

REVIEW | *Where Are You Going? The Neurobiology of Navigation*

Role of the head-direction signal in spatial tasks: when and how does it guide behavior?

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Submitted 27 July 2017; accepted in final form 12 March 2018

Weiss S, Derdikman D. Role of the head-direction signal in spatial tasks: when and how does it guide behavior? *J Neurophysiol* 120: 78–87, 2018. First published March 14, 2018; doi:10.1152/jn.00560.2017.—Since their discovery, mammalian head-direction (HD) cells have been extensively researched in terms of sensory origins, external cue control, and circuitry. However, the relationship of HD cells to behavior is not yet fully understood. In the current review, we examine the anatomical clues for information flow in the HD circuit and an emerging body of evidence that links neural activity of HD cells and spatial orientation. We hypothesize from results obtained in spatial orientation tasks involving HD cells that when properly aligned with available external cues, the HD signal could be used for guiding rats to a goal location. However, contradictory inputs from separate sensory systems may reduce the influence of the HD signal such that animals are able to switch between this and other systems according to their impact on behavior.

cognitive map; head-direction cells; hippocampus; orientation; spatial behavior

INTRODUCTION

Numerous everyday activities in an organism's life require some sense of direction, from ants having to navigate large distances back to their nests, to African elephants traveling large distances to exact locations of remote waterholes, to migrating birds returning to their nest site after spending winter in another continent. The requirement for navigational precision over long distances suggests that self-motion cues alone cannot account for such abilities because they are inherently inaccurate and prone to accumulation of errors. The evolutionary demand for directional awareness is so great that Darwin postulated the existence of a specific brain structure dedicated to this function: “The manner in which the sense of direction is sometimes suddenly disarranged in very old and feeble persons, and the feeling of strong distress, which as I know, has been experienced by persons when they have suddenly found out that they have been proceeding in a wholly unexpected and wrong direction, leads to the suspicion that some part of the brain is specialized for the function of direction” (Darwin 1873).

Behavioral experiments in spatial learning in rodents yielded the first evidence for allocentric (i.e., world based, and not egocentric) directional representation by mammals in Tol-

man's sunburst maze (Tolman et al. 1946), as part of a series of spatial tasks attesting to the idea of a cognitive map. In this task, rats were trained to find a reward on a right-angled track that was not visible from the starting location. In probe trials, the track connected to the starting location was replaced with multiple track arms protruding in different directions. Rats typically chose arms that were pointing in the direction of the rewarded location in the training trials, despite the fact that the rewarded location was not visible from the starting point (note however that because a light cue was also present above the reward location, cue-based navigation cannot be excluded).

The cognitive map, as proposed by Tolman (1948), is supposed to contain an allocentric representation of the external space and the agent's position within it. The ability to use shortcuts was in Tolman's view an indicator of a maplike spatial representation. [Note however that Grieves and Dudchenko (2013) found that rats, being neophobic, did not really use novel shortcuts.] With the discovery of place-selective cells in the rodent hippocampus (HPC) by O'Keefe and Dostrovsky (1971), the concept of the HPC as the site of the cognitive map emerged (O'Keefe and Nadel 1978) and became prevalent. Hippocampal place cells were found to encode specific locations in an environment, and multiple place fields can potentially map out the environment such that the animal's position could be decoded from the read out of firing rate of cell populations. Several years later, directional selective cells were discovered in the dorsal presubiculum (dPrS; also known

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as postsubiculum) of rats by Ranck (1984) and were characterized in detail by Taube et al. (1990a, 1990b). Head-direction (HD) representation can be computed from the activity of multiple azimuth selective cells, called HD cells. Each HD cell is selective for a specific azimuth range or preferred firing direction (PFD). Populations of cells create a network representing the entire range of possible azimuth headings. HD cells code for the azimuth of the rat's head in allocentric coordinates, in accordance with Tolman's cognitive map. However, these cells are not contained in a single dedicated brain structure as Darwin predicted, but rather are distributed in a complex neural circuit. This circuit is capable of transforming self-based sensory data into a world-based representation of a current direction. A wealth of experimental neural data on mammalian HD cells has been published in multiple species (Finkelstein et al. 2015; Jacobs et al. 2010; Robertson et al. 1999; Taube et al. 1990a; Yoder and Taube 2009), and its full description is beyond the scope of this review. [For a more thorough discussion of HD cell literature, see reviews by Finkelstein et al. (2016), Laurens and Angelaki (2018), and Winter and Taube (2014) and books by Dudchenko (2010) and Wiener and Taube (2005).] However, the exact relationship of the activity of HD cells to behavior has yet to be fully understood. A long-standing question is, how and when is the HD system used for guiding orientated behavior? Is the use of HD cells for navigation dependent on learned associations to rewarded locations? Or, is it an innate system that is in permanent control over the spatial orientation of the animal, always dictating navigational choices?

To discuss how the HD system relates to orientation behavior, we will first outline how the HD signal originates and what the flow of information between different components in the circuit is. From there we will move to a discussion of what is known about the connection of this system to behavior. In the context of this short review, we will focus on visual and vestibular influences, because these are the predominantly researched modalities in the context of sensory inputs to the HD circuit (Clark et al. 2012; Dudchenko and Taube 1997; Kudrimoti et al. 1996; van der Meer et al. 2010; Yoganarasimha et al. 2006). For a more detailed account on the origin of the HD signal, see reviews by Taube (2007) and Winter and Taube (2014). As described below, vestibular input can give a rough inaccurate measure of angular head velocity (AHV), whereas visual input can provide information from salient visual features and landmarks in the environment, as well as directionality of optic flow.

ORIGINS OF THE HEAD-DIRECTION SIGNAL

Spatial orientation is a process of self-localization within one's environment. A key component of this process is establishing a current heading. In order for this signal to be used effectively, it must be routinely, and ideally continuously, updated. The possible sensory inputs for generating a directional signal are a combination of visual, proprioceptive, and vestibular signals: self-motion, optic flow, and fixed visual landmarks, if any are available (Calton and Taube 2009; Clark and Taube 2012; Dugué et al. 2017; Huang et al. 2017; Rondi-Reig et al. 2014; Shin et al. 2011; Wilber et al. 2015; Winter and Taube 2014; Zhu et al. 2016).

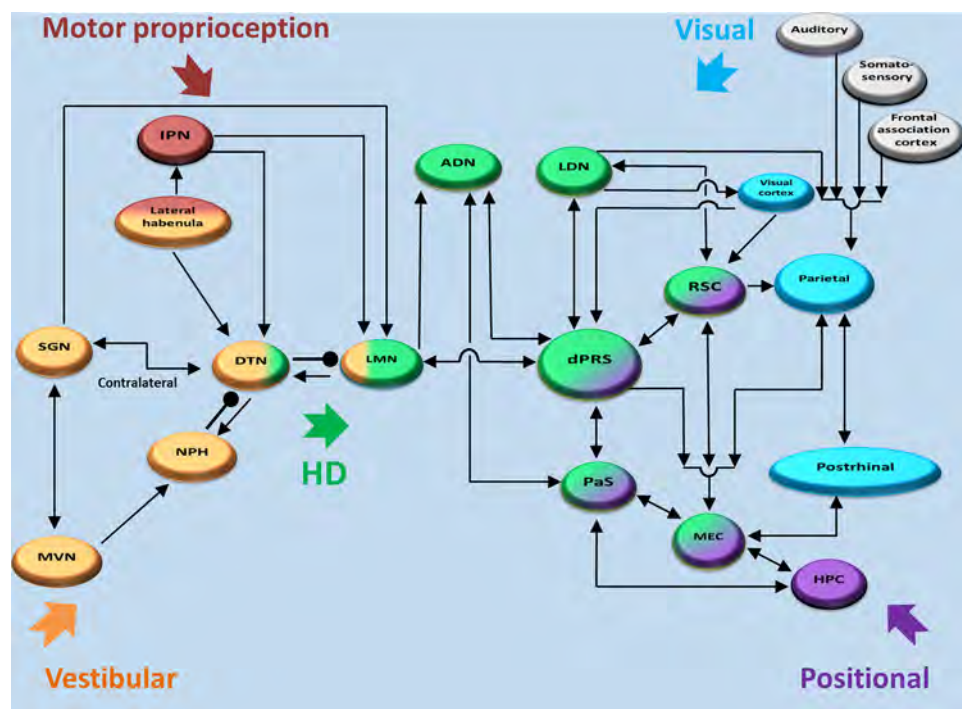
Tolman's sunburst experiment suggested that rats keep track of remembered locations and relative direction from their

current position to those locations, even if they are not visible, provided that an external salient cue or landmark can still be indicative of the relative goal location, such as a global cue in the experimental room. Therefore, it is postulated that the representation of direction is first and foremost relative to an absolute external coordinate system, and not confined to self-centered cues alone. Given that sensory inputs are predominantly self-referenced and egocentric, it follows that if a system is to function properly, the egocentric sensory representation must be transformed into a world-based allocentric representation through anchoring in some manner to the external environment.

To implement this transformation, the HD system comprises integrated compartments of information flow. Its origin is thought to be mainly vestibular: AHV signals are carried by angular-velocity sensitive cells in the medial vestibular nucleus (MVN), projecting to the nucleus prepositus hypoglossi (NPH) and supragenual nucleus (SGN). NPH cells inhibit cells in the dorsal tegmental nucleus (DTN), whereas SGN cells project to the contralateral DTN. The DTN also serves as a site for converging proprioceptive signals from the lateral habenula and interpeduncular nucleus. [The full account of anatomical projections upstream of DTN is beyond the scope of this review. For further details, see Clark and Taube (2012), Winter and Taube (2014), and Yoder and Taube (2014).] In turn, DTN cells inhibit cells in the lateral mammillary nucleus (LMN). These two nuclei are considered as the major region for the generation and maintenance of the HD signal and contain a mixture of AHV and HD cells. LMN cells project to the anterodorsal nucleus of the thalamus (ADN) (Seki and Zyo 1984; Taube 1995) and receive AHV input from SGN, as well as feedback from regions containing HD cells, such as dPrS. Visual information enters the HD system through projections from visual cortices to retrosplenial cortex (RSC), dPrS, and parietal cortex (Lozano et al. 2017; Wilber et al. 2014) and can provide visual feedback to the LMN through dPrS projections described in Huang et al. (2017), although it is noted that Calton et al. (2008) found no effect of parietal lesions on landmark control of HD cells in ADN. Visual feedback is crucial, because the AHV signal is relatively imprecise and prone to accumulation of errors over time during angular path integration, as is observed in the dark or before eye opening (Bjerknes et al. 2015; Tan et al. 2015, 2017). HD cells recorded in rat pups before postnatal day 16 may display directional selectivity but lack stability, whereas after eye opening, tuning curves are immediately sharper. This suggests that the maturation of the HD circuit is achieved before eye opening, but visual input is required to correct for signal drifting due to uncorrected self-motion cues. Further information, carried over from cerebellar and cortical areas such as auditory, somatosensory, and possibly frontal association cortices, projects to the parietal cortex and may enter from there into the HD system (Calton and Taube 2009; Rondi-Reig et al. 2014) (Fig. 1).

Directional information flowing into the HD circuit converges on the dPrS and reciprocally connected areas [ADN, lateral-dorsal nucleus of the thalamus (LDN), RSC, parasubiculum (PaS)] that serve as a hub providing directional signals to the HPC via the medial entorhinal cortex (MEC). The dPrS receives feedback from the hippocampal formation both directly via the PaS and indirectly via the RSC. In this way, the dPrS is in an ideal position to provide feedback to the gener-

Fig. 1. The head-direction (HD) circuit comprises several multimodal inputs and feedback projections, clustered by main modality of information contained within. Dark brown, motor proprioception; orange, vestibular; green, HD; blue, visual; purple, positional information. Black arrows represent excitatory connections. Black circles represent inhibitory connections. Based on reports by Calton and Taube 2009; Clark and Taube 2012; Dugué et al. 2017; Huang et al. 2017; Rondi-Reig et al. 2014; Shin et al. 2011; Wilber et al. 2015; Winter and Taube 2014; Zhu et al. 2016).



ative DTN-LMN coupling from integrated visual and positional information. This integration of information from different modalities may also account for the key feature of the HD circuit: it encodes direction in world-based coordinates despite receiving inputs and providing feedback to areas that encode mainly egocentric coordinates (vestibular, proprioceptive, and visual). The role of the DTN-LMN complex in generation of the HD signal was further emphasized by inhibition of NPH-to-DTN projections (Butler et al. 2017), resulting in loss of stability of HD cells recorded in the ADN, but without abolishing the HD signal. In this case it appears that the DTN-LMN complex is sufficient to still generate a directional signal, but lack of vestibular input cannot be compensated by other input pathways.

Thus the anatomical connectivity scheme (Fig. 1) holds clues on the flow of information between systems and compartments of the directional signal. For example, hippocampal and entorhinal projections can potentially provide reciprocal feedback between the positional and the HD systems through the PaS. This information could be used to correct for inaccuracies in spatial representations of either system or aid in planning of future trajectories. The flow of information also depends on how different inputs are processed and encoded into the relevant reference frame in each level in the generation and maintenance of the directional signal. The main influences on the HD signal that emerge out of the anatomical connectivity scheme are visual (through RSC, parietal and postsubthal) and vestibular (originating in MVN cells and entering through LMN). Both contribute to the ability to track heading (Yoder et al. 2011) through separate pathways, with possible integration of different modalities at key transition points between sensory compartments (lateral habenula, LMN, RSC, parietal). Specifically, the RSC was recently indicated as a site for convergence for multiple sensory and memory systems involved in spatial tasks (Calton and Taube 2009; Hunsaker and Kesner 2018). Electrophysiological recordings have unveiled cells respond-

ing to a combination of HD and positional information (Alexander and Nitz 2017; Jacob et al. 2017), possibly through inputs from the hippocampal formation. This finding is in accordance with the results of Kubik et al. (2012), who found a reduction of Arc gene expression in the RSC after inactivation of hippocampal CA1.

Although hippocampal inputs may occasionally serve to update the HD system, most current models focus on the contributions of continuous vestibular and visual inputs. The prominent theory for how integration of vestibular and visual information is accomplished is through a scheme in which cells are organized as a continuous attractor network, best described as a ring model (Bassett and Taube 2001; Kim et al. 2017; Knierim and Zhang 2012; Peyrache et al. 2015; Skaggs et al. 1995; Song and Wang 2005; Stringer et al. 2002; Xie et al. 2002; Yoshida and Hasselmo 2009). Ensembles of HD cells with different preferred firing directions, communally representing all possible directions, can be abstractly depicted as a ring of population activity. The current direction is represented as a bump of heightened activity on this activity ring, with external excitatory inputs driving the bump along the azimuthal axis and local inhibition maintaining the bump when no inputs are present. This type of model can account for sustained activity in the absence of external cues; each cell is excited by cells with a similar PFD and inhibited by cells with a different PFD. The combined activity of this network represents the current heading. However, with no external inputs to the ring, the bump would theoretically be static. To shift the bump and update its location, AHV cells in the vestibular system push the bump in the direction of head turns. Some models of HD networks describe triple-layer connectivity, with an inner layer of HD cells with excitatory inputs from outer layers of AHV cells and of visual information (Calton and Taube 2009). These connections can be viewed as fixed weights inputs, or at the very least slowly changing, because rapid changes at this level will entail strong variability in the responses in the computed

head direction. Visual inputs can be more adaptively weighted, to account for relative saliency of visual cues in a given environment (Knight et al. 2013; Page et al. 2013) (Fig. 2).

HEAD-DIRECTION CELLS AND BEHAVIOR

After outlining the anatomical connectivity and signal flow of HD information, we move to discuss possible interactions of the HD system with behavior in spatial tasks. Numerous experiments have dealt with the tuning properties of HD cells and the specific internal and external cues that might serve as guides for controlling the PFD of cell ensembles (Chen et al. 1994; Clark et al. 2012; Goodridge et al. 1998; Kudrimoti et al. 1996; Shinder and Taube 2014; Taube et al. 1990b).

However, relatively few studies confronted with the questions of how and whether these cells drive rodent spatial behavior. Reproducing Tolman's classical sunburst experiment, Muir and Taube (2004) affirmed that HD cells coded for the global coordinates, consistent with the behavioral strategy in the maze. Little change in PFD of cells was noted between the train and probe trials. Visual cue rotations around a radial maze (Dudchenko and Taube 1997) showed that when the HD system was able to follow the rotation of visual cues, indicating a rewarded location, rats appeared to use the HD signal to reach the goal location. However, when the HD system failed to accurately follow visual cues, rats did not shift from going to a previously learned location. Similarly, muscimol inactivation of ADN in a radial maze containing two baited arms impaired task performance despite familiarity with task and the environment (Harvey et al. 2017), further implicating the involvement of HD cells in the task. In mice performing a Morris water maze, muscimol inactivation of ADN produced a shift from local to globally based strategies (Stackman et al. 2012). More extensive manipulation in the form of excitotoxic lesions of the ADN and LDN resulted in impairments in a variety of spatial tasks, but not in object recognition (Wilton et al. 2001). Mizumori and Williams (1993) recorded HD cells in the LDN of rats performing a spatial task in a radial maze. The authors observed an inverse relationship between the directional selectivity of cells and number of errors during learning. van der Meer et al. (2010) showed that large shifts in PFD

following rotation of the rat resulted in larger errors in heading accuracy when rats used self-motion cues in a path integration task. Valerio and Taube (2012), using blindfolded rats in a similar path integration task, observed that the degree of error in heading accuracy matched the error in PFD of HD cells. Posttrial, for small shifts in PFD ($<50^\circ$), HD cells returned to their original alignment. However, for large shifts ($>50^\circ$), HD cells retained the erroneous PFD and carried it over to the next trials. [The detailed neural mechanisms for path integration are beyond the scope of this review. For more information on path integration, see Etienne and Jeffery (2004) and McNaughton et al. (2006).] Despite the results of Dudchenko and Taube (1997), Golob et al. (2001) found no consistent correlation to behavior in a reorientation task. Shifts in HD did not necessarily induce corresponding shifts in behavior. Lesions of the DTN were shown to produce impairments of spatial tasks (Clark et al. 2013; Frohardt et al. 2006). A more recent study by Butler et al. (2017) used halorhodopsin to inhibit the cells projecting from NPH to the DTN in rats performing the food retrieval task. Inhibition of the NPH-to-DTN pathway during the return phase to a refuge caused drift in ADN HD cells and increased heading errors in darkness, but not in light conditions with visible cues present. NPH inhibition on the return phase led to loss of stability in ADN HD cells and errors in the food retrieval task. Lesions of the LMN produced no impairment in a visually guided spatial landmark task but did affect reversal learning in a water maze task (Harland et al. 2015). Overall, both lesion and inactivation experiments point to the role of the NPH-DTN-LMN circuit, both in persistence of the HD signal in the absence of external input (by local attractor-network-type mechanisms) and for maintaining the accuracy of directional representations. We note that the term "maintenance" refers to keeping an accurate representation, whereas the term "persistence" refers to the fact that a directional signal can hold in the absence of external input, possibly by a local attractor-network-type of mechanism. The studies mentioned above and their relevance to the relation of HD cells to behavior are summarized in Table 1.

