Neural compass or epiphenomenon? Experimental and theoretical investigations into the rodent head direction system

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Abstract

How does the brain convert sensory information into abstract representations that can support complex behaviours? The rodent head-direction (HD) system, whose cell ensembles represent head direction in the horizontal plane, is a striking example of a "cognitive" representation without a direct sensory correlate. It can be updated by sensory inputs from different modalities, yet persists in the absence of external input. Together with cells tuned for place, the HD system is thought to be fundamental for navigation and spatial information processing.

However, relatively few studies have sought to characterise the connection between the HD system and spatial behaviour directly, and their overall outcome has been inconclusive. In the experiments that make up the first part of this thesis, we approach this issue by isolating the self-motion component of the HD system. We developed an (angular) path integration task in which we show that rats rely on their internal sense of direction to return to a trial-unique starting location, allowing us to investigate the contribution of the HD system to this behaviour without influences from uncontrolled external cues.

Using this path integration task, we show that rats with bilateral lesions of the lateral mammillary nuclei (LMN) are significantly impaired compared to sham-operated controls. Lesions of the LMN, which contains HD cells, are known to abolish directional firing in downstream HD areas, suggesting that impairment on the task is due to loss of HD activity. We also recorded HD cell activity as rats are performing the path integration task, and found the HD representation to correlate with the rats' choice of return journey. Thus, we provide both causal and correlational experimental evidence for a critical role of the HD system in path integration.

For the second part of this thesis, we implemented a computational model of how the HD system is updated by head movements during path integration, providing a novel explanation for HD cells' ability to anticipate the animal's head direction. The model predicts that such anticipatory time intervals (ATIs) should depend on the frequency spectrum of the rats' head movements. In direct comparison with experimental recording data, we show that the model can explain up to 80% of the experimentally observed variance, where none was explained by previous models. We also consider the effects of propagating the HD signal through multiple layers, identifying several potential sources of anticipation and lag.

In summary, this thesis provides behavioural, lesion, and unit-recording evidence that during path integration, rats use a directional signal provided by the head direction system. The neural mechanisms responsible for the generation and maintenance of this signal are explored computationally. The finding that ATIs depend on the statistics of head movements has methodological implications and constrains models of the HD system.

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Declaration

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

(*Matthijs van der Meer*)

In memoriam

A.A.M.M. van der Meer, polymath, friend, father.

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Chapter 1

Introduction: head direction cells and the brain

In the foreword to the recently published "head direction cell book" (Wiener and Taube 2005) James Ranck Jr. tells the story of how these remarkable cells were discovered:

> Sunday, January 15, 1984, I lowered the electrode and recorded from the first of the rats. I was astounded to find a head direction cell. It was so clear that I felt confident about its characteristics within a few minutes: the firing was in absolute direction in the horizontal plane (yaw), independent of pitch, roll, and location; it was independent of the few behaviors observed that afternoon; and all the firing occurred within about 90°.

Ranck made a movie of a recording sessions of this rat, including audible clicks when the cell fired, and showed it at the 1984 Society for Neuroscience meeting. He notes:

> It was a big hit. A lot of people came to see it and many said "Wow" or the equivalent. I was especially pleased that one of the guards at the convention center spent most of his time watching the tape. You don't have to be a neuroscientist to be struck and entertained by the firing of these cells.

Ranck's last remark has been proven true time and time again; to some extent, it is also true for movies of Hubel and Wiesel's visual cells, which fire when a bar of light in a particular orientation moves in a particular direction. However, if you *are* a neuroscientist, there is something especially remarkable about a head direction cell: you can't *sense* head direction[1]. How does this cell know which way the rat is facing?

The "neural compass" provided by the head direction system is a compelling example in support of the computational paradigm so influential in neuroscience over the last couple of decades. Its main principle is that if what is happening inside the brain is to be useful to

[1] Unless you have a magnetic sense, perhaps, but when Ranck carried a magnet into the recording room, it didn't disturb the cell's firing.

an organism, there must be some correspondence between brain activity and aspects of the world the organism interacts with. In other words, to understand the brain, we must find out what is *represented* there, how those representations arise, and how they are used for behaviour. I subscribe to this view, and the work described in this thesis is an attempt to contribute to both questions, applied to the head direction system: how is the head direction signal constructed, and what is it for?

The head direction system, a model system?

Why study the head direction system? The "meta-sensory" property of head direction cells (i.e. the lack of a direct sensory correlate) is an important reason for its appeal. This signal ultimately has to be constructed somehow, yet it can be maintained apparently in the absence of any sensory inputs. (Later experiments showed that the head direction signal persists when the rat is not moving, even in darkness.) Some of the neural mechanisms now thought to underlie this property of the head direction system, "attractor dynamics", are believed to be a general scheme also important for other cognitive abilities which don't need obvious sensory input to work, such as working memory and planning. The fact that the head direction system seems to be representing something that is relatively simple (a one-dimensional continuous variable of which we understand the mathematics) compared to more ephemeral concepts like thoughts and plans, promises to give us insight into how these systems might work in general.

Another point is that the representation of space appears to be pretty important in mammalian brains. Head direction cells, and their "place cell" relatives, are found in many different brain structures, lesions of which are known to cause not just disruptions in navigational skills, but also more general memory deficits. The link between spatial processing and memory for events and experiences is starting to be explored in detail, and understanding the head direction system is part of that enterprise.

Structure and contents of this thesis

This is a document in three parts, broadly addressing two questions: how is the head direction signal generated, and what is it used for? The first three chapters, constituting Part I, are an introduction to the head direction system, with the first (Chapter 2) reviewing the relevant physiology and anatomy, Chapter 3 discussing computational models in relation to the results reviewed, and Chapter 4 reviewing theories of navigation and the evidence for a role for the head direction system in them. While there have been several comprehensive reviews of the head direction system, in particular the recent "head direction cell book", from which this work has benefited greatly, the review part of this thesis is an attempt at a more integrated (and necessarily less comprehensive) approach. Although the physiology

and modelling review chapters are separated out, the aim is discuss all major physiology results in a modelling context, finishing with 10 open questions these models pose about the generation of the head direction signal. Some of these questions, related to anticipation, are addressed in Part III, using computational and analytical techniques (Chapters 7 and 8).

A specific contribution of the Part I review chapters is the re-interpretation of a number of experimental results using an idea which is not itself new (the distinction between *drift* and a change in *reference direction*), but has not been applied to the head direction system. Using this idea, an explicit hypothesis about the function of the head direction system in behaviour is developed (the "neural compass hypothesis"), which is tested using behavioural, lesion, and recording techniques in the experimental Part II of the thesis (Chapters 5 and 6).

A summary of contributions and an overall discussion is provided in the concluding Chapter 9.

Part I

Review

Chapter 2

Physiology of the rodent head direction system

2.1 Basic properties

Head direction (HD) cells, found[1] in the rodent and primate brain (Ranck Jr. 1984; Taube et al. 1990a; Robertson et al. 1999; Khabbaz and Tank 2004), do as their name suggests: they are neurons whose primary firing correlate is the animal's head direction[2]. Head direction cell tuning curves are typically constructed by recording neural activity from animals freely moving in a contained environment (traditionally a cylindrical bucket with a white cue card affixed to the wall, Figure 2.2 on page 7, left) while their position and head direction are tracked by an overhead camera. Spikes recorded from putative HD cells can then be analysed in relation to head direction by a computer program to construct a tuning curve. This kind of analysis shows that HD cells are tuned for *allocentric* direction, that is, a particular bearing relative to a reference direction. They do not fire at a fixed bearing relative to a landmark at finite distance (*egocentric* direction); this distinction is illustrated in Figure 2.1 on the next page. Maximal firing occurs along parallel lines, irrespective of the animal's position (red arrows in Figure 2.2a). What determines the reference direction is an important question discussed in detail in later sections.

Like so many cells in the brain, head direction tell tuning curves are approximately Gaussian in shape: they are maximally active when the animal's head is facing that particular cell's preferred firing direction, away from which activity gradually falls off to almost silent levels.

[1] Encouragingly to all young researchers in the field having trouble getting their recording electrodes in the right place, their discovery was something of an accident: James Ranck Jr. inadvertently placed his electrodes in the adjacent postsubiculum when trying to hit the subiculum (Ranck Jr. 2005).

[2] This term conventionally refers to head direction in the horizontal (yaw) plane, although neurons sensitive to roll and pitch have been found (e.g. Stackman and Taube 1998), these are typically not referred to as head direction cells, and although true head direction cells behave in interesting ways in three dimensions (during locomotion in a non-horizontal plane), this is a nonstandard case reviewed elsewhere (Taube 2005).

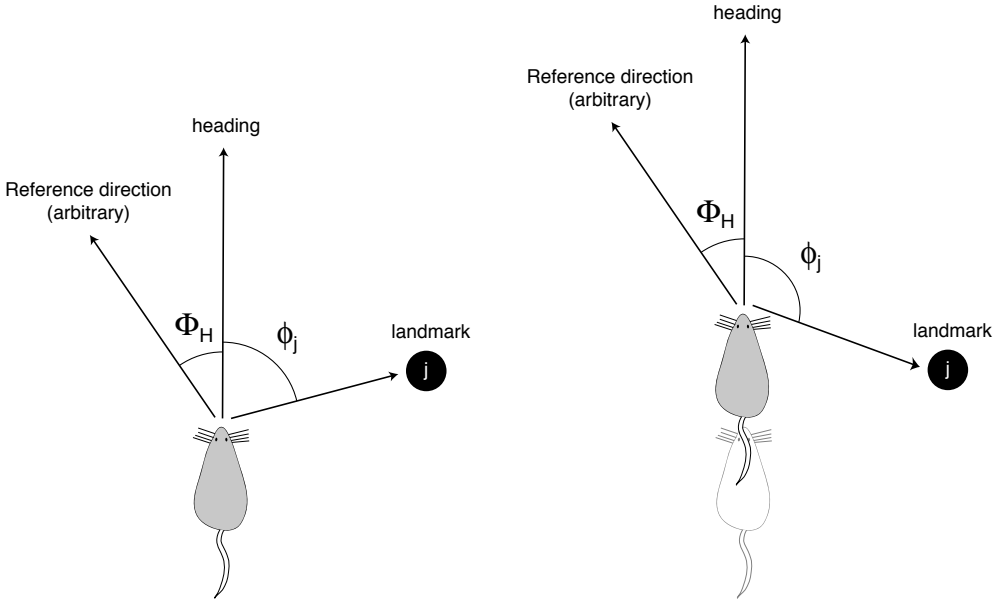

Figure 2.1: Egocentric and allocentric bearing. As a rat moves with a constant heading, its egocentric bearing ϕ_j relative to a landmark j changes (compare ϕ_j in the left and right panels), while its allocentric bearing relative to a reference direction (Φ_H) remains constant. Because head direction cell firing does not depend on the position of the animal (i.e. the same head direction cells would be active in both panels), head direction cells encode allocentric, not egocentric, bearing. (Adapted from Redish 1999.)

Their active range is between about 60° and 180°, depending on the anatomical locus of the HD cell in question and the exact definition of active range; see Figure 2.2 on the following page for an example HD cell tuning curve. It is worth keeping in mind that tuning curves are typically constructed over relatively long time intervals (8-16 minutes) and thus might obscure possible activity changes that occur on finer timescales; some examples of such dynamics are discussed in later sections. In general, however, the HD signal is extremely robust. Taube et al. (1990a) report a signal-to-noise ratio[3] of up to 7299.7, HD cells fire persistently without perceptible adaptation for long periods when the animal is still, their activity does not appear to be related to other variables[4] or the animal's behavioural state (when awake), and their tuning curves can remain stable for long periods (>15 days).

Different HD cells have different preferred directions, so that the directional range is evenly covered, that is, no directions appear to be overrepresented relative to others (Taube et al. 1990a; Baird et al. 2001). Thus, a population of HD cells can be visualised by arranging them in a ring, where their position on the ring corresponds to their preferred firing direction (Figure 2.3 on page 8, right). In this arrangement, the population of currently active

[3] For a HD cell, the ratio of its peak firing rate relative and its background firing rate.

[4] However, the firing of some HD cells is also correlated with angular head velocity and/or (linear) speed. This is discussed in later sections.

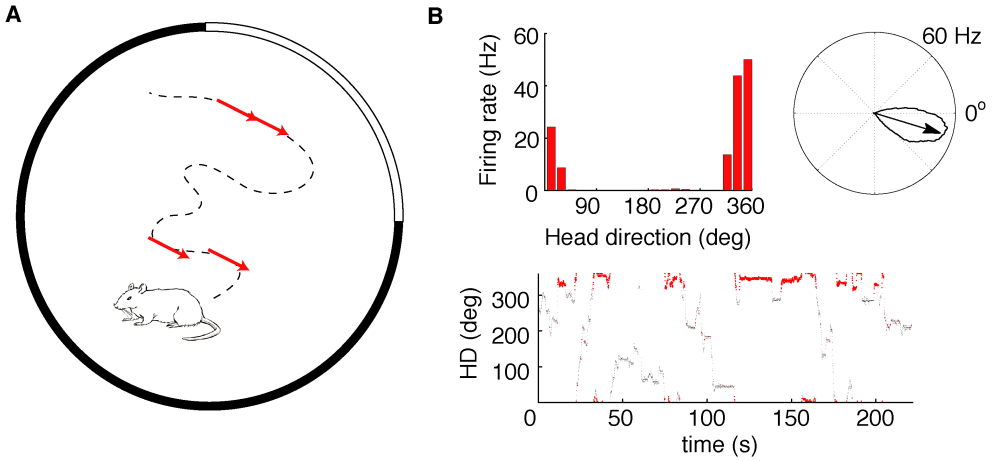

Figure 2.2: Basic firing properties of a head-direction cell (recording session `4322_1p`). **A**: Schematic representation of a head direction cell firing (red arrows) when the animal's head is facing some direction in the horizontal (yaw) plane, south-east in this example. Firing is not oriented towards a point; rather, it firing occurs along parallel lines (i.e. towards a point infinitely far away). **B**: Example tuning curve in standard bar plot form (top left) and polar coordinates (top right) showing its approximately Gaussian shape with a preferred firing direction at around 320° (top left). In a plot of head direction over time (bottom), with spikes indicated as red dots, the restricted firing range of the cell is apparent. A small number of spikes appear outside the cell's firing range: this could be the result of sub-optimal cell isolation (e.g. some noise signals are mistakenly treated as originating from this cell).

cells will form a Gaussian-shaped activity packet[5], sometimes called a "hill of activity" or "bubble", on the ring. As the animal changes its head direction the activity packet moves with it, representing the animal's head direction like a compass. The direction represented can be extracted, for instance, by taking the circular mean of the cells' positions in the ring, weighted by their firing rate: this is known as the "population vector" (Georgopoulos et al. 1983, although in general, more efficient and more plausible methods are possible, e.g. Deneve et al. 1999). Experimentally, Johnson et al. (2005) showed that the animal's momentary head direction can be inferred or "reconstructed" (Brown et al. 1998) from the activity of several simultaneously recorded HD cells, indicating that rats, in principle, have access to a "neural compass"[6].

Using this ring model, we can consider the state of the head direction system *as a whole* instead of at the level of single cells. For instance, the reference direction of the HD system is determined by the (angular) relationship of which way the rat is facing and the location of the activity packet in the ring. A change in reference direction means that a different

[5] In fact, of necessarily the same shape as the tuning curve of an individual cell, assuming that the activity packet tracks the animal's head direction perfectly. A single cell's directional tuning curve is uniquely defined by the shape of the activity packet as it moves around the ring.

