

Does the vestibular system contribute to head direction cell activity in the rat?

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Abstract

Head direction cells (HDC) located in several regions of the brain, including the anterior dorsal nucleus of the thalamus (ADN), postsubiculum (PoS), and lateral mammillary nuclei (LMN), provide the neural substrate for the determination of head direction. Although activity of HDC is influenced by various sensory signals and internally generated cues, lesion studies and some anatomical and physiological evidence suggest that vestibular inputs are critical for the maintenance of directional sensitivity of these cells. However, vestibular inputs must be transformed considerably in order to signal head direction, and the neuronal circuitry that accomplishes this signal processing has not been fully established. Furthermore, it is unclear why the removal of vestibular inputs abolishes the directional sensitivity of HDC, as visual and other sensory inputs and motor feedback signals strongly affect the firing of these neurons and would be expected to maintain their directional-related activity. Further physiological studies will be required to establish the role of vestibular system in producing HDC responses, and anatomical studies are needed to determine the neural circuitry that mediates vestibular influences on determination of head direction.

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1. Introduction

In order for an animal to navigate accurately in an environment, it must be aware of its location within that environment as well as its directional heading. A growing body of work in the rat suggests that “head direction cells” (HDC) located in the lateral mammillary nuclei (LMN), anterior dorsal nucleus of the thalamus (ADN), postsubiculum (PoS), and several other regions of the brain provide the neural substrate for the determination of head direction. Evidence supporting this assertion is summarized in several recent reviews [1–3] and will not be repeated in this manuscript. The activity of rat HDC varies as a function of the animal’s head direction in the horizontal plane and is

independent of its location in the environment and ongoing behavior. Various sensory signals have been suggested to participate in shaping the firing patterns of HDC including vestibular and visual inputs and internally generated cues [1–3]. However, recent lesion studies [4,5] indicated that inactivation of labyrinthine inputs abolished the direction-related activity of HDC, suggesting that the vestibular system plays an essential role in producing HDC responses. This finding is supported by behavioral data that show that elimination of vestibular inputs impairs navigation when visual cues that can be used as landmarks are absent [6]. Furthermore, relatively direct pathways have been proposed that could relay vestibular signals to brain regions containing HDC [37,38]. Nonetheless, responses of vestibular nucleus neurons to horizontal head rotations are considerably different from those of HDC, requiring a complex transformation of signals by the circuitry that transmits signals between the two groups of neurons. The purpose of this review is to critically evaluate data regarding the role of the vestibular system in generating HDC activity and to

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propose future research that will more firmly establish the contribution of vestibular inputs to spatial cognition.

2. An overview of the response properties of HDCs

In 1990, Taube et al. [7] reported that cells in the rat PoS were most active when the animal faced a specific direction in its environment. The peak of this activity was described as the “preferred direction” of an HDC, and the directional sensitivity of the cell was found consistent over several recording sessions. The discovery of HDC fit well with 20 years of work on hippocampal place cells in rodents; the neural bases of both location in space (coded by place cells) and directional heading (coded by HDC) were thought to be established.

Over the course of the subsequent 10 years, cells with similar directional selectivity as PoS HDC were found in rat lateral dorsal thalamic nucleus [8], dorsal striatum [9], retrosplenial cortex [10,11], ADN [12], and LMN [13]. However, the most widely studied HDC are located in the LMN, PoS, and ADN, as they are considered to be the most basic components of a circuit that could provide the animal with current directional heading information. The firing properties of cells in these different areas are relatively similar, although there are some differences that will not be discussed here (see Ref. [2]).

Several models related to the generation and maintenance of HDC activity have been proposed including those based on theoretical and computational ideas [14–16] and those based on electrophysiological and anatomical data [1,2]. Although these models vary in scope and content, they all suggest ways in which sensory information may be necessary and sufficient to support normal HDC activity.

Numerous experiments have been performed in order to determine the extent to which HDC activity responds to sensory, behavioral, and environmental manipulations (for a review, see Ref. [2]). HDC activity has been found robust and reliable, provided the animal maintains a perception of environmental stability. Evidence suggests that HDC activity is independent of body position relative to the head, as well as the animal’s location within an environment. HDCs are active while the animal is moving or still, and there is no indication that adaptation of firing rate occurs if the animal continues to face a preferred direction. Firing rate decreases from maximum as the rat moves its head to either side of an HDC’s preferred direction, until it reaches a baseline firing rate approximately 45° away from the preferred direction.

Visual input is important for normal HDC activity, although it seems to be unnecessary for its generation and maintenance. The directional specificity of these cells remains consistent within and between recording sessions in the light, although there is evidence that drift may occur in the dark [17,18]. The preferred direction of an HDC within an environment can be manipulated by rotating or moving

salient visual cues, although the cues themselves are not required for HDC activity [19].

The animal’s perception of cue stability also seems to be essential for reliable HDC responses [18]; the extent to which a known cue is perceived as stable defines the amount of control it will exert over the directional firing of an HDC. Interestingly, the direction-related activity of HDC appears to be in register with the place-specific firing of hippocampal place cells. This finding suggests that HDCs in rat are part of a larger, cognitive mapping system that is based on representations of place and heading [20].

3. Evidence suggesting that vestibular inputs are involved in the generation of normal HDC activity

Two studies have demonstrated that the directional sensitivity of many HDC remains stable when the substrate the animal is standing upon is rotated quickly in the dark [21,22]. This stability in directional sensitivity during rapid shifts in body position requires perception that the movement has occurred, presumably through inertial cues. Such evidence has been used to argue that the vestibular system contributes to directional sensitivity of HDC [21,22]. However, animals were freely moving during these experiments, allowing for the possibility that inertial cues arising from sources other than the vestibular system affected the firing of HDC. Furthermore, because the animals’ heads were not restrained and could be moved during the rotation, the particular vestibular stimuli produced in these studies are difficult to gauge. Thus, although these data support the notion that the vestibular system contributes to HDC activity, the findings are not definitive.

The strongest evidence suggesting that the vestibular system has a direct and profound influence on the firing of HDC comes from a lesion study conducted by Stackman and Taube [5]. These investigators demonstrated that bilateral ablation of vestibular inputs through injection of sodium arsenite outside the inner ear abolished the directional firing properties of HDC. Consistent with this result, Stackman et al. [4] recently showed that inactivation of vestibular hair cells abolished directional sensitivity of HDC in PoS. Taken at face value, these data suggest that the vestibular system has a fundamental influence on normal HDC activity. However, as discussed in the next section, these findings are not easily reconciled with current data regarding inputs to vestibular nucleus neurons and plastic changes that occur in the vestibular system following removal of labyrinthine inputs.

A third line of evidence to suggest that the vestibular system contributes to the directional sensitivity of HDC comes from circuit analysis using conventional monosynaptic anatomical and lesion techniques. These methods have demonstrated a potential pathway through which vestibular signals can be relayed to brain regions containing HDC. This pathway is illustrated in Fig. 1. As noted previously, HDC are

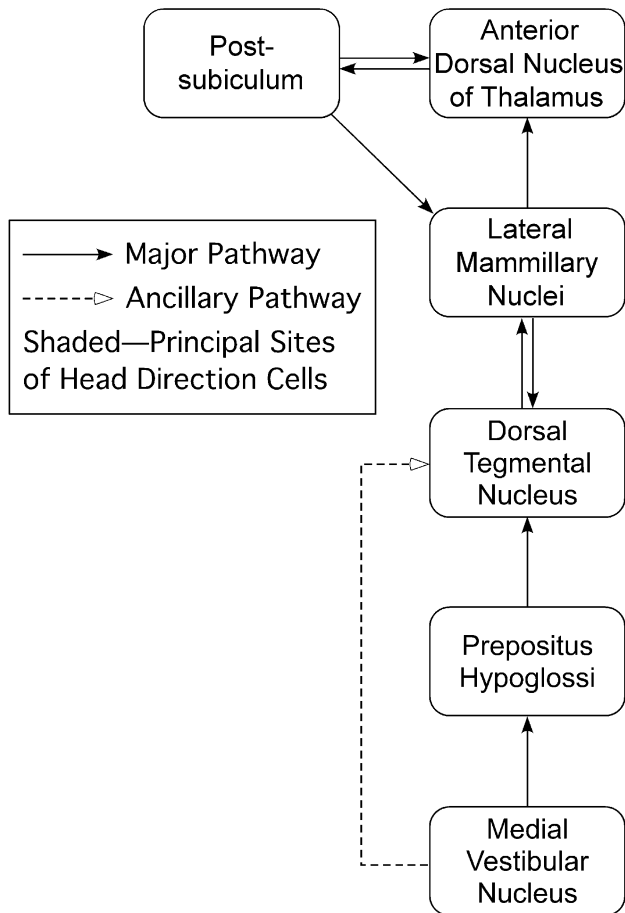


Fig. 1. Relatively direct pathway that may relay vestibular signals to brain regions containing HDCs (indicated by shading). Adapted from Refs. [37,38].

located primarily in three brain structures: LMN, ADN, and PoS. Lesions of LMN abolish the directional firing properties of ADN neurons [23,24], and in turn, lesions of ADN eliminate directional sensitivity of PoS neurons [25]. Thus, any signals from the vestibular nuclei would presumably first be processed by LMN neurons and then relayed to cells in ADN and PoS. Conventional neuroanatomical techniques have demonstrated a large input to LMN from the dorsal tegmental nucleus of Gudden (DTN) [26–28]. The DTN receives inputs from prepositus hypoglossi (PH) [26,29,30], a region of the caudal medulla adjacent to the vestibular nuclei that processes vestibular signals related to horizontal head velocity [31,32]. Thus, vestibular signals could potentially be transmitted from the vestibular nuclei to PH, and then to DTN, and then to HDC in LMN, ADN, and PoS. Vestibular information may also reach DTN through direct afferents from the medial vestibular nucleus, although anatomical studies have shown that this pathway is less prominent than that from PH [28].

