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A new perspective on the head direction cell system and spatial behavior

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Highlights:

- Damage to the head direction circuit produces only modest impairments in spatial behavior.
- Head direction cells predict spatial behavior in some tasks, but not others.
- New evidence suggests that there are different kinds of head direction cells.
- Different head direction cells may underlie different spatial abilities.

Abstract

The head direction cell system is an interconnected set of brain structures containing neurons whose firing is directionally tuned. The robust representation of allocentric direction by head direction cells suggests that they provide a neural compass for the animal. However, evidence linking head direction cells and spatial behavior has been mixed. Whereas damage to the hippocampus yields profound deficits in a range of spatial tasks, lesions to the head direction cell system often yield milder impairments in spatial behavior. In addition, correlational approaches have shown a correspondence between head direction cells and spatial behavior in some tasks, but not others. These mixed effects may be explained in part by a new view of the

head direction cell system arising from recent demonstrations of at least two types of head direction cells: 'traditional' cells, and a second class of 'sensory' cells driven by polarising features of an environment. The recognition of different kinds of head direction cells may allow a nuanced assessment of this system's role in guiding navigation.

Key words: Head direction cells, spatial cognition, landmarks, navigation

In the mammalian brain, there is a remarkable type of neuron which fires in a compass-like way. These head direction cells, as they are known, show a high rate of firing when an animal, such as a rat or mouse (in whom most of the work on these cells has been done) faces one direction, but show little or no firing in other directions (Figure 1). Different head direction cells exhibit different 'preferred firing directions' such that the entire 360^{o} range is represented. Despite having one of the highest signal-to-noise ratios of any neuron in the brain, and despite being found in a series of brain regions from the brainstem to the cortex, what these cells actually do for the animal has not been determined. In this review, we consider the mixed evidence linking head direction cells and spatial behavior. We will argue that variability in these findings may be explained by the recent demonstrations of two types of head direction cells, and an appreciation of differences in task demands and the distributed representation of direction in the brain.

Head direction cell basics

On January 15th, 1984, Dr James Ranck Jr. encountered, serendipitously, the first head direction cell (Ranck, 2005). Ranck was attempting to record from the rat subiculum, but his recording electrodes ended up in the adjacent postsubiculum. The cell he encountered fired

when the rat's head faced one direction, with a 90^{o} range in the horizontal plane, and this firing appeared to be independent of the animal's behavior or position within the environment. Ranck found additional head direction cells in this and in subsequent animals, and the first full papers describing these cells were published in 1990 with Jeffrey Taube, Robert Muller, and John Kubie (Taube et al., 1990a; 1990b).

In these and subsequent studies, the characteristics of head direction (HD) cells were established. Briefly, these cells fire when the rat's head faces a specific direction relative to the recording environment, and do so regardless of the position of the rat's body. Like the spatial firing of place cells - neurons in the hippocampus that represent specific locations - head direction cell tuning is anchored to visual landmarks in the environment. In essence, they behave as a neural compass, though one that is anchored to familiar landmarks, and not a magnetic field.

Though familiar landmarks exert stimulus control over the preferred firing direction of HD cells, earlier studies suggested that these cells are not visually responsive per se. HD cells maintain, for a period of time at least, a stable firing direction in the dark (Goodridge et al., 1998; Knierim et al., 1998). They also maintain a similar preferred firing direction as the animal walks from one local environment to another in which different visual cues are available (Taube and Burton, 1995). Evidence suggests that lesions or temporary inactivation of the vestibular system causes a loss of directional firing of HD cells (at least those recorded in the anterior thalamus and the postsubiculum) (Stackman and Taube, 1997; Stackman et al., 2002). Thus,

'traditional' head direction cells require vestibular inputs, and rely on familiar landmarks to maintain stability.

Since their initial description in rats, head direction cells have been found in the mouse (Khabbaz et al., 2000), chinchilla (Muir et al., 2009), bat (Finkelstein et al., 2015), and rhesus macaque monkey (Robertson et al., 1999). Indirect evidence also suggests that head direction cells are present in the human brain (Shine et al., 2016). Remarkably, directionally tuned neurons are also observed in the fruit fly, *Drosophila melanogaster* (Seelig and Jayaraman, 2015). Together, these observations suggest that head direction cells are both an evolutionarily conserved and an evolutionarily convergent system. The range of organisms in which head direction cells are found also implies that they serve an important function for mobile organisms, though that function has yet to be established definitively.

Brain areas containing head direction cells

Since their identification in the postsubiculum, head direction cells have been identified in a series of interconnected brain regions (Figure 2). The head direction signal is believed to originate in connections between the dorsal tegmental nuclei and the lateral mammillary nuclei, and then project to the anterior thalamus, the postsubiculum, and the medial entorhinal cortex. Head directions cells are also found in retrosplenial cortex, parasubiculum, lateral dorsal thalamus, nucleus reuniens, dorsal striatum, medial precentral cortex, and posterior parietal cortex (e.g., Sharp et al., 2001a; Wilbur et al., 2014; Mehlman et al., 2018; see Taube, 2007 for review). At the time of writing, head direction cells have been identified in 11 brain

regions.

Earlier studies have shown that head direction cells in separate brain regions differ, specifically with regard to the width of their directional tuning and the interval in which cells 'anticipate' the animals current head direction (Blair & Sharp, 1995; Taube & Muller, 1998; Stackman & Taube, 1998, 2003; Sharp, 2005). For the former, broader directional tuning was observed in head direction cells of the lateral mammillary nucleus, followed by narrower tuning in the anterior dorsal thalamus and the postsubiculum, although variability was seen within each area as well. Despite these differences, the traditional head direction cell system has been conceived as being both unitary and hierarchically organised (Clark & Taube, 2012). Within this view, establishing a clear link between head direction cells and behavior should be possible, but as described below this has proved not to be the case.

The relationship between head direction cells and other classes of spatial cells

Head direction cells are not only of intrinsic interest, they are also a key component of a broader neural circuitry involved in representing the animal's location in the environment (for recent reviews see Grieves and Jeffery, 2017; Poulter et al., 2018). This circuit includes place cells, neurons in the hippocampus that represent an animal's location, the locations of others (Omer et al., 2018; Danjo et al., 2018), and sequences of stimuli (Aronov et al., 2017; for review see Eichenbaum, 2017). Lesions to specific parts of the head direction circuit cause place fields (the locations where individual place cells fire) to be unstable relative to visual landmarks (Calton et al., 2003) and to lose their sensitivity to locations that look similar but which face

different directions (Harland et al., 2017). The head direction system is essential for the spatial firing of grid cells, neurons in the medial entorhinal cortex and adjacent regions that tile environments with discrete, regularly spaced firing fields (Winter et al., 2015; for review see Rowland et al., 2016). The relationship between head direction cells and border/boundary vector cells, neurons that fire in parallel and at a specific direction relative to a barrier in the animals environment, has yet to be empirically determined. However, an allocentric directional representation is thought to be essential for the spatial anchoring of these cells (Barry et al., 2006), and they in turn are thought to anchor the putative path integration based firing of grid cells (for review see Savelli and Knierim, 2019). In short, the directional representation provided by head direction cells likely underlies the neural representation of location.

Evidence linking head direction cells and behavior: lesion studies

Given their prominence and robust signaling of current (or upcoming) head direction in allocentric space, it is natural to ask what head direction cells actually do for the animal. Broadly, this question has been addressed either by removing a part of the head direction circuit and observing the behavioral consequences, or by correlating HD cell directional firing and behavioral choices in response to changes in the environment (a point also noted by Butler et al., 2017). As described below, both approaches have provided mixed evidence for a direct relationship between HD cells and behavior. This stands in contrast to lesions of the hippocampus, which yield profound deficits on a range of spatial tasks. To account for this, we argue that there are two directional representations in the brain. One is the traditional head direction cell system, linked closely to the vestibular system and internal, self-motion

information. The second is a 'sensory' head direction cell, tied closely to polarising features of the environment. These two systems, together with variations in task demands and redundancy with the head direction circuit, may help to explain the range of findings from the previous lesion studies and correlational studies.

Dorsal tegmental nuclei lesions

In rats, lesions of the earliest point in the brain where head direction cells are found, the dorsal tegmental nucleus (DTN; Figure 2), impair the ability to return to a 'home' location after an excursion to find food. However, the animals still perform at above chance levels on such a homing task following these lesions, and their errors are not random (Frohardt et al., 2006). Dwyer et al. (2013) likewise found impairments in a homing task and in a direction task in a T-shaped maze following electrolytic lesions of the DTN, though this damage extended to brain areas beyond the DTN in some instances. These findings are consistent with a role for HD cells in an animal's ability to sense its direction. One limitation in this evidence, however, is that it is unclear whether the impairments were due to damage to HD cells per se, as these comprise only a small percentage of the neurons in the DTN (12.5% in Sharp et al., 2001b; 11% in Bassett and Taube, 2001), while the majority (~ 75% of DTN neurons) encode head velocity.

Lateral mammillary nuclei lesions

The findings from removal of the mammillary bodies (in rodents), the next stage in the HD circuit after the DTN, are likewise inconclusive. Lesions of the entire mammillary body complex (including both the lateral mammillary nuclei (LMN), where HD cells are found, and the medial

mammillary nuclei (MMN), where they are not) produce a modest impairment in alternating directions on a T-maze, but this impairment is smaller than that seen with fornix or large anterior thalamic lesions (Aggleton et al., 1995). Lesions specific to the LMN, the portion of the mammillary bodies containing HD cells, have no effect on a traditional T-maze alternation task and result in only a mild and transient effect on a matching-to-sample task in a Morris water maze (Vann, 2005). Subsequent work confirmed this lack of effect on a T-maze, though a small impairment was observed when LMN lesioned animals were required to alternate directions across adjacent mazes (Vann, 2011). In this same study, lesioned animals showed only a transient impairment in a shape-based Morris water maze task. Work by Harland et al. (2015) has shown that LMN lesions have no effect on identification of a correct direction relative to a salient visual landmark in a novel digging task, and only a transient effect on relearning a Morris water maze task. On radial arm mazes in environments with extra-maze visual cues, no impairment was observed in LMN-lesioned animals (Vann, 2018) or in animals with degeneration of the mammillary bodies caused by mutation of the Foxb1 transcription factor gene (Radyushkin et al., 2005) (though in this study impairments were observed in a circular, table-top Barnes maze). Recent work, however, has shown that lesions of the LMN diminish the rat's capacity to distinguish locations based on their directional orientation (Harland et al., 2017; Smith et al., 2018).

Anterior thalamic nuclei lesions

A larger number of studies have assessed the effects of removing the anterior thalamus on spatial learning. Broadly, lesions restricted to portions of the anterior thalamus that contain HD

cells (principally the anterior dorsal thalamus, but also the anterior ventral thalamus (Tsanov et al., 2011)) yield initial impairments in spatial learning on a T-maze and a Morris water maze that improve with training (Aggleton et al., 1996; Van Groen et al., 2002). No impairment was observed with anterior thalamic lesions on a radial arm maze task (Beracochea et al., 1989), though impairments in a reference memory version of this task have been observed following temporary inactivation of the region (Harvey et al., 2017). In mice, such inactivation of the anterior thalamic region is associated with indirect swim paths in the Morris water maze (Stackman et al., 2012). Impairments in homing were also observed with anterior thalamic lesions, though these appear less severe than those following DTN lesions (Frohardt et al., 2006). Combined lesions of the anterior dorsal thalamus and the lateral dorsal thalamus, where HD cells have also been described (Mizumori and Williams, 1993), yield impairments in T-maze alternation and on a variant of the Morris water maze task (Wilton et al., 2001). Larger lesions of the anterior thalamic nuclei, including portions of the anterior thalamus where HD cells have not been found, yield greater impairments (Aggleton et al. 1996; for full review see Aggleton and Nelson, 2015).

Postsubiculum, retrosplenial cortex, and medial entorhinal cortex lesions

Lesions of the cortical regions in which HD cells are found yield mixed effects on tasks which depend on a sense of direction. For example, Taube et al. (1992) found that rats with lesions of the postsubiculum were impaired in performance of a radial arm maze and a Morris water maze, but in both instances, performance of lesioned animals improved with training. Kesner and Giles (1998) found that rats with combined post- and parasubiculum damage were

impaired in remembering which maze arm they'd recently visited on a radial maze, and similar lesions also resulted in deficits in Morris water maze and T-maze alternation (Liu et al., 2001; Bett et al., 2012). However, removal of the postsubiculum in rats does not impair their ability to return to a home site in a testing environment without extra-maze visual landmarks (Bett et al., 2012).

Likewise, for the retrosplenial cortex, impairments have been observed in some instances (e.g., Harker and Whishaw, 2004a; Vann & Aggleton, 2004), but not others (e.g., Neave et al., 1994). For example, rats with complete lesions of the retrosplenial cortex produce more errors during learning of a working-memory radial arm maze task compared with control animals, though the performance of the two groups was equivalent at the end of training (Vann & Aggleton, 2004). Subsequent maze-rotation probe sessions in this and another study (Pothuizen et al., 2008) suggest that although rats with retrosplenial cortex lesions can perform the task, they make less use of distal visual landmarks compared with control animals (see also Nelson et al., 2015). In the Pothuizen et al. study, the lesioned animals were impaired in alternation across T-mazes in the dark, suggesting an impaired directional sense. Evidence from neuronal imaging studies also indicates that the dysgranular retrosplenial cortex is active during a radial maze task performed in the light (where distal landmarks are presumably used), whereas the granular retrosplenial cortex is active in both light and dark maze performance (indicating a contribution to both visual and nonvisual spatial strategies) (Pothuizen et al., 2009). This parcellation of the retrosplenial cortex is noteworthy, given the distribution of a new class of head direction cells discussed below. Finally, the formation of stable neuronal activation patterns in the retrosplenial cortex is associated with better memory performance in a reference memory

version of the task (Milczarek et al., 2018). In general, it is likely that differences in lesion techniques, lesion extent and spatial strategy determine whether a spatial impairment is observed following retrosplenial cortex damage (Aggleton and Vann, 2004; Harker and Whishaw, 2002; Harker and Whishaw, 2004b; Pothuizen et al., 2008; Vann and Aggleton, 2002; Vann and Aggleton, 2004).

Lesions of the entorhinal cortex

For entorhinal cortex lesions, the literature is complicated by differences in lesion technique and the anatomical specificity of damage. Earlier studies used electrolytic, aspiration, or radiofrequency lesions, and tended to report larger impairments in spatial tasks, though these effects were occasionally transient (Ramirez and Stein, 1984; Schenk and Morris, 1985; Rasmussen et al., 1989; Kesner and Giles, 1998; Ramirez et al., 2007; Nagahara et al., 1995; Parron et al., 2006).

More specific lesions of the entorhinal cortex with neurotoxins (typically, glutamate receptor agonists such as ibotenic acid or NMDA) produce no or only modest impairments in spatial learning. For example, rats with ibotenic acid lesions of the subiculum and entorhinal cortex showed no deficit in learning the location of rewarded arms on a radial arm maze, though some sparing was suggested in the most dorsal level of the entorhinal cortex (Bouffard and Jarrard, 1988). Cho et al. (1993) found that ibotenic acid lesions of the entorhinal cortex (including the lateral and medial entorhinal cortices) in mice impaired performance of a recently learned discrimination between pairs of arms on a radial maze, but not a discrimination learned four weeks prior to the lesions. Hölsher and Schmidt (1994) found that quinolinic acid lesions of the

medial entorhinal cortex impaired radial maze learning and reversal, but these impairments were transient. In Pouzet et al. (1999), rats with NMDA lesions of the entorhinal cortex learned a radial maze task, but showed a slightly higher error rate during initial acquisition and during reversal learning. On a T-maze, Rothblat et al. (1993) found that alternation was not impaired following NMDA infusions in the parahippocampal region, though sparing of medial portion of the entorhinal cortex was evident in this study. Similarly, NMDA lesions of the entorhinal cortex produced no impairment in a matching-to-position task on a T-maze, though again some sparing of the dorsal entorhinal cortex was present (Marighetto et al., 1998).

In other studies, rats with lesions of the entorhinal cortex were either not impaired or only mildly impaired in learning the location of a submerged platform in a Morris water maze task (Hagan et al., 1992; Pouzet et al., 1999; Burwell et al., 2004). Steffenach et al. (2005) argued that the lack of pronounced spatial impairments following neurotoxic lesions of the entorhinal cortex were due, in part, to potential sparing of the dorsolateral band of this structure (where spatially tuned neurons such as grid cells are observed). They trained animals using a Morris water maze and found that lesions of the dorsolateral band abolished this memory, though the lesioned animals learned a new hidden platform location almost as readily as control animals. Hales et al. (2014) found that rats with extensive lesions of the medial entorhinal cortex were impaired initially in learning the Morris water maze task compared to control animals, but this impairment was not evident after five days of training. However, in contrast to Steffenach et al., large impairments in acquisition of a new platform/cue configuration were observed in the medial entorhinal cortex lesioned rats. Together, these studies with specific lesions of the

medial entorhinal cortex suggest that spatial learning is still possible in the absence of this structure, though it may be slower and more rigid.

Evidence linking head direction cells and behavior: recording studies

The second main line of evidence linking head direction cells to behavior is based on correlational studies between the two. In general, this literature indicates that there is a correlation between changes in HD cells' firing directions and changes in spatial behavior in some tasks, but less so in others (Weiss and Derdikman, 2018).

Radial arm maze tasks

The first study suggesting a link between HD cells and behavior was by Mizumori and Williams (1993). They recorded cells in the lateral dorsal thalamus which showed directional firing during performance of a radial arm maze task. Two cells were followed across training on the task, and their extent of their directionality was positively correlated with performance on the maze.

Additional support for a correlation between HD cells and behavior was reported by Dudchenko and Taube (1997). They trained rats on a radial maze task that was surrounded by a black curtain, upon which hung a white 'cue' curtain serving as a polarizing, distal cue. Rats were trained to find a reward on one arm of the maze, and then probe sessions were conducted in which the cue curtain was rotated by either 90^{o} or 180^{o}. In most instances, rotation of the cue curtain was associated with a corresponding shift in the preferred firing direction of the head

direction cells and the animals' maze arm choices.

In 2004, Muir and Taube recorded HD cells on a single-route maze, where the rat was led on an indirect route to obtain a water reward. They were then tested on the 'Sunburst' version of this maze where several different routes were possible (one of which led directly to the reward location). Early maze work by Edward Tolman has used this apparatus to demonstrate that rats could demonstrate knowledge of the direction in which a reward was located (Tolman et al., 1946). However, Muir and Taube found no consistent relationship between HD cells and the rat's choices on the Sunburst maze. Instead, HD cell firing directions appeared anchored to the start of the maze - which was the same in both the training and Sunburst mazes - while the choices made by the animals varied across trials.

Square or rectangle orientation tasks

A different pattern of results was obtained by Golob et al. (2001). They trained rats to find a water reward in a specific corner of a square box that was equipped with a 'cue' card on one wall. Rats learned this task, but shifts in head direction preferred firing directions during performance of the task were not associated consistently with shifts in the corner chosen. When tested in a rectangle with the same cue card - reward corner association, the rats generalized from the square environment, and chose the same correct corner 78% of the time, despite changes in the firing direction of HD cells in 92% of these manipulations. In a second experiment, a lack of consistency between the behavior of head direction cells and that of the rat's choices was again observed on the majority of trials. Taken together, in the square or

rectangular apparatus, there was not a clear relationship between the firing of HD cells and spatial behavior.

In a more recent study, the results were similarly mixed. Weiss et al. (2017) tested reorientation in a rectangular environment (similar to the task used by Golob et al., 2001, and originally developed by Ken Cheng (1986)). Following disorientation, head direction cells were stable over blocks of trials while the rat's corner choices varied. However, the rats' performance improved as a function of the number of trials in which the head direction cell firing direction remained stable. Thus, individual corner choices were not strictly tied to the behavior of head direction cells, though when the latter were stable, behavioral accuracy improved.

Homing tasks

Van der Meer et al. (2010) assessed the correlation between head direction cell changes and homing behavior on a large, circular platform. Rats left a submerged 'nest' on the periphery of the platform, and retrieved a food reward in the center of the platform. They then returned to the nest via a direct path, and consumed their reward there. Typically, rats make relatively direct returns to a 'home' location after such excursions (Whishaw et al., 2001). In the Van der Meer et al. study, rats were confined to the center of the platform for a delay, and during some of these the platform was rotated by 90^{o} slowly. Overall, rotation resulted in a corresponding shift in the rats' behavior, and in those animals for which HD cells were recorded, a correlation between firing direction changes and nest choices was observed.

Valerio and Taube (2012) likewise examined the relationship between head direction cells recorded in the anterior dorsal thalamus and behavior in a homing task. In their study, blindfolded rats were trained to leave a refuge box at the periphery of a large, circular apparatus, find a food reward within the apparatus, and return to the refuge to consume this. The authors found that shifts in HD cell firing directions during the search for the food reward compared to within the refuge (before each for each trial) were strongly correlated with the amount of error in the animal's return trip to the refuge.

Finally, Butler et al. (2017) sought to provide causal evidence for a link between the head direction cell system and behavior by optogenetically inactivating a critical input to the circuit, the nucleus prepositus hypoglossi (NPH), during a homing task. They found that the amount of HD cell firing direction drift following inactivation of the NPH (recorded separately) correlated with the directional error in the subsequent homing task. Though indirect, this suggests that changes in the head direction cell system correspond to changes in homing directions.

Summary of recording/behavior studies

Taken together, the recording studies above suggest that head direction cell representations are more strongly correlated to performance in homing tasks than to performance on discrete choice tasks. This could be accounted for by differences in the cues available during these tasks. For example, in the Golob et al. experiment described above, rats' choices in the square or rectangular apparatus were controlled by the cue card therein.[1] The same cue card exerted

less stimulus control over the HD cells, as evidenced by instability in firing direction across trials (where the cue card did not move) and some mismatches in HD cell rotations during card shifts. One possibility, as discussed below, is that there are different types of HD cells, and some are less strongly controlled by visual landmarks (such as a cue card) than others. In homing tasks, in contrast, the testing environments typically lack polarizing landmarks (being large, circular table tops, curtained off from the rest of the laboratory room), or the animals are tested in darkness or with blindfolds. Thus, it is possible that traditional HD cells that are driven more by vestibular or self-motion inputs are more closely tied to behavior in tasks which are not landmark based.

A second factor for the lack of clear-cut impairments following damage to the head direction circuit is that spatial tasks can be solved in different ways, and only some of these spatial strategies may require the head direction cell system. For example, the T-maze alternation task is attractive in its simplicity, with the rat or mouse first choosing one arm of the T, and on the next run choosing the other arm. However, this task can be solved by choosing alternate directions (West then East; e.g., Douglas, 1966), or by the detection of intramaze cues on the maze arms, or by the choice of alternate locations (Futter and Aggleton, 2006). Only the first of these may require a representation of direction, and this is consistent with the somewhat larger deficits observed with T-maze alternation in the dark with retrosplenial cortex lesions (Pothuizen et al., 2008; Nelson et al., 2015). Likewise, mice lacking NMDA receptors in the dentate gyrus and CA1 hippocampus showed evidence of intact spatial learning (on a traditional Morris water maze task), but impaired ability to use spatial information to choose between

similar locations (Bannerman et al., 2012). This suggests a dissociation between the representation of spatial information, and its use to guide behavior.

In addition, there may be redundancy in the head direction signal. Whereas complete lesions of the hippocampus remove most, if not all of the representations of location provided by place cells, damage to a specific portion of the head direction cell circuit (for example the anterior dorsal thalamus) may spare the directional representation found in other brain regions (e.g., the lateral mammillary nuclei).

A potential resolution: multiple directional representations in the brain

The preceding review of the literature suggests that 1) damage to specific head direction cell brain regions in some instances produces relatively modest, transient impairments in spatial behavior, and 2) correlated changes in HD firing directions and spatial behavior are observed in some spatial tasks, but not all. This pattern of results is surprising, given the strength of the head direction signal, its representation within a large neural circuit, and the directional demands of the behavioral tasks used. Lesions to the hippocampus, in contrast, produce consistent, devastating impairments on a range of spatial tasks (for review see Dudchenko, 2010). Our argument is that the lack of a clear relationship between head direction cells and behavior stems from there being more than one directional representation in the brain. As described below, recent studies provide evidence for at least two representations of head direction (see also Taube, 2017).

In the first of these, a hint that there may be different types of head direction cells was observed in an elegant study by Giocomo et al. (2014). They found that along the dorsal-ventral axis of the medial entorhinal cortex, head direction cells in layer III showed sharp (narrow) directional tuning dorsally, and much wider tuning ventrally. This observation parallels previous demonstrations of a dorsal-ventral expansion of both grid cells and place cells (Hafting et al., 2005; Jung et al., 1994; Kjelstrup et al., 2008). Interestingly, no such changes in directional tuning were seen in layers V-VI of the MEC, or the presubiculum, along the dorsal-ventral axis. In these regions, the head direction cells showed that same sharpness of turning throughout. At the very least, these results indicate that there is a range of directional representations in layer III of the MEC.

A more recent, unambiguous demonstration of different 'kinds' of head direction cells is found in a study by Jacob et al. (2017). They recorded from head direction cells in the dysgranular retrosplenial cortex in a two chamber apparatus connected via a middle doorway. Remarkably, a subset of HD cells fired in opposite directions in each of these rectangular-shaped chambers, despite the animal having walked between the two (Figure 3A). Moreover, some cells showed bidirectionality within a single compartment. This bidirectionality, either within a single chamber or across two connected chambers, stands in contrast with the responses of 'traditional' HD cells recorded in the postsubiculum or the anterior thalamus. These possess a single preferred firing direction that is maintained across connected chambers in the absence of conflicting landmarks (see also Taube and Burton, 1995; Dudchenko and Zinyuk, 2005). As the two chambers in the Jacob et al. study were equipped with identical cue cards at opposing wall

ends, one possibility is that the firing direction of the bidirectional HD cells was anchored to these visual landmarks (Figure 3A). As both bidirectional HD cells and traditional HD cells (i.e., those maintaining the same preferred firing direction in both chambers) were recorded simultaneously in this study, both representations are present in the same brain area.

Overall, the findings of Jacob et al. provide clear evidence for two different kinds of head direction cells: traditional cells that are driven by (presumably) vestibular inputs, and sensory cells, driven (presumably) by sensory inputs.[2] Cells that were bidirectional in a single environment (within-compartment cells) could likewise be driven by visual inputs, such as the corners of the environment, or could represent yet a third class of HD cells. However, although the directional firing of bidirectional cells recorded by Jacob et al. appears to be anchored to either the visual landmarks within an environment or the corners of the environment, visual inputs are not necessary for this firing as it is maintained in the dark. This suggests that bidirectional cells are multi-modal. Intriguingly, directional firing was less obvious when these same cells were recorded in a square open platform. As such an environment contains four equivalent corners, it is possible that there is a limit to the number of polarising features that can be represented at the same time and still allow a cell to be directional (Page and Jeffery, 2018). This again contrasts with vestibular head direction cells, where directionality is maintained in an open field (e.g., Whitlock and Derdikman, 2012).

A third recent study also suggests that different directional representations are found in the mammalian brain. Olson et al. (2017) recorded from neurons in the rat dorsal subiculum, and

found that a subset of cells in this region fired along an axis of a triple T-maze with return arms (Figure 3B). Thus, for example, a given subicular cell might fire when the animal is travelling both East and West on alleyways within the maze (and other cells fired along other axes, with firing peaks about 180^{o} from one another). The preferred 'axis' of these cells was anchored to the room, as rotations of the maze by 90^{o} resulted in the cells firing on different alleyways, but in the same direction with respect to the room. Axis-tuned neurons did not fire in a directional way when recorded in an open, circular arena in the same room. These cells thus appear to encode the animal's axis of travel on a maze. Axis cells have similarities with bidirectional cells in that they fire in two opposite directions in both the light and the dark in an environment with a polarising shape, but they exhibit less directionality in an open field environment. It is unclear whether axis cells are thus a variant of the bidirectional cells (or vice-versa), or whether they constitute another unique representation of direction. To distinguish between these possibilities, it will be necessary to record both of these cells within one experiment.

A fourth study indicating that there are different types of head direction cells is that of Kornienko et al. (2018). They recorded from the MEC and parasubiculum of mice during exploration of a square environment where one of two patterns of lights was displayed on the walls. The patterns alternated every two minutes for the entire session. Some HD cells exhibited different tuning curves for the two different visual patterns - that is, they shifted preferred firing direction every two minutes. At the same time, other HD cells maintained a stable preferred firing direction across both visual patterns. The former cells were theta-modulated, while the latter were not. Difference responses to the two patterns of lights were

observed with simultaneously recorded HD cells. These results indicate that within the same brain region and at the same time, different HD cells can be anchored to different cues. Simply put, some HD cells followed the visual cues, while at the same time other HD cells did not.

A reappraisal of the head direction cell system

Since their first demonstration, it has been assumed that the head direction circuit is unitary. HD cells were thought to be driven by a combination of familiar external landmarks, and internal integration of movement-related information, and this was true for all HD cells equally. These and other properties suggested that the head direction cell system is an internal system, driven by attractor dynamics, and corrected by external sensory inputs (e.g., Zhang, 1996; Peyrache et al., 2015). Previous work has demonstrated that traditional head direction cells in different regions exhibit differences, for example in their tuning widths, anticipatory firing, and modulation by turning direction (e.g., Stackman and Taube, 1998). Despite these, according to the single attractor model, all cells within the head direction cell circuit provide a consistent read out of the animal's current (or slightly anticipated) direction. Thus, if one head direction cell's preferred firing direction changes following a manipulation of the environment, such as displacement in a visual landmark, all other head direction cells are assumed to change in the same way.

The recent demonstrations by Jacob et al., Olsen et al., and Kornienko et al., however, indicate that there are at least two functional types of head direction cells in the brain. Presumably, these arise from a different weighting of internal vs. external inputs to specific head direction

cells (Figure 4). Broadly, one class of cells may be considered 'vestibular' head direction cells - driven primarily by internal dynamics and the vestibular system, and corrected by external landmarks. These are the traditional head direction cells of both earlier recording studies and computational models. The second class is 'sensory' head direction cells - driven primarily by external landmarks. Within-compartment bidirectional cells (with two firing directions in a single environment; Figure 5) and axis cells may be variants of the sensory head direction cells, as both lose directional tuning in an open field. However, it is also possible that they represent distinct forms of directional representation.

As sensory head direction cells have thus far been observed only in cortical regions, it is possible that different brain regions possess different types of HD cells. Thus, a mixture of sensory and vestibular HD cells may be found in cortical regions (e.g., retrosplenial cortex, medial entorhinal cortex, parasubiculum), while vestibular HD cells may be the only type of directional cells observed subcortically (e.g., in the dorsal tegmental nucleus, lateral mammillary nucleus, anterior thalamus). This distinction is not absolute, as only traditional (vestibular) head direction cells were observed in the postsubiculum, which is a cortical region (Jacob et al., 2017). Also, even vestibular HD cells can be controlled by visual landmarks, and recent findings from Yoder et al. (2017) suggest that this information enters the circuit at the level of the lateral mammillary nucleus. Finally, it is also possible that parallel ascending circuits, such as those observed in the connections between the mammillary nuclei and the anterior thalamic nuclei (Aggleton et al., 2010, Jankowski et al., 2013), give rise to theta-modulated vs. non-theta modulated head direction cells which differentially respond to visual

and self-motion inputs.