The results reviewed above suggest the following narrative: the HD system is a continuous and persistent signal that is anchored to salient visual features in the environment. Vestibular input, being a less accurate measure, is used more for maintenance and persistence of the HD signal. Rats might be able to learn to use the HD system for guiding their behavior, but it is dependent on associations formed between any orientation and reward or task outcome. This idea was recently explored by Weiss et al. (2017). When HD cells were recorded in the MEC of rats performing a reorientation task in a rectangular arena, HD readout was indicative of behavior, as a function of its directional orientation in the recent past. This result was strongest when alignment of HD cells to the external environment was most similar to that observed in oriented open-field recordings conducted in the same test arena. The PFD of the HD cells was remarkably stable in between reorientation events, consistent with previous work demonstrating strong stability of HD even when grid cells and place cells remap (Whitlock and Derdikman 2012). The coherence of HD cell ensembles was preserved despite periods of disorientation epochs by rapid angular movement, when rats were spun and deprived of visual cues before some trials. After deliberate disorientation epochs, the PFD of cells either remained rela-

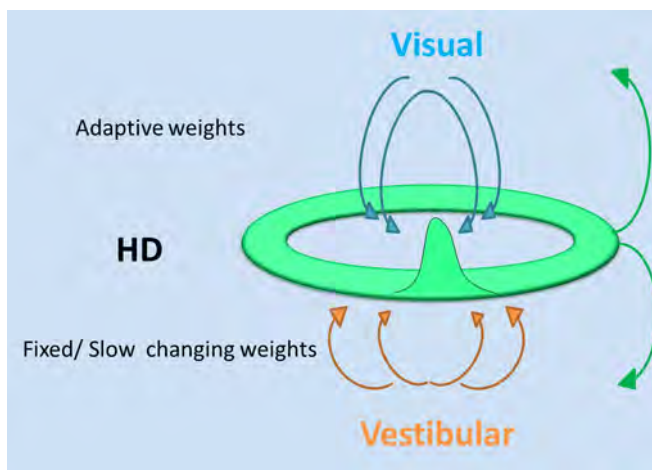


Fig. 2. Ring attractor model for head-direction (HD) cells. Visual (light blue) and vestibular (orange) inputs drive a bump of activity in HD cell ensemble (green).

Table 1. Key experiments linking head-direction signal and behavior, arranged by types of experimental manipulation

Recording Site	Manipulation	Task	Effect on HD Cells	Correlation of Neural Activity to Behavior	Reference
<i>Shift of external cues</i>					
LDN		Radial arm maze in light and dark	In absence of visual cues, HD cell tuning drifted	During learning, directional specificity was correlated to task performance	Mizumori and Williams (1993)
ADN	Cue rotation	Radial arm maze	HD cells either followed cue rotation or failed to do so	When HD cells followed cue rotation, there was an increase in correct arm choice	Dudchenko and Taube (1997)
ADN, dPrS	Switch from right-angled to sunburst maze	Sunburst maze	No shift in HD PFD was observed		Muir and Taube (2004)
<i>Disruption of self-motion signals</i>					
ADN	Disorientation outside of arena	Reorientation task	HD cells rotated on some trials but not others in an unpredictable manner	No clear correlation to behavior	Golob et al. (2001)
ADN/dPrS	Passive rotation in a cylinder	Homing task	On some trials, HD cells shifted their PFD	Large shifts in HD PFD associated with larger heading errors during return phase	van der Meer et al. (2010)
ADN	Blindfold	Food retrieval task	PFD of HD cells occasionally drifted from initial position	Large shifts in HD PFD associated with larger heading errors during return phase; HD cells maintained shifted PFD on subsequent trial	Valerio and Taube (2012)
MEC	Disorientation inside arena	Reorientation task	PFD of HD cells predictably realigned in reference to geometric axis containing reward location	Increase in probability of correct choice when HD cells maintained correct alignment; correct choice ratios increase with HD reliability	Weiss et al. (2017)
<i>Lesion and genetic mutation studies</i>					
	Lesions of ADN and LDN	T maze, Morris water maze, object-in-place task		Impaired performance in spatial tasks	Wilton et al. (2001)
	LMN lesion	Object recognition		No deficits found	
		Visually guided spatial landmark task		No impairment	Harland et al. (2015)
		Water maze		Impaired reversal learning	Harland et al. (2015)
<i>Inactivation studies</i>					
ADN	Disorientation	Morris water maze		Loss of bias toward local cues	Stackman et al. (2012)
	Muscimol inactivation of ADN	Morris water maze		Shift of navigational strategy from local to global cues	Stackman et al. (2012)
	Muscimol inactivation of ADN	Radial arm maze		Impaired performance after muscimol injection despite task familiarity	Harvey et al. (2017)
	Optogenetic inhibition of NPH	Food retrieval task		Inhibition during return phase of task led to increase in heading errors	Butler et al. (2017)
ADN	Optogenetic inhibition of NPH	Open-field task	Loss of stability in round arena		

HD, head direction; LDN, lateral-dorsal nucleus of thalamus; ADN, anterodorsal nucleus of thalamus; dPrS, dorsal presubiculum; PFD, preferred firing direction; MEC, medial entorhinal cortex; LMN, lateral mammillary nucleus; NPH, nucleus prepositus hypoglossi.

tively unchanged, or reset, to a predictable orientation: aligned with the geometric axis that contained the rewarded goal location, yet 180° away from the original PFD (Fig. 3). The results of Weiss et al. (2017) show that the contribution of the HD system to behavior is not determined only by anatomical and connectivity constraints but rather is a dynamic process. The value of the HD system for goal-directed navigation is hence dependent on outcomes of its use in the recent past.

At this point, it is worth noting that, most likely, the HD system is not the sole network used for directional orientation, and additional heading estimation methods can also direct rats to their targets. Such mechanisms might rely on upstream directional signals initially present in the generation of the HD signal. These signals originate from sensory inputs, which are inherently egocentric.

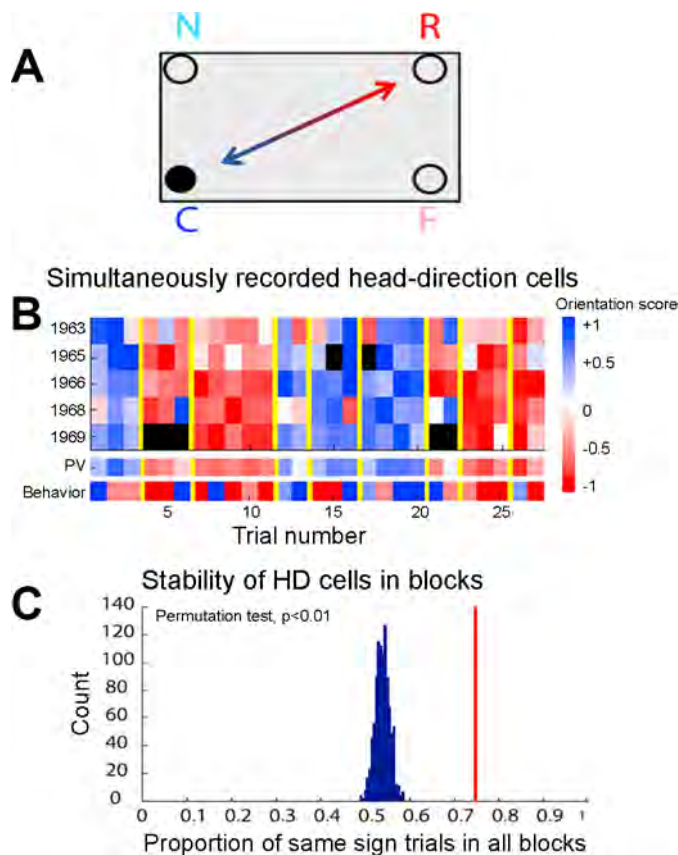


Fig. 3. A: diagram of experimental apparatus. Rectangular arena 60 × 120 cm. C, correct choice; N, near error; F, far error; R, rotational error. Color-coded arrow represents alignment of head-direction (HD) population: blue, aligned with correct corner; red, aligned to a rotational transformation of reference frame. B: population activity of simultaneous HD cells in rat medial entorhinal cortex recorded during reorientation task. HD cells maintain reference frames between disorientation epochs, displaying misalignment in some blocks but not random activity. Individual cells are labeled by numbered rows. Cell and population vectors (PV) are color coded by orientation score as in A (one bin per trial). Behavioral outcome is color coded by corner choice as indicated by letter annotation in A. Yellow lines note disorientation epochs. C: significant stability of directional representation during test trial blocks. Blue bars are population data of 1,000 permuted trials from same recording session; red line is the observed proportion of same-sign trials (positive or negative performance scores). [Reprinted from Weiss et al. (2017) with permission.]

PARALLEL DIRECTIONAL ORIENTATION SYSTEMS COMPETE FOR DOMINANCE OVER BEHAVIOR IN SPATIAL TASKS

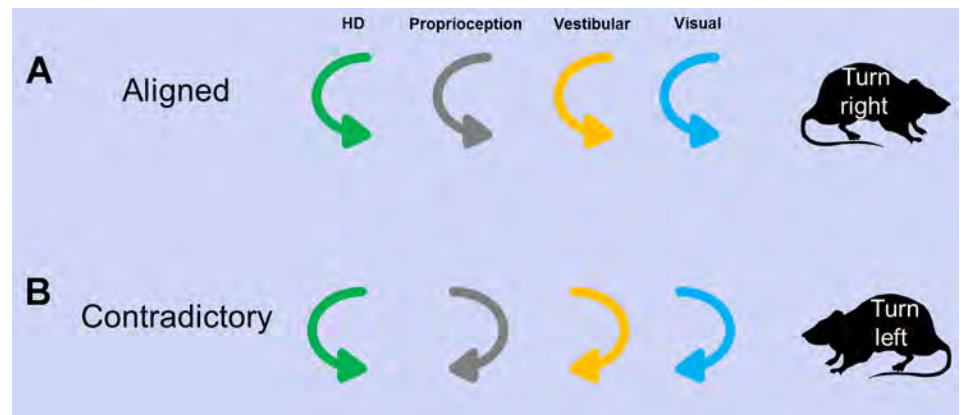
Egocentric driven navigation is typically linked to the activity of cells in the striatum. Striatal lesions and caudate nucleus inactivation studies induce procedural, response-type learning deficits in spatial tasks and introduce a behavioral bias away from an egocentric spatial reference frame (Packard et al. 1989; Packard and McGaugh 1992, 1996). The allocentric hippocampal and egocentric striatal pathways are independent, and dissociable parallel orientation systems may allow for switching between navigational strategies for maximum optimization of search patterns or reducing cognitive load. However, when hippocampal and striatal pathfinding strategies are conflicted, rats display increased vicarious trial and error (VTE) (Schmidt et al. 2013), a typical rodent behavior of pausing in place and orienting toward possible future routes, mainly at choice points. This result highlights that spatial decision-making is not under the exclusive control of either system but rather is influenced by both systems, as parallel mechanisms for processing spatial information, reward prediction, and route planning. Such processing by multiple reference frames is likely mediated by the parietal cortex, RSC, or the subicular complex (Jacob et al. 2017; Olson et al. 2017; Wilber et al. 2014).

The determining factor is therefore an issue of signal reliability (Dudchenko and Taube 1997; Weiss et al. 2017). The redistribution of the impact on behavior between parallel spatial memory systems is most probably context specific, with either prior experience in a given environment or outcome-dependent activity yielding a bias toward the use of one system over the other. Support for this notion can be found in the dissociation between use of heading vs. place information, as demonstrated by Julian et al. (2015).

We offer the following interpretation of existing literature reviewed above (Fig. 4): the HD system is a continuously updated signal. Although its origins are rooted in sensory self-based information, the resulting convergence of these inputs is a transformed world-based directional representation. This representation is visually anchored to salient features in the environment. When properly aligned with available external cues, the HD signal could be used for guiding rats to a goal location. However, contradictory inputs from separate subsystems may reduce the reliability of the HD signal and lead to a reduction in the reliance on HD in spatial tasks. Therefore, the functionality of the HD system in spatial orientation can be viewed as a dynamic process, based on its functional value at any given time point, rather than a constant guide of spatial behavior. The parameter that is being tracked is the reliability of each system in predicting reward location, based on previous experience in the very recent past. In certain cases, temporary misalignment of true heading and directional representation can result in loss of orientation. The ability of the HD system to recover from and still function as a guide for behavior depends on the extent of preserved relational information. Two major states are identified in this context: type I and type II disorientation.

In type I disorientation (unrecognized), there is no conscious perception of spatial disorientation. We refer to this state as “misorientation,” because it may appear to subjects that no

Fig. 4. Competition between allocentric head-direction (HD) signal and egocentric sensory only inputs. **A**: the HD signal is aligned with sensory information. In this state, rats are able to use it as a guide for behavior. **B**: multi-modal sensory information is more coherent than the HD signal but is contradictory to the HD signal. In this case, the dominance of the HD signal over behavior is lost.



problem exists, although their actions will lead them in an erroneous direction (Previc and Ercoline 2004). This is a state of misalignment of perceived heading and true heading while maintaining knowledge of spatial relationships between external cues. Such a state can occur when cues are no longer visible for prolonged periods of time (Dudchenko 2010). Misorientation can be expressed by synchronous network activity of an ensemble of HD cells. That is, PFD is expected to be collectively skewed in a similar degree across cells. Behaviorally, misorientation may result in systematic azimuth errors. However, because this state does not render the HD system unusable, it is possible that the population activity, although different from its original form, can still guide an animal in making correct directional choices, despite having a new reference point. Indeed, both results were observed by Weiss et al. (2017).

In type II disorientation (recognized), subjects are aware of the disorientation and attempt to correct their actions. We refer to this state as “disorientation,” because subjects are aware that their sense of direction is flawed and may compensate using available external cues (Previc and Ercoline 2004). In this state, directional representation is lost, or perhaps even the knowledge of spatial relationships can be lost, unstable, or inaccessible (Dudchenko 2010). Disorientation might be expressed either as reduced responsiveness of cells to changes in azimuth or by asynchronous activity between cells in an ensemble, meaning each cell’s PFD will remap to a new azimuth, independently from the PFD of other cells. This state signifies a failure of the directional system and may result in rewiring of the functional connectivity within the HD circuit as new positional-directional relationships are learned, because the two are intricately coupled (O’Mara and O’Mara 2017). Behaviorally, we expect disorientation to produce a period of confusion, longer latency to choice in spatial tasks, and reversion to cue-dependent navigation, later followed by recovery.

A third form of disorientation, which we will not discuss in detail, is type III (incapacitating), in which coordination of vestibulo-ocular function is disrupted. In humans, this type of disorientation is accompanied by nystagmus and activation of vestibulospinal reflexes, motion sickness, and strong emotional sensations of fear (Previc and Ercoline 2004).

In disorientation, rats are unable to use the HD signal to accurately orient themselves because of a vestibular driven drift or visual resetting of the network activity; they may revert to other navigational strategies rather than follow an unreliable signal. However, in misorientation, directional stability and

coherence are still maintained despite a shift in relative PFDs of all cells (meaning they all still fire in phase and no further drift occurs). In this case, it is possible for rats to readjust and slowly learn to reliably use the signal once again (Weiss et al. 2015, 2017). Hypothetically, this rationale enables switching between orientation strategies as a constant optimization process based on accurately predicting direction to goal locations (Fig. 4).

Even so, If the legibility of the current heading signal is maintained, and it is representing the current heading, the HD system has a key advantage over other spatially informative systems, mainly in that it is integrating sensory information from multiple egocentric sensory systems and converting these signals into an allocentric reference frame, possibly by integration with boundary information in the dPrS (Gofman et al. 2017; Lever et al. 2009; Peyrache et al. 2017). This integration may also be essential for the anchoring of grid cells to physical features, such as boundaries in the external environment (Derdikman 2009; Weiss et al. 2017), or for disambiguating visually identical locales (Harland et al. 2017) or scenes by hippocampal place cells. Finally, in conjunction with positional information, a reliable HD signal can serve for improving the accuracy of heading components in preplay of future trajectories, in keeping a vector to hidden goal locations by hippocampal place cells (Sarel et al. 2017) or to series of future locations by conjunctive grid and HD cells (Kubie and Fenton 2012).

OPEN ISSUES AND FUTURE DIRECTIONS

Potentially, the representations generated by the HD system can also serve for other localization processes, such as fine motor commands similar to those seen in the reach-to-grab task (Guo et al. 2015) or directional joystick task (Morandell and Huber 2017), where a directional component in a goal-directed task may also involve hippocampal functions in early learning stages. Specifically, to keep track of movement direction, velocity, and spatial positions of goal locations, essentially whenever angular path-integration computations are required. One prediction of this line of thought is that hippocampal involvement should be evident in spatiomotor tasks, especially when visual information is absent. Another open issue is the extent of hippocampal feedback to the HD system. This is especially relevant to understanding the factors involved in realignment of HD cells after visual or vestibular ambiguity. The exact mechanism driving realignment of HD cells is so far unknown; however, it appears that mammillary bodies (MB),

RSC, and subiculum may be crucial in this context. A recent study (Kinnavane et al. 2018) found novel collateral connections from dorsal subiculum to medial MB and RSC, which are uncharacteristic of previously described subicular connectivity patterns. Such findings may indicate possible pathways for simultaneous hippocampal feedback to both cortical and sub-cortical areas. By updating RSC and MB with the same input, synchronization and realignment of spatial frames may be achieved. Further work is needed to understand the functional significance of these findings in relation to spatial tasks. Although most studies described above have focused on the influence of inputs to the hippocampal formation (Table 1), it may be beneficial to dissect the influence of hippocampal inputs to the HD system at different levels, focusing on MB, ADN, and RSC. This line of research may serve to update our current view of the contribution these connections have to the HD network (as described in Fig. 1). For example, in the context of the reorientation task, visual inputs fed into the hippocampal formation may be compared with positional and directional information (Fig. 4) to attenuate feedback to RSC and MB and, in turn, change the weights of visual and vestibular effects on the HD system (Fig. 2). Further anatomical and functional studies are required for a more complete understanding of the interaction of the directional and positional systems. Yet, as these systems can be dissociated (Julian et al. 2015), it should be possible to differentiate both behavioral and neural responses to inhibition of specific feedback pathways between the two systems. An additional avenue of research is how interactions of the RSC and subicular complex affect the transformation of egocentric to allocentric information. Potential processes include gating of sensory information into the HPC by RSC or changes to the thresholds of RSC responses to different sensory inputs by subicular outputs.

In summary, the HD system, when properly aligned, offers a high degree of accuracy for prediction of future trajectories or replay of recent past that is difficult to achieve by stimulus response memory systems or sensory systems alone. This predictive power is dependent on the recent-past value of the system, as established by the outcome of previous goal-directed trajectories. It is still to be determined how HD signal reliability is processed in the brain. Further investigation of the neural circuits involved may have implications extending beyond the use of HD signals and reveal general principles guiding additional influences of consistency of spatial or other cues on behavior.

GRANTS

This research was supported by Israel Science Foundation Grants 955/13 and 2344/16, a Rappaport Institute grant, an Allen and Jewel Prince Center for Neurodegenerative Disorders of the Brain grant, and an Adelis Foundation Technion-Weizmann Collaboration grant.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.W. prepared figures; S.W. and D.D. drafted manuscript; S.W. and D.D. edited and revised manuscript; S.W. and D.D. approved final version of manuscript.

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