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Processing the Head Direction Cell Signal: A Review and Commentary

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ABSTRACT: Animals require information about their location and directional heading in order to navigate. Directional information is provided by a population of cells in the postsubiculum and the anterior thalamic nuclei that encode a very accurate, continual representation of the animal's directional heading in the horizontal plane, which is independent of the animal's location. Recent studies indicate that this signal 1) arises either in the anterior thalamic nuclei or in structures upstream from it; 2) is not dependent on an intact hippocampus; 3) receives sensory inputs from both idiothetic and landmark systems; and 4) correlates well with the animal's behavior in a spatial reference memory task. Furthermore, HD cells in the anterior thalamic nuclei appear to encode what the animal's directional heading will be about 40 ms in the future, while HD cells in the postsubiculum encode the animal's current directional heading. Both the electrophysiological and anatomical data suggest that the anterior thalamic nuclei and/or the lateral mammillary nuclei may be the sites of convergence for spatial information derived from landmarks and internally-generated cues. Current evidence also indicates that the vestibular system plays a crucial role in the generation of the HD cell signal. However, the notion that the vestibular system is the sole contributor to the signal generator is difficult to reconcile with several findings; these latter findings are better accounted for with a motor efference copy signal.

KEY WORDS: Orientation, Navigation, Postsubiculum, Anterior Thalamus, Papez Circuit, Vestibular System, Motor Efference Copy.

INTRODUCTION

One of the more challenging topics in neuroscience today is understanding how sensory and motor information is integrated in the nervous system to culminate in accurate behavioral responses. Proper integration of this information is important for not only correct motor responses, such as placing your hand on a visually presented target, but is also critical for the ability to successfully navigate from one place to another. In order to navigate successfully, an organism requires knowledge about its orientation in the environment with respect to a set of cues. These cues can be derived from either external features of the environment, such as landmarks, or they can be derived from internally

generated cues about the animal's movements through space. Internally generated cues are often referred to as idiothetic cues and include information from the vestibular apparatus, proprioceptive receptors, motor efference copy, and optic flow. The use of idiothetic cues enables an organism to continually monitor its movements through space and provides the basis for a method of navigation called path integration. While path integration is an effective means of navigation, its accuracy diminishes over long distances and times because any small error made by the animal gets compounded over time. Therefore, to improve their navigational accuracy animals rely on landmarks to reset and update their orientation. In sum, animals utilize information from two distinct spatial systems for successful navigation: landmarks and path integration.

To maintain spatial orientation, an organism's central nervous system must be able to integrate and transform sensory information from several different modalities. For example, sensory information first received by the head and body in an egocentric (body-centered) coordinate frame must be transformed into a reference frame based on allocentric (world-centered) coordinates. In addition, spatial information concerning landmark and idiothetic cues has to converge at some level within the brain. For instance, information regarding angular and linear head motion must be integrated with information concerning the organism's orientation with respect to visual landmarks in the environment. The final process produces a spatial representation for orientation that is based on an allocentric reference frame. Many investigators believe that to achieve this egocentric-allocentric transformation, both humans and animals somehow maintain a mental representation (or cognitive map) of the environment, and depend on this map when transforming and interpreting sensory cues [30].

The brain sites for the coordinate transformation have not been definitively determined, but areas of the hippocampal formation, thalamus, and posterior parietal cortex are most likely involved. Two types of spatial information are essential for orientation: location and directional heading. Previous studies have identified cells in the hippocampal formation that encode the animal's location within the environment; these cells are referred to as place cells [29]. Although the firing rates of place cells are modulated by the animal's directional heading in some appara-

tuses [21], the cells do not convey information about the animal's directional heading when the animal is in an open field [28]. Thus, other types of cells in the nervous system are required in order to encode information about the animal's directional heading.

HEAD DIRECTION CELLS

Previous studies have identified a population of neurons in the rat postsubiculum (PoS) that discharge as a function of the animal's head direction (HD) in the horizontal plane, independent of its behavior and location in the environment [32]. For example, a particular neuron might discharge whenever the animal points its head northeast, no matter where it is located. As such, these cells are ideally suited to provide information about the animal's ongoing directional heading in the environment. Later studies have characterized the properties of these cells in more detail [49,50]. The direction of maximum response (preferred direction) for individual cells is always in the horizontal plane, but the preferred direction varies from cell to cell and all directions appear to be represented equally. The range of elevated firing is typically about 90°, and decreases linearly away from the preferred direction. Responses are generally independent of 1) pitch or roll of the head up to 90°, 2) direction of movement, and 3) trunk position relative to the head. The firing patterns remain stable across recording sessions many days apart. HD cell responses appear to exhibit a high degree of intersensory convergence from visual, vestibular, tactile, and proprioceptive modalities. For example, the preferred direction of all cells are maintained when the animal moves about, even in darkness, but can be simultaneously rotated in register with a similar rotation of the surrounding visual landmarks. A representative HD cell is depicted in Fig. 1A (solid line with dots). This article reviews recent experiments addressing 1) how an animal uses these cells during a spatial task, and 2) how the HD cell signal is derived and processed from known sensory inputs.

RELATIONSHIP OF HD CELL ACTIVITY TO BEHAVIOR

One series of experiments examined the relationship between the activity of HD cells and ongoing spatial behavior as an animal learned a spatial reference memory task [6a]. Animals were trained on an eight-arm radial maze in which water reinforcement was available at the end of one designated arm while simultaneously recording from HD cells. Results showed that there was little change in the HD cell's firing characteristics throughout the learning period. When the salient room cue was rotated, both the animal's behavioral choice of maze arms and the HD cell's preferred firing direction shifted a similar amount. These results provided correlational evidence to support the notion that HD cell activity is involved in guiding an animal's spatial behavior. Conceptually, the animal learned to use information about its current spatial orientation within the maze in order to guide its behavioral response.

CONTRIBUTIONS OF DIFFERENT SENSORY SYSTEMS TO THE HD CELL SIGNAL

Another area of research has addressed the contributions of different sensory systems to the HD cell signal. In one study we found that HD cells maintained stable directional discharge when a rat moved from a familiar environment to a novel chamber ([46] Fig. 1A). Because there were no familiar landmarks in the novel environment that would have enabled the cells to maintain their preferred direction, the cells must have been receiving input regarding the animal's own movements through the environment. This result implies that the HD cells were receiving information from internally generated (idiothetic) sensory cues and that the animals were using path integration mechanisms to keep track of their directional heading.

HD cells have also been monitored under conditions in which a conflict situation was introduced in relation to the established orientation landmarks and the animal's internally generated sen-
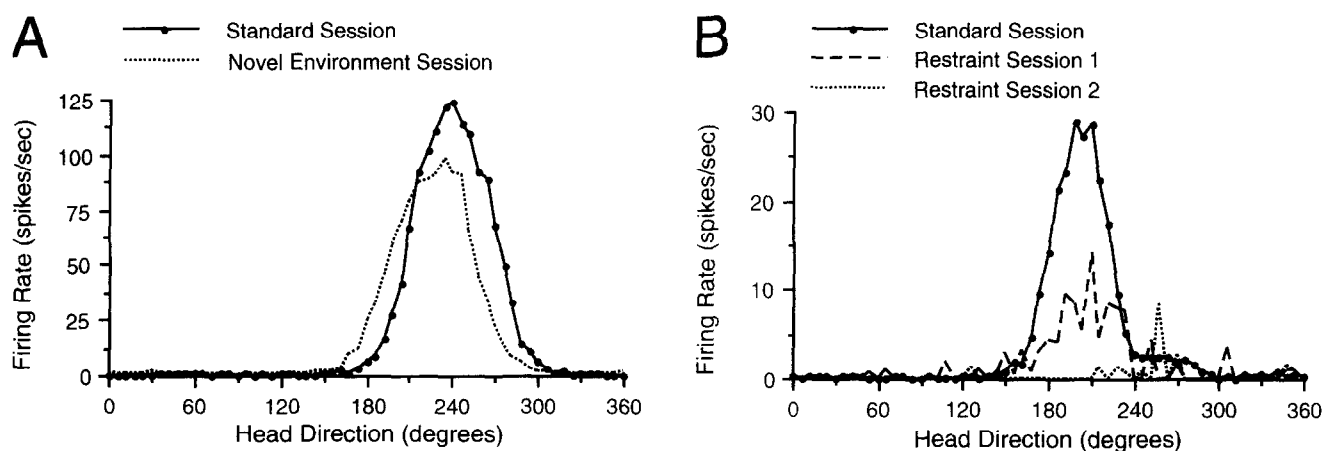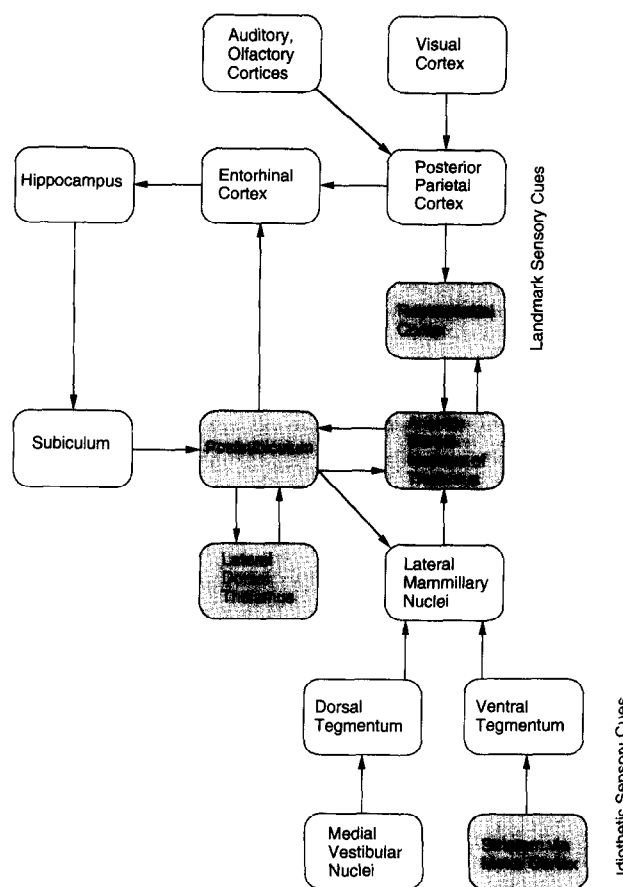

FIG. 1. Representative HD cells in the PoS (A) and ATN (B) recorded in the cylinder for 8 min (standard session). Each graph plots the cell's firing rate as a function of the animal's head direction with respect to the recording room in 6° intervals (points on the solid line). Note that each cell had a different peak firing rate and that the firing rate decreased linearly away from the preferred direction. The PoS cell had a high peak firing rate around 125 spikes/s, while the ATN cell had a lower peak firing rate around 30 spikes/s. (A) This cell was initially recorded in the cylinder. A door was then opened, which allowed the animal to run through a passageway into a rectangular-shaped chamber. The dotted line shows the cell's responses when the animal was monitored in the passageway/rectangle. Note that the cell's preferred direction and peak firing rate remained relatively stable in the novel chamber. (B) This cell was monitored during two restraint sessions where the animal was held firmly in the experimenter's hands and passively rotated around the center of the cylinder. In the first restraint session (dashed line) the cell's firing rate decreased by 50%, while in the second restraint session (dotted line), the cell ceased discharging at head directions near the preferred direction.

sory cues [14]. For example, animals were initially trained to retrieve food pellets in a cylinder containing a single salient cue. Following recording of an HD cell, the animals were removed and the floor paper changed. The animal was then reintroduced into the chamber without the salient cue and the cell's activity monitored a second time. If the cell's preferred direction shifted, then the salient cue was returned to its original position while the animal remained in the apparatus. Under these conditions, the HD cell's preferred direction shifted back to its original relationship with the cue, indicating that HD cells preferentially used information concerning landmark cues as opposed to information from internally generated cues. Furthermore, simultaneous recordings from multiple cells in different sessions showed that the preferred directions remained "in register" with one another. Thus, when one HD cell shifted its preferred direction a specific amount, the other HD cell also shifted its preferred direction by the same amount, indicating that the HD cell population was being activated together as a unit.

HD CELL CIRCUITRY: WHERE IS THE SIGNAL GENERATED?

Given that HD cells receive information from both visual landmarks and internal sensory information, the question arises: where in the central nervous system do these two types of information converge? Furthermore, where is the HD cell signal generated? HD cells were initially discovered in the PoS (also referred to as the dorsal presubiculum) [32,49]. Figure 2 shows the three primary areas that project to the PoS. These areas are: 1) subiculum, 2) anterior thalamic nuclei (ATN), and 3) lateral dorsal thalamic nuclei [51]. The major projections of the PoS are to: 1) entorhinal cortex, 2) ATN, 3) lateral dorsal thalamic nuclei, and 4) lateral mammillary nuclei. Previous studies have reported the presence of place cells, but not HD cells in the subiculum [3,35]. In contrast, directionally tuned neurons were reported in the lateral dorsal thalamic nuclei [27], and recent recording studies in our laboratory have identified the presence of HD cells localized to the anterior dorsal portion of the ATN [45]. Quantitative analysis of ATN cells showed they had similar discharge characteristics as PoS HD cells. The one exception was that for many cells, passive rotation of a hand-held restrained animal led to the cessation of cell discharge when the animal's head was oriented in the preferred direction (Fig. 1B), which suggests that some type of proprioceptive or motor input is necessary to drive ATN HD cells. In addition, each HD cell in the ATN, as well as the PoS, had a characteristic peak firing rate at the preferred direction that was unchanged from session to session. The peak firing rates for all cells ranged from 5 to 120 spikes/s. The significance and functional implications of these observations are still unclear.

Although the presence of HD cells in the ATN and lateral dorsal thalamic nuclei indicate the importance these structure may play in processing the directional signal, the origin of the HD cell signal remains unclear because there are reciprocal connections between the PoS and ATN, and between the PoS and lateral dorsal thalamic nuclei. To determine what brain structures are critical for processing the HD cell signal, we have conducted three series of lesion studies that have selectively disrupted one area while simultaneously recording HD cells in either the PoS or ATN. Our results showed that 1) lesions of the lateral dorsal thalamic nuclei did not disrupt HD cell activity in the PoS [10], 2) lesions of the PoS did not disrupt HD cell activity in the ATN [13], but 3) lesions of the ATN led to the absence of identifying HD cells in the PoS [12]. These lesion studies suggest that the

FIG. 2. Block diagram summarizing the major connections involved in processing the head direction cell signal. Shaded blocks indicate areas where directionally tuned neurons have been identified. The model shown proposes that information from idiothetic cues are processed in brainstem areas and then projected dorsally to the lateral mamillary and anterior thalamic nuclei. In contrast, information concerning the spatial relationships of landmarks is processed in cortical structures, particularly in the retrosplenial and posterior parietal cortices. These two types of information then converge at the level of the anterior thalamus, or possibly the lateral mamillary nuclei, which receives projections from the PoS. Note the involvement of brain structures traditionally considered as part of the Papez circuit.

PoS HD cell signal is dependent on inputs from ATN HD cells. Furthermore, the functional role served by the prominent reciprocal connections between the lateral dorsal thalamic nuclei and the PoS awaits elucidation.

A second approach to the issue of where the signal is generated has yielded some interesting findings. A time-shift analysis, which shifts the spike series forwards and backwards in time in 1/60th-s intervals with respect to the animal's HD, showed that ATN HD cell discharge was optimized (in terms of the maximum peak firing rate and minimum directional firing range) when the spike series was shifted forward in time by about 40 ms [48]. This result indicates that ATN HD cell discharge was better at predicting where the animal was going to point its head than where the animal previously pointed its head. In contrast, PoS HD cell discharge was optimal when the time shift was zero. These results could be interpreted as being consistent with the notion that the PoS HD cell signal is derived from HD cell discharge in the ATN, because the HD cell signal could be pro-

cessed in a serial manner starting in the ATN and ending in the PoS. However, alternative explanations can be postulated. For example, the 40 ms time shift observed for ATN HD cells could occur because these cells receive information from two sources: 1) an 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 40 ms. This scheme has recently been postulated by Blair and Sharp [4] (see below). However, this scheme is difficult to reconcile with the above lesion studies, because lesions of the PoS (the source of the current directional heading signal) do not abolish HD cell discharge in the ATN.

Another important issue is: what role does the hippocampus contribute to the directional heading system? Anatomical findings have shown the absence of an ATN projection to the hippocampus and subiculum [57] and only sparse, if any, projections from the subiculum to the ATN [23,56]. These findings diminish the likelihood that the subiculum (or the hippocampus for that matter) plays a critical role in the generation of the HD cell signal. Because the subiculum receives its major inputs from the hippocampus, we have recently tested this hypothesis by recording from PoS HD cells in animals with neurotoxic lesions of the hippocampus [11]. Our results have indicated that lesions of the hippocampus do not disrupt the HD cell signal in the PoS. Interestingly, the preferred directions of HD cells remained stable across days when the lesioned animal was placed in a novel environment. Taken together, these findings indicate that not only is the HD cell signal generated by structures outside the hippocampus, but that these extrahippocampal structures must be capable of encoding new information concerning landmarks. This notion is contrary to prevailing views of hippocampal function, which postulate that it is critical for learning the relationships among different stimuli, as well as encoding the contextual features of relevant ongoing events [7,16,41]. Learning the spatial features of a novel environment and the spatial relationships amongst different stimuli would certainly qualify as functions the hippocampus should be performing according to these investigators. It is, thus, surprising to observe the stability in the HD cell's preferred direction across days in the novel environment in the hippocampal-lesioned animals. These findings indicate that current theories of hippocampal function may need modification or may be limited to include only certain types of information. Furthermore, the findings raise the important question of where in the brain is information about new spatial relationships encoded and stored.

INVOLVEMENT OF THE PAPEZ CIRCUIT

What are the projections to the anterior dorsal area of the ATN? Several anatomical studies have shown that this area receives three major inputs: 1) the lateral mammillary nuclei, 2) the posterior cingulate cortex, which in rats is referred to as retrosplenial cortex, and 3) the postsubiculum [34,40,51]. The ATN also sends reciprocal connections back to the retrosplenial cortex [38,58]. Interestingly, Chen et al. [6] have recently reported that a small percentage of cells in the retrosplenial and medial pre-striate cortices discharge in relation to the animal's directional heading. These cells maintained their directional discharge in the dark, and the firing rates of some cells were modulated by the types of movements the animal made, such as motion straight ahead vs. head turns to the left or right.

The retrosplenial cortex has extensive connections with areas of the posterior parietal cortex that contain highly processed vi-

sual information from the occipital lobes. In particular, this information appears to encode the spatial relationships of objects with respect to eye and head positions. For example, the receptive fields of cells in parietal area 7a of primates can be modulated either by the animal's eye position [2] or by the animal's head position [5]. These neurons in conjunction may signal the direction of gaze with respect to the animal's body and 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 ATN and PoS via the posterior parietal and retrosplenial cortices. Indeed, Mishkin and Ungerleider [24] postulated that visual information beyond the primary and secondary visual cortices 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, while the second stream analyzed the perceptual features of the object and enabled the subject to identify what the object was. 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. Taken together, spatial information concerning visual landmarks may project to the hippocampal system through a pathway starting in the posterior parietal lobe and then proceeding to the retrosplenial cortex, ATN, PoS, entorhinal cortex, and, finally, into the hippocampus. This pathway is different from the route postulated through the temporal lobes and entorhinal cortex, which is considered the more conventional route of how cortical spatial information reaches the hippocampus. It is noteworthy that the retrosplenial cortex, ATN, and PoS are all parts of the classical Papez circuitry, which is summarized in Fig. 2. These observations imply that an important function served by this circuit is the processing of spatial information. Consistent with this notion are behavioral findings showing that animals with lesions of the ATN, PoS, mammillary nuclei, or retrosplenial cortex are impaired in the spatial version of the water maze task [43,44,47].

WHERE DO THE LANDMARK CUES AND IDIOTHETIC SENSORY CUE STREAMS CONVERGE?

Because both the PoS and ATN HD cells appear to receive sensory information concerning idiothetic cues, it becomes important to determine which types of idiothetic cues are used, and over what neural pathways this information reaches limbic system structures. Most investigators have believed that vestibular and motor efference copy cues are conveyed to the hippocampal formation through polysynaptic pathways starting in somatosensory and motor areas of the thalamus. Information from the thalamus is then projected to several areas within the parietal cortex, and finally on to the hippocampal formation through the perirhinal and entorhinal cortices (for review, see [54]). However, there are alternative pathways from the brainstem to the hippocampal formation that are more direct, and have not received much attention.

Liu et al. [17] reported projections from the medial vestibular nuclei, which encodes information from the horizontal semicircular canal, to the dorsal tegmental nucleus. Thus, information about the animal's angular head acceleration in the horizontal plane has direct access to the dorsal tegmental area. Interestingly, both the dorsal and ventral tegmental nuclei send major projections to the mammillary nuclei [31]. In particular, the dorsal tegmental nucleus projects preferentially to the lateral mammillary nucleus [17]. Recall that it is the lateral mammillary nucleus that sends direct projections to the anterior dorsal portion of the

ATN [1,34]—the same area where we identified HD cells. Furthermore, the postsubiculum also contains a dense projection to the lateral mammillary nucleus [37].

In terms of motor information for a motor efference copy signal, the supplementary motor and motor cortices have extensive connections with the striatum, which in turn, sends a major projection to the ventral tegmental area (reviewed in [15]). In addition, the midbrain reticular formation, which contains some motor circuitry, also projects to the dorsal tegmental nucleus [33]. Thus, the anatomical connections are present within the tegmental brainstem areas for motor and vestibular information to be conveyed rather directly, through its connections with the lateral mammillary nuclei, to the ATN and PoS (see Fig. 2). Unfortunately, there have been no experiments that have recorded single neurons from the mammillary nuclei in freely moving animals, and behavioral studies involving lesions of the mammillary nuclei have not provided a clear functional role for this structure.

Because organisms low on the phylogenetic scale can navigate using path integration (reviewed in [9]), it is possible that navigational systems based on idiothetic cues and path integration have evolved before more complex navigational systems utilizing landmarks. Furthermore, the navigational systems that use idiothetic sensory cues may be processed in brainstem and diencephalic structures, while cortical areas are more involved in processing landmark information. Indeed, the amount of information processing required for understanding the spatial relationships amongst a set of landmark cues is probably considerable, as it requires several cognitive processes. First, the subject must perceive and identify the object. Second, a subject must interpret the object as a useful item to use for a landmark (i.e., the subject would not want to use as a landmark an object that moves around all the time). Finally, an analysis of the spatial relationships of the object in the context of the current environment must occur. Thus, the neural machinery required for these multiple cognitive processes is certainly more suited for cortical processing than brainstem processes. Given the anatomical observations that the ATN is centrally located within the brain to receive both cortical (retrosplenial) and subcortical inputs (mammillary nuclei), perhaps the ATN and lateral mammillary nuclei are the sites of convergence for the landmark and idiothetic information streams (see Fig. 2). In this scheme, head directional information reaching the hippocampus via the PoS and entorhinal cortex would already be highly processed and, thus, be ready for integration with other types of information, such as learning where to go for a reward.

IMPORTANCE OF THE VESTIBULAR SYSTEM FOR NAVIGATION

Our studies described above with the dual-chamber apparatus showed the importance of idiothetic cues for maintaining HD cell discharge when the animal enters a novel environment. This finding raises the question of which idiothetic cues are important? At the behavioral level, several studies have shown that vestibular information is important for both orientation and navigation in animals. For example, Miller et al. [24] demonstrated that rats with vestibular lesions were impaired in a spatial task that required them to accurately monitor their motion through space as they were passively transported on a wheeled cart. Mittelstaedt and Mittelstaedt [26] showed that the desert mouse was capable of compensating for angular rotation of its environment and successfully returned to its nest in the dark. More recently, Matthews and colleagues reported that fornix-lesioned [20] and labyrin-

thectomized [19] animals were impaired in a spatial task that required them to monitor their angular rotation.

Single-unit studies from place and HD cells have shown that a cell's place field, and the HD cell's preferred direction, do not remain stable between recording sessions when an animal is trained under conditions where it is always brought into the room after first being disoriented [18]. These authors argued that path integration into a novel environment was necessary in order to form a stable spatial representation of that environment. According to their model, the vestibular system was the primary mechanism involved in path integration [22]. Indeed, recent recordings from hippocampal place cells have shown that vestibular system stimulation is capable of influencing place cell activity in the hippocampus [36,55]. The data in a recent report by Blair and Sharp [4] also concurred with this premise for HD cell activity. Using an analysis based on the rat's angular head velocity in conjunction with monitoring HD cell activity, they reported that ATN HD cell discharge predicted the animal's future directional heading, while PoS HD cell activity signaled the animal's current head direction. Furthermore, they proposed that the mechanism that accomplished this operation was the integration in time of a head velocity signal generated by angular head motion, which was added to the PoS signal, indicating current HD in order to anticipate the animal's future directional heading. Taken together, these findings indicate that the vestibular system may play a pivotal role in enabling an animal to path integrate as well as influencing the neural circuitry involved in encoding the animal's spatial orientation. Consistent with this proposal is preliminary evidence from our laboratory indicating the absence of ATN HD cells in rats with neurochemical-induced lesions of the vestibular apparatus [42]. Furthermore, in a subset of rats ATN HD cells were isolated and then the vestibular apparatus was lesioned. In these cases, disruption of the vestibular system appeared to abolish the normal directional firing of ATN neurons.

POTENTIAL CONTRIBUTIONS OF OTHER INTERNAL SYSTEMS TO HD CELL DISCHARGE

Although the discussion to this point makes clear that many types of sensory information can exert influence over the firing of the HD cells, it is not clear how these various types of input interact. McNaughton et al. have suggested that vestibular input serves to update the firing of HD cells in a continuous manner, while landmark information is used periodically to "reset" the firing of the cells so they are properly aligned with cues in the environment. Resetting is necessary because of the error that accumulates in the idiothetic signal over time. On the other hand, landmarks themselves cannot be employed effectively to sustain HD cell firing because the same cues are not continuously available to the animal. It is well known, for example, that HD cells can maintain their firing rates and preferred direction even when the animal is looking away from the landmark cue that exerts stimulus control, or when it is removed altogether [50]. Thus, a fundamental issue in understanding the mechanisms underlying HD cell discharge is: what is the nature of the neuronal inputs that initiate and then sustain HD cell discharge?

Our finding that labyrinthectomies disrupted the HD cell signal provides strong evidence that the vestibular system plays a critical role in the generation of the signal. However, there are a number of problems that would arise if this system were the only generating mechanism available to HD cells. For example, the finding that the ATN HD cell signal was optimal when it was predicting the animal's future head direction is difficult to reconcile with a pure sensory code, because any sensory code would

have to be generated after, not before, the animal turns its head. (Recall that the optimal time shift reported for ATN HD cells by Taube and Muller [48] and Blair and Sharp [4] was about 40 ms.) If the animal was turning its head continuously at a constant speed, then it might be possible for vestibular information to signal where the head will be pointing some milliseconds in the future. However, even in this circumstance, the directional heading could still not be predicted for the 40 ms at the beginning of the head turn. Furthermore, most head turns in a rat are very brief—on the order of 100 ms. Thus, the animal is seldom in a state where it is turning its head continuously for long time periods. With a head turn encompassing 100 ms, the animal would not be capable of predicting its future directional heading for almost half this amount of time based on a vestibular signal.

Other evidence that is difficult to reconcile with the notion that the vestibular system is the sole contributor to the generation of the HD cell signal are findings showing that cell discharge was disrupted when the animal was restrained and passively rotated. Under these conditions, the vestibular system is still intact and should be able to convey information about the animal's head turns as the experimenter rotates the animal back and forth. Nonetheless, ATN HD cell discharge was usually abolished. Another troublesome issue concerns what would sustain HD cell activity when the animal is still. It is important to note that the hair cells in the semicircular canals would not be activated when the animal's head is not turning. In addition, individual HD cells show very little, if any, adaptation when the animal maintains a constant directional heading in the cell's preferred direction (unpublished observations). Thus, some other mechanism is required to sustain HD cell discharge under these conditions. Taken together, these findings are difficult to reconcile with the notion that the vestibular system is the sole mechanism that initiates or sustains HD cell discharge.

These observations suggest that a motor efference copy signal may also play a significant role in generating HD cell discharge. Such a signal can better account for both findings discussed above: 1) that HD cells in the ATN discharge ahead of the animal's directional heading, and 2) that HD cells cease discharging under restraint conditions. The involvement of locomotion and motor systems in HD cell activity may explain why a small population of HD cells was recently identified in the striatum [54], a structure usually considered important for motor functions. Interestingly, the area of the striatum where HD cells were identified was the same area that receives direct projections from the anterior dorsal thalamic nuclei where HD cells have been identified [52]. The involvement of motor systems in processing spatial information may also explain why hippocampal place cell discharge is abolished when an animal is passively moved into the cell's firing field [8].

Sustained cell discharge when the animal is not moving or turning its head, however, is just as difficult to reconcile with a motor efference copy signal as with a vestibular signal. To enable steady-state discharge when the animal is not moving, it is possible that HD cells have a self-generating, tonic discharge rate once they are initially activated. In this case, the cells would only cease discharging when the animal turned its head to another direction. Alternatively, the HD cells could be interconnected in a ring-like network, where cells with similar preferred directions have excitatory synaptic connections and cells with preferred directions about 180° opposite would inhibit one another ([39] Zhang, unpublished observations). These authors have shown that a network of such cells can sustain HD cell firing in the absence of landmarks and without a dynamic change in head movement. Either of these mechanisms would account for the

finding that HD cells generally have peak firing rates that are invariant across different environmental situations. Finally, we conclude by pointing out that motor systems alone cannot be the critical factor for the generation of the HD cell signal, because our findings show that labyrinthectomies (which presumably do not disrupt the motor system) abolish HD cell activity in the ATN. Thus, a combination of vestibular and motor signals may be the inputs that generate HD cell discharge. Once the signal is generated, landmark cues can be utilized to reset the reference frame used by these cells.

SUMMARY

In conclusion, the HD cell signal encodes a very accurate, continual representation of the animal's directional heading. Recent studies indicated that this signal 1) arises either in the ATN or in structures upstream from it, 2) is not dependent on an intact hippocampus, 3) receives sensory inputs from both idiothetic and landmark systems, and 4) correlates well with the animal's behavior in a spatial reference memory task. Furthermore, HD cells in the ATN appear to encode what the animal's directional heading will be in the future, while PoS HD cells encode the animal's current directional heading. The electrophysiological and anatomical data indicate that brain areas within the Papez circuit play an important role in conveying and processing spatial information concerning the animal's directional heading. In addition, the ATN and/or the lateral mammillary nuclei may be the sites of convergence for spatial information derived from landmarks and idiothetic sensory cues. Although the vestibular system plays a critical role in the generation of the HD cell signal, it alone has difficulty accounting for several findings involving HD cell discharge. A motor efference copy signal can account for some of these findings.

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COMMENTARIES

This article is a fine summary of some very interesting and important experiments from the authors' lab. These experiments are beginning to tease apart the circuitry involved in the generation of the directional selectivity of head direction cells. This selectivity clearly arises from the convergence of multiple sources of information, including the vestibular, visual, and motor systems, and thus provides an outstanding opportunity to discover how the brain integrates such multimodal input to produce an abstract cognitive percept like a "sense" of direction.

Both behavioral and neurophysiological experiments suggest that an animal's sense of location and direction results from a complex interaction between internally generated, self-motion cues (idiothetic cues) and external sensory cues (primarily visual landmarks) (for a brief review see [1]). Over the past few years, McNaughton and colleagues have developed a model of this interaction, in which we postulate that the primary drive upon head direction cells and place cells comes from the animal's internally generated self-motion cues, which underlie the navigational strategy known as path integration [3,6,22a]. According to the model, the vestibular system provides the primary input to update the firing of head direction cells as the animal navigates in a new environment (although we recognized the potential influence of other idiothetic cues such as proprioceptive cues and motor efference copy). Initially, visual landmarks have no influence over these cells. However, as the rat explores the new environment, synaptic connections between coactive cells representing the current visual input and the current head direction are strengthened. If the animal maintains a consistent mapping between its internal sense of direction and the external cues each time it enters the environment, these connections will eventually become strong enough to override the vestibular input when the system drifts out of calibration.

We believe that many of the results presented in this article provide strong support for our model, especially the demonstration of a complete abolishment of directional tuning in the ATN after a lesion of the vestibular apparatus (main article reference [42]). However, the interesting finding that ATN HD cells reflect the future head direction (whereas PoS HD cells reflect the current head direction) (main article references [4,48]) is a puzzle, because our models do not predict the existence of this property, and a computational analysis by Zhang of a similar model [58a] demonstrates that such cells are not required for the model to function well. The current authors and Blair and Sharp (main article reference [4]) apparently disagree on the functional significance of this finding, and it will be interesting to see future experiments designed to address this question.

Our major disagreement with the authors is in their ending statement that a motor efference copy signal can account for the known properties of HD cells "better" than a vestibular signal. Although there are clearly nonvestibular idiothetic influences on these cells, we do not agree that the proposed primary role of motor efference copy accounts for the data better than the proposed primary role of the vestibular system. For example, the complete abolishment of HD activity in the ATN with a vestibular lesion is consistent with behavioral data showing that such lesions impair navigation ([4,5]; main article references [19,24]) even though motor systems are presumably intact. The abolishment of ATN HD tuning (main article references [18,45]) and hippocampal place cell firing (main article reference [8]) under conditions of restraint appears, on the surface, to suggest that motor efference copy is more important than vestibular input, as the vestibular system is intact under these conditions. However, hippocampal place cell firing returns as soon as the rat is released from tight restraint, even before the rat begins to move (Foster, Castro, and McNaughton, unpublished observation). In addition, both place cells and head direction cells do maintain their tuning properties when the animal is passively moved or rotated, as long as the animal is not tightly restrained. It, thus, appears that some type of "motor set"—the preparedness for motion—has an influence over the responses of these cells, rather than any copy of actual motor commands.

The authors argue that the sustained discharge of HD cells while the animal is stationary is a problem for the vestibular hypothesis. However, the motor efference copy hypothesis has the exact same "problem," so this argument does not weigh heavily in favor of either hypothesis. As the authors state later, there really is no problem here, anyway, for an attractor neural network can easily account for the sustained discharge of HD cells under conditions where the animal is stationary [6,58a]. The argument that a pure vestibular input is difficult to reconcile with the finding that ATN HD activity predicts future head direction has some merit, but it is not entirely persuasive because the functional significance of this finding is still not known. Thus, we agree totally with the authors' statement that idiothetic inputs other than vestibular input must play a role in the generation and maintenance of HD tuning; however, the data and arguments in favor of motor efference copy playing a primary role over the vestibular system are not compelling.

The finding that hippocampal lesions do not affect PoS HD cell tuning (main article reference [11]) is particularly interesting and important, but we would caution about drawing too strong a conclusion that the hippocampus plays no role in the normal functioning of the HD cell system based on this single experiment. Although an early version of our group's model hypothesized that hippocampal place cells were "local view" cells that served to recalibrate the HD cell system (main article reference [22]), subsequent experiments in our lab and in other labs have made the "local view" hypothesis no longer tenable. More recent versions of the model [3,6,22a] postulate that the HD cells are updated most likely by neocortical sensory cells, not hippocampal cells. Although we are in agreement with the authors on this point, we must disagree with the logic of the authors' conclusion that the maintenance of PoS HD cell