In order for this proposed circuitry to support HDC activity rostrally, inputs from the horizontal semicircular canals (a signal related to angular head velocity) must be transformed into neuronal responses by HDC related to horizontal head position. There is some evidence to suggest

that the neural pathways shown in Fig. 1 are capable of such a transformation of signals. Neurons in DTN have activity correlated with horizontal angular head velocity [33,34] although it is important to note that these angular velocity responses are different from those of neurons in the vestibular nuclei or PH [32,35,36]. The velocity sensitivity of vestibular nucleus neurons to horizontal head movement (approximately 0.7 spikes/s per $^{\circ}$ /s [35]) is over five times greater than that of DTN neurons [33]. Furthermore, some DTN neurons, but not vestibular nucleus or PH neurons, have asymmetric responses to horizontal head rotations; the firing rate of these cells is positively correlated with angular head velocity during head turns in one direction, but not the other [33,34]. It has been postulated that these asymmetric responses represent an important step in the transformation of the signals from horizontal semicircular canals into head direction signals, and a model has been proposed regarding how the integration of symmetric and asymmetric angular velocity signals from DTN by LMN neurons could produce responses related to head direction in the horizontal plane [33].

The existence of such a relatively direct pathway linking the vestibular nuclei with regions containing HDC is critical for labyrinthine signals to play a powerful role in regulating the responses of these neurons. However, a caveat is that transneuronal tracing techniques have not been used to demonstrate that neurons in LMN receive inputs from those cells in the DTN that in turn receive inputs from PH. In other words, if injection of a transneuronal tracer into LMN produced labeling in DTN and subsequently in PH, then the circuit proposed in Fig. 1 would be confirmed.

4. Evidence indicating that vestibular inputs do not play a predominant role in generating head direction signals

As noted in the previous section, a model has been proposed to indicate how signals from horizontal semicircular canals could be transformed into head direction signals by a neural circuit including PH, DTN, and LMN. However, this model does not take into account the fact that neurons receiving signals from horizontal semicircular canals may also process other powerful signals, including those related to eye movements [37,38]. In all mammals that have been considered, eye movement related signals are quite prominent in many PH neurons, which are a component of the circuitry that produces saccades [39]. It seems unlikely that neurons receiving powerful signals related to eye movements would be useful in determining head direction. It should be noted, however, that rats have not been a common model animal for the examination of control of eye movements, and it is possible that a subpopulation of vestibular nucleus and PH neurons lacking eye movement sensitivity provides inputs to DTN neurons in this species.

As indicated above, the responses of DTN neurons to horizontal rotations differ from those of vestibular nucleus or PH neurons, particularly in that some (albeit not all) DTN neurons, unlike PH or vestibular nucleus neurons, have asymmetric responses to the rotations. Although these differences in responses could represent the initial transformation of horizontal semicircular canal inputs into head direction signals by DTN neurons, it is unclear how direct inputs from PH could generate the complex head velocity-related responses exhibited by cells in DTN. One possibility is that symmetric angular head velocity cells in either PH or DTN in some way alter the firing of a subpopulation of DTN cells such that they exhibit asymmetrical responses to horizontal head rotations in different directions. Another possibility is that the transformation of horizontal semicircular canal signals could begin prior to DTN, perhaps by a subpopulation of PH neurons that has not yet been characterized. Furthermore, it is noteworthy that only limited anatomical evidence suggests that angular head velocity signals are relayed directly from PH to DTN, and it is feasible that these inputs reach DTN through pathways other than those from PH. For example, DTN is known to receive major afferent projections from the interpeduncular nucleus and minor projections from the supragenualis nuclei, lateral habenula, and reticular formation [28]; neurons in any of these areas could potentially provide angular head velocity signals directly to cells in DTN or modulate the inputs received from PH. Moreover, DTN receives a reciprocal connection from LMN, and LMN is known to contain cells that are sensitive to angular head velocity [13] that could potentially modulate the firing of DTN neurons. Transneuronal tracing studies will be useful in resolving whether direct or indirect pathways convey inputs from the vestibular nuclei to the circuitry that produces signals related to head position.

It is curious that bilateral removal of vestibular inputs abolishes the directional sensitivity of most HDC [4,5], as visual inputs and perhaps other sensory cues strongly affect the firing of these cells and would be expected to sustain their directional-related activity [12,18,19,21,22]. Furthermore, some HDC, particularly those in ADN, receive strong corollary discharge signals related to movement, as evidenced by the fact that their maximal responses may begin prior to passing through the cells' preferred firing directions [40]. One argument that could be posed to explain why removal of vestibular inputs eliminates directional sensitivity of HDC, despite the fact that the neurons receive other signals regarding head position, is that the vestibular inputs are critical for maintaining the background excitability of the neurons. It might be expected that bilateral peripheral vestibular lesions would eliminate spontaneous firing within the central vestibular system. To the contrary, vestibular nucleus neurons quickly (within 24 h) regain a level of spontaneous activity approximately equal to that prior to the lesion even after total elimination of labyrinthine inputs [41–43]. This return of spontaneous activity presumably reflects the fact that vestibular nucleus neurons integrate sensory signals from a wide

variety of sources including muscle, skin and viscera [44], and the visual system [42]. Additionally, because of the presence of these sensory inputs, vestibular nucleus neurons can still respond to whole-body movement and optokinetic stimuli following bilateral labyrinthectomy [42,43]. Although recordings have not been made from PH neurons following the bilateral removal of vestibular inputs, the fact that many of these cells receive strong optokinetic inputs [32,45] suggests that they presumably would retain spontaneous activity and probably would still respond to visual stimuli. Thus, although the body of relevant physiological literature does not discount the possibility that removal of vestibular inputs might affect directional sensitivity of at least some HDC, it is difficult to reconcile this literature with the observation that bilateral peripheral vestibular lesions completely eliminate head direction responses. Stackman and Taube [5] also noted this discrepancy.

There are several potential explanations regarding the apparent contradictions between lesion and physiological experiments with regards to the importance of vestibular inputs in establishing the directional sensitivity of HDC. Although the majority of vestibular nucleus neurons regain their spontaneous activity following removal of vestibular inputs, it is possible that the subpopulation of neurons influencing the head direction circuitry does not recover spontaneous firing. Furthermore, it is feasible that despite the fact that several signals are integrated in determining head direction, labyrinthine inputs are critically involved in this integration and cannot be replaced by vision, other senses, or movement-related commands. Yet another possibility is that injection of sodium arsenite outside the inner ear, which was used to eliminate vestibular inputs in previous studies considering the effects of these signals on HDC activity [4,5], can result in low levels of the toxin diffusing into the cerebral spinal fluid and killing a population of sensitive neurons in the central nervous system. In this case, the loss of directional sensitivity of HDC following injection of sodium arsenite into the ear would be due to an unintended destruction of central nervous system neurons and not due to removal of vestibular inputs.

Other observations have been proposed as evidence suggesting that the vestibular system does not play a powerful role in regulating the firing of HDCs. It has been reported that tightly restraining a rat and rotating it manually eliminates or vastly reduces the direction sensitivity of HDC (see Refs. [2,3] for a review of these data). However, it is unclear whether these rotations were rapid enough to produce substantial modulation of horizontal semicircular canal activity. Horizontal head rotations typically include components at instantaneous frequencies >1 Hz ($360^\circ/\text{s}$), and semicircular canal afferents respond maximally only during such rapid rotations [36]. In addition, effects of stress associated with tight restraint could potentially diminish HDC responses to rotational stimuli. For these reasons, holding a rat and rotating it manually may not elicit vestibular inputs that are powerful enough to modulate the firing of HDC.

5. Resolving the role of the vestibular system in the generation of HDC activity

Although some evidence suggests that the vestibular system plays an important role in producing the directional sensitivity of HDC, other data appear to contradict this assertion. Further experiments are required to determine the role played by the vestibular system in determining head direction. One useful set of experiments would involve injection of transneuronal tracers into regions containing HDC to verify that relatively direct pathways exist to relay vestibular inputs to these brain areas. Physiological experiments could also be conducted to compare the firing and directional sensitivity of individual HDC during active head movements and passive rotations; such passive rotations should be conducted on head-restrained animals placed on a turntable capable of providing high-velocity, controlled movements. It is also important to differentiate the influence of visual from vestibular cues; if the vestibular system alone is sufficient for the generation and maintenance of normal HDC activity, then HDC should respond to rapid rotations of the animal conducted with the head fixed in both the light and dark. Findings from these experiments would be useful in determining the extent to which the vestibular system participates in determining HDC activity, and may potentially open an important new research direction. Comparisons of the processing of vestibular signals by HDC and neurons that mediate vestibulo-ocular, vestibulo-spinal, and vestibulo-autonomic responses will also likely reveal valuable new information regarding the physiology of the vestibular system.

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