The existence of different kinds of head direction cells may help to explain the mixed results observed in traditional lesion and behavior studies, though these distinctions may be relative. For example, lesions to brain regions that contain only vestibular head direction cells might be expected to produce deficits in tasks that are performed in darkness or in the absence of external polarizing landmarks, for example in returning to a nest sight based on self-motion information (homing). Some of the findings described above are consistent with this. For example, Frohardt et al. (2006) showed that lesions of the DTN, a brainstem region early in the head direction circuit, yields impairment in homing. An additional factor may be that at the level of the DTN, there is less redundancy in the representation of head direction, compared with upstream structures such as the ATN (where lesions produce a less dramatic impairment in homing). In contrast, such lesions may have less of an effect on tasks that can be solved using external landmarks such as a visual cue or the shape of the testing environment. For example, Harland et al. 2015 found that animals with LMN lesions had no difficulties using a visual cue to identify a specific rewarded location from many alternatives. From a recording perspective, the firing direction of traditional HD cells may be less strongly anchored to specific external landmarks compared to visual HD cells, as suggested by the results of Jacob et al., and thus the former's relationship to behavior controlled by these same landmarks may be variable.

At the other end of the circuit, lesions of brain regions containing sensory head direction cells - such as the dysgranular retrosplenial cortex - would be expected to impair spatial tasks that

require the use of visual landmarks. Indeed, such lesions appear to diminish the stability of anterior thalamic head direction cells recorded in the presence of a salient visual landmark (Clark et al., 2010). Behaviorally, support for this prediction is found in the observation that rats with retrosplenial cortex lesions are impaired on a radial arm maze task when the maze is rotated midway through the rats' choices (Pothuizen et al., 2008). Such a result suggests that the lesions of this brain area interfere with the animal's use of distal visual landmarks to choose the correct maze arms. Likewise, the ability to learn the location of a hidden platform within a Morris water maze, which also depends on the use of extra-maze, distal landmarks, is impaired following lesions of the retrosplenial cortex (for review see Harker and Whishaw, 2004). However, in both the Pothuizen et al. study and in the studies reviewed by Harker and Whishaw, it is noted that retrosplenial cortex lesions also impair alternation in the dark and path integration tasks (such as homing). This suggests that the retrosplenial cortex contributes to both landmark-based and self-motion-based spatial processing. One possibility, suggested by the results of Pothuizen et al. (2009), is that the dysgranular retrosplenial cortex (where bidirectional head direction cells were reported by Jacob et al., 2017) is specifically involved in visual landmark processing, whereas the granular retrosplenial cortex is involved in both visual and non-visual spatial memory.

In recording studies, it may be that behavior in discrete choice, landmark-based tasks, such as that of Golob et al. (2001), is better correlated with sensory head direction cells than vestibular head direction cells. In the Cheng rectangle reorientation task used by Weiss et al. (2017), it may be speculated that, following disorientation, in some instances vestibular head direction

cells (and grid cells) reorient, while sensory head direction cells do not. Thus, the corner chosen by the animal immediately following disorientation may be better predicted by the responses of the latter. With ensuing trials, the two systems may become aligned, or the animal may in some way revert to the use of traditional head direction cells. Further empirical work is required to address this possibility.

Future directions

The demonstration of different kinds of head direction cells points to several new direction for research. First, do sensory head direction cells maintain directional tuning in the absence of vestibular inputs? This input is essential for traditional (vestibular) head direction cells, but the properties of the sensory cells suggest that they are less strongly tied to self-movement inputs. Second, fundamentally, do vestibular head direction cells underpin some types of spatial tasks (for example, homing), while sensory head direction cells underpin others (visual landmark based tasks)? As the preceding review suggests, the precise role of the head direction cell system in behavior has been difficulty to establish. A clear possibility is that different spatial tasks rely on different directional representations. Third, what is the precise circuitry that gives rise to sensory head direction cells? Presumably, visual and sensory inputs are required for these cells, and thus these cells may be sensitive to disruptions of these inputs. As a related point, are traditional head direction cells the only type of directional cells observed in the DTN -> LMN -> ATN ascending circuit? Finally, the findings described above could indicate that there are multiple representations of directionality across different brain regions. It will be of interest to determine whether these can be accommodated under the 'traditional' and

'sensory' classification proposed here, or whether a further typology is required.

Summary

Recent recording studies have suggested that head direction cell system is not unitary. Although this is likely to be an incomplete characterization, we suggest that head direction cells can be classified as either traditional/vestibular HD cells (in that they are driven primarily, but not exclusively by internal and vestibular inputs) or sensory head direction cells (driven primarily by external landmarks or polarising features of an environment). Such a conceptualization may help to account for the variable relationship between head direction cells and directional behavior, as the latter may be controlled by different cues under different circumstances.

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Footnotes

[1] In a subsequent behavioral experiment within the Golob et al. study, rats *were* able to select the correct corner of a square apparatus *even when the cue card was removed*. Coupled with the observation that the rats' choices followed the cue card shifts, this suggests that while the cue card exerts the strongest control over behavioral choices (at least in well-trained animals), other sources of information, such as a putative internal sense of direction, are sufficient to guide behavior in the absence of a cue card. One wonders, then, if the Golob et al. experiment were re-done without a cue card, whether a stronger link between corner choices and

preferred firing directions would be observed.

[2] This is not an absolute distinction. Traditional cells are driven by vestibular and self-motion inputs as the animal moves from one environment to another, but this can be overridden by familiar visual landmarks (Dudchenko and Zinyuk, 2005).

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Figure captions

Figure 1. The directionally-tuned firing of a head direction cell The specific direction in which an HD cell fires is termed its preferred firing direction. The linear plot (A) and the polar plot (B) are of the same cell recorded as a rat foraged for scattered food morsels in an octagonal enclosure.

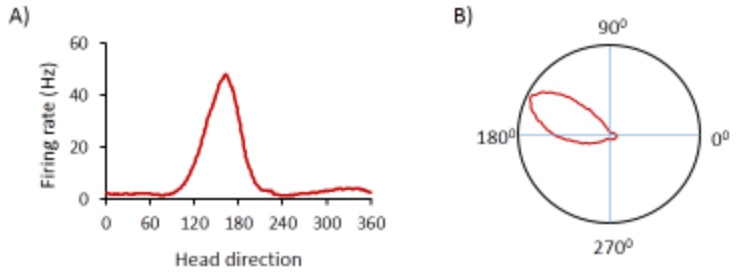

Figure 1

Figure 2. The head direction cell circuit The head direction signal is thought to originate in the connections of the dorsal tegmental nucleus and the lateral mammillary nucleus, and then ascend via thalamic nuclei to cortical regions. We argue that additional head direction signals, dependent on landmarks, are observed in cortical regions.

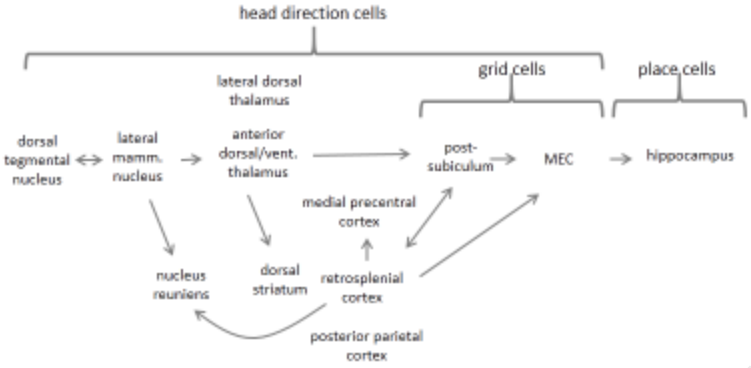

Figure 2

Figure 3. Evidence for different types of head direction cells A) Recent findings by Jacob et al. (2017) suggest that not all head direction cells respond in the same way. Briefly, when a rat moves from one rectangular compartment to a second, some head direction cells maintained their same firing directions, while others showed a flipped direction. B) Olsen et al. (2017) showed that neurons in the subiculum fired in a directional way along the animal's axis of travel on a maze.

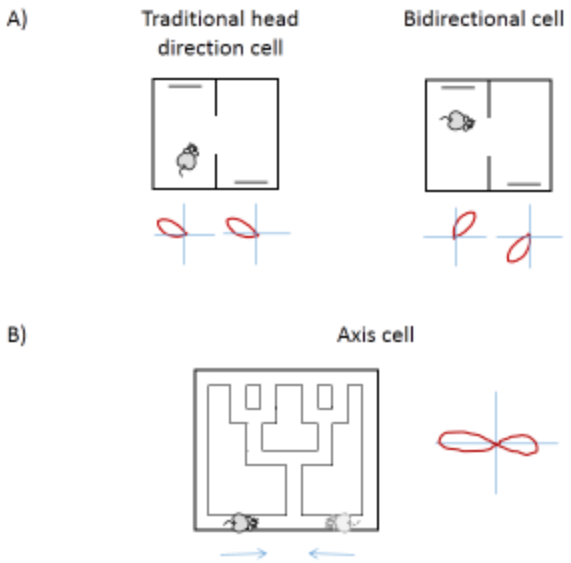

Figure 3

Figure 4. Differential inputs to vestibular and sensory head direction cells Recent evidence suggests that there are at least two functional types of head direction cells. In the first type, the traditional head direction cell, vestibular inputs may be stronger drivers of preferred firing directions than visual inputs, though the latter still exert an influence. For the second type, referred to here as sensory head direction cells, external sensory inputs outweigh vestibular/self-motion inputs in controlling preferred firing directions.

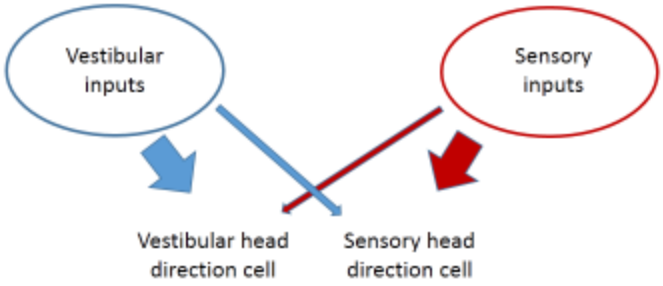

Figure 4

Figure 5. Example of a head direction cell with two firing directions This cell shows two peaks in directional firing, at about 180° from one another, similar to the bidirectional and axis cells described in the text. This recording was conducted in a maze with four, identical, parallel rooms, and is from electrodes that were intended to reach the medial entorhinal cortex.

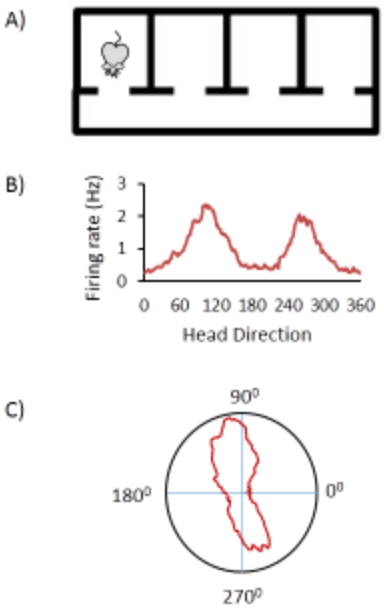

Figure 5