[6] The fact that something is represented in the brain does not necessarily mean it is used: current methods does not allow us to determine what decoding method, if any, the brain is actually using in this case. Section 4.3 and Chapters 5 and 6 treat the issue of the behavioural relevance of the HD system in detail.

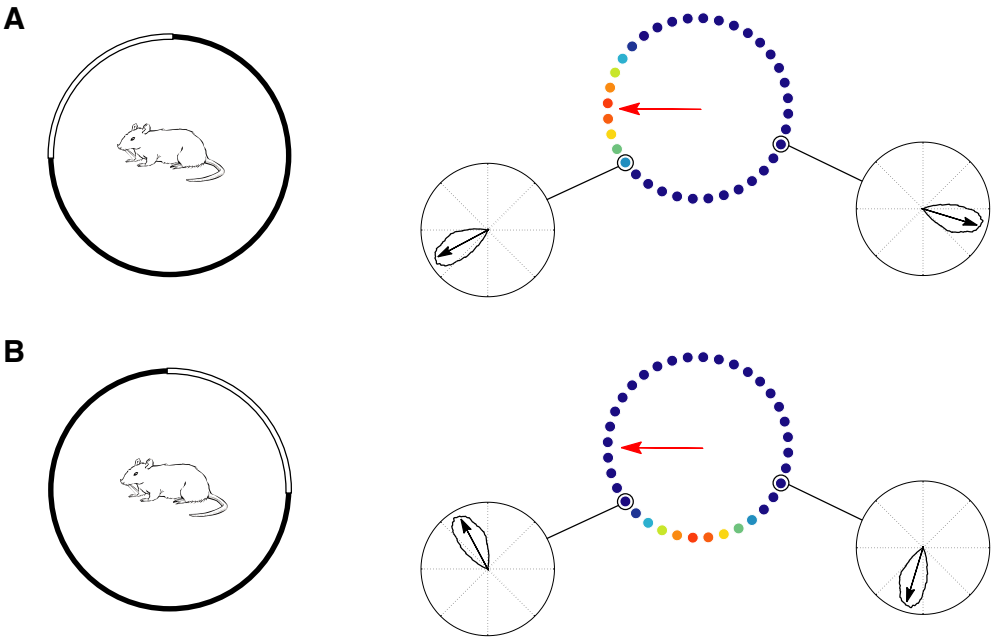

Figure 2.3: Schematic illustration of a changed in reference direction caused by rotation of a prominent cue ("cue card") on a packet of activity in a ring of head direction cells. **A**: Rat facing west with the (white) cue card in the north-west position (left). When head direction cells are arranged in a ring so that their angular position on the ring corresponds to their preferred firing direction (right) the active subset of cells will represent the rat's current allocentric head direction. Activity ranges from low (blue) to high (red); the directional tuning curves of two cells in the ring are shown. In this example, the "west" cells are chosen to be active when the rat is facing west (red arrow). When the cue card is rotated 90° clockwise, this is no longer the case (**B**): after rotation, when the rat is facing west, the "south" cells in the ring are active. Individual tuning curves appear to be "anchored" to the cue card, with their preferred firing directions having rotated following the cue card. Note that arranging HD cells in this way is done for convenience and does not imply a topographical arrangement in the brain. The initial location of the bubble when the rat is facing a particular direction (west in this case) can be chosen arbitrarily without loss of generality: HD cells in the brain have no label that says "I am a *South* cell", and in the absence of such an absolute reference, changes in reference direction are always relative to a previous reference direction.

population of HD cells is active while the rat is facing the same way as before; this is illustrated in Figure 2.3.

The directional tuning of HD cells is remarkable in itself: no perceptible signal in the world directly provides allocentric head direction information[7]. How do head direction cells "know" which direction the animal is facing? In our current understanding of the head direction system, this ability arises though the integration of two different kinds of information. First, information about the animal's own movements, notably from

[7]Apart from the earth magnetic field perhaps, but Ranck's magnet anecdote (Ranck Jr. 2005) and disorientation experiments (e.g. Mittelstaedt and Mittelstaedt 1980; Zugaro et al. 2003; Chapters 5 and 6, this thesis) find no electrophysiological or behavioral evidence for the use of such a signal.

the vestibular system, but possibly from other sources such as proprioception or motor efference copy as well. Such internal sources are referred to as *idiothetic* information. Second, external (principally, but not necessarily, visual) information from the outside world. In current theories of navigation and the head direction system (Gallistel 1990; McNaughton et al. 1996; Taube 1998; Redish 1999; McNaughton et al. 2006; see Chapter 4 for a review) idiothetic information supports a continuous, "procedural" angular path integration process, continuously updating the animal's head direction based on internal cues. The term angular path integration refers to the idea that at some level, the HD system must be performing a mathematical integration operation on angular head velocity information to yield a consistent representation of head direction. On its own, this process is thought to be prone to error; to compensate, this representation can be periodically or "episodically" updated by taking a visual "fix" of the environment using external (*allothetic*) information.

The simplest type of evidence that rats use self-motion cues to maintain a representation of head direction comes from recording of HD cells in darkness (e.g. Mizumori and Williams 1993; Chen et al. 1994; Goodridge and Taube 1995), which show that under these conditions, HD cells maintain a stable preferred firing direction for some time. For this to be the case, the movement of the activity packet in the HD ring must (roughly) match the angular head movements of the rat. However, this angular path integration process is not perfect: error seems to accumulate over time in dark conditions, such that over a 8-minute recording session, HD cells' preferred directions drift by an average of 30° (Goodridge and Taube 1995), which is substantially more than the average drift during light conditions. In the ring model, this drift corresponds to the activity packet in the HD ring having moved by 30° relative to its initial location when the rat was facing the same way, whereas perfect angular path integration would correspond to the activity packet always being in exactly the same location relative to the rat's directional heading. In principle, different mechanisms can contribute to such drifts in the HD system; these will be discussed in section 3.1 in the next chapter.

Perhaps to compensate for these limitations to angular path integration in darkness, the HD system doesn't rely on self-motion cues exclusively. Indication that visual information is important for the head direction signal starts with the observation that, when a rat is returned to a familiar environment, head direction cells will adopt their previous preferred direction from that environment (Taube et al. 1990a; Golob and Taube 1997). On the population level, this means that the activity packet is at the same place in the HD ring when the rat is facing the same way, that is, the system adopts a previous reference direction. When a prominent cue in the environment (e.g. the white cue card in Figure 2.3 on the previous page) is rotated, the preferred firing direction of HD cells can be made to rotate by the amount the card was rotated: cells seem "anchored" to the cue, and the activity packet

changes place in the HD ring (Figure 2.3 on page 8). Demonstrating the dual character of the system, HD cells aren't affected by removal of this same cue that can act as the reference point (Goodridge and Taube 1995): the reference direction of the HD system (the location of the activity packet in the ring) can be set by visual information, but the system doesn't require this information for maintenance of a directional signal.

Both drift and a change in reference direction result in a change of the relationship between the angular location of the activity packet in the HD ring and the rat's directional heading. This means that they can not always be distinguished experimentally; however, the fact that no drift occurs during light conditions, and that previous reference directions can be retrieved, implies that drift and reference direction changes are different processes. Furthermore, drift accumulates gradually over a session (Goodridge and Taube 1995; Knierim et al. 1998), as would be expected from error in the procedural-like angular path integration process, whereas changes in reference direction happen episodically and rapidly (in less than 100 ms, Zugaro et al. 2003).

Whenever multiple head direction cells have been recorded simultaneously during a preferred direction change, their preferred directions have changed coherently (i.e. all by the same amount, Taube et al. 1990b; Taube and Burton 1995; Goodridge and Taube 1995; Knierim et al. 1998; Yoganarasimha et al. 2006), suggesting that the HD system represents head direction relative to a single reference direction, in a ring arrangement as illustrated in Figure 2.3. One could imagine multiple reference directions being tracked, e.g. one signalling head direction relative to the cue card, one relative to the room, one relative to the home nest, etc., but the HD system does not appear to work that way.

Thus, basic physiology of the HD system suggests its ability to maintain a directional signal arises from a combination of idiothetic (internal) and allothetic (external) information. Idiothetic information is responsible for the angular path integration process acting in response to head movements, while external information is used to correct for errors and to set the reference direction of the system. The anatomical arrangement of the system, reviewed in the next section, mirrors this dual update structure. A more detailed discussion of the sources of information interacting with the HD system is split between this chapter (experimental review, sections 2.3 and 2.4) and the next (models, sections 3.1.2 and 3.1.3).

A diversion: place cells

It should be noted that head direction is one of two (from a navigational perspective, complementary) types of allocentric spatial information represented in the brain. "Place cells", whose primary firing correlate is the animal's location in an environment, were originally discovered in the hippocampus (O'Keefe and Dostrovsky 1971; Ranck Jr. 1973; O'Keefe 1976), but robust place representations are also present in entorhinal cortex

(Quirk et al. 1992; Fyhn et al. 2004; Hafting et al. 2005), in particular its superficial layers, which project to the subfields of the hippocampus (reviewed in Witter and Amaral 2004). Classic hippocampal place cells tend to have well-defined tuning curves localised to one particular place in an environment ("place fields"), whereas spatial cells in entorhinal cortex are more distributed, ranging from fairly diffuse firing fields (Quirk et al. 1992; Fyhn et al. 2004) to a remarkable periodic triangular grid pattern (called "grid cells", Hafting et al. 2005). Where head direction cell activity can be conceptualised as a hill of activity on a (one-dimensional) ring, which is then moved around as the animal turns, location-selective activity can be viewed as a hill of activity on a (two-dimensional) sheet (Samsonovich and McNaughton 1997; Fuhs and Touretzky 2006). As the animal moves, this hill can move in two dimensions, representing the current position of the animal[8].

Such location-selective cells share several fundamental properties with head direction cells. Their activity persists in the absence of input, and appears to be updated by idiothetic and external cues in a similar way (O'Keefe 1976; Muller and Kubie 1987; Taube et al. 1990b; Cressant et al. 1997; Zugaro et al. 2001)[9]. When recorded with head direction cells simultaneously, both cell types were found to rotate with the cue, remaining "in synchrony" even during underrotations or other non-standard cases (Knierim et al. 1998; Yoganarasimha and Knierim 2005; Sargolini et al. 2006)[10]. Just as HD cells can retrieve their previous preferred firing direction when returned to a familiar environment, cells in the hippocampus and entorhinal cortex can retrieve their previous firing location, such that each cell is active in the same place of the environment as before. Such observations suggest that the head direction and place systems are closely linked, and may be part of an integrated navigation system (Gallistel 1990; McNaughton et al. 1996; Redish 1999; Jeffery and Burgess 2006).

However, an important difference between head direction cells and place cells becomes apparent when an animal is placed in a different environment. The head direction system will typically adopt a new reference direction, such that a cell which previously fired when facing east now fires facing north-west. Such a reference shift preserves the relationship between HD cells' preferred firing directions, i.e. even though a cell's preferred firing direction ϕ_i may change, the relationship between preferred firing directions ($\{\phi_i - \phi_1 \ldots \phi_i - \phi_N\}$) remains unchanged. In other words, different head direction cells change their preferred directions coherently (by the same amount). In contrast, in the hippocampal place representation of this new environment, the relationships between the locations of place cells' firing fields can be completely decorrelated: this is known as "remapping". For

[8] Like in the case of an animal's head direction for HD cells, the location of the animal can be accurately reconstructed by recording the activity of a sufficiently large ensemble of place cells (Wilson and McNaughton 1993; Brown et al. 1998; Fyhn et al. 2004).

[9] In fact, many of the experimental apparati and manipulations used in HD system experiments were first developed for place cells.

[10] However, for hippocampal place cells in particular, the situation can be more complex, discussed below.

instance, two cells which were active in neighbouring locations before, could fire far away from each other, or one or both may have become silent, after remapping. Hippocampal remapping can take various forms, with the recent distinction between global and rate remapping in subfield CA3 (Leutgeb et al. 2005a) a useful demonstration of the two extremes: complete decorrelation of firing locations (global remapping) at one end, and decorrelation of firing rates, but not locations (rate remapping) at the other. However, remapping is a complex phenomenon and how the many instances of remapping in the literature (e.g. Muller et al. 1991; Bostock et al. 1991; O'Keefe and Burgess 1996; Gothard et al. 1996; Skaggs and McNaughton 1998; Wood et al. 1999; Knierim 2002; Anderson and Jeffery 2003; Moita et al. 2004; Leutgeb et al. 2005b to name a few) are to be understood in a single framework is an important issue in current hippocampus research, with the properties of remapping in entorhinal cortex only beginning to be studied in detail. In a compelling demonstration of the relative simplicity of the HD system as compared to place cells, Yoganarasimha et al. (2006) show that when they rotated one set of cues one way and another set the opposite way, the place cell representation became split, with some place cells rotating with one cue, some place cells with another, and some cells doing something else (this had been shown earlier, e.g. Knierim 2002). The head direction representation, however, maintained internal coherency, all shifting preferred firing direction by the same amount.

The idea that the hippocampus has independent representations of different environments is common to several theories addressing the firing properties of hippocampal cells, and has been referred to as "multiple maps" (O'Keefe and Nadel 1978), "charts" (Samsonovich and McNaughton 1997), or "reference frames" (Redish 1999)[11]. Indeed, the ability of the hippocampus to recall a previous reference frame upon entry to an environment is an important model of understanding hippocampal function at the neural ensemble level (Knierim 2006); for instance, old animals are impaired on this, frequently recalling the wrong reference frame (Barnes et al. 1997; Wilson et al. 2005). As is the case for the reference direction of the HD signal, rats appear to keep the same hippocampal reference frame during experiences in a given environment, only changing abruptly (remapping) in response to changes in that environment (e.g. cue or shape manipulations referred to above)[12].

However, what the exact relationship is between HD system reorientation and hippocampal remapping remains to be clarified, although we know that HD cells can retrieve environment-specific preferred directions without a hippocampus (Golob and Taube

[11] Here I will adopt Redish's term; although there are some subtle differences between these theories, they are not important for the discussion here.

[12] However, at timescales of days to months, there are changes (Lever et al. 2002); whether this is also to the case for entorhinal location-selctive cells, which might be more specialised for spatial representations than the hippocampus, it not yet known.

1997) whereas HD lesions impair the hippocampus' ability to form a stable representation between sessions in the same environment (Calton et al. 2003). Whether this last finding represents a deficit in retrieving the appropriate orientation of the correct reference frame, or a deficit in retrieving the correct reference frame at all, remains to be determined. Recording studies of entorhinal spatially-selective cells, at the interface of the place and direction systems, are likely to be important.

Two recent studies have identified populations of cells which jointly represent position and head direction[13]: Cacucci et al. (2004) found place-by-direction cells ("TPD cells") in the pre- and parasubiculum[14], and Sargolini et al. (2006) found conjunctive grid $\times$ HD cells in the deep layers of medial entorhinal cortex. Both these cell types conjunctively encode place and head direction, such that they are only active when the animal is in a particular place *and* facing a particular direction. Such cells are further evidence that the place and head direction systems are tightly linked, and part of a larger spatial navigation system.

In summary, while the HD system is only capable of changing its reference direction in response to changes in the environment (where the preferred firing direction of all HD cells changes coherently), the hippocampus *may* change its representation coherently in register with HD system reorientation; however, it may also exhibit various degrees of remapping.

2.2 Functional anatomy: dual streams of information

Head direction cells are found in about 10 different brain areas, but there are four or five, centred on the classic Papez circuit (Papez 1937) in the limbic system, that can be thought of as forming the spine of the system. As illustrated in Figure 2.4 on the next page, these areas, in order, are the dorsal tegmental nucleus[15] (DTN, specifically its ventral part) in the brainstem, the lateral mammillary nucleus (LMN), the anterodorsal thalamic nucleus (ADN), the postsubiculum (PoS, referred to as the dorsal presubiculum by some authors), and the medial entorhinal cortex (MEC)[16].

The properties of HD cells found in these areas are broadly the same[17]: approximately

[13] Place cells with directional firing fields have been known for some time (e.g. McNaughton et al. 1983), but that appears to be an environment-specific phenomenon and not an inherent property of the cell (Brunel and Muller 2005).

[14] In fact, most of them in postsubiculum (dorsal presubiculum), where HD cells are also prominent.

[15] I will be referring to these anatomical loci in the singular rather than the plural for simplicity; however, at all levels of the HD system these loci are present bilaterally, and have extensive commissural fibres connecting the hemispheres in several places.

[16] With HD cells in MEC being a relatively recent discovery, this area has been less studied in the context of the HD system, and it might be debated whether this area merits inclusion as part of the spine of the system. Because MEC is the likely pathway for HD information to the hippocampus, and a likely site for the path integrator, I have chosen to include it.

[17] It must be noted that one group reported finding no classic head direction cells in DTN (Bassett and Taube 2001b), and the standard cue control and darkness experiments have not been reported for DTN HD cells.

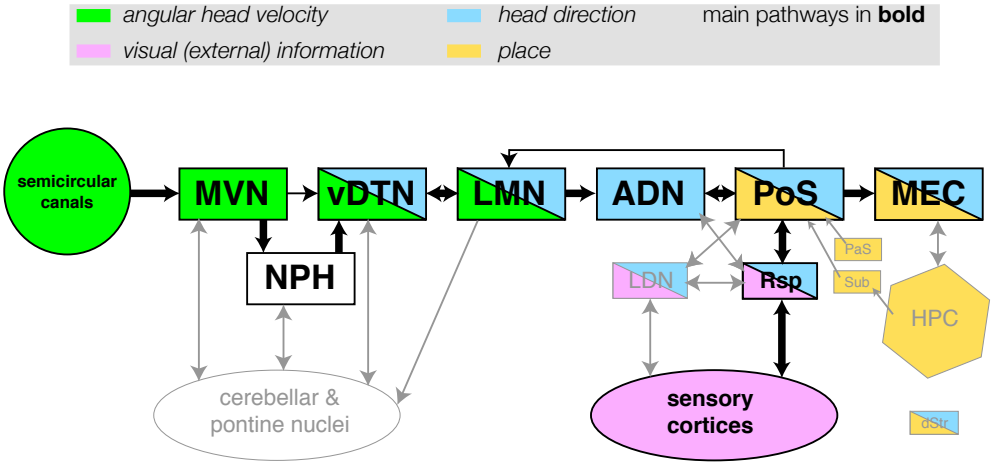

Figure 2.4: Schematic circuit diagram of the head direction system. Head direction cells (light blue) are found in several brain areas, with self-motion information (green) coming in from the brainstem end, and external sensory information (pink) coming in from the cortex end. Boxes indicate specific brain areas (identified by their abbreviations, expanded below), arrows indicate projections (either inhibitory or excitatory, or both), and circles indicate groups of structures. The main structures and pathways are indicated in bold black, areas thought to be auxiliary are in light grey. Abbreviations: MVN, medial vestibular nucleus; vDTN, ventral dorsal tegmental nucleus (of Gudden); NPH, nucleus prepositus hyperglossi; LMN, lateral mammillary nucleus; ADN, anterodorsal thalamic nucleus; PoS, postsubiculum (dorsal presubiculum); MEC, medial entorhinal cortex; HPC, hippocampus; Rsp, retrosplenial cortex; LDN, laterodorsal thalamic nucleus; PaS, parasubiculum; Sub, subiculum; dStr: dorsal striatum.

Gaussian tuning curves for head direction, and relatively stable in darkness yet controllable by visual cues. There is a tendency for tuning curve width to decrease through the system, from relatively broad tuning curves in DTN to narrower ones in MEC, in addition to a number of other subtle differences. One of these, the degree to which HD cells in different areas anticipate the animal's head direction, will be discussed in more detail (section 2.5 on page 27); another is the presence of various secondary firing correlates (e.g. absolute angular head velocity, linear running speed, response to restraint), which are reviewed briefly in section 2.3 on page 17. Outside the main HD areas, HD cells have also been found in the laterodorsal thalamic nucleus (LDN, Mizumori and Williams 1993), retrosplenial or posterior cingulate cortex (Rsp, Chen et al. 1994; Cho and Sharp 2001), dorsal striatum (Wiener 1993), hippocampus (Leutgeb et al. 2000)[18], and other anterior thalamic nuclei (Yoganarasimha and Knierim 2005; Yoganarasimha et al. 2006). However, in some cases it is not clear whether those cells meet the criteria for being classified as classic HD cells, e.g. some of the cells in Wiener (1993) may be cells responding to a particular cue or maze arm, and Chen et al. (1994) report incidental two-peaked HD cells. The mazes used in these studies make it difficult to be sure these cells were really HD cells. With the

[18] Reports of HD activity in hippocampus are relatively rare, and it is possible that such activity is in fact recorded from axons originating in entorhinal cortex.

exception of Rsp and LDN, where additional lesion studies have been done, the properties of HD-specific activity in these areas have been less studied.

The spine of the HD system can be ordered based on a series of technically challenging combined lesion-recording experiments, illustrated in Figure 2.5 on the following page, showing for several HD areas, that lesioning it abolishes downstream directional firing. Specifically, Bassett and Taube (2001a) lesioned DTN and found no directional activity in ADN[19]. LMN lesions abolish HD activity in ADN (Blair et al. 1998; Blair et al. 1999). Goodridge and Taube (1997) lesioned ADN and found no HD cells in PoS, but doing the reverse experiment, lesioning PoS and recording from ADN, yielded intact directional firing[20]. MEC HD cells have only recently been found (Sargolini et al. 2006) and no associated lesion results focusing on the HD system have been reported; however, PoS sends a very focused projection to the deep layers of MEC (Köhler 1985; van Groen and Wyss 1990a; Caballero-Bleda and Witter 1994), where the highest density of HD cells has been found, suggesting that MEC HD activity is likely to depend on an intact PoS. Lesions of LDN did not result in loss of HD activity in PoS (Golob et al. 1998). Preliminary results indicate that Rsp lesions leave ADN HD activity intact (Bassett and Taube 1999)[21], which implies that LDN and Rsp are not part of the main HD pathway.

These lesion results are consistent with the existence of direct anatomical pathways, which have been well studied historically (Gurdjian 1927; Papez 1937; Guillery 1955). DTN is reciprocally connected with LMN (Cruce 1977; Groenewegen and van Dijk 1984; Shibata 1987; Allen and Hopkins 1989; Hayakawa and Zyo 1990; Hayakawa and Zyo 1992), LMN projects to ADN (Fry and Cowan 1972; Shibata 1989; Hayakawa and Zyo 1989; Gonzalo-Ruiz et al. 1992; Shibata 1992), and ADN is reciprocally connected to PoS[22] (Swanson and Cowan 1977; van Groen and Wyss 1990a; Witter et al. 1990; Shibata 1993a). Ultrastructural studies suggest that all these projections are excitatory, except DTN to LMN, which is thought to be inhibitory (Allen and Hopkins 1989; Wirtshafter and Stratford 1993). In no area have interneurons (recurrent connections, non-projection neurons) been found; however, it has been suggested that individual HD areas may form indirect recurrent loops through nearby areas (Hopkins 2005).

All main areas receive other inputs apart from other HD areas, with LMN probably the most isolated, in only receiving major inputs from DTN and PoS, although it itself projects to several other brainstem nuclei besides DTN (reviewed in Bassett and Taube 2005). DTN is reciprocally connected to several brainstem nuclei (Bassett and Taube 2005), but

[19] This is a preliminary report, and in general, showing a negative result of this kind can be complicated by cell sampling bias and other factors.

[20] However, PoS lesions had some subtle effects on ADN HD cells as well as hippocampal place cells, apparently abolishing the influence of visual information on these systems (see sections 2.4 and 2.5).

[21] Similarly to PoS lesions, with some subtle effects on external cue control.

[22] This reciprocal connection is part of the fornix bundle, something not often mentioned in studies reporting the effects of fornix lesions.

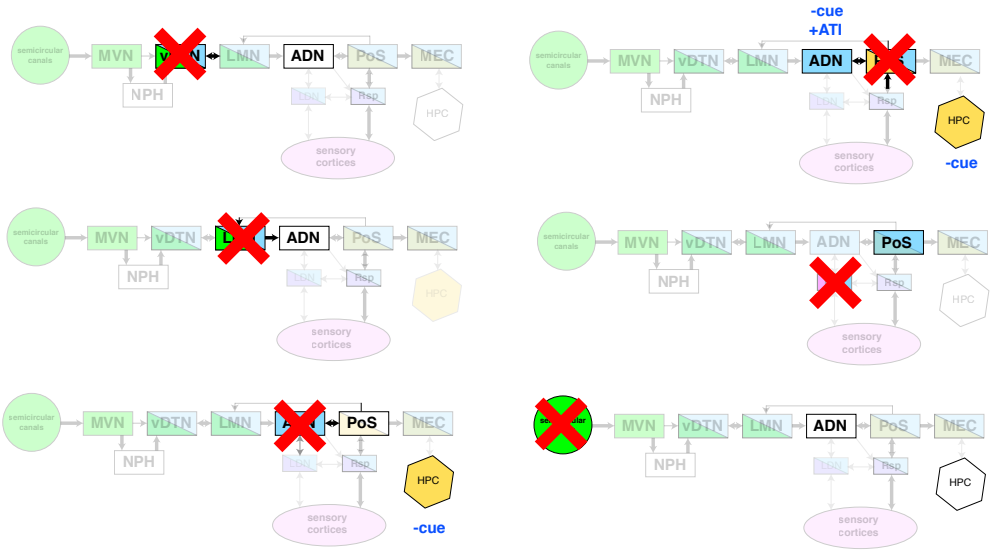

Figure 2.5: Schematic of the effects of lesions within the HD system. For each subpanel, the area lesioned is indicated by the red cross; area(s) recorded from are in black (with areas not examined greyed out). If directional or place activity was found in this area is indicated by colour (blue for direction, orange for place). During postsubiculum (PoS) recordings, cells were screened for directional activity, so no explicit reports on whether the place component of place-by-direction cells was still intact are available. Abbreviations as in Figure 2.4 on page 14; "-cue" refers to an effect on cue control, i.e. rotations of the standard cue card having a reduced effect compared to control animals (discussed in section 2.4). "+ATI" refers to an increase in anticipatory time interval found in ADN after PoS lesions (Goodridge and Taube 1997).

importantly, there is a possible pathway for vestibular information (a likely source of the angular head velocity update signal for the angular path integration process), either directly from the medial vestibular nuclei (MVN), from MVN to the nucleus prepositus hypoglossi (NPH) to DTN (Brown et al. 2005; Bassett and Taube 2005), or, following a recent suggestion, through the supragenual nucleus (Biazoli et al. 2006).

ADN receives glutamatergic and GABAergic inputs from other thalamic nuclei (Groenewegen and Witter 2004; Gonzalo-Ruiz and Lieberman 1995), from retrosplenial cortex (although this is a minor projection compared to the retrosplenial input to PoS, Vogt et al. 2004), medial prefrontal cortex (Groenewegen and Witter 2004), the frontal eye field (Guandalini 2001), and at least serotonergic, cholinergic, and muscarinic inputs (Sikes and Vogt 1987; Gonzalo-Ruiz et al. 1995; Gonzalo-Ruiz et al. 1995) from several sources. There is sparse evidence for muscarinic and dopamine receptors in LMN (Vilaró et al. 1990; Gonzalo-Ruiz et al. 1992), but the functional significance of these is not clear, although combined administration of serotonergic and muscarinic antagonists appear to disrupt the HD signal (Murawski et al. 2004).

PoS receives inputs from Rsp, the subiculum, and sensory cortical areas (van Groen and Wyss 1990c; van Groen and Wyss 1992; van Groen and Wyss 2003; Witter and Amaral 2004).

LDN receives inputs from LGN, visual cortical areas, and the hippocampal formation (Groenewegen and Witter 2004; Shibata 1996; Thompson and Robertson 1987a). LDN is reciprocally connected with PoS and Rsp (Thompson and Robertson 1987b; Groenewegen and Witter 2004). Rsp receives inputs from various parietal sensory cortex areas, as well as projections from PoS, subiculum, and ADN, where it is notable that Cho and Sharp (2001) found HD cells in the dysgranular subdivision of Rsp, while ADN projects to granular Rsp only (van Groen and Wyss 1990b; Shibata 1993b). PoS, Rsp and LDN are thought of as the "visual" (or allothetic) end of the HD system, because of their prominent inputs from visual and sensory areas.

In conclusion, anatomical and lesion evidence suggests that on first approximation, the areas in the spine of the HD system are related essentially in a simple feed-forward manner, where DTN is the first area where head direction information is present, which is then simply propagated through the system, with any "break" in the chain abolishing directional firing downstream from it[23]. The flow of information from the vestibular system, which provides inputs to the DTN end of the system, is consistent with this arrangement, and indeed, vestibular lesions abolish HD activity (Stackman and Taube 1997). This suggests that vestibular information is essential for the maintenance of a directional signal. At the other end of the system, the fact that the HD signal can be updated by external cues is consistent with the many sensory cortical inputs to HD areas, PoS, Rsp and LDN in particular. Note that the projection from PoS to LMN allows for a way of visual information to update HD signals all the way through the system's spine. Hence, reflecting its dual-natured physiology (Section 2.1), the HD system contains two "streams of information" (Bassett and Taube 2005). The primary ascending stream, propagating vestibular information from the brainstem through the Papez circuit to the hippocampal formation and overlying cortical areas, and the secondary, descending stream, propagating external (visual) information from the hippocampal formation and cortex down to the brainstem.

2.3 Idiothetic information

Idiothetic information, consisting of internal cues about the animal's movement, is thought to be critical for angular path integration. The main source of idiothetic information to the head direction system is vestibular, thought to originate primarily from the semicircular canals in the labyrinth. Anatomically, primary vestibular afferents from the hair cells in the semicircular canals project to the medial vestibular nucleus (MVN) in the brainstem (for a review, see Vidal and Sans 2004). Cells in the MVN fall into several different classes with different firing properties, but a large population of MVN neurons has angular head velocity (AHV) as its primary firing correlate (Melvill Jones and Milsum 1971; Fuchs and Kimm

[23] This notion is further supported by anticipatory time interval analysis, discussed in section 2.5.

1975, see Highstein et al. 2005 for a recent review). In principle, (relative) head direction can be derived from AHV by mathematical integration: a body of anatomical, recording and lesion studies support the notion that the HD system does something amounting to this. According to some studies, the MVN sends a direct projection to DTN (Liu et al. 1984; Hayakawa and Zyo 1985, but see Brown et al. 2005); certainly the MVN has a strong indirect pathway to DTN via the nucleus prepositus hyperglossi (NPH; Liu et al. 1984; McCrea and Baker 1985). NPH has cells tuned for angular head velocity (Blanks et al. 1977; Lannou et al. 1984), but is mainly associated with eye movements (Baker and Berthoz 1975; Delgado-García et al. 1989; Kaneko 1997, see McCrea and Horn 2005 for a recent review). A recent suggestion (Biazoli et al. 2006) proposes the supragenual nucleus as a possible relay station of AHV information. However, no lesion or recording studies in these areas which could clarify the flow of AHV information to the HD system have been done.

Whichever way angular head velocity information (AHV) may get there, a substantial proportion of cells in both DTN and LMN are sensitive to AHV (Stackman and Taube 1998; Blair et al. 1998; Bassett and Taube 2001b; Sharp et al. 2001). A number of different AHV-sensitive neurons have been reported; there are neurons whose primary firing correlate is AHV ("AHV-only" cells) in addition to AHV-modulated HD cells. AHV-only cells have been found in both LMN and DTN, and there are reports of AHV modulation in PoS (Sharp 1996). Bassett and Taube (2001b) report two different classes of AHV cells in DTN, "symmetric" and "asymmetric" AHV cells, where symmetric AHV cells increase their firing with absolute angular head velocity, and asymmetric cells fire selectively for turns in one direction only (so two kinds of asymmetric cells exist). Sharp et al. (2001) also report AHV cells in DTN, but they only find asymmetric cells. LMN AHV cells are symmetric (Stackman and Taube 1998).

HD cells found in DTN (Sharp et al. 2001) and LMN (Stackman and Taube 1998) are both reported to be modulated by angular head velocity. Stackman and Taube (1998) find that HD cells in the left hemisphere increase their firing rate during clockwise turns, and right hemisphere cells for counterclockwise turns, although Blair et al. (1998) do not report this effect. DTN HD cells are also modulated by 'ipsilateral' head turns (Sharp et al. 2001), although this is from a small and noisy sample.

Neural network models of the HD systems have proposed several ways in which these AHV-modulated cells could contribute to updating of the HD signal in an angular path integration process that yields direction. This integration is thought to occur in the interaction between DTN and LMN, whose reciprocal connections are thought to be essential for such angular path integration circuits (see Chapter 3 for detailed discussion on models of the HD system). Certainly, asymmetric AHV cells represent a useful step in transforming (integrating) a raw AHV signal into head direction.

Thus, recording evidence shows that the HD signal is closely related to AHV information, because some HD cells are AHV-modulated, and AHV-only cells are colocalised with HD cells in DTN and LMN. Although the exact anatomical pathway of vestibular information to these specific cells is not known, the general connectivity of the areas involved is consistent with the HD system receiving vestibular information. In support of the importance of this information for the generation and/or maintenance of the HD signal, lesion studies of the vestibular system have shown abolished HD activity in ADN (Stackman and Taube 1997; Muir et al. 2004). This result has generated some discussion as to why vestibular lesions seem to abolish directional firing given the influence of external cues, which is known to be strong enough to reset it after drift. Furthermore, HD firing persists when the animal is still, presumably in the absence of vestibular input. One possibility may be that background firing rates are needed to support HD activity (as noted by Brown et al. 2002), but it seems that MVN background firing rates recover after bilateral labyrinthectomy (Waespe et al. 1992; Ris and Godaux 1998; Yates et al. 2000). As noted by Brown et al. (2002), it's still possible that the specific neurons providing inputs to the HD system do not recover, or that labyrinthectomy by sodium arsinalate causes some unintended damage elsewhere. Redish (1999) interprets the effects of labyrinthectomy as that the HD network becomes "decoupled" from the external world, i.e. that it still forms a coherent representation, but it no longer relates to the rat's actual head direction. This would be consistent with a report by Muir et al. (2004), who found firing of two previously isolated HD cells remained correlated after plugging of the semicircular canals. However, if decoupling is the only effect of vestibular lesions, it is not clear why visual input would not be able to reset and/or stabilise the HD signal, at least for a little while. It could be that previous experiments have not looked on the fine timescales needed to resolve this, given that visual fixes are thought to happen only episodically (i.e. relatively infrequently) and deficient angular path integration may immediately obscure any transient reorientation. Alternatively, it is possible that in the absence of angular path integration, the influence of cues can be "unlearned", an idea compatible with experiments discussed in section 3.1.3 on page 39[24].

Perhaps the most compelling evidence that the HD system actually uses vestibular information to update its direction signal comes from a number of recording studies, which addressed the HD system's ability to maintain HD representations during passive rotations in darkness (Blair and Sharp 1996; Goodridge et al. 1998; Knierim et al. 1998; Zugaro et al. 2000). In this type of experiment, the animal is subjected to an externally-induced passive rotation, e.g. of the complete recording chamber. The HD system is able to track such turns, provided they are fast enough, presumably above the vestibular threshold (Blair and Sharp 1996), although not perfectly. This functional but imperfect updating is consistent

[24] In their model of the HD system, Song and Wang (2005) report that the equivalent of a vestibular lesion causes loss of a coherent activity packet. However, they did not consider the recovery of background firing rates.

with freely moving recordings in darkness, where an average preferred firing direction drift of 30° over 8 minutes has been reported (Goodridge and Taube 1995). Comparable results have been found for hippocampal place cells, where blind and anosmic rats were found to maintain stable firing fields (Hill and Best 1981; Save et al. 1998), and the place representation could track passive rotations Sharp et al. (1995, Jeffery et al. (1997).

Seemingly in conflict with the importance of vestibular information to the HD signal, Golob and Taube (1999) reported that HD cells recorded in darkness from rats with hippocampal lesions exhibited significant drift in HD cell PFD relative to unlesioned controls. Similarly, they found that when lesioned rats walked into a novel environment (where normal rats exhibit a small PFD shift of 18° on average), PFDs shifted seemingly randomly. These results suggest that the hippocampus may be required for angular path integration in the absence of external cues, and raises the question of how HD cells behave in darkness in PoS-lesioned animals (which Goodridge and Taube (1997) did not address in their combined PoS-lesion, ADN-recording study)[25].

Apart from vestibular influences, there are studies showing effects of active locomotion on the firing rates of HD cells: Zugaro et al. (2001) compared peak firing rates during active and passive locomotion and found them to be higher in the active case. There is also evidence of theta modulation in HD cells (Arleo et al. 2005, chapter 6, this thesis). ADN HD cells have been reported as losing their directional firing when animals are restrained (Taube 1995) or asleep (Engle and Calton 2004). However, the functional significance of these findings is not clear.

2.4 Interactions with external information

Cue control

As noted earlier, when a rat is returned to a familiar environment, HD cells reorient to their previous preferred firing direction (PFD) in that environment: the system recalls its reference direction. The simplest demonstration that this is due to visual control is the classic cue card rotation experiment (Figure 2.3, originally introduced in a place cell experiment by Muller and Kubie 1987, done for head direction cells in Taube et al. 1990b). In this experiment, when a prominent polarising cue (typically a white card on the wall of the recording chamber) is rotated prior to rat being returned to the environment, the preferred firing direction of head direction cells follow the cue (illustrated in Figure 2.3 on page 8): the cue is said to "control" the firing of the cells.

Detailed examinations of HD cell PFD drifts show that when an animal is simply returned

[25] This is a puzzling and potentially important observation which, for reasons unknown to the author, appears to have been largely ignored in the subsequent literature.

to a familiar, unchanged environment, the system drifts by an average of 5° (Taube et al. 1990a; Taube 1995)[26]. This is significantly less than the systematic underrotation observed when the cue card is rotated 90° and the rat gently disoriented before being returned, where mean differences of 18.9°, 13.2°, and 9.8° (relative to the expected 90° shift for true cue card control) have been reported (Taube et al. 1990a; Taube 1995; Dudchenko et al. 1997). This underrotation has been interpreted as evidence of interaction with cues other than the cue card, which have not been rotated (Taube 2005).

In an extension of the basic cue card rotation experiment, Goodridge and Taube (1995) disoriented the rat and removed the cue card before returning the rat to the environment. This caused the HD cell PFD to change, but when the cue card was reinserted, the cell's original PFD (relative to the cue card) was resumed. This shows that under these conditions, (a) the control exerted by a familiar cue can be strong enough to act even when the animal is not (re)introduced into the environment but actively walking around, and (b) whatever other cues there are beyond the (removed) cue card, these were not enough for HD cells to revert to their previous PFD, despite their apparent influence on the underrotations observed when the cue is rotated.

An important observation regarding cue control is apparent from a place cell experiment by Jeffery and O'Keefe (1999), who rotated the cue card (by 90°) *in the presence* of the rat. Compared to the case where the rat could not see the card being moved (they covered the rat while it remained in the recording chamber[27]), this only rarely caused place fields to follow the cue: about 20% of the time, compared to 100% of the time when the rat did not see the cue move. Hence, place cells (and likely HD cells, too) do not simply respond passively to the cue; instead, it appears rats have a representation of the stability of the cue in this case. Results of a similar experiment by Rotenberg and Muller (1997), who rotated a cue 45° in the presence of the rat, found that in this case place cells would follow it, but they would not follow 180° rotations, as if the rat had some representation of the degree of confidence or accuracy of the idiothetic signal, correcting small but not large mismatches between internal and external information. Further evidence of this idea comes from Knierim et al. (1998), who turned the lights off and allowed the HD system to drift before turning them back on. In this case, when the amount of drift was small (<45°) the system oriented back to the cue card about half the time. For larger drifts, however, cue control was almost non-existent. This dependence on the degree of mismatch between the idiothetic and visual signals has a neat interpretation in terms of network models of the HD system, discussed in section 3.1.3 on page 39.

(As an aside, previous studies using a similar paradigm (Mizumori and Williams 1993; Chen

[26] It is not clear whether this is more than would be expected by chance of a Poisson-spiking HD cell of a realistic firing rate interacting with realistic rat movements.

[27] So there are two potential factors here: the rat observing the cue being rotated, and the absence/presence of a covering episode with associated procedure and time delay.

et al. 1994), where the lights were turned off, found slightly different results. In Mizumori and Williams (1993), LDN HD cells would always reset to their original orientation when the lights were turned back on, even if the darkness-induced drift was large (90°). In contrast, Chen et al. (1994) rotated visual cues (they used a different recording setup to Knierim et al. 1998) when the lights were turned off, and found that Rsp HD cells tended to ignore the cues, and sometimes change preferred direction unpredictably; as noted before, however, it is not clear in all cases whether these were genuine allocentric HD cells.)

Beyond the simple cue card, several experiments have addressed the issue of what cues rats use to "set" the orientation of the HD signal. Auditory or substratal cues appear ineffective (Goodridge et al. 1998; Zugaro et al. 2000) and rats seem to prefer distal cues over proximal ones (Knierim et al. 1998; Zugaro et al. 2001), broadly consistent with similar experiments done with place cells (e.g. Cressant et al. 1997).

Cue learning

There are some interesting issues relating to under what conditions cue control (i.e. the ability of a a particular cue, usually the classic white cue card, to set the orientation of the HD system) develops. Goodridge et al. (1998) varied the amount of time rats were exposed to a novel environment with a cue card before rotating it, and their results indicate that such cue control develops within 8 minutes, and sometimes as soon as 1 minute. An influential idea is that the forming of such associations between the environment and the rat's internal sense requires a "stable directional framework", i.e. the location of the cue has to be consistent with idiothetic information and other landmarks (McNaughton et al. 1996; Gallistel 1990). This idea, when applied to the HD system, is supported by results from Knierim et al. (1995), where rats were systematically disoriented before being placed in a standard cue card cylinder. Under these conditions, their HD system could not be controlled by the cue card, even after many sessions, while a non-disoriented control group had normal cue control.

This result has a compelling interpretation in the context of theoretical models of the HD system (section 3.1.3). However, it raises the question of why, if in the case of (Goodridge et al. 1998) cue control develops in less than 8 minutes, disorientation matters at all; the sessions in Knierim et al. (1995) were 8 minutes, and presumably even a previously disoriented animal maintains a stable directional framework *within* a session, which would mean ample time for the cue to develop control. As suggested by Dudchenko et al. (1997), one question is whether in the Knierim et al. study, the cue never had control in the first place, or whether it had control but subsequently lost it. Because Knierim et al. only recorded from the disorientation group after many sessions, these possibilities could not be distinguished. However, in the Jeffery and O'Keefe (1999) study mentioned earlier, it was

also found that rats learned to ignore the cue after several rotations even when they never actually saw it move[28]. This is consistent with the loss of cue control rather than it never developing.

Loss of cue control still presents a challenge, however. When a sufficiently strongly learned cue is rotated, the cells follow it, and thus the cue and the cells remain in a consistent arrangement. How can this arrangement lead to loss of cue control? One possible explanation is to consider that there might be additional (uncontrolled) cues apart from the prominent rotated cue (in agreement with HD PFD underrotations in response to cue rotation, Taube 2005). Indeed, it is interesting to note that in the Knierim et al. study, an additional difference between the group being disoriented and the control group was that in the disorientation group, the cue card cylinder was not enclosed by curtains, thus potentially giving the animal access to other cues in the room and their relationship to the cue card. Another possibility is that when the location of the activity packet in the HD ring is inconsistent with the cue, the influence of the cue gradually decreases, whereas if it is concsistent, it increases. Such a model (detailed in section 3.1.3), which could be explored in simulations, could also be consistent with the lack of HD activity after vestibular lesions, where the lack of angular path integration in combination with periodic (non-continuous) visual updates would cause mismatches between the cue and the activity packet.

Further indication that we do not fully understand the details of cue learning comes from a study by Dudchenko et al. (1997), who found essentially the opposite result from the Knierim et al. study, that disorientation treatment did *not* reduce cue card control. Behaviourally, the effects of disorientation on task acquisition appear to depend on the type of reinforcement (appetitive or aversive) used (Martin et al. 1997; Dudchenko et al. 1997; Gibson et al. 2001; Golob and Taube 2002), suggesting that some aspects of cue control cannot be explained by the model proposed by Knierim et al. (1995).

Connected environments

It is possible the procedure of introducing a rat to an environment, and the many variables involved in it (variations in entry point, disorientation procedures, previous experience, etc.), interacts with how the animal treats that environment (e.g. Poucet 1993; Hynes et al. 2000), and thus may be a factor in the discrepancies highlighted above. A slightly different type of experiment, where an animal walks between environments, provides a perspective which avoids this issue. Extending an earlier experiment by Taube and Burton (1995), Dudchenko and Zinyuk (2005) had rats walk from a familiar ("A") into a novel environment ("B"). This resulted in a small change in HD PFD, consistent with earlier results (always less than 30°, about 18° on average). In separate sessions, rats were independently introduced to

[28] Although it might be argued that these rats were not disoriented, such that they could treat the cue as unstable based on their idiothetic HD signal rather than relative to other cues.

a different environment ("C"), such that HD cells had different preferred firing directions in A compared to C, consistent with previous results. When rats walked from B to C, their HD cells adopted the PFD from environment C, indicating that under those conditions, previous experience of the environment determines the extent to which it is able to affect the HD signal (small shift when walking into a novel environment: large shift back to previous PFD when walking into a familiar environment). It is interesting to compare this result, where HD cells can shift their preferred direction by large (>135°) amounts, to that obtained by Knierim et al. (1998) (discussed above) who found that a cue would only reset the HD system to its previous orientation after small (45° or smaller) drifts.

Some further slightly puzzling results related to what happens when a rat enters a novel environment come from a study by Stackman et al. (2003), who showed that the ability to maintain a stable PFD when entering a novel environment depended on walking there rather than being passively transported. In walking rats, an average PFD shift of about 20° was found, whereas in passively transported rats, PFDs shifted randomly, even in light conditions. While Stackman et al. (2003) interpret this result as showing the importance of motor efference copy or proprioceptive information, it is known that gentle passive movement can update the HD signal (see Section 2.3) and that animals can return to a starting location after a similar passive outward journey (e.g. Etienne et al. 1986).

In resolving these apparent discrepancies, it may be helpful to be mindful of the distinction between a HD representation drifting (e.g. because of angular path integration error), without the animal changing its reference direction, and the HD representation changing reference direction, encoding direction either relative to something that has moved (the cue card) or to something different (as in when the rat walks into a familiar environment). Using this idea, it is possible that the passively transported animals in Stackman et al. (2003) treat the novel environment as being on a different (newly constructed) reference frame, while actively moving animals do not switch reference frames. It could also be argued that the fact that Stackman et al. (2003) observe significant drift in the first two minutes when the rat is inside the novel environment is inconsistent with any drifts being the result of failure to integrate angular head velocity information during passive transport. Thus, the observed differences in HD shift may not be due to an angular path integration deficit, but in a different way of segmenting the environment. Such an interpretation is clearly illustrated in Dudchenko and Zinyuk (2005): when animals walk into a familiar environment, their HD cell PFDs shift by a large amount, but to interpret this as an angular path integration deficit would be inconsistent with animals' ability to carry over a PFD when walking into a familiar environment, elegantly shown in the same experiment. This interpretation also provides a possible explanation for why Dudchenko and Zinyuk (2005) find large (>135°) PFD shifts when the animal walks from A to C; these are the result of a change in reference direction, unlike the Knierim et al. (1998) study, where in the same reference frame, visual

cues compensate for drift (and only small (<45°) shifts are observed). Experimentally, drift and reference frame shifts may be distinguished by recording from a sufficiently large population of HD cells, such that the location of the activity packet in the ring can be tracked on a fine timescale (Brown et al. 1998; Johnson et al. 2005).

Cue conflicts

What if internal and external cues are explicitly put into conflict by rotating both the cue and the rat? In a second experiment, Knierim et al. (1998) rotated the recording cylinder (again, a cylinder with cue card) with the rat in it. As long as the rat cannot see cues outside the cylinder, this introduces a conflict: the rat's vestibular system tells the rat it has been rotated, but the cue card tells the rat its position relative to it has not changed. (To see that this leads to a conflict, imagine an activity packet in a ring.) The question is, which type of information "wins"? Knierim et al. (1998) found that when the apparatus rotation was small (45°), HD cells (and place cells) tended to follow the cue (i.e. change their preferred firing direction). For larger rotations (at least 135°), however, the HD cells tended to ignore the cue[29]. This result seems consistent with the effect of turning the lights back on after encouraging HD system drift in darkness (discussed above) where the cue was able to correct for a small, but not a large, drift. In neural network models of the HD system, both these results can be explained in principle (Section 3.1.3). However, there are also reports of the visual system always appearing to dominate over the idiothetic signal. Jeffery and O'Keefe (1999) rotated both the cue and the rat (by various different respective angles) while the rat was covered inside the recording chamber, and found that the cue nearly always controlled the firing locations of place fields. The reasons for this discrepancy are unclear.

Anatomy of landmark control

What are the brain structures associated with landmark control? As suggested by the anatomy of the system (Figure 2.4 in section 2.2 on page 13), the postsubiculum (PoS) and retrosplenial cortex (Rsp) have been implicated as being important. Goodridge and Taube (1997) lesioned PoS and found HD activity in ADN to be apparently normal (although, as noted earlier, they did not record in the dark). However, they found that ADN HD cell PFDs shifted unpredictably in response to cue card rotations. Similarly, Calton et al. (2003) recorded from hippocampal place cells after lesioning PoS, and found that their between-session stability (i.e. the same cell firing in the same place), but not within-session stability was impaired. The fact that place fields were stable within a session in the presumed absence of a HD signal is interesting, because to reliably fire in the same location might

[29] Knierim et al. report some instances of "delayed cue control", where a HD cell's preferred firing direction did not change immediately after the rotation, but did so later.

be thought to require a path integration mechanism to keep track of place, which in turn requires a representation of heading direction (see section 4.2). However, it is possible that in light conditions, place cells in this experiment were relying on various external cues to maintain stable firing fields. No place cell recordings in darkness after HD system lesions have been reported. It is also not known whether the lack of between-session stability is the result of a failure to retrieve the correct reference frame, or merely a result of the correct reference frame lacking a constant reference direction. Retrosplenial cortex lesions are reported to have similar effects to PoS lesions (Bassett and Taube 1999), while posterior parietal cortex (which provides input to Rsp) lesions had a very mild effect on cue control (Golob and Taube 1999).

In contrast to these results, Golob and Taube (1997) recorded from HD cells and showed that rats could encode and recall preferred orientations for three different environments, even when they didn't have a hippocampus. Taken together, these results suggest that the hippocampus relies on the HD system for some aspects of its function, however, the details of the interaction between the HD system and the hippocampus and its implications for navigation and memory are still under active investigation, with entorhinal cortex likely to be important.

As a separate way in which external inputs may interact with the HD system, it also appears that rats can use optic flow information to update their HD system (Wiener et al. 2004). This may help account for differences in HD cell stability in darkness versus in light that aren't due to episodic fixes from the "landmark system", but the details or anatomical substrates of this ability aren't clear.

Synthesis

It is clear that visual information (the white cue card in most experiments), although not necessary for the maintenance of directional activity, can exert influence on the HD system. From drifts observed in darkness, this influence is thought to be important for keeping an accurate representation over longer periods. The visual influence over HD cells, shown most simply as a PFD drift after rotation of the cue card, appears to be acquired quickly in a single session; however, various conditions can cause it to be ineffective. In particular, a consistent finding is that repeated disruption of the relationship between the HD system and the cue (either by rotating the rat, the cue, or both) appears to lead to reduction or total abolishment of cue control. Some discrepancies between different experiments complicate the picture somewhat; however, the basic associative cue learning model, discussed in section 3.1.3 on page 39, provides a useful paradigm which highlights issues that warrant further exploration. An important distinction which sheds light on some potentially discordant results in the literature is that between drift and shifts in reference

direction. Drift builds up gradually and may only be corrected for by visual cues when the mismatch between the internal and external signals is small. In contrast, reference shifts, which are episodic and can occur when the animal enters a novel environment or in response to changes, can be arbitrarily large and do not reflect an angular path integration deficit.

2.5 Anticipation

Description

A remarkable property of head direction (HD) cells in several brain areas is that they appear to *anticipate* the animal's HD. If the HD signal was simply sensory-derived, it would be expected to lag head direction by some amount, due to propagation delays and processing, analogous to e.g. the visual system (Oram et al. 2002). In the HD system, these anticipatory time intervals (ATIs) can reach up to about 100 ms in individual recording sessions (Blair et al. 1997; Stackman and Taube 1998).

What does it mean to anticipate head direction? In the HD literature, ATIs are obtained by a time-slide method, where spikes from a head direction cell are shifted relative to the head direction samples. Some measure of the cell's directional selectivity (e.g. mutual information, tuning curve width, peak firing rate, difference between clockwise and counterclockwise tuning curves) is then optimised as a function of this time shift, with the optimal time shift being the cell's ATI. For cells in LMN and to a lesser extent ADN and Rsp, the directional content of the cell is optimal when its spikes are shifted some amount into the future; i.e. the cell anticipates (illustrated in Figure 2.6 on the following page). Note that this does not imply any "active" prediction in the sense that a HD cell starts firing when the animal's head is still just before it initiates movement: this just says that over a whole recording session, time slide analysis indicates the HD signal is predictive. In the absence of active prediction processes, it can be noted that the fact that HD can be predicted at all results from angular head movements having some inertia or "predictability" (i.e. a non-zero autocorrelation).

For LMN, averages of 38.5 (Blair et al. 1998) and 66.6 ms (Stackman and Taube 1998, note erratum) have been reported, with the values for ADN and Rsp about 25 ms (Cho and Sharp 2001; Taube and Muller 1998; Blair et al. 1997; Blair and Sharp 1995), and PoS slightly lagging (-5 ms, Taube and Muller 1998). ATIs in DTN have not been as well characterised as in other areas, but Sharp et al. (2001) report that some individual DTN cells show lag and others show anticipation, with no evidence that the population mean was different from zero anticipation, but this was based on a small sample of cells. Note that the ATI difference of 20-30 ms between ADN and PoS in particular, which in principle could be a monosynaptic connection (section 2.2), seems larger than expected by transmission

and synaptic delays; this is explored in Chapter 8. It is also notable that the highest ATIs are found at the vestibular end of the system, decreasing as the signal is propagated down the system's spine.

A salient feature of HD anticipation is the large amount of variability associated with it. This is particularly noticeable when the same cell is recorded for several sessions in an identical environment: Blair and Sharp (1996) report values ranging from 25 to 95 ms. Similarly, average ATIs reported by the same group range from 20 to 45 ms (Taube and Muller 1998; Bassett et al. 2005), and estimates from different groups can differ by 30 ms (Stackman and Taube 1998; Blair et al. 1998). Both Blair et al. (1997) and Taube and Muller (1998) report that there is greater variability between different cells than within cells (recorded multiple times), suggesting that each cell to some extent has a specific ATI value. Another feature of HD cell anticipation is that the magnitude of anticipation does not appear to depend on absolute angular head velocity, as shown in a plot in Taube and Muller (1998) and by Blair et al. (1997) reporting no correlation between ATI and average AHV. This property is relevant for models of anticipation, discussed in section 3.2.

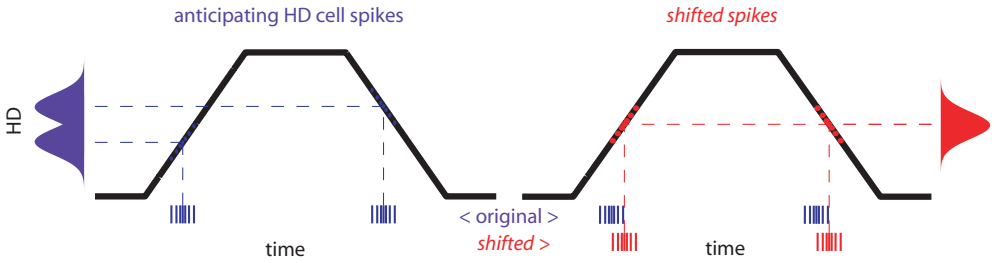

Figure 2.6: Schematic of an idealised anticipating HD cell. The black line represents head direction over time, i.e. the model rat is making a left-still-right movement. An anticipating HD cell would fire something like the blue spikes, generating a bimodal tuning curve. When these spikes are shifted into the future (red spikes) the two modes of the tuning curve move closer together until they overlap perfectly: instead of firing just before the animal's head faced a particular direction, the shifted spikes are optimally aligned with the "anticipated" direction.

Apart from average angular head velocity, no other correlations between behavioral variables and ATI have been reported. However, for ADN HD cells, Blair et al. (1997) report that the amount by which individual cells anticipate is correlated with two related properties of their tuning curve: the extent to which the tuning curve has two nearby peaks instead of one when the animal is still (illustrated in the left panel of Figure 3.3 on page 43), and the amount of deformation that occurs when the animal is turning. This relationship has been the focus of modelling studies, reviewed in section 3.2. LMN HD cells do not show this two-peakedness, but Blair et al. (1998) report a narrowing of their tuning curves during turns (clockwise for cells recorded from the right hemisphere and counterclockwise for left), not found by Stackman and Taube (1998). They do not report whether the extent to

which this happens is variable or related to anticipation. Rsp HD cells showed a broadening of the tuning curve when turning towards the brain hemisphere where the cell was recorded from (Cho and Sharp 2001) but no correlation of this with ATI was found.

In the situation where one has access to the activity of many HD cells (for instance in simulations), the ATI can also be defined on population level, by comparing the animal's actual HD directly to the HD signal reconstructed (or decoded) from HD cell activity. A population ATI may then be found by e.g. minimising the error between these two signals as a function of time, similar to the single cell case. For the population case, the result can be more reliable by reflecting the activity of all cells in the population, but it will also depend on the decoding method used. For instance, Xie et al. (2002) report that in their model, a "max" decoding method, which simply takes the PFD of the most active cell as the coded HD, was more anticipatory than a population vector method which weighted cell PFDs by their firing rates.

Interpretation

The fact that HD cells seem to anticipate has been interpreted as evidence for a motor efference copy and/or proprioceptive signal (Taube et al. 1996; Taube 1998; Brown et al. 2002), although early models suggested that anticipation could also be generated by circuitry not requiring such a signal (Blair and Sharp 1995; Blair 1996; Redish et al. 1996). Such circuitry could be combined with mechanisms needed for angular path integration, such that no mechanisms specific for generating the ATI would be needed (see section 3.2 on page 41 for detailed discussion.) In an experiment appearing to conflict with a role for motor efference copy or other "active" processes in generating the ATI, Bassett et al. (2005) showed that the ATI actually increases during passive movement (for a specific hypothesis of why this might happen, see chapter 7). Although these authors didn't test the contribution of optic flow signals to the ATI (e.g. by doing the same experiment in darkness), this suggests that stimulation of the vestibular apparatus alone might be enough to generate anticipation. Although no reports of ATIs in darkness are available to support this further, the fact ATIs seem highest closest to the source of vestibular information, with it decreasing as the HD signal ascends from the brainstem to the cortex, seems consistent with this idea.

It is worth noting that a similar anticipation property has been found in several other population-coding systems representing a continuous variable, e.g. motion perception extrapolation (Nijhawan 1994), motor control of hand movements (Wolpert et al. 1995), and hippocampal place cells (Muller and Kubie 1989; Sharp 1999; Battaglia et al. 2004). Possible mechanisms underlying such anticipation and the head direction ATI in particular are explored in chapters 7 and 8. However, even in these other cases, it remains somewhat

of a mystery whether there is any specific use for such anticipatory signals.

Chapter 3

Models of the head direction system

3.1 Ring attractor networks

To account for the properties reviewed in section 2.1, a basic model of the head direction (HD) system needs a way to maintain a directional signal in the absence of input, a way of updating it in response to movement, and a way of resetting it in response to visual input. The first theoretical proposal of how this could work (McNaughton et al. 1991) described the HD system as a linear mapping of head direction and angular head velocity at time t to head direction at time $t + dt$. As a neurophysiological mechanism by which this mapping could be implemented, they proposed *HH'* cells, head direction cells which were modulated by angular head velocity; one population increasing their activity during left turns, another for right turns. Such *HH'* cells are also a key ingredient of a more detailed model (Skaggs et al. 1995), which unlike the earlier McNaughton et al. model, proposed specific circuitry for maintaining and updating the HD signal (top panel of Figure 3.1 on the next page).

Although Skaggs et al. (1995) did not report any simulation results, their proposal contains the necessary elements for a basic but neurally plausible model. Every HD model with sufficient neurophysiological detail to date has included *HH'* cells in some way, although mathematically equivalent, simplified versions (which violate some plausibility criteria) are possible. Apart from *HH'* cells, all computational models of the head direction system share another conceptual element (again, of which specific implementations may differ), in that they implement a continuous attractor network. In the case of the HD system, such a network is often referred to as a "ring attractor", because HD is a one-dimensional, circular variable that can be represented by the angular position of active units on a ring (Figure 2.3 on page 8 and Figure 3.1 on the next page). A ring attractor is like a standard "point attractor" network (Hopfield 1982) in that it has a number of stable states where a subset of its units is persistently active in the absence of external input. Unlike a point

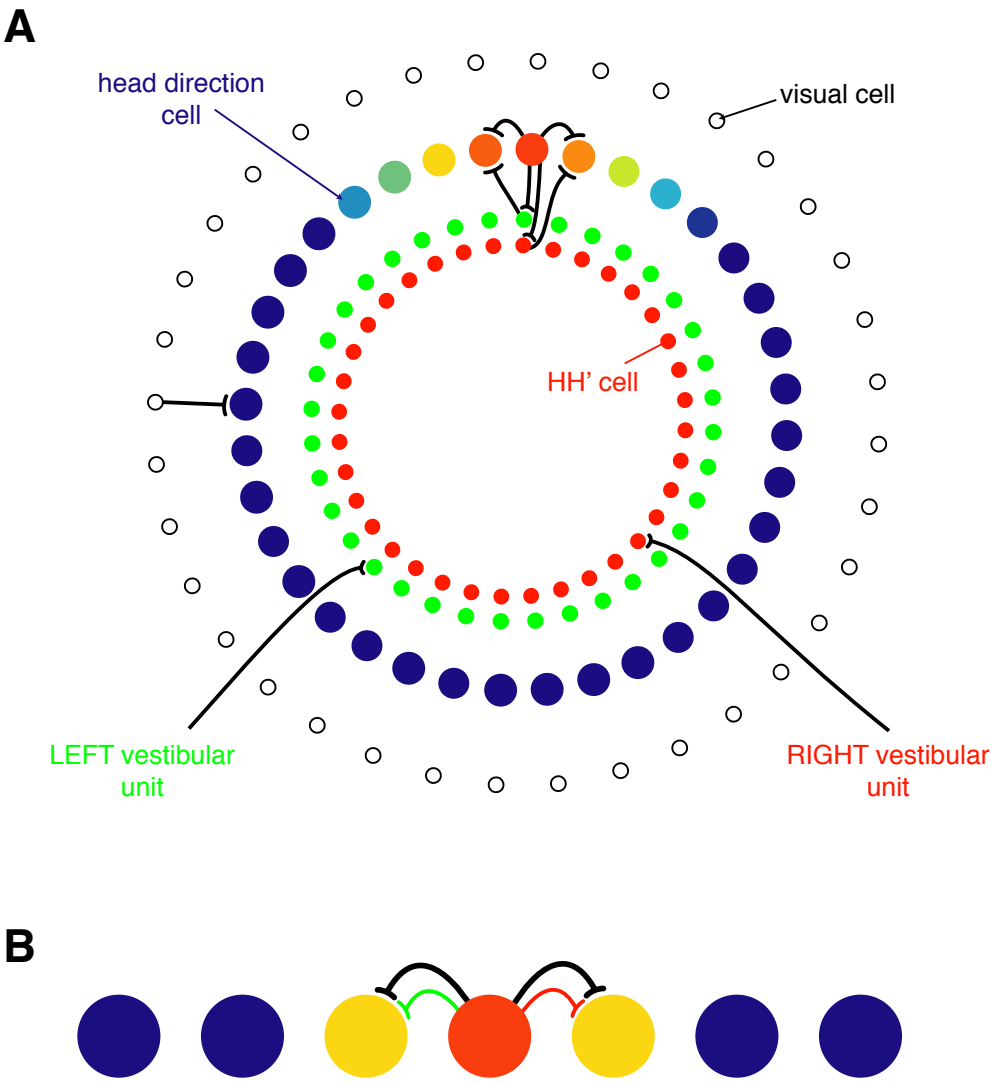

Figure 3.1: Two early models of the head direction (HD) system. **A**: The canonical network model, first proposed in this form by Skaggs et al. (1995). It contains three cell types (all arranged with their preferred firing directions (PFDs) corresponding to their angular position on the circle for convenience): head direction cells (middle ring of large filled circles, with dark blue indicating inactivity and red indicating activity on a cold-hot colormap), visual cells (outer ring), and HH' cells (inner two rings, green for left turns, red for right turns). The model contains three sets of excitatory connections to HD cells: each HD cell projects to its neighbours with similar preferred directions ("symmetric connections", only connections to two neighbours drawn), each HD cell receives inputs from visual cells which may be active when the rat faces e.g. a cue card ("visual inputs", only connection to one HD cell drawn), and each HH' cell sends "asymmetric connections" to HD cells to the left (left-turn HH' cells) and right (right-turn HH' cells). HH' cells receive input from HD cells with corresponding preferred firing directions, as well as a vestibular angular head velocity signal. For simplicity, connections are only drawn for one cell. The symmetric connections ensure persistent activity in the absence of input, the visual inputs allow for visual updates, and the asymmetric connections allow for idiothetic updates. **B**: Simplified form as used by Zhang (1996) and others, with only a linearised subsection of the complete ring shown, so cell PFD now varies from left to right. There is only one cell type (HD cells) and a recurrent weight matrix, consisting of fixed symmetric connections (black) responsible for maintaining the activity packet, and variable asymmetric (red, green) connections responsible for moving it around. The symmetric weights are excitatory between nearby cells and inhibitory between cells with different preferred firing directions, creating a single activity bump.

attractor system, however, a ring attractor has a *continuum* of stable states[1]: the network is constructed in such a way that stable "packets of activity" can exist centred at any unit. Such an activity packet (also referred to as "hill of activity", "bubble", or "bump"), consists of a subset of HD cells being active, with the HD cell with a preferred firing direction corresponding to the centre of the packet being the most active, and the cells on its edge firing only slightly above the background firing rate – the location of the packet represents the animal's estimated directional heading. Note that in models the HD cells are usually laid out in a ring topography, where neighbouring cells have similar preferred orientations, but this is done for clarity purposes only, and no evidence of a topographical layout of HD cells in the brain has in fact been found.

In the Skaggs et al. (1995) model, stable bump states are achieved and maintained with recurrent connections between the HD cells. If the connection weights are chosen appropriately (discussed in more detail in the next section), activity will be constrained to a Gaussian-shaped activity packet, with the cells outside the packet silent. When this arrangement is "at rest" (i.e. no incoming vestibular or visual input), the model maintains a stable, coherent[2] representation of active HD cells. Details of maintenance mechanisms are discussed in the following section.

This activity profile is transferred to the two populations of *HH'* cells, which are responsible for moving the activity packet around. Note how each population has *offset*, or asymmetric, connections back to the HD cells in the direction corresponding to their input type ("left" or "right"). If both *HH'* populations are equally active, the HD layer activity packet will receive equal input in both directions and thus remain stationary. However, if one population of *HH'* cells becomes more active than the other, this balanced arrangement is disturbed, and the activity packet will be pushed in the corresponding direction, thus updating the HD representation. The details of update mechanisms are reviewed in section 3.1.2 on page 37.

The canonical model also includes a way for external sensory inputs to set the location of the activity packet. This is implemented by a number of visual input (or more generally, "local view detector") units, which directly connect to cells on the HD ring. In its simplest conceptualisation, these units represent salient landmarks visible to the rat from its current directional orientation, e.g. a "white cue card" unit is turned on when the rat is facing the cue card. If the inputs from such units is strong enough and can selectively activate a particular set of HD cells, the location of the activity packet in the ring will be "reset" to that location every time the visual input units are active (i.e. when the rat looks at it). Although such a scheme necessarily assumes some pre-processing of the input (e.g. by having units recognising an object), a potentially more serious problem is that for this scheme to work

[1] Graphically, its energy profile is a continuous valley wherein the system can move freely, like the punt or "kick-up" at the bottom of a wine bottle, rather than a set of small, discrete "wells".

[2] That is, all the cells agree on what head direction they are encoding, as opposed to half the active cells encoding "North" and the other half encoding "South" (Jackson and Redish 2003).

reliably, such "resets" need to happen when the rat is facing some *allocentric* direction. In contrast, a simple implementation of when the visual units are active might result in the HD system being reset when the rat is at some *egocentric* bearing relative to the cue card, because it can look at the cue card from different allocentric bearings. This would not result in the known, allocentric, firing behaviour of HD cells. Despite this limitation (the model effectively requires the rat to only be able to rotate, but not move), this model is helpful in considering experimental results relating to cue control, discussed in section 3.1.3 on page 39.

3.1.1 Maintenance mechanisms

With respect to creating and maintaining stable activity packets in fully functioning HD models, one type of model essentially follows the proposal by Skaggs et al. (1995), using recurrent connections within a HD cell layer[3]. The first model of the HD system to include simulations (Zhang 1996) used recurrent all-to-all connections of the "on-centre-off-surround" or "Mexican hat" type, i.e. cells with similar preferred directions excited each other, and cells with different preferred directions inhibited each other. An appropriately chosen matrix of connection weights, with shape (Zhang uses a cosine, but a difference of Gaussians is also common) and strength as the important parameters, can constrain activity to a realistically shaped activity packet. In this single-layer scenario, both excitation and inhibition are needed to achieve the desired shape and pseudo-winner-take-all behaviour where there can only be one bump (so that incoherent states, e.g. simultaneous North-and-South, are impossible). The strengths are usually hand-tuned, although in certain mathematically convenient cases phase diagrams can be constructed which show the possible regimes as a function of model parameters (Hansel and Sompolinsky 1998).

In the Zhang model, both excitation and inhibition are implemented in a single recurrent connection weight matrix. A simple way to get the packet to be stable is to make the weight matrix reflection-invariant, i.e. from a given unit with preferred firing direction ϕ_i, the weights to units $\phi_i + d$ and $\phi_i - d$ are identical[4]: excitatory for small d, inhibitory for large d. Hence, these connections can be referred to as "symmetric connections", responsible for the generation and stabilisation of the bump. These weights need to be rotationally symmetric in order for the bump to be stable at any point in the ring: whatever connections originate from a single unit, they must be the same (but shifted) for every unit in the ring, i.e. $w(\phi_i, \phi_j) = f(|\phi_i - \phi_j|)$. If these demands on the weight matrix are not met, the system is not

[3] It must be noted that networks of this class, which use interactions between inhibitory and excitatory "neural fields", have been studied in a more general context (Wilson and Cowan 1973; Amari 1977) and applied to other systems, e.g. saccade planning in the superior colliculus (Droulez and Berthoz 1991) and working memory (Zipser et al. 1993). Treatment here is restricted to the application of these ideas to the HD system specifically.

[4] This isn't a strict requirement, more complex solutions are possible.

a true continuous attractor, and a number of point attractor states will form instead, causing the system to drift and only be stable at those points. This problem also occurs in other, similar models, e.g. of working memory (Zipser et al. 1993; Compte et al. 2000) and the velocity integrator circuit of the vestibulo-ocular reflex (Cannon et al. 1983). A number of solutions have been proposed to reduce bump drift due to weight noise (e.g. Koulakov et al. 2002); for the HD system specifically, the use of NMDA receptors, with their relatively slow channel dynamics, has been found to reduce drift (Song and Wang 2005), but it seems likely a biological system will never achieve a perfect continuous attractor. In this regard, modellers have pointed to experimental evidence that the HD system is not able to track perfectly in darkness (e.g. Goodridge and Taube 1995, see section 2.3 on page 17 for a review), suggesting that some drift towards point attractors might occur in the biological system. It may be difficult to attribute this experimentally observed drift entirely to noisy attractors, however; an alternative source of error may be that the update signal used to move the activity packet is imperfect, or that the packet doesn't move the correct amount in response to the signal (these possibilities are discussed in the next section). Vestibular neurons, which are thought to provide an important idiothetic update signal, are known to adapt on several different timescales (e.g. adaptation in the vestibular organs themselves, as well as in secondary neurons), which would make accurate tracking difficult unless compensated for by other sources. Chapter 7 describes a HD system model that explicitly considers error in the vestibular update signal.

Several subsequent models have used arrangements similar to Zhang (1996) to create stable bump states[5]. Redish et al. (1996) separated out excitatory and inhibitory neurons, while Goodridge and Touretzky (2000) and Stringer et al. (2002) used uniform inhibition. For an implementation of such a continuous attractor with recurrent excitation and uniform inhibition, see Chapter 7. An elegant proposal by Xie et al. (2002) used a different "double ring" arrangement, where two separate HD cell populations create a single attractor together. In this model, the symmetric connections to each HD cell come from two different sources: HD cells with a slightly different preferred firing direction (PFD) to one side from the same ring, and HD cells with a different PFD to the other side from the other ring. This is illustrated in panel C in Figure 3.2 on the next page.

Two recent models (Boucheny et al. 2005; Song and Wang 2005) used another way of generating Gaussian-shaped bump states, based on specific offset inhibitory connections. Such a scenario is potentially more consistent with the known anatomy of the HD system, where no recurrent collaterals have been found at any level, and the projection between DTN and LMN is inhibitory. This "cross-inhibition" arrangement is shown in Figure 3.2d. A given cell in the (excitatory) population of HD cells with PFD ϕ_i receives maximal

[5]That is not to say they did not do anything new; sometimes the reported innovations were not in the symmetric weight mechanism.

inhibitory input from a "left" turn cell with PFD $\phi_i - d$ and from a "right" turn cell with PFD $\phi_i + d$, in addition to a constant uniform excitatory drive. Excitatory cells project to both populations of inhibitory cells with the same PFDs. When the activity of both inhibitory populations is balanced, this has the effect of creating a stable hill of activity in the excitatory population; maximal inhibition occurs to both sides of the hill (the offset amount d is critical in achieving this).

Circuit diagrams aside, a general difference between the maintenance mechanisms used in different models is the amount of biological realism. This can range from using rate-based units with both excitatory and inhibitory effects (as in Zhang 1996) to a conductance-based spiking model with realistic AMPA, NMDA, GABAa and GABAb dynamics (Song and Wang 2005). However, the fact that a model is at a higher level of description does not mean it cannot be implemented using more realistic machinery; every level allows for particular questions to be explored.

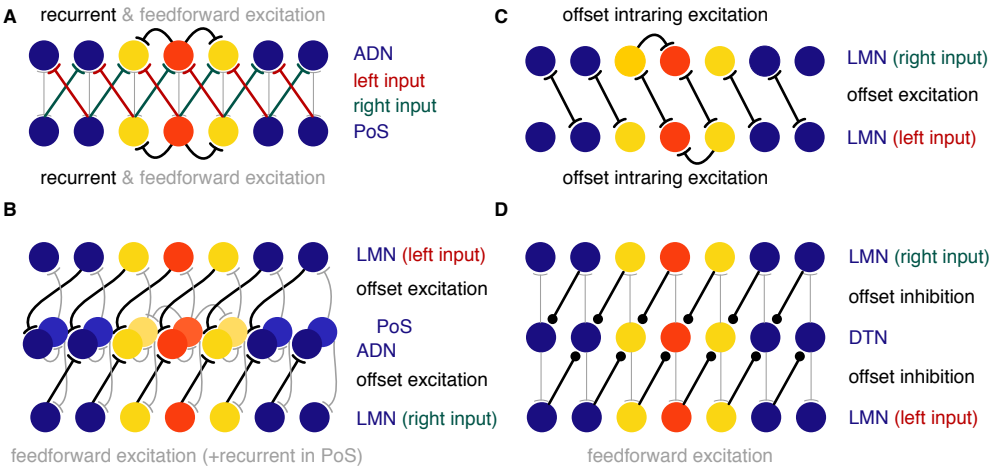

Figure 3.2: Schematic diagrams of the main head direction network models, layout as Figure 3.1b. **A**: Redish et al. (1996) use two attractor layers (implemented with recurrent excitation) and reciprocally connected with non-offset connections (grey arrows). Offset connections from the "PoS" layer to the "ADN" layer (red, green arrows) are directly modified in response to angular head velocity (AHV) input. **B**: Goodridge and Touretzky (2000) use two populations of "LMN" neurons; the "left" population has left offset connections to the "ADN" layer and increases firing rate during left turns (right for the "right" population). The LMN and ADN layers have no attractor dynamics, but ADN projects to PoS, which does (recurrent connections not shown), and projects back to LMN (grey arrows). **C**: Xie et al. (2002) use a "left" and a "right" ring, where the left ring (increased activity during left turns) receives right-offset connections from the right ring, and left-offset connections from itself (vice versa for the right ring). **D**: The "left" LMN population in Song and Wang (2005) has right-offset inhibition a DTN layer, which projects back to LMN (vice versa for the "right" population). Neither the LMN or DTN layers have recurrent connections. All models additionally have a form of global inhibition (excitation in panel **D**) which is not shown here.

3.1.2 Idiothetic update mechanisms

Stable states are one ingredient; the other essential component for direction-specific firing is that the bump needs to be moved around, such that different HD cells become active when the head of the animal faces a different direction. In principle, like the original Skaggs et al. (1995) network, all models effectively implement this update mechanism by adding an asymmetric component to the symmetric weight arrangement responsible for stabilising the bump. In the Skaggs et al. (1995) model, this is done by offset connections from the *HH'* cells (left offset for the "left" *HH'* cells, right offset for the "right" *HH'* cells) to the HD cells. In Zhang (1996), this is not accomplished by any plausible neural mechanism as such, but by literally adding an asymmetric component (in fact, the derivative of the symmetric weight profile) to the weight matrix, shown schematically in Figure 3.1b. Redish et al. (1996) used a similar implausible mathematical shortcut (Figure 3.1a), directly manipulating the strength of offset connections between two attractor layers. In their scheme, an "ADN" HD cell with preferred firing direction (PFD) ϕ_i receives two offset inputs, one which is active during clockwise turns and originates from a "PoS" HD cell with PFD $\phi_i - d$, and one from a PoS HD cell with PFD $\phi_i + d$ which is active during counterclockwise turns. Non-offset connections between the layers ensure that in the absence of input, the two representations synchronise (if there were only offset connections, the HD representation in the originating layer would never get updated).

It is possible to imagine circuits that accomplish the same goals without violating plausibility constraints: this has been one way in which models of the HD system have progressed. For instance, the Zhang and Redish models modified synaptic strengths instantly and directly, but in subsequent models the same result is achieved using circuits where firing rates, not synapses, are changed in response to input. Another area of improvement has been to increasingly identify populations of cells having particular properties with specific anatomical locations. For instance, Goodridge and Touretzky (2000) propose two populations of "LMN" cells, one left population which increases firing rate during left turns (idem dito for right turns) which could be easily accomplished by a feedforward vestibular input. The LMN units do not have attractor dynamics, so by themselves would not be able to sustain a stable activity packet. In the model, attractor dynamics are placed in PoS, which sends a projection to the LMN layer. The "left" LMN units send left-offset connections to the ADN layer (also without attractor dynamics), which in turn projects to the PoS layer, moving the bump (see Figure 3.2b for a diagram).

The Xie et al. (2002) and Song and Wang (2005) models share this approach of identifying two populations of LMN cells, one increasing their firing rate with left turns and another with right turns. In the Xie et al. model, these populations (rings) have offset recurrent excitatory connections, as well as offset excitatory connections between them (Figure 3.2c), which results in a stable attractor when combined with appropriate global inhibition. The

update is then achieved by providing more input to one ring than to the other. In the Song and Wang model, the two LMN populations send offset inhibition to the "DTN" population (which has a constant excitatory drive), which update the DTN activity packet in a similar way, where differential input to the two LMN populations breaks the symmetry of the stable state. There will be no stable state if the two inputs are not perfectly balanced; apart from the imperfect continuous attractor network mentioned in the previous section, such update asymmetry is another likely source of HD system drift in a biological system.

For all head direction system models, it is important that the amount the activity packet travels in response to input is calibrated. In HD models, it is typically assumed that the input signal is angular head velocity (AHV), such that in the model, the activity packet has to travel at a speed proportional to the magnitude of input (ideally over a wide range of turning velocities) and set such that the network achieves integration of AHV into HD. How fast the activity packet travels in response to the input can be referred to as the *gain* of the model: unity gain would correspond to perfect integration, i.e. if the input is AHV, then the decoded output is HD. HD cells will only have stable tuning curves is this condition is at least approximately met, although visual updates ("fixes") using external cues can help, depending on their accuracy and frequency. There is little data available on what speeds and what kinds of turns animals can actually track accurately; the fact that they regularly move at speeds up to 720°/s (Xie et al. 2002) does not automatically imply that their HD system is able to keep up. Passive rotation data is only available from experiments where rotation velocity has not been explicitly controlled (Blair and Sharp 1996; Knierim et al. 1998; Bassett et al. 2005) and suggest animals can probably track basic movements of up to at least 200-300°/s, but how this ability depends on other factors such as input frequency is unknown.

In early models (Redish et al. 1996; Goodridge and Touretzky 2000) the idiothetic update mechanism did not work well with a constant gain (Zhang (1996) did not simulate a realistic HD profile); an empirical relationship had to be derived for how much input signal to give the model for AHV inputs of different magnitude. In later models, this issue has largely been resolved through careful tuning of model parameters (e.g. Xie et al. (2002) report accurate tracking at speeds in excess of 4000°, and in the detailed model of Song and Wang (2005) saturation occurs at 1670°) although nonlinearities in the gain necessarily appear for extreme AHV values. Data on how stable the biological system is would help to assess how much parameter tuning is required to achieve realistic results. The issue of how a useful gain (and, more generally, the appropriate connection weights) for updating the HD network in response to idiothetic inputs could be learned is addressed by two similar studies (Stringer et al. 2002; Hahnloser 2003), proposing that visual supervision could interact with local synaptic plasticity rules to produce the desired result. A recent study (Yu et al. 2006) found that head direction cell tuning curves shifted backwards as rats ran

on a circular track, providing evidence for the existence of plasticity rules in the HD system that could support such learning.

3.1.3 Visual update mechanisms

With a way to create a stable activity packet and the ability to move it around, continuous attractor models can in principle explain the basic HD cell property of persistent directional firing. Following the proposal by Skaggs et al. (1995), Zhang (1996) also provides simulations of how visual input can change the preferred direction of HD cells. By providing external input to some point in the HD ring when the rat is facing a simulated cue (see Figure 3.1 on page 32), the activity packet can be set to that point. As illustrated in Figure 2.3 on page 8, when a cue that is strong enough in this sense is rotated, the relative location of the activity packet in the HD ring will be rotated by that same amount. This is because the rat is now facing a different way when it is looking at the cue, while the activity packet is reset to the same location in the ring as before, thus changing the PFDs of the HD cells. As noted earlier, this model relies on a number of simplifications, in particular that local view input from a single cue is sufficient to set allocentric head direction correctly. However, rats are known to have a wide field of view (estimated at up to 300°, Prusky and Douglas 2005), so the same cue is presumably sensed from any number of allocentric bearings, further complicated if the cue is visible from different positions as well. A recent robot implementation (Strösslin et al. 2005) which processes V1-like representations of the visual world to track allocentric heading (and position) accurately, shows that in principle, these limitations can be overcome and the assumptions of the simple visual update model are not unreasonable.

In the simple visual update model, updates can happen in two qualitatively different ways (Zhang 1996; Song and Wang 2005). For strong visual inputs, if the location of the input is close to the activity packet, it will move smoothly to the visual input location. If the input is far away, the packet will die out at the old location, while appearing at the new location. Because of the "Mexican hat"-like weight profile required to maintain stable states, the input strength required to move the packet is smaller than that required to completely reset it. Thus, a subtle effect can be observed for visual inputs strong enough to move the packet, but not strong enough to make it appear at an entirely new location. Potentially, this effect could explain a number of experimental results, reviewed in section 2.4 on page 20, where in case of a small mismatch between idiothetic and visual information, the visual inputs "win", but in case of large mismatches, the idiothetic information wins. However, in simulations, the strength of input required to get this effect is in a very restricted range, and no direct tests of this idea, which would require controlling the strength of the visual input and the degree of mismatch, have been done experimentally. Another potentially troublesome issue is the observation that a polarising cue card never seems to be able to

control place cell firing when it is moved by a large amount in the presence of the rat (90° in Jeffery and O'Keefe (1999), 180° in Rotenberg and Muller (1997). In different paradigms, like the standard cue rotation experiment (Taube et al. 1990b; Muller and Kubie 1987) HD cells reliably rotate 90° relative to a previous preferred firing direction. This suggests that the standard model of visual input to the HD system (Figure 3.1) is too simple, and rats can decide to ignore a cue if they judge it to be unstable.

Another interesting point concerns the way in which landmarks become associated (and un-associated) with particular directions in the HD model. The basic case assumes that a "visual cell" is active when the rat is facing a certain direction in space (in the room reference frame), simulating sensory input that is unique to that head direction. The visual cell has Hebbian plastic connections to all HD cells, such that those connections projecting to active HD cells are strengthened, and those projecting to inactive HD cells are weakened. If the idiothetic angular path integration mechanism is accurate enough (and given enough time and appropriate learning rule), the same HD cells will be consistently active when the visual cell is on, allowing the connections from that visual cell to become strong enough to set the system: the visual cell has acquired "cue control". Knierim et al. (1995) did an experiment in which they disoriented rats before placing them into a cylinder with a prominent cue card; in these rats, the cue never gained control over HD cell preferred directions. The authors interpreted this as the result of the cue associating itself with a different set of HD cells in each session (the disorientation ensuring that the HD signal had a random orientation each session), which given an appropriate balance of potentiation and depression, would lead to insufficiently consistent activation of the same cue-to-HD cell connections. However, in this explanation, it is not clear why the cue did not gain cue control in the first session, which was 8 minutes, sufficient for cue control in apparently similar conditions in Goodridge et al. (1998). As suggested in section 2.4, it is possible that both the case where rats are disoriented before entry Knierim et al. (1995) and where the cue card is rotated repeatedly in without the rat looking (Jeffery and O'Keefe 1999) create a time window where the position of the cue and the position of the activity packet are temporarily inconsistent, until they are aligned again by a visual fix. An appropriate learning rule (in particular, an appropriate balance between of potentiation and depression), might then result in the influence of the cue diminishing with each such briefly mismatched window; such a scenario would require computational exploration.

Another way in which the visual update model appears to be too simple is that it does not explicitly distinguish between correcting for drift and switching reference frames. While this could be seen as a feature, these processes are dissociable experimentally, and the model cannot account for the finding that in Knierim et al. (1998), large mismatches between idiothetic and external inputs are ignored, while in (Dudchenko and Zinyuk 2005), PFDs reliably switch by 135° or more when a rat enters a familiar environment.

A further challenge for the simple model of visual cells projecting to the HD ring comes from the effect of HD system lesions on hippocampal place cells. Golob and Taube (1997) showed that in animals with hippocampal lesions, HD cells can store and recall environment-specific preferred directions. Lesions of PoS cause intersession instability in hippocampal place cells, i.e. the correct map and/or orientation for that environment isn't recalled correctly (Calton et al. 2003). As suggested by several theories (McNaughton et al. 1996; Touretzky and Redish 1996) this finding is consistent with the idea that the hippocampus relies on the head direction system for setting the reference direction of the hippocampal map, and possibly also for retrieving the correct map (although more simultaneous units recorded from hippocampus would be needed to confirm this possibility)[6]. Such an interpretation would be consistent with the role of PoS in aligning the head direction signal with visual landmarks, with the hippocampus lacking a dedicated similar input for aligning its map. However, the situation is not that simple. Calton and Taube (2005) also investigated the effect of ADN lesions on hippocampal place cells, and although they found a small reduction in intersession place cell stability, this impairment was mild relative to PoS-lesioned animals. Since ADN lesions are thought to abolish head direction activity in PoS (Goodridge and Taube 1997), this is an interesting result. It must be concluded that either the visual inputs to PoS HD cells are strong enough to activate HD cells in order to transmit this reference direction information to the hippocampus, in which case it is unclear why such directional activity is not observed after ADN lesions as discussed earlier[7], or that there are non-HD cells in PoS responsible for relaying this information. The latter case implies that the hippocampus does not rely on the HD system to set its directional orientation, in spite of the strong correlations in reference direction reported between the two systems (Knierim et al. 1998; Yoganarasimha and Knierim 2005).

3.2 Anticipation and deformation

As reviewed in section 2.5 on page 27, head direction cells in several areas anticipate the animal's head direction by up to 100 ms. LMN HD cells anticipate the most (39-67 ms), ADN and Rsp cells a moderate amount (25 ms), and PoS HD cells appear to code for current head direction or lag slightly. This anticipation property has been useful in guiding neural network models of the HD system.

Simulations by Redish et al. (1996) showed that offset connections (section 3.1.2) between layers of HD cells generate anticipation, with the amount of anticipation in the receiving

[6]However, these theories also require a head direction signal in order to have any consistent place cell activity at all. Perhaps retrosplenial or striatal head direction activity remains intact after PoS lesions, and may be capable of supporting hippocampal path integration. It would be interesting to see the effects of darkness on the intrasession place cell stability of PoS-lesioned animals.

[7]it is possible Goodridge and Taube (1997) didn't do analyses needed to see such effects, only looking for "classic" HD cells.

cell layer proportional to the offset d. It is worth noting that the canonical HD model (Figure 3.1 on page 32) also contains offset connections, from the *HH'* cells to HD cells. Conceptually, the Redish et al. (1996) is a simple adaptation of this, with the main change being that in addition to the HD cell layer, the *HH'* layer contains attractor dynamics, and instead of the *HH'* units being modulated by AHV, the connections *between* the two layers are AHV-modulated.

Refining this result, Goodridge and Touretzky (2000) used offset connections from LMN to ADN to reproduce the tuning curve deformations exhibited by ADN cells (skewness during turning and two-peaked tuning curve when still, Blair and Sharp 1995; Blair et al. 1997). They found these deformations resulted in 28 ms of ATI for one particular cell tried, while the experimental ATI was 47 ms, suggesting other mechanisms beyond deformation act to generate anticipation. (Especially since the cell chosen was the one exhibiting the most deformations.) Also, they found that ADN deformations could not be reproduced in a configuration where LMN leads ADN (which contained no recurrent connections) and is the sole input to it. Essentially, offset connections from LMN to ADN were needed to reproduce the correct tuning curve shapes in ADN, but these same connections would cause ADN to lead LMN. However, when they added in PoS connections to ADN, realistic tuning curve shapes could be reproduced. Recordings from ADN HD cells in PoS-lesioned animals (Goodridge and Taube 1997) do not address tuning curve deformations, but they do report an ATI increase. This could be consistent with Goodridge and Touretzky (2000)'s result that without PoS input, ADN HD cells are more anticipatory because the offset connections from LMN dominate.

Both Blair et al. (1997) and Taube and Muller (1998) report that ATIs do not appear to depend on angular head velocity, i.e. that during slow turns HD cells anticipate by the same amount (time) as during fast turns. The Goodridge and Touretzky model reproduces this, although it is possible that their empirical method of setting the strength of the offset connections (the gain of how much the mode updates in response to a given input), which they set separately for inputs of different angular head velocities, may have contributed to this result.

Both the Song and Wang and Xie et al. models also found that their offset connection schemes resulted in anticipation. Song and Wang attributed this in part to using instantaneous angular head velocity as input (as other models have done), while in a biological system this signal would be subject to some transmission delays and low-pass filtering. They found that with mild low-pass filtering of the AHV signal before it was used as input, they could reduce anticipation from 25 ms to around zero. Xie et al. find similar values using instantaneous

update[8].

Thus, several models using offset connections have reported that this mechanism generates anticipation relative to an instantaneous AHV input signal. It seems that anticipation is an automatic by-product of such connections, due to deformation of the activity packet (Goodridge and Touretzky 2000). This is illustrated schematically in the left panel of Figure 3.3.

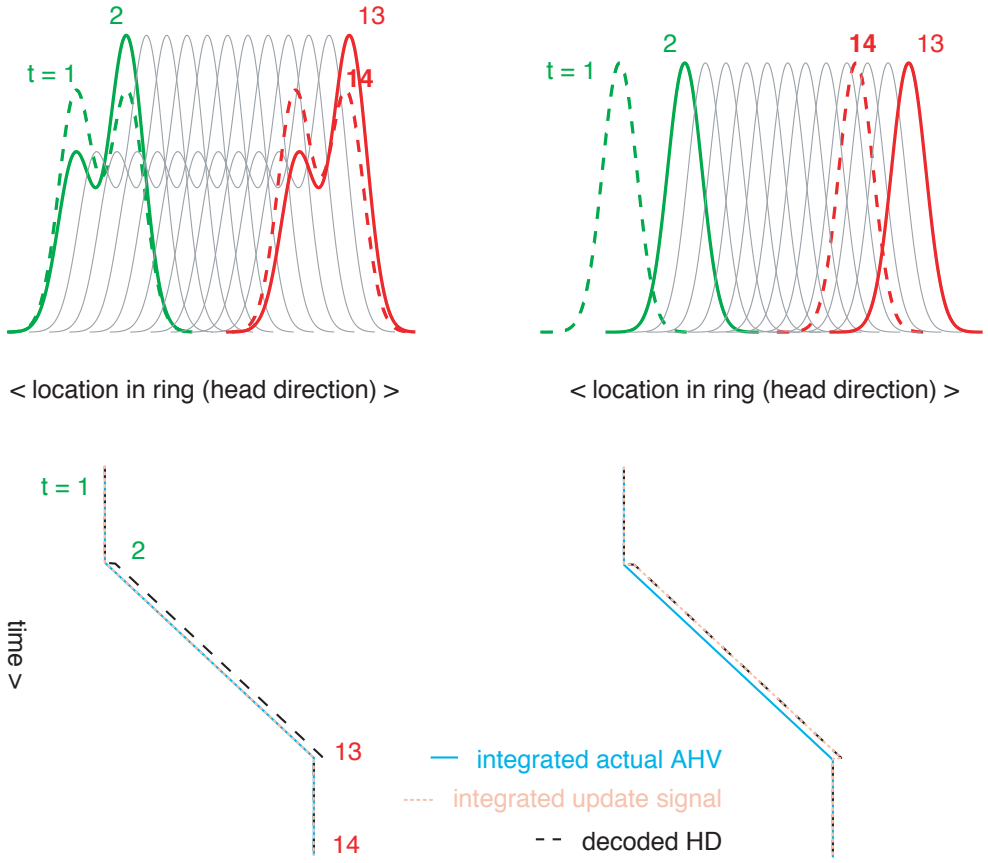

Figure 3.3: Anticipation can result from two separate mechanisms. **Left**: Deformation of the activity packet. The top panel shows an activity packet, with vertical position indicating coded head direction. In this example, the bump at rest (1, dashed green line) has the two-peaked shape characteristic of some anticipating ADN cells. At the start of a turn, the bump deforms (2, solid green line), causing a "jump" in coded head direction. This is illustrated in the lower panel, again with HD as vertical position and time flowing from top to bottom. The dashed line corresponds to decoded HD. During the turn, the bump moves as normal (top panel, grey bumps). When the turn stops, the bump regains its normal shape and the decoded HD makes a jump back (14, red lines). **Right**: Input with angular acceleration component. In this case, there is no deformation of the tuning curve, and the decoded HD tracks the input perfectly. If the input signal is constructed such that it anticipates the original signal, the decoded output is anticipatory.

[8]They make the point that anticipation will depend on the decoding method used: using the maximum instead of the population vector will yield greater anticipation. This is correct, but since experimental ATIs are calculated on the single cell level, not yet directly relevant.

However, deformation is not the only possible mechanism for generating anticipation. If the input signal updating the HD network was itself anticipatory with respect to the reference signal, the decoded HD would also be anticipatory, without requiring deformation. This idea was suggested by Zhang (1996), and also implemented in Song and Wang 2005. They included a generic angular acceleration term in the idiothetic angular head velocity (AHV) update signal. In this way, the bump does not have to deform to be anticipatory (illustrated in Figure 3.3, right); the anticipation results from a modification in the input signal before it reaches the HD system. The result obtained by Goodridge and Touretzky (2000), who found that the deformations of the most deforming ADN cell could only account for 28 ms of anticipation, supports the notion that these deformations are not the only source of anticipation (the experimentally observed value for that cell was 47 ms). In addition, LMN cells anticipate more than ADN cells (39-67 ms on average, with some individual cells approaching 100 ms), and show a different deformation pattern. LMN HD cells on the left side of the brain become narrower during ipsiversive (left, or counterclockwise) turns, and vice versa (Blair et al. 1998, note erratum). How much, if any, anticipation this narrowing of tuning curves could contribute has not been addressed, but since Stackman and Taube (1998) did not report this effect, some experimental clarification would be desirable.

The fact that ADN HD cell tuning curves would deform was actually predicted by the first model to use offset connections (Redish et al. 1996), and subsequently confirmed by (Blair et al. 1997)[9]. Unfortunately, some reports on such fine characteristics of HD cell tuning curves have been inconsistent. For instance, in addition to inconsistent reports on the tuning curve narrowing effect discussed in the previous section, Stackman and Taube (1998) report that LMN HD cells increase their firing rate during ipsiversive turns[10], while Blair et al. (1998) merely report that cells have higher firing rates during turns than when the animal is not moving. The two most anatomically detailed models (Song and Wang 2005; Goodridge and Touretzky 2000) both rely on *HH'* cells, i.e. HD cells asymmetrically modulated by AHV, as reported by Stackman and Taube (1998) for LMN and Sharp et al. (2001) in DTN (although this was a small sample). It is noteworthy that Stackman and Taube (1998) found that the direction of asymmetry was strongly correlated with which hemisphere cells were in, suggesting that one hemisphere is responsible for turns one way, yet Blair et al. (1999) found that unilateral LMN lesions left ADN HD cells generally unaffected.

Because recording data from LMN were not available at the time, Redish et al. (1996) only accounted for anticipation in ADN, generating anticipation by AHV-modulated offset connections from PoS to ADN. However, LMN HD cells anticipate more than

[9] However, it is now clear that even though the prediction turned out to be correct, some aspects of this theory have had to be updated since, discussed below.

[10] As if they received excitatory input from Type I vestibular neurons (which increase their firing rate during an ipsiversive head turn) from the same hemisphere and/or from Type II neurons on the contralateral side.

ADN cells (section 2.5 on page 27). While PoS sends a projection to LMN that could in principle be offset, a lesion study by Goodridge and Taube (1997) showed that ADN anticipation does not depend on an intact PoS, in fact anticipation in ADN doubled from about 18 to 36 ms (exact values depend on the measure used). This suggests that, unless ADN anticipation is generated independently of LMN anticipation, PoS is not involved in anticipation generation. However, this does not doom the offset connection hypothesis; a possible anatomical locus for offset connections could be between DTN and LMN. Since these connections are thought to be inhibitory (section 2.2 on page 13) this wouldn't work literally as proposed by Redish et al. (1996). Song and Wang (2005) use offset inhibitory connections, but don't report any relationship between their offset parameter and anticipation, although they do report that when using instantaneous AHV to update their HD network, it anticipates by 25 ms, presumably because of the offset nature of the cross-inhibition.

Apart from the question of how much the anticipation in LMN is due to deformation, and how much to the properties of the input signal, there are some further issues with regard to anticipation. Tuning curve shapes in ADN seem to suggest that some of their anticipation is due to offset, but that would imply that it should be more anticipatory than LMN. This may be attributable to PoS, but ADN HD cells in PoS-lesioned animals don't seem to anticipate more than LMN cells: Goodridge and Taube (1997) report 32 ms, while the estimate for LMN anticipation from the same lab is 67 ms (Stackman and Taube 1998). However, the LMN estimate in Blair et al. (1998) is 39 ms, in which case when various delays are additionally taken into account, the PoS-lesioned ADN ATI may be compatible with offset connections from LMN. Additionally, ADN receives inputs from other areas, notably Rsp, which might affect form and ATI of the signal in ADN. The prediction would be that when all these inputs are severed, ADN should be more anticipatory than LMN. However, the experimental variability is ATI estimates is a problem in working out such details, especially when comparing data between labs.

Among models which have associated specific cell types to particular areas, a weakness of the coupled attractor models (Redish et al. 1996; Goodridge and Touretzky 2000) is that they rely on recurrent excitation, and that their layout is incompatible with the effects of PoS lesions on ADN tuning curves (Goodridge and Taube 1997). In the Song and Wang (2005) model, directionally tuned inhibitory (*HH'*) neurons are a critical ingredient; the only known plausible location for these would be in DTN, where only a small number of HD cells have been found. These do seem to fit the *HH'* pattern, although the role of the various types of AHV cells found in DTN (Sharp et al. 2001; Bassett and Taube 2001b) is unclear in this model, given that DTN also lacks recurrent connections and those cells thus are unlikely to provide AHV input to DTN HD cells. The LMN HD cells in this model are symmetric-AHV modulated, however, Stackman and Taube (1998) additionally report

asymmetrically-modulated HD cells (*HH'* cells) in LMN, which are not needed in the Song and Wang model.

3.3 Synthesis and unresolved issues

From reconciling the general "ring attractor" architecture with known anatomical constraints, the overall model that emerges is that a stable, coherent HD signal is generated by cross-inhibition in the loop between DTN and LMN, performing angular path integration in response to a vestibular-derived AHV input signal[11]. Anticipation in LMN may be generated by a combination of deformations due to cross-inhibition and anticipation already present in the input AHV signal. LMN projects the HD signal to ADN (with offset connections, which interact with PoS and possibly other inputs to produce the characteristic ADN tuning curve shapes), ADN to PoS, PoS to EC. Visual information is comes in to PoS and can be propagated up to DTN via the PoS-LMN-DTN pathway.

A number of details remain to be worked out in the modelling domain; nevertheless, the current state of the art highlights some issues that could be addressed experimentally. Questions related to the role of head direction cells for navigation and spatial behaviour are discussed in the next chapter.

My top 10 of open questions arising from modelling studies of the HD system is as follows:

- Why do hippocampus lesions affect HD cell stability in the dark? Specifically, is this because of an angular path integration deficit (which would be at odds with current models of such a process in the HD system) because of a pathological interaction with the visual input system, or something else? Since hippocampal signals presumably enter the HD system through PoS, comparisons with PoS-lesioned animals would be useful (for which ADN recording data already exists, but not recorded in darkness, Goodridge and Taube (1997).
- The role of some AHV-modulated HD cells, and some AHV-only cells is not understood in the current model of Song and Wang (2005): in particular, both types of DTN AHV cells and well as *HH'* cells in LMN don't appear to be needed. The AHV cells may be part of another system, and the LMN *HH'* cells may be responsible for driving offset connections to ADN.
- How are the failure of cues rotated in the presence of the rat to control HD PFDs, and the loss of cue control in repeatedly moved cues, to be understood? How do rats "decide" to use or ignore particular cues? Simulations of such scenarios using different learning rules and visual update mechanisms could help in exploring this issue; fine-

[11] A slight worry is that DTN HD cells seem relatively rare.

timescale reconstruction using ensemble recordings in rats with vestibular lesions (and in normal rats) would be helpful in constraining computational explorations.

- How are ADN tuning curve deformations consistent with observed anticipatory time intervals, in particular after PoS lesions? One possibility may be that after PoS lesions, ADN HD cells are in fact more anticipatory than LMN HD cells, due to offset connections from LMN to ADN. This would be consistent with simulation results (Goodridge and Touretzky 2000), although the exact ATIs predicted will also depend on various delay factors (see Chapter 8 for an exploration of such issues). Alternatively, ADN may be influenced by other HD areas such as Rsp. Do the proposed offset connections from LDN to ADN have any purpose if they are not part of the update mechanism or generate anticipation?
- What is the input signal in the angular path integration process? How close is this to the animal's actual AHV? This would allow us to distinguish sources of error (drift) in the HD system due to this signal and noisy attractors. It is also relevant to anticipation (see Chapter 7): specifically, how much anticipation in LMN is due to offset connections and deformation, and how much is due to the input signal?
- What are the factors underlying anticipation variability? The same HD cell recorded in the same environment for 16 minutes can yield ATIs 70 ms different between two sessions.
- How are the characteristics of HD cells in Rsp, LDN, and Str to be understood? The ATI reported for Rsp cells is close to that found in ADN has been interpreted as suggesting that Rsp activity may be generated independently. However, ATI variability may be a problem in a strong interpretation of this, and offset connections could "create" anticipation in an area whose activity is directly derived from a less anticipatory population of HD cells.
- What are the other cells in HD areas for, if only up to 40% of cells in PoS, and less in other areas, are HD cells? Comparisons of the effects of ADN and PoS lesions on hippocampal place cells suggest these cells (in PoS at least) may be involved in providing local view information to the hippocampus. Recording studies and appropriate analysis methods can address this.
- What is the role of HD cell firing modulation by the theta rhythm, active locomotion, and restraint?
- "Philosophical" questions, such as why there are so many HD areas, and whether anticipation serves any purpose.

Experimental confirmation of the ideas implemented in models of the HD system would be of interest, for instance, investigation into the circuit that generates and updates bump

states. Offset cross-inhibition between DTN and LMN is currently the most plausible proposal; this could be tested with specific pharmacological manipulations combined with recording e.g. by local injections of bicuculline or other GABA antagonists in LMN, where inputs from DTN are thought to form inhibitory synapses. In figuring out the precise circuitry of the angular path integration component of the system, what would really be useful is to find out which type of cell projects to which other type of cell. Do HD cells in one area project directly to HD cells in the next area? Do AHV cells in DTN project to HD cells in LMN? Questions of this type, requiring integration of functional and anatomical information, are extremely difficult to address experimentally, especially at the single cell level required in the case of the HD system. Multiple single-unit recording could potentially be a tool; in hippocampal recordings, it is sometimes possible to work out that two cells are connected by cross-correlating their spiking activity (Csicsvari et al. 1998). However, the odds of finding a connected pair will be likely be much lower when attempting to record from two different areas (like in the HD system), instead of from a single area containing interneurons.

Large-scale multi-unit recording could also contribute useful information to other open questions. Given a sufficient number of head-direction cells, appropriate analysis (e.g. fine-timescale reconstruction, Johnson et al. 2005) of the head direction signal under various conditions could reveal details of drift when still, error when moving, and corrections by external input. A quantification of the drift in the system is of interest from a theoