b, 1992b; Shibata, 1993, 1994). The projections from the subiculum terminate in layers I, II, and V of PoS (van Groen and Wyss, 1990b), projections from the anterior thalamic nuclei terminate in layers I–III and V of PoS (van Groen and Wyss, 1995), and projections from the lateral dorsal thalamus terminate in layers I, III–V of PoS (van Groen and Wyss, 1992b). The major efferent projections of the PoS are to the superficial layers of entorhinal cortex, ADN, AVN, lateral dorsal thalamus, and lateral MN (Swanson and Cowan, 1977; Donovan and Wyss, 1983; Thompson and Robertson, 1987b; Shibata, 1989; van Groen and Wyss, 1990a,b, 1992b, 1995). Thus, both the anterior and lateral dorsal thalamic nuclei have reciprocal connections with the PoS. The projections to layer III of entorhinal cortex originate from the superficial layers of PoS, while the projections to layer I of entorhinal cortex arise from the deep layers of the PoS (Caballero-Bleda and Witter, 1993). The projections to the anterior thalamic nucleus arise from the deepest layer of PoS, and projections to the lateral MN originate from intermediate layers of PoS (Donovan and Wyss, 1983). In addition to these major connections, the PoS also receives inputs from visual areas 17 and 18, retro-

splenial cortex, and anterior cingulate cortex (Vogt and Miller, 1983), and sends projections to areas 17 and 18 (Vogt and Miller, 1983), lateral posterior thalamus (Swanson and Cowan, 1977), and layers I, III, and IV of both retrosplenial and anterior cingulate cortices (Meibach and Siegel, 1977; Swanson and Cowan, 1977; Vogt and Miller, 1983; van Groen and Wyss, 1992a). The projections to the visual cortex arise from the deep layers of PoS, while the visual cortex projections terminate in layers I and III of PoS (Vogt and Miller, 1983).

Given the presence of HD cells in the PoS and that the PoS sends a major projection to the superficial layers of the entorhinal cortex, it is curious that no direction-specific activity has been reported from this region (Quirk *et al.*, 1992). It is possible, however, that the specific PoS cells which project to the entorhinal cortex are *not* direction-selective. It is also important to note that not all cells within the deep layers of PoS show directional selectivity. Indeed, the precise projections of HD cells in any of the brain areas where HD cells have been identified are unknown. This situation underscores the importance for future studies to determine the exact projections of HD cells.

The anterior thalamic nuclei receive inputs from the PoS and MN, and have reciprocal connections with the anterior cingulate and retrosplenial granular (areas 29a–c) cortices (Sripanidkulchai and Wyss, 1986, 1987; Shibata, 1993; van Groen and Wyss, 1995). Within the anterior thalamic nuclei, there is a high degree of specificity for both the afferent and efferent projections. In particular, the medial MN projects to all three anterior thalamic nuclei, but the lateral MN projects only to the ADN (Seki and Zyo, 1984; Shibata, 1992). Afferents from the cingulate and retrosplenial cortices terminate in all three anterior thalamic nuclei (Domesick, 1969; Beckstead, 1979; van Groen and Wyss, 1990c). The AVN and ADN have reciprocal connections with

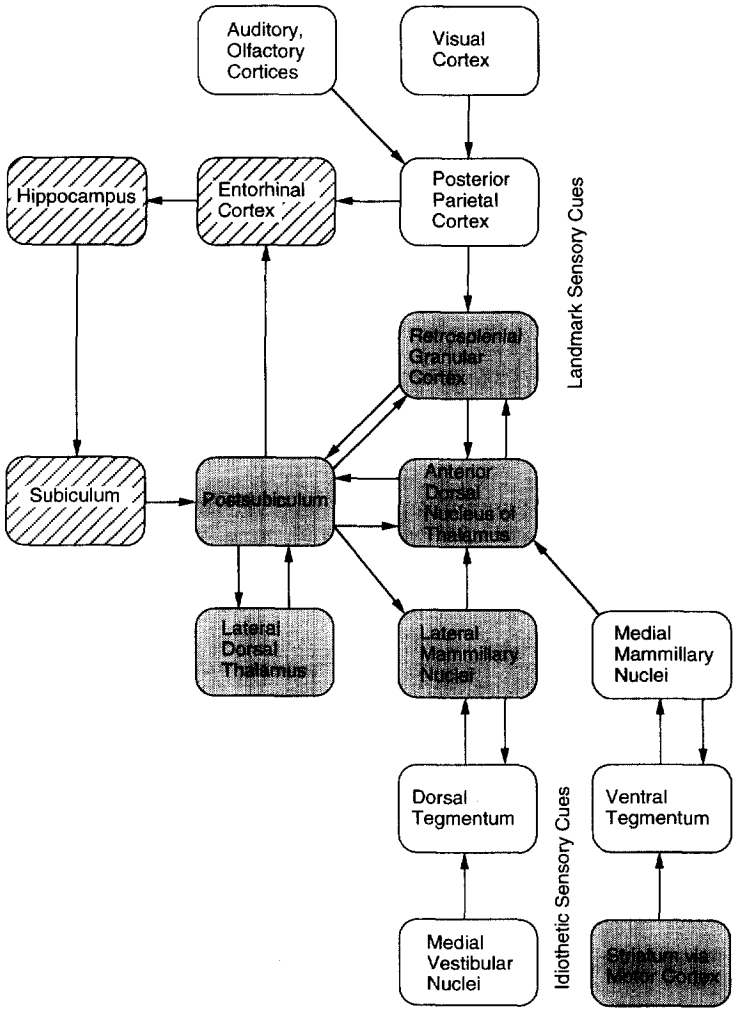

Fig. 5. Summary of the principal nuclei and connections of areas involved in the HD cell circuit. Shaded blocks indicate areas where HD cells have been identified. Cross-hatched blocks indicate areas where place cells have been identified. This block diagram can also be used as a conceptual framework in understanding how the directional signal may be processed.

retrosplenial granular cortex (areas 29a–c), whereas the anterior medial thalamic nucleus has reciprocal connections with the anterior cingulate and retrosplenial dysgranular cortex (area 29d) (Domesick, 1972; Beckstead, 1976; van Groen and Wyss, 1992a). The ADN's projection to the retrosplenial granular cortex terminates in layers I, III, and IV (Shibata, 1993; van Groen and Wyss, 1995), while the projection back to the ADN from the retrosplenial cortex originates in layer VI (Sripanidkulchai and Wyss, 1987). There is also a GABAergic projection from the thalamic reticular nucleus to the ADN (Gonzalo-Ruiz and Lieberman, 1995).

The lateral MN has reciprocal connections with the dorsal tegmental nucleus and receives other major inputs from the PoS, parasubiculum, pontine periacqueductal gray, and septal region (Hayakawa and Zyo, 1984, 1990; Shibata, 1987; Allen and Hopkins, 1989; Gonzalo-Ruiz *et al.*, 1992). Its principal projections are to the dorsal tegmental nucleus and ADN (Seki and Zyo, 1984; Shibata, 1987, 1992; Hayakawa and Zyo, 1990). The major connectivity of the PoS, limbic thalamic areas, and the lateral MN are summarized in Fig. 5.

10.2. Lesion Studies

An important issue concerning HD cells is how the directional signal is generated. What brain areas are critically involved in its processing and what function does each brain area contribute to the signal? Many of the brain areas where HD cells have been identified lie within the classical Papez circuit and are interconnected with one another. Figure 5 illustrates the areas (shaded gray) and principal pathways where HD cells have been identified. Because many of these areas are reciprocally connected, it has been difficult to determine the origin of the signal. In an effort to clarify the critical areas involved in its processing, lesion studies have been conducted in which one brain area was lesioned and HD cells recorded in another area. The findings to date are summarized in Table 2. A plus sign in the Results column indicates that HD were identified in the lesioned animal; a minus sign indicates that no HD cells were identified.

Taken together, these lesion studies indicate that the ADN is critical for the establishment of the directional signal in the PoS. Although Mizumori *et al.* (1994) has shown that lateral dorsal thalamic lesions reduce location-specific firing of place cells in the hippocampus, the studies by Golob *et al.* (1998) show that such lesions have little impact on HD cell activity in the PoS. Thus, the functional role served by the prominent reciprocal connections between the lateral dorsal thalamus and PoS remains to be elucidated. In addition, despite their prominent connections with the ADN, the roles that the retrosplenial cortex and the lateral MN play in the generation of the directional signal have not been investigated, and this area warrants further study because HD cells have been identified in both structures. Similarly, no lesion studies have been conducted in the striatum in conjunction with HD cell recordings in the limbic system. Thus, the functional role of the striatum in processing the directional signal also remains unknown.

10.3. Optimal Time Shifts In Lesioned Animals

The optimal time shift analyses also provide some clues as to how the directional signal may be processed. As described in Section 4, ADN HD cells anticipate the animal's directional heading, while PoS HD cells encode the animal's current directional heading. Interestingly, the time shift analyses conducted for the lateral MN HD cells show that they anticipate the animal's directional heading to a greater degree than ADN HD cells (Leonhard *et al.*, 1996). If the directional signal is processed in a serial manner, then these findings suggest that the directional signal may be processed from lateral MN → ADN → PoS, which is consistent with both the anatomical and lesion studies. Alternatively, given the feedback connections from the PoS to the ADN and lateral MN, it is possible that the directional signal may prove to be processed in a parallel manner. Interestingly, when the PoS was lesioned the ADN HD cell firing anticipated the animal's directional heading by a larger amount of time compared to cells in non-lesioned animals (Goodridge and Taube, 1997), indicating that the anticipatory quality of the ADN signal cannot be attributed to a feedback projection from the PoS. The larger anticipatory values observed in ADN HD cells from PoS-lesioned animals may result from the projections of lateral MN HD cells, because lateral MN HD cells anticipate the animal's directional heading by larger amounts than ADN HD cells. Lesions of the lateral dorsal thalamus or the hippocampus did not change the optimal time shifts for PoS and ADN HD cells (Golob *et al.*, 1998; Golob and Taube, unpublished observations).

Table 2. Effects of selective brain lesions on HD cell discharge

Area lesioned	HD cells recorded in	Results*	Reference
PoS	ADN	+	Goodridge and Taube, 1997
ADN	PoS	-	Goodridge and Taube, 1997
Lateral Dorsal Thalamus	PoS	+	Golob *et al.*, 1998
Hippocampus	PoS, ADN	+	Golob and Taube, 1997a
Vestibular apparatus	ADN	-	Stackman and Taube, 1997
Vestibular apparatus	PoS	-	Stackman and Taube, unpublished observations

*Plus sign indicates that HD cells were identified in the lesioned animal; minus side indicates that *no* HD cells were identified in the lesioned animal.

10.4. Lesions And Cue Control

A HD cell's preferred direction can be controlled by salient landmarks in the environment; thus rotation of a salient visual cue will lead to a similar shift in a HD cell's preferred direction (see Section 6.1.1). An important finding from the lesion studies was that the preferred directions of ADN HD cells in PoS-lesioned animals did not shift following rotations of the cue card, suggesting that the cue card exerted less control over these cells in PoS lesioned animals (Goodridge and Taube, 1997). Furthermore, although the preferred directions of these cells were stable within a single 8 min recording session, the cells preferred directions were not stable *between* different sessions in the cylinder, as the frequency of shifts observed in a cell's preferred direction across sessions was significantly greater than in intact animals. Interestingly, the control exerted by the cue card was *not* disrupted in ADN HD cells by lesions of the hippocampus (Golob and Taube, 1997a) or in PoS HD cells by lesions of the lateral dorsal thalamus (Golob *et al.*, 1998). Because the PoS receives its major inputs from the lateral dorsal thalamus, anterior thalamic nuclei, and subiculum (which in turn receives its primary input from the hippocampus), these findings, taken together, suggest that the PoS plays an important role in modulating and/or processing visual information onto ADN HD cells. The finding that total cue control was not lost by lesions of the PoS would suggest that the PoS may play a role in selecting which landmark to use among a set of potential cues. Although the white cue card was the most salient and the only intentional cue within the recording room, there were other cues the rat could have used, such as olfactory markings on the floor, texture cues from the cylinder wall, or auditory cues from the recording equipment. Finally, it is noteworthy that PoS lesions frequently disrupted cue control of hippocampal place fields, further suggesting that the PoS may play a role in selecting which cues to use as landmarks (J.P. Goodridge, R.W. Stackman, W.B. Archey, J.S. Taube, unpublished observations).

10.5. Directionality And Hippocampal Place Cells

Previous studies have shown that place cell discharge can be modulated by the animal's directional heading within the cell's place field (O'Keefe and Dostrovsky, 1971). This finding is most frequently observed when animals perform tasks involving stereotypic linear motion, such as the radial arm maze task (McNaughton *et al.*, 1983; Breese *et al.*, 1989; Wiener *et al.*, 1989). However, this modulation is not found when hippocampal place cells are recorded in an open field (Muller *et al.*, 1987), although place cells recorded in the subiculum and parasubiculum have sometimes been shown to contain a secondary directional correlate, even when the animal is monitored in an open field (Sharp and Green, 1994; Taube, 1995b). Subsequent studies have explored these differences further. Muller *et al.* (1994) monitored the same hippocampal place cell in both an open field and on a radial arm maze, and found that the cell only showed directionality on the radial maze. Similar findings were also reported for hippocampal place cells by Markus *et al.* (1995). These authors also showed that the details of the visual environment had little influence on whether place cells showed a secondary directional correlate. Furthermore, place cells could display directionality in an open field if the animal searched for food at fixed locations and their paths were relatively stereotypic from trial to trial. In sum, investigators currently agree that place cells tend to show directionality when the animal is performing a task that involves linear motion in a stereotypic manner, but will *not* show directionality when the animal is an open field and its movements are much less patterned. Furthermore, these findings indicate that there are *not* distinct populations of place cells, with one group sensitive to the animal's directional heading. Rather, there is something fundamentally different about the type of information encoded by place cells when the animal is on a linear track compared to when it is in an open field (see Mehta *et al.*, 1997, for a recent discussion of this issue).

Another important issue concerns the effect of removing the directional signal on hippocampal place cell firing? McNaughton *et al.* (1995) postulated that if information about directional heading was absent, place cells would fire in a fixed radius about a prominent landmark; thus the place field would be annular in shape. In preliminary studies, Dudchenko *et al.* (1995) and Archey *et al.* (1997) tested this hypothesis by monitoring hippocampal place cells in animals with bilateral lesions of the PoS or ADN. They found that place cells continued to show location-specific firing with both types of lesions. Furthermore, when these animals were monitored in the cylinder without a cue card, place fields remained intact, although they sometimes rotated to a new position. Importantly, there was little evidence showing that the place fields became annular in shape. An unexpected finding from these lesion studies, however, was that many place cells showed directionality within their place fields even in an open field (Archey *et al.*, 1997). This effect was more pronounced in animals with ADN lesions than in animals with PoS lesions. This result is counterintuitive since directional heading information has presumably been severely compromised, if not abolished, by the lesions in these animals. In essence, place cells in these lesioned animals appear to encode more the local view from a particular location. While these findings remain puzzling, further research on this issue is warranted because it could provide an understanding of the precise type of information encoded by place cells.

10.6. HD Cells And Episodic Spatial Memory

How might the hippocampus influence HD cell activity in the PoS and ADN? The PoS receives a major projection from the subiculum (Sorenson and Shipley, 1979), which is the primary output target of the hippocampus. Previous studies that have monitored single-unit activity in the subiculum have reported only location-specific firing correlates, although some subicular cells were modulated by the animal's directional heading *within the place field*

of the open field environment (Barnes *et al.*, 1990; Mizumori *et al.*, 1992; Sharp and Green, 1994). In addition, anatomical findings have not shown an ADN projection to the subiculum (Wyss *et al.*, 1979) and only sparse, if any, projections from the subiculum to the ADN (Meibach and Siegel, 1977; Donovan and Wyss, 1983; Witter *et al.*, 1990). However, it is possible that hippocampal place cells could influence or contribute to the PoS HD cell signal, either through their spatial processing or mnemonic functions. Golob and Taube (1997a) reported that lesions of the hippocampus did not disrupt the HD cell signal in either the PoS or ADN, indicating that the HD cell signal must be generated by structures external to the hippocampus. The authors also reported that each HD cell established a new preferred direction when the lesioned animal was placed into a novel environment, and more importantly, this new preferred direction usually remained stable across days in the novel environment. This finding is surprising because one would expect that animals without a hippocampus would have difficulty recalling their previous spatial context, particularly if their only experiences in that environment were subsequent to the lesions (see Kim and Fanselow, 1992). Thus, the stability in the preferred direction spanned a length of time that usually results in memory impairments in animals with hippocampal lesions (O'Keefe and Nadel, 1978; Squire and Zola-Morgan, 1991; Cohen and Eichenbaum, 1996). This stability apparently reflects the encoding and retrieval of new spatial information about the environment by HD cells, and suggests that some types of episodic spatial information can be stored and maintained over time without a hippocampus. These findings are consistent with the notion postulated by McNaughton *et al.* (1995; Skaggs *et al.*, 1995) who argued that the binding together of spatial relationships among different environmental features through experience takes place in the cortex.

To further determine whether the hippocampus is required for the storage of episodic spatial information, Golob and Taube (1997b) 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 orienting cue. When an 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 hr delay, the cue was rotated by 90° and the HD cell was monitored again. Golob and Taube (1997b) reported 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. These results show that the hippocampus is *not* required for the establishment of stimulus control by a novel cue in ADN HD cells.

10.7. HD Cell Activity And Lesions Of The Vestibular System

Several investigators have postulated that the vestibular system plays an important role in updating the HD cell signal when an animal turns its head (McNaughton *et al.*, 1991, 1995; Skaggs *et al.*, 1995; Blair, 1996; Touretzky and Redish, 1996). Consistent with this notion are findings that humans with vestibular dysfunction have an impaired sense of directional orientation (Heimbrand *et al.*, 1991; Brookes *et al.*, 1993) and animals with vestibular damage are impaired in orientation and navigational tasks (Potegal *et al.*, 1977; Miller *et al.*, 1983; Matthews *et al.*, 1989). To explore the role of the vestibular system in HD cell discharge, Stackman and Taube (1997) examined HD cell properties in labyrinthectomized animals. Interestingly, lesions of the vestibular system, through intra-tympanic injections of a neurotoxin, abolished the directional firing properties of ADN HD cells. The time course of disruption in the directional firing properties paralleled the loss of vestibular function as assessed by a contact-righting reflex. The disruption of directional firing was quite evident despite the continued presence of all the visual landmarks within the room. Furthermore, vestibular lesions also disrupted the influence of angular head velocity upon ADN single unit firing rates. Based on the findings that bilateral vestibular nerve transection (Waespe *et al.*, 1992) or unilateral labyrinthectomy (Ris *et al.*, 1995) only disrupted the modulation of firing in vestibular neurons, but did not interfere with their high tonic firing rates, the loss of directional activity in the ADN following chemical labyrinthectomy is unlikely to be due to the absence of a tonic discharge signal from the vestibular nuclei. Rather, it is the loss of modulation in the vestibular signal that appears to culminate in the disruption of the directional signal. Finally, recent work by Stackman and Taube (unpublished observations) have shown that disruption of the directional signal can also be brought about by temporarily inactivating the vestibular system through intra-tympanic injections of tetrodotoxin. In sum, 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.

How vestibular information reaches the hippocampal formation or limbic thalamic areas is poorly understood. Anatomical studies of the cortical projections of the vestibular nuclei have been confined mostly to the cat and primate and very little is known about these pathways in the rat (for review, see Wiener and Berthoz, 1993). The conventional pathway described in primates and cats entails vestibular information conveyed from the vestibular nuclei to the parietal insular vestibular cortex (PIVC) via the ventral posterior thalamus (Abraham *et al.*, 1977; Lang *et al.*, 1979; Grüsser *et al.*, 1990a). In turn, the vestibular cortex provides information to the ADN and other limbic system structures via its connections, either directly with the posterior cingulate cortex, or indirectly through area 7 of the parietal cortex (Guldin *et al.*, 1992; Olson and Musil, 1992a). In support of these pathways, neurons in the ventral posterior thalamic areas can be modulated by angular rotation of the animal (Büttner and Henn, 1976; Büttner *et al.*, 1977) and

vestibular stimulation can evoke responses in neurons in the primate parietal sulcus (Schwarz and Fredrickson, 1971). Furthermore, Grüsser *et al.* (1990a) reported that neurons in the PIVC respond to angular rotation of the animal's head, but, interestingly, not to static head tilt or linear motion. The PIVC is not an exclusive area for vestibular processing, however, because neurons within this area can also be modulated by visual and tactile stimulation of the neck and shoulder (Grüsser *et al.*, 1990b). Based on the anatomical inputs to the PIVC, Grüsser *et al.* postulated that the PIVC serves to recognize and control head and body position in space. To date, most of the structures connected with the PIVC are not recognized as having major direct pathways to limbic areas involved in spatial information processing, although Insausti *et al.* (1987) reported a direct projection from the insula to the entorhinal cortex. Nonetheless, the presumed vestibular pathways to the hippocampal formation are through multisynaptic projections to the perirhinal and entorhinal cortices.

Evidence for these vestibulo-cortical pathways in the rat have yet to be demonstrated, but the presence of cells in the rat posterior parietal area encoding angular head motion is consistent with the findings in primates (McNaughton *et al.*, 1994). Alternatively, other anatomical studies have revealed a shorter route by which vestibular information may reach the ADN. In rats, the medial vestibular nuclei, which receive a large input from the horizontal semi-circular canal and is ideally suited for providing information concerning angular head velocity in the horizontal plane, projects to the dorsal tegmental nucleus (Liu *et al.*, 1984), which in turn projects to the lateral MN (Shibata, 1987; Allen and Hopkins, 1989; Gonzalo-Ruiz *et al.*, 1992). Because the lateral MN projects directly to areas of the ADN where HD cells have been localized (Seki and Zyo, 1984; Shibata, 1992), Taube *et al.* (1996a) postulated that angular head velocity information may reach the ADN through this subcortical route.

10.8. Lesions In Areas Containing HD Cells Lead To Impairments In Spatial Tasks

The presence of HD cells in several structures of the Papez circuit suggests that these areas are important components of a neural network mediating spatial and navigational abilities. One question that arises is whether animals with lesions in selected components of this circuit are impaired in spatial tasks requiring the use of directional information. Several studies have tested rats with various brain lesions in the Morris water maze task, a task in which the rat needs to find a hidden platform in a large tank filled with cloudy water. In general, lesions in any part of the HD circuit led to post-operative acquisitional deficits (PoS: Schenk and Morris, 1985; Taube *et al.*, 1992; ADN: Sutherland and Rodriguez, 1989; lateral MN: Sutherland and Rodriguez, 1989; retrosplenial cortex: Sutherland *et al.*, 1988; lateral dorsal thalamus: Palmer and Sutherland, 1994). Lesions in areas that project to the HD circuit also led to deficits in the Morris water task. For example, rats with parietal cortex lesions were impaired in acquiring the standard version of the water maze task (random entry point), as well as learning to escape onto the platform even when released from the same entry point each time; rats were also mildly impaired at retention of this task, when training occurred prior to the lesions (Kolb and Walkey, 1987; Kolb *et al.*, 1994; Save and Moghaddam, 1996; but see Kolb *et al.*, 1983). In addition, disruption of vestibular information by mildly spinning a rat before testing in the Morris water task led to performance deficits (Semenov and Bures, 1989). Lesions of the vestibular system also impair performance on various types of spatial tasks that require accurate directional orientation (Potegal *et al.*, 1977; Miller *et al.*, 1983; Matthews *et al.*, 1989).

Other studies have examined the performance of animals with brain lesions in other types of spatial tasks that employed the use of spatial working memory, either in a radial arm maze or spatial alternation task. In most cases again, lesioned animals showed deficits in task acquisition when trained post-operatively (PoS: Taube *et al.*, 1992; ADN: Aggleton *et al.*, 1995; but see Beracochea *et al.*, 1989; lateral MN: Rosenstock *et al.*, 1977; Saravis *et al.*, 1990; Sziklas and Petrides, 1993; Aggleton *et al.*, 1995; but see Jarrard *et al.*, 1984; retrosplenial cortex: Markowska *et al.*, 1989; but see Neave *et al.*, 1994; lateral dorsal thalamus: Mizumori *et al.*, 1994).

10.9. Integration Of Findings And A Conceptual Model

How can the lesion, behavioral, and firing property studies be incorporated into a conceptual framework? The anatomical diagram in Fig. 5 provides a useful starting point. The lesion studies clearly show the importance of the ADN for generating HD cell discharge in the PoS, as lesions of the hippocampus, lateral dorsal thalamus, or PoS do not abolish directional-specific firing in the ADN. The labyrinthectomy findings also show the critical role played by the vestibular system in generating the signal.

How does the parietal cortex, which is traditionally viewed as a spatial processing area, fit into this scheme? In primates, the posterior cingulate cortex is connected with both the ADN and areas of the posterior parietal cortex that contain highly processed visual information from striate cortex. Many neurons within the posterior parietal area appear to encode the spatial relationships of objects with respect to eye and head positions. For example, the receptive fields of neurons within area 7a of primates can be modulated either by the animal's eye (Andersen *et al.*, 1990) or head position (Brotchie *et al.*, 1995). These neurons, working in concert, may signal the direction of gaze with respect to the animal's body, information that would be useful for determining where a visual object is in space. Because visual landmarks are capable of exerting control over HD cell firing, it is possible that information from the visual cortex projects to the ADN and PoS via the posterior parietal and retrosplenial

cortices. Indeed, Mishkin *et al.* (1983) postulated that visual information beyond the visual cortex was processed in two general streams of information: one stream analyzed the spatial characteristics of an object and determined where the object was in space, whereas the second stream analyzed the perceptual features of the object and enabled the subject to identify the object. While the perceptual stream was localized to ventral cortical structures in the temporal lobe, the spatial stream was localized more dorsally in the posterior parietal lobe. There is a similar flow of information from posterior parietal cortex → retrosplenial cortex → ADN in the rat (Reep *et al.*, 1994). Taken together, information concerning the egocentric location of visual landmarks may be transformed and used to update the animal's directional heading in an allocentric frame of reference. This information could then be projected to the hippocampal system through a pathway starting in the posterior parietal lobe and proceeding to the retrosplenial cortex → ADN → PoS → entorhinal cortex → hippocampus. In this manner the hippocampus can integrate highly processed information regarding the animal's directional heading with perceptual information conveyed through the inferior temporal cortex. This integrated material can then be used by the hippocampus to help guide the animal's spatial behavior.

This notion, however, is difficult to reconcile with the finding that ADN HD cell activity was not well-controlled by the cue card in PoS-lesioned animals (Goodridge and Taube, 1997). Furthermore, if one postulates that visual landmark control over HD cell firing arises from either the lateral dorsal thalamic or hippocampal (via subiculum) projections onto PoS HD cells, then it is difficult to explain why the lateral dorsal thalamus or hippocampal lesions did not affect cue control over PoS HD cells. One possible explanation is that the PoS lesions may have led to an inability to accurately discriminate which landmarks to use for orientation. In this situation, ADN HD cells would still have had landmark information available to them, but the cells were unable to detect which landmark to use. Alternatively, because the PoS projects to the retrosplenial cortex, it is possible that the PoS lesions disrupted the normal flow of information from the retrosplenial cortex to the ADN.

While landmark information may be conveyed to the hippocampus via the ADN → PoS → entorhinal pathway, the anatomical connections also suggest that information concerning the animal's head movements (i.e., idiothetic cues) may enter the limbic system through subcortical structures, such as the dorsal tegmental area. Whereas vestibular information may reach the limbic system via the dorsal tegmental projections to the lateral MN, motor information for a motor efference copy signal may be conveyed to the limbic system via three possible pathways. One route is from the midbrain reticular formation, which is known to process some motor information, to the laterodorsal tegmental nucleus; this latter area also projects to the lateral MN (Satoh and Fibiger, 1986). Second, the striatum, another brain area associated with motor functions, contains projections to the ventral tegmental nucleus (Heimer *et al.*, 1995), which projects primarily to the medial MN (Hayakawa and Zyo, 1984; Shibata, 1987) and then to the ADN (Shibata, 1992). The third possibility is the cortical pathway from motor cortex to area 29c of retrosplenial cortex (Vogt and Miller, 1983), which in turn projects to the ADN (van Groen and Wyss, 1990a). Taken together, because the ADN receives subcortical inputs via the dorsal tegmental area and lateral MN, and cortical inputs from the retrosplenial cortex, the ADN appears to serve as a convergence point for landmark and idiothetic information before it is passed on to the PoS, entorhinal cortex, and hippocampus. If all idiothetic information originates in subcortical structures, then lesions of the lateral MN or dorsal tegmental area should abolish accurate path integration (at least in terms of directional heading).

The role the striatum plays in this circuitry remains unclear, although it may provide some motor information to the HD network. It is likely, however, that striatal HD cells are "downstream" from ADN HD cells because there are no short pathways from the striatum to the ADN. Indeed, van Groen and Wyss (1995) reported direct projections from the ADN to the striatum. Thus, it is possible that the presence of HD cells in the striatum reflects contributions from this pathway. Examining whether striatal HD cells best predict the animal's future or past directional heading could confirm this notion.

11. BRAIN AREAS INVOLVED IN PATH INTEGRATION

What brain areas play a role in maintaining a cell's preferred direction when the animal moves into a novel environment? To explore this issue, HD cells have been monitored in animals with lesions of the PoS or hippocampus while exploring the dual-chamber apparatus (see Section 8.1). Results have shown that the amount of shift in the cell's preferred direction between the familiar and novel environments was much greater in animals with lesions of the PoS or hippocampus than in intact animals (Golob and Taube, 1996; Goodridge and Taube, 1997). These results suggest that both the PoS and the hippocampus are involved in path integration mechanisms that enable an animal to maintain an accurate spatial representation between two contiguous environments, and are consistent with recent hypotheses that the hippocampus is important for the utilization of idiothetic-based cues during navigation (McNaughton *et al.*, 1996; Whishaw *et al.*, 1997; cf., Alyan *et al.*, 1997). For example, Whishaw *et al.* showed that rats with fimbria–fornix lesions did not return to their home area in a direct route following retrieval of food in an open-field—a task which is thought to require the use of path integration. A recent conceptual model by Redish and Touretzky (1997a) proposed that path integration occurred in a loop comprising the hippocampus, subiculum, parasubiculum, and the superficial layers of entorhinal cortex.

12. RELATIONSHIP OF HD CELL ACTIVITY AND BEHAVIOR

One important issue concerning HD cells is what role they play in an animal's behavior. Are they actively involved in guiding navigational behavior? Evidence suggesting a link between HD cells and behavior was recently provided by Dudchenko and Taube (1997) using a radial arm maze and spatial reference memory task. Animals were trained to run down a particular maze arm relative to a visible landmark cue to obtain a water reward. Following rotation of the cue, the animal's maze arm selection and the HD cell's preferred direction shifted in tandem relative to the salient visual cue. Furthermore, when the HD cell's preferred direction did not shift relative to the cue, neither did the animal's behavioral response. These findings are similar to comparable studies with hippocampal place cells (O'Keefe and Speakman, 1987), and provide a necessary first step in demonstrating that HD cells may contribute to a neural system involved in guiding the animal's spatial behavior.

Two studies have explored the relationship of HD cell activity to spatial learning while an animal learned a behavioral task. Mizumori and Williams (1993) trained two rats to perform a working memory radial arm maze task while recording HD cell activity in the lateral dorsal thalamus. Cell monitoring continued during the entire two week training period. For each training session, the number of incorrect arms the animal selected was determined and the HD cell was given a "directionality score" reflecting the degree of directionality it exhibited. The investigators reported that the directionality score was negatively correlated with the number of errors; thus, higher directionality scores were observed in sessions where animals made fewer errors. In contrast to these results, Dudchenko and Taube (1997) monitored ADN HD cell activity over two weeks while animals acquired the spatial reference memory task described in the above paragraph. Results showed that HD cell firing properties, such as peak firing rate, directional firing range, and background firing rate remained relatively stable throughout acquisition. Based on these results, the authors postulated that the coding of directional heading information was independent of the neural systems involved in task acquisition, and that over time, an animal learns to use information provided by the directional system to guide its behavioral responses. Whether different task contingencies or brain areas studied contributed to the differences between these two studies remains to be determined.

13. OTHER BEHAVIORAL CORRELATES OF HD CELLS

Another important issue concerns whether HD cell activity is modulated by the animal's on-going behavior, other than aspects of motor movements. This issue is important because place cells in the hippocampus show multiple behavioral correlates, sometimes even within the same environment (Best and Thompson, 1984; Wiener *et al.*, 1989; also see Berger and Thompson, 1978; Hampson *et al.*, 1993; Markus *et al.*, 1995). For example, many place cells may show location-specific firing in one paradigm, but show time-locked discharge to specific task-related contingencies in other paradigms. One study has also shown that changing the reward location frequently leads to a shift in the place cell's place field (Breese *et al.*, 1989; Markus *et al.*, 1995; cf., Speakman and O'Keefe, 1990). Despite these multiple and plastic representations encoded by place cells, HD cell discharge appears to be quite different, since no study has reported any significant modulation of HD cell activity during performance of a spatial or non-spatial task (Mizumori and Williams, 1993; Wiener, 1993; Dudchenko and Taube, 1997). Except for the movement related correlates described above (see Section 3.3), no study has reported that HD cell discharge was time-locked to a specific behavioral event. Furthermore, moving the reward location to a different radial maze arm also does not lead to a change in the cell's preferred direction, peak firing rate, or directional firing range (Dudchenko and Taube, 1997). In sum, HD cell discharge in each brain area appears to be controlled by very different behavioral parameters than hippocampal place cells.

14. DEVELOPMENT OF SPATIAL ORIENTATION

Several studies have explored the relationship between HD cell activity and the development of an animal's perceived spatial orientation. Studies with rats and humans have demonstrated that the geometry of the environment plays an important role in establishing an organism's orientation. For example, in a task where one corner of a rectangular environment is rewarded, rats make systematic rotational errors and choose one of two 180° opposite corners. These errors occur despite the presence of a salient cue on one wall which, in theory, should disambiguate the two locations and allow for accurate performance (Cheng, 1986; Margules and Gallistel, 1988). Similarly, young children aged 18–24 months also make the same type of rotational errors as the adult rats (Hermer and Spelke, 1994, 1996). By the time humans reach adulthood, however, they accurately perform this spatial reference memory task with ease. To further examine differences in spatial abilities across species, Vallortigara *et al.* (1990) tested 12 day old chicks and found that they preferentially used the salient non-geometric cues over geometric cues (the shape of the enclosure) when both sets of cues were present. These studies suggest that a hierarchy of spatial information may exist that determines the type of cues an animal will use for orientation. In some species, geometric cues are dominant in determining orientation while in other species, or at later times during development, non-geometric features of the environment come to dominate.

The extent to which an animal is disoriented when it is brought into an environment plays an important role in establishing not only its perceived spatial orientation, but also its ability to incorporate

novel landmarks cues into its spatial representation. The difference in performance between disoriented and non-disoriented rats was clearly demonstrated by Cheng (1986) and Margules and Gallistel (1988). In Cheng's study, the rats never had access to cues outside the test apparatus (extra-maze cues) and presumably were not cognizant of their orientation with respect to the external world. These rats chose the incorrect, but geometrically opposite, corner almost as often as the correct corner. However, when the same experiment was conducted in a well-lit room with abundant cues, thus allowing the rats to be cognizant of their orientation with respect to the external world, the rats showed relatively accurate performance (Margules and Gallistel, 1988). Biegler and Morris (1993) also demonstrated that landmark stability, relative to other spatial cues, is important for determining whether an animal will use the landmark to guide its spatial behavior. When a landmark that defined the location of a reward was not perceived to be in a stable spatial framework, the animal's performance in finding the reward was poor. However, when the landmark was consistently in the same position relative to a second landmark, animals showed accurate performance. Apparently, the mere association between a reward and a landmark was insufficient to establish accurate performance; the landmark had to be perceived within a stable spatial framework before it could lead to correct behavior.

Knierim *et al.* (1995) extended these findings to the neural level. These authors monitored HD and place cells from two groups of rats in a cylinder containing a single salient visual cue attached to the wall. One group of rats was hand carried from their cages and placed into the apparatus. Rats in the second group were disoriented on every trip into and out of the recording room (by placing them in an opaque box and gently spinning them back and forth while being carried to the recording environment), and thus were not allowed to form a stable spatial representation between the recording apparatus and the outside world. The authors found that the preferred directions of HD cells and the place fields of place cells recorded from disoriented animals frequently failed to establish a consistent relationship with the cue card, despite the fact that the cue card was the only intentionally introduced stable reference point. Based on these findings Knierim *et al.* postulated that visual landmarks exert control over orientation only after an animal has learned an association between the visual landmark information and its "internal sense" of directional heading as provided by idiothetic cues. When the rats are deprived of forming this link through disorientation, the cells will never form a stable spatial association with the cue card. It is only through active exploration that an animal will establish a consistent relationship between spatial information from landmarks and its own perceived spatial orientation (Poucet, 1993). These findings were consistent with the view that in learning about the spatial relationships of an environment, animals first rely primarily on idiothetic cues, and that landmarks gain control of spatial behavior only after sufficient experience in linking information from idiothetic cues with spatial information from landmarks (Alyan and Jander, 1994).

If the above hypothesis is correct, then rats that are consistently disoriented at the start of an experiment should not be capable of learning to go to a particular location relative to a fixed landmark. Martin *et al.* (1997) and Dudchenko *et al.* (1997b) tested this hypothesis by examining the effects of disorientation on the acquisition of different spatial reference memory tasks. Both studies found that in an appetitively motivated radial arm maze task where one arm was consistently baited, animals that were disoriented before each trial were impaired in their ability to acquire the task relative to animals brought to the test apparatus in a clear container and not disoriented.* However, disoriented animals were able to learn an aversively-motivated Morris water maze and a water version of the radial arm maze under similar training conditions, suggesting that the effects of disorientation may interact with the quality or quantity of motivation involved in a given task. These results suggested that appetitive and aversive spatial tasks are dissociable, and that any impairment due to disorientation is specific to the appetitive radial arm maze task. While the results from the appetitive radial arm maze task can be viewed as consistent with the notion of Knierim *et al.* (1995), the findings in the water maze are difficult to reconcile with their view.

To determine whether the behavioral impairment on the standard radial arm maze task was associated with a lack of landmark stimulus control over the preferred orientations of HD cells, following completion of the behavioral experiments, Dudchenko *et al.* (1997a) monitored HD and place cells in the same animals that showed significant acquisition deficits. Landmark control in the radial arm maze and in a cylinder were assessed by rotating the visual cue card with the animal out of view and then examining the cell's preferred direction. Animals underwent disorientation treatment before and after each recording session. Despite the disorientation, rotation of either the cylinder's cue card or the curtain (for the radial arm maze sessions) resulted in a corresponding shift in the cell's preferred direction. Similar findings were also reported for place cell place fields. These results suggest that the establishment of stimulus control by a landmark does not require a learned association between that landmark and the linkage with idiothetic information. Thus, instability in the HD system is unlikely to account for the impaired performance of the disoriented animals in the radial arm maze. Rather, the impairments are more likely attributed to the animal's inability to utilize stable representations of the environment provided by the HD and place cells.

Another question that arises from these issues is what length of time does an animal need to be

* Animals which were simply placed in an opaque container and carried into the testing room also had difficulty acquiring the task, and suggests that they needed to visually link the two environments in order to perform the task.

exposed to a novel landmark before for it develops control over the cell's preferred direction? Goodridge *et al.* (1998) trained and recorded rats in the cylinder without the cue card. All rats were consistently disoriented before being brought into the recording room. After identifying a HD cell, the investigators introduced the cue card for different lengths of time—1, 3 or 8 min. A cue card rotation session was then conducted to determine if the cue card had gained control over the cell's preferred direction. All 8-min card exposure sessions resulted in a corresponding shift in the cell's preferred direction, while about half of the 1- and 3-min exposure sessions led to a shift. Thus, only a single exposure to a novel cue for a few minutes was frequently sufficient time to enable the cue to acquire stimulus control over HD cell responses. These results were consistent with the findings in the dual chamber experiment discussed above (see Section 9) where only a short exposure to the landmarks in the rectangle was sufficient for them to gain control over the cell's preferred direction in the subsequent conflict experiments (Taube and Burton, 1995). Finally, the reason for the inability of the HD cells to consistently use the cue card for orientation in Knierim's *et al.* study is unclear. The only notable difference between the two studies was the strain and sex of rat they used—Goodridge *et al.* (1998) used female Long-evans rats while Knierim *et al.* (1995) used male Fisher 344 rats.

15. INTERACTIONS AND COMPARISONS WITH PLACE CELLS

There are several interesting points to consider when comparing HD and place cells (for a detailed comparison between the two types of spatial cells, see Table 1 of Muller *et al.*, 1996). Knierim *et al.* (1995) demonstrated that the spatial representation of the environment as encoded by HD and place cells was strongly coupled. Thus, when a shift occurred in the HD cell's preferred direction following a disorientation protocol, a similar shift also occurred in the place field of a simultaneously recorded place cell, suggesting that the same neural information drove the two cells. As with HD cells, place fields also shift when a prominent visual cue is rotated (O'Keefe and Conway, 1978; Muller and Kubie, 1987). Additionally, a place cell's response remains relatively stable when either the visual cues are removed or the animal is recorded in the dark, although sometimes the place fields rotate somewhat to a new unpredictable angular position under these conditions (O'Keefe, 1976; Hill and Best, 1981; O'Keefe and Speakman, 1987; Quirk *et al.*, 1990; but see Markus *et al.*, 1994).

There are several notable differences between HD and place cells in addition to the different types of spatial information they encode. First, a given HD cell will discharge in all environments, while a given place cell will only discharge in selected environments (Kubie and Ranck, 1983). Second, place cells can show discharge in a time-locked manner to specific non-spatial events or other behaviors emitted by the animal. In contrast, HD cell discharge is not modulated by these events or behaviors. Third, on a subjective level, HD cell discharge appears more "regular" and predictable than place cell firing. HD cells will consistently fire at a specified rate whenever the animal points it head in the cell's preferred direction. In contrast, place cell firing is more irregular—for example, sometimes the cell may fire 8–10 spikes when the animal moves through the place field, while at other times, the cell may fire only 2–3 spikes when the animal runs what appears to be the same path through the place field.

16. NEURAL NETWORK MODELS

Several investigators have proposed network models for how the HD cell signal is generated and updated over time. All of the models are based on some type of attractor network (Skaggs *et al.*, 1995; Blair, 1996; McNaughton *et al.*, 1996; Redish *et al.*, 1996; Sharp *et al.*, 1996; Zhang, 1996). This network contains a "ring" of HD cells that are interconnected with both excitatory and inhibitory connections; each of the networks differ somewhat on how the inhibitory connections are modeled. All of the attractor network models will self-generate a "hill" of excitation that corresponds to one directional heading. The hill of excitation can then be moved around to different angles depending on external influences, such as inputs from the vestibular or visual landmark systems. Each of the attractor networks can accurately simulate the firing rate vs. HD tuning curves of experimental data. Zhang (1996) presented a mathematical model using a "dynamic shift" mechanism to account for HD cell firing in the ADN. His model was able to account for the anticipatory discharge observed in ADN cells by varying the connection strengths amongst cells. The connection strengths for each cell depend upon the direction, speed, and acceleration of the animal's head turn. Redish *et al.* (1996) also demonstrated that two attractor networks which were coupled together using a series of "offset" connections can simulate the anticipatory properties of ADN cells. Offset connections are excitatory pathways between an HD cell of one attractor network and HD cells tuned to preferred directions on either side of it in the second attractor network. In the Redish *et al.* (1996) model, the anticipatory nature of ADN cells is achieved by a set of offset connections projecting from the PoS to the ADN. Although each ADN HD cell contains two sets of offset connections—one for clockwise head turns and one for counter-clockwise head turns—only one set is active at a given time depending on the direction the head is turning. Cell activity can continue when the animal's head is still by having a set of matching connections (cells tuned to the same preferred direction) between the PoS and ADN.

Another important feature of an attractor network is the manner by which the hill moves to a different directional heading. Movement to a new stable state occurs either by having the hill pass through all the intermediary angles (i.e., directional headings in between the initial and final preferred directions) or by an abrupt shift without passing

through the intermediate angles. In the latter condition, the hill at one directional heading decreases as the hill at another directional heading increases. Abrupt shifts in a cell's preferred direction have been observed in many studies. For example, in the cue conflict situations (see Section 9), when the cue card was reintroduced into the enclosure (Goodridge and Taube, 1995), or when the rat locomoted back into the passageway/rectangle environment (Taube and Burton, 1995), the cell's preferred direction was observed to have already changed by the time the animal made its first pass through the new preferred orientation. Thus, all the directional shifts observed by these researchers were abrupt ones. Although the preferred direction never appeared to pass through intermediary angles as it shifted to a new direction, it is possible that the shift occurred too quickly to be detected by the recording methods.

Zhang (1996) and Redish and Touretzky (1997b) reported that when an abrupt shift occurred in their network models, an HD cell would pass through a short phase (on the order of 150–200 msec) where the cell would discharge at a lower firing rate in one of two different directional headings—its initial preferred direction and the preferred direction it was shifting to. This observation could be tested experimentally by examining whether HD cell discharge in the initial preferred direction decreased gradually when it was undergoing a shift to a new orientation. In addition, for both models, when the shift to a new orientation was small, the cell's preferred direction shifted to the new orientation by passing through the intermediate directions. This prediction can also be tested experimentally by recording from several HD cells simultaneously and determining whether HD cells with intermediate preferred directions discharged during the shift. Interestingly, humans experiencing visual reorientations do not report being spun through a series of intermediate orientations, although it is possible that the perception of the intermediate orientations are suppressed in a manner analogous to how a perceived visual image is suppressed during a saccade. In sum, while these observations do not preclude the possibility of an attractor-type network, they do indicate that any network model must contain inputs or gates that can shift the hill to a new directional heading in the order of a few hundred msec.

In a preliminary report Skaggs (1997) reported how HD cells would respond when one of two salient visual cues was rotated. If one cue was rotated by a small amount, the model predicted that the HD cell system would shift to a new orientation that was the "average" of the two salient cues. However, if one of the cues was rotated by a large amount, then the HD cell system would align with only one of the cues and appear to ignore the other cue. The averaging process was sometimes observed in the cue conflict situation of the dual-chamber apparatus experiments discussed above in Section 9, although in most instances the HD cell system remained aligned with one of the two environments (i.e., the rotated cylinder condition or the rectangle) (Taube and Burton, 1995).

While many of the findings discussed in this review are consistent with these network models, there are several findings that are difficult to reconcile with them. These findings include:

1. Some of the models can account for the anticipatory nature of the ADN HD signal (Redish *et al.*, 1996; Sharp *et al.*, 1996; Zhang, 1996), but these models use cells which all have the same fixed lead time. As mentioned in Section 4, each ADN HD cell appears to be tuned to a specific lead time; thus all cells within the ADN are not uniformly tuned to the same anticipatory shift (Blair *et al.*, 1997; Taube and Muller, 1998).
2. Both the Blair and Sharp (1995; Sharp *et al.*, 1996) and Redish *et al.* (1996) models have difficulty accounting for the lesion study by Goodridge and Taube (1997), who reported that ADN cells had increased anticipatory shifts following PoS lesions. Both models require an intact PoS to achieve anticipatory firing in the ADN.
3. Self-generating attractor networks predict that disruption of projections into the network should not abolish the directional signal, since it is self-generated by neurons within a brain region and the inputs are viewed more as a modulatory influence where the hill is moved around, but are not responsible for generation of the hill. Thus, any disruption of the network would be expected to either freeze the hill in place, or have the hill continually moving. In the former situation, freezing the hill would mean that some HD cells should be in a tonic state of activation and discharge constantly, while other HD cells would be permanently silent and never discharge. Following the labyrinthectomies, no previously identified HD cells were found to contain steady states of continual firing (Stackman and Taube, 1997). In the situation where the hill is continually moving, one would expect to observe periodic bursts of activity among HD cells in lesioned animals. While bursty cells were observed in vestibular-lesion animals, they did not originate from cells which initially showed directional activity (Stackman and Taube, 1997). HD cells in the ADN never showed the periodic burst pattern following the vestibular lesions.
4. The results from the passive restraint experiments (see Section 5), and the experiments where the rat is passively transported on a cart into a novel chamber (see Section 8.2), are problematic for some of the network models because these models use only the vestibular system to provide information about angular motion, and in both experiments the vestibular system was intact, but HD cell activity was abnormal.
5. One key feature of the attractor networks is the inhibitory connections between HD cells that have opposite preferred firing directions. While there may be an extensive local inhibitory network within the PoS, there is little evidence for such a network within the ADN or lateral MN. The major inhibitory synapses in both the rat ADN and lateral MN arise from GABAergic neurons that are external to these structures. For the ADN, the afferent projections originate in the

reticular thalamus (Gonzalo-Ruiz *et al.*, 1991; Shibata, 1992), a pathway that is not present in the cat (Steriade *et al.*, 1984). The ADN also contains a projection back to the reticular thalamus (Seki and Zyo, 1984). All GABA containing neurons within the lateral MN are thought to arise from the dorsal tegmental area, as systemic inhibition of GABA metabolism 90 min prior to paraformaldehyde fixation removes all GABA immunoreactive cells within the lateral MN (Gonzalo-Ruiz *et al.*, 1993; Wirtshafter and Stratford, 1993).

17. DIRECTIONAL CORRELATES IN OTHER SPECIES

To date, HD cells have only been reported in rats. This circumstance is mostly attributed to the fact that studies in non-human primates have generally not recorded from areas where HD cells have been identified in rats. Recordings in primates, however, have revealed several interesting types of spatial cells. Rolls and O'Mara (1995) reported neurons in the hippocampus and parahippocampal region that were responsive to where the monkey was looking in its environment. Other hippocampal neurons appeared to discharge depending on where a stimulus was shown (Rolls *et al.*, 1989) or the animal's whole-body movements through space (O'Mara *et al.*, 1994). Other recording studies in non-hippocampal areas have also reported interesting cell types that contain spatial correlates, but in each case the correlates are based on retinal-, head-, or body-centered coordinates. Examples include neurons in the posterior parietal cortex (area 7) that respond to: (1) the location of an object in head-based coordinates, as well as the orbital position of the eye (Andersen *et al.*, 1985) and (2) both visual stimuli and saccades, but are also modulated by the animal's head position in body-centered coordinates. These neurons may encode the animal's direction of gaze (Brotchie *et al.*, 1995). Neurons in the dorso-medial superior temporal cortex (area MSTd) respond to visual information that is expanding away from a focal area of space; this type of coding could provide information about the direction of movement through space (Bradley *et al.*, 1996). Finally, the activity of neurons in the posterior cingulate cortex in various species have also been shown to be modulated by either the direction of eye movement or the orbital position of the eye and are more clearly linked to sensory, rather than motor, processes (rabbit: Sikes *et al.*, 1988; cat: Olson and Musil, 1992b; primate: Olson *et al.*, 1993). Note, though, that all these types of spatial correlates are referenced to the animal in some manner. Although these signals may play a role in generating the HD signal, a major coordinate transformation is required in order to obtain a HD signal based on world-centered (allocentric) coordinates. Where this coordinate transformation takes place is not currently known.

It is beyond the scope of this review to provide a summary of the spatial properties of cells in non-mammalian species. Nonetheless, it is noteworthy that some species of insects are capable of remarkable feats of navigation and path integration (e.g., ants: Wehner and Srinivasan, 1981; Müller and Wehner, 1988; bees: Gould, 1986). Similarly, certain species of birds appear able to detect the Earth's magnetic field and use this information for homing and navigation (for review, see Bingman, 1990). Interestingly, the responses of some cells in several groups of nuclei in the pigeon and bobolink are effected by changes in an artificially applied magnetic field (Semm *et al.*, 1984; Semm and Demaine, 1986; Beason and Semm, 1987; for an interesting series of articles discussing the evidence for and against magnetic sensitivity in birds, see *Animal Learning and Behavior*, 1987, volume 15, issue 2).

18. FUNCTIONAL IMAGING STUDIES IN HUMANS

The brain areas involved in topographical orientation in humans have recently begun to be investigated using functional imaging techniques such as PET and functional MRI. Most of these studies have used movie films or virtual-reality environments to determine which brain areas are activated. Using PET, Maguire *et al.* (1998) observed activation of the right hippocampus, bilateral parahippocampal region, and the precuneus in a task where subjects viewed a film of novel urban environments and later had to identify whether they had seen various scenes from still photographs. In another paradigm, Maguire *et al.* (1998) had subjects explore a virtual reality environment under two conditions. In the first condition, the subjects explored a complex shaped environment that was devoid of objects and textures. In the second condition, the subjects explored a similar environment but one that contained textures and numerous salient objects. In both conditions, researchers reported widespread activation in several areas including occipital, medial parietal, and occipito-temporal regions, but the right parahippocampal region was only activated in the condition when objects and textures were present.

Using fMRI Aguirre *et al.* (1996) also tested subjects' topographical memory and found activation in the parahippocampal region during both the learning and recall phases of the task. Interestingly, in a second study Aguirre and D'Esposito (1997) found a difference between activation sites depending on the type of knowledge utilized by the subject. Consistent with the lesion studies above, they reported that dorsal brain areas (superior, inferior, and posterior parietal) were activated more when the subject had to make judgments regarding the spatial configuration of items and that ventral areas (parahippocampus, inferior temporal, occipital) were activated more when the subject had to make judgments about the visual appearance of the items.

In a recent PET study Maguire *et al.* (1997) tested London-based taxi cab drivers while they were recalling complex routes around London (a familiar environment) and when they were recalling well-known landmarks, some of which they had experienced many times previously and some of which they had never visited before and did not attach a

distinct spatial association to. For the tasks requiring recall of items that utilized topographical information (routes around London and well-known landmarks), the authors found activation in parahippocampal gyrus, posterior cingulate cortex, precuneus, and cerebellum, the same areas reported in the fMRI and other PET studies discussed above. Taken together, these studies indicate that recall of either topographical episodic or topographical semantic memory activates a common set of neural substrates. In addition to these activated areas, Maguire *et al.* reported that the right hippocampus was activated during the recall of specific routes by the taxi cab drivers. Although the previous studies did not show specific activation in the hippocampus, the authors attributed this result to the fact that in this study, the subjects had to rely on long-term memory involving more complex routes than in the virtual reality maze tasks.

19. TOPOGRAPHICAL DISORIENTATION IN HUMANS

The clinical literature contains numerous cases of humans who have topographical disorientation. The extent to which this disorder arises from an impaired sense of direction is unclear and probably varies depending on the nature of the deficit. A diagnosis of topographical disorientation can include a number of symptoms: (1) loss of awareness in the spatial relationships of objects to one another, (2) visual object agnosia—an inability to recognize objects or landmarks, (3) unilateral neglect—inattention to portions of external space, (4) loss of topographic memory—the failure to retrieve topographical knowledge, (5) loss of the ability to draw or verbally describe a route, but with the retention of navigational abilities. Because visual object agnosia and unilateral neglect are attributed to impaired perceptual systems, the classification of a pure topographical disorder is usually reserved for disabilities that can be distinguished from perceptual difficulties. Topographical disorders are generally classified into one of two broad categories: topographical agnosia and topographical amnesia (for historical reviews and descriptions see Paterson and Zangwill, 1945; Benton, 1969; De Renzi, 1982). Topographical agnosia is sometimes further subclassified into two groups. In one group, the patient usually feels lost and does not recognize familiar features as landmarks, although they retain the ability to identify classes of objects such as buildings or terrain features. In the second group, patients usually recognize the items as landmarks, but are not cognizant of their spatial relationships. In topographical amnesia the patient is unable to learn and recognize routes, as well as the spatial relationships of novel items. This disorder is also frequently subdivided into two levels: 1) deficits in learning and recalling the spatial relationships of items, and 2) difficulties in remembering specific landmarks. Although the latter condition contains mnemonic elements similar to topographical agnosia (i.e., the inability to recognize and identify items as landmarks), there is a fine distinction between these two conditions. The mnemonic deficit in agnosia reflects the inability to recognize an object as having spatial significance, and the disorientation schema is defined as a higher perceptual disorder. In contrast, with topographical amnesia, the deficit lies more in the patient's sense of familiarity with the landmark. Patients usually report they are unfamiliar with a particular place because they have never seen or been there before. What is common to both disorders is that there is no general mnemonic impairment for other categories, as the memory loss appears confined only to items of spatial importance. Finally, note that an impairment in any of these processes would culminate in feelings of disorientation, difficulty at route finding, and getting lost.

In general, the brain areas damaged in patients displaying topographical disorientation usually include portions of the hippocampal, parahippocampal, medial occipital, or posterior parietal regions. Which of these areas are critical for manifesting the disorder is unclear and usually depends on whether the patient is classified with topographical agnosia or amnesia. Furthermore, because topographical disorientation can arise from various cognitive deficits and different cognitive batteries test different functions, it is easy to understand how ambiguities have arisen in ascribing various spatial functions to different brain areas. Nonetheless, damage to the extrastriate cortex in the medial occipital and fusiform areas is usually associated with topographical agnosia and is frequently, but not always (see McCarthy *et al.*, 1996), accompanied by some degree of prosopagnosia (Cogan, 1979; Hécaen *et al.*, 1980; Cummings *et al.*, 1983; Landis *et al.*, 1986). In contrast, patients with damage to the posterior parietal lobe usually are classified with having the second form of topographical agnosia—they can recognize landmarks, but have a poor understanding of their spatial configuration with one another (De Renzi, 1982; Hublet and Demeurisse, 1992). The deficits are readily apparent when they are asked to draw sketch maps representing the spatial relationships of objects. Interestingly, a recent study reported three cases with a similar clinical picture following damage to the posterior cingulate cortex (Takahashi *et al.*, 1997), which is comparable to retrosplenial cortex in rats.

Patients with damage to parahippocampal and surrounding temporal lobe regions have also been reported to have topographical disorders. These patients are usually classified as having topographical amnesia and in each case a mnemonic component to the deficit can be identified. Pallis (1955) and Whiteley and Warrington (1978) reported patients who had difficulty in recognizing and recalling landmarks, but had no difficulty in drawing or verbally describing the route. However, when they were confronted with the actual route, they couldn't perform it—presumably because they couldn't recognize the landmarks, although these patients had normal memory for other classes of information. Habib and Sirigu (1987) reported four cases classified as topographic amnestics with the common damaged area as the right parahippocampus/temporal lobe. In particular, these patients had difficulty navigating unfamiliar environments. Finally, it

should be noted that not all cases of topographical disorientation fall into well-defined categories. For example, Bottini *et al.* (1990) reported a patient who had a lesion in the splenial area of the corpus callosum that extended to the right temporal lobe. Although this patient was classified as having topographical amnesia and was able to recognize familiar landmarks, he was unable to describe the map of his apartment or well-known routes in town. Furthermore, he could not learn new routes. A case of topographical amnesia was also reported for a patient with an angioma in the right cingulate cortex (Cammalleri *et al.* 1996).

Several studies have examined spatial abilities in patients who have undergone medial temporal lobe resection (usually for intractable epilepsy). Because the lobectomies usually included the hippocampus and portions of the overlying parahippocampal cortex, it is difficult to ascribe deficits to a particular region. Nonetheless, impairments in such patients can best be characterized as poor spatial working memory (Smith and Milner, 1981; Abrahams *et al.*, 1997; Feigenbaum *et al.*, 1996). They can navigate accurately in familiar surroundings, but get lost in new ones. Similarly, with their eyes closed they have difficulty pointing to remembered locations of objects they have just viewed. A recent study also showed that patients with similar temporal resections were impaired at topographical judgments after navigating through a virtual-reality environment (Maguire *et al.*, 1996a).

Patients with Alzheimer's disease, a disease often associated with hippocampal and parahippocampal degeneration, often feel disoriented, frequently get lost, and have poor spatial knowledge (De Leon *et al.*, 1984). Indeed, Alzheimer originally reported that his demented patients were frequently disoriented as to time and place and had difficulty navigating familiar environments, such as their homes (cited in Bick *et al.*, 1987). Henderson *et al.* (1989) showed that patients with Alzheimer's disease had a higher incidence of symptoms characterized as spatial disorientation compared to aged matched controls. Tests examined the frequency of (1) wandering, (2) getting lost indoors, (3) getting lost on familiar streets, and (4) being unable to recognize familiar surroundings. Although the authors attributed the deficits to right inferior parietal damage, no evidence was provided to support this notion and given that the patients had Alzheimer's disease, it is more likely that they had considerable hippocampal pathology, as well as damage to the PoS (Kalus *et al.*, 1989; Akiyama *et al.*, 1990) or limbic thalamus (Braak and Braak, 1991). Finally, it is worth noting that not all patients with bilateral medial temporal lobe dysfunction are reported to be topographically disoriented, as is demonstrated by the classic cases of H.M. and R.B. (Milner *et al.*, 1968; Zola-Morgan *et al.*, 1986). Whether these subjects indeed had intact topographical abilities or the examiners were simply not aware of the deficits because of the absence of formal spatial testing is unclear.

Unfortunately, none of the above clinical studies experimentally examined a patient's path integration abilities or their sense of direction in a large-scale environment. The one area where clinical patients have been tested for their sense of direction involves patients with vestibular system damage. These patients usually have a poor sense of direction while in the dark, but show no deficits in lit conditions (Brookes *et al.*, 1993; Heimbrand *et al.*, 1991). Thus, with cortical areas intact, they have no difficulty navigating around familiar environments in the light and appear to have a normal representation of space. Finally, although the ADN appears to play a key role in the HD signal, I am unaware of any clinical studies of patients with damage confined bilaterally to this nucleus.

20. CONCLUSIONS AND KEY UNANSWERED QUESTIONS

In conclusion, HD cells represent an allocentric spatial signal concerning the animal's directional heading. The firing properties of these cells make them attractive candidates for studying how the central nervous system processes higher cognitive functions. Specifically, this spatial signal provides a model system for examining how primary sensory information, entering through various sensory pathways, is transformed into a "higher level cognitive signal" representing the organism's spatial orientation. The mechanisms that accomplish this transformation are unknown. Although HD cells have been identified in several brain areas, each area's functional contribution to the signal and to the animal's behavior are poorly understood. It appears that the signal arises from the ADN, or structures afferent to it, and that both vestibular and motor information play important roles in generating the signal. Given the prominent projections from the lateral MN and retrosplenial cortex to the ADN, it will be important for future studies to conduct lesion experiments in these two areas while recording cells in the ADN. If the vestibular signal is conveyed to the ADN via the dorsal tegmental nucleus and lateral MN, then lesions of either structure should abolish directional activity in the ADN.

There are several other important issues that await clarification and warrant further study.

1. How does the brain use the information provided by HD cells to guide the animal's behavior? In addressing this issue, it will be useful to develop more demanding navigational tasks that require the animal to utilize its sense of directional orientation.
2. Although visual landmarks exert strong control over a cell's preferred direction, HD cells also receive salient inputs from idiothetic cues. Under normal circumstances, the two types of cues act together, but the question remains where in the brain do the two systems converge? In addition, how does the information from one cue system come to dominate over the information from the other system? And finally, how and where in the brain are the computations involved in path integration performed?
3. Why do different HD cells have different peak firing rates and what functional implications does this serve in the HD network?

4. Because HD cells appear to encode directional heading within the azimuth plane, the question arises how these cells or other cells in the brain encode directional heading in the pitch and roll planes. In addition, how are different height elevations encoded? Is it similar to encoding the relationship between two rooms that are next to one another?
5. Because eye movements probably play a small role in attentional and orientation systems in rats compared to primates, it will be important for future studies to demonstrate the presence of HD cells in a primate model—either human or nonhuman.
6. Do HD cells fire during sleep? To date, there have been no reports concerning the nature of HD cell discharge during sleep. Given the interesting finding that place cells which were active together during awake periods when exploring a novel environment were reactivated during ensuing periods of slow-wave sleep (Wilson and McNaughton, 1994), it would be interesting to determine how HD cells discharge during sleep.

Answers to each of these questions will advance our knowledge of the neural mechanisms underlying spatial cognition. Studying the neural mechanisms underlying the HD cell signal provides an excellent opportunity for# understanding how the mammalian nervous system processes a high level cognitive signal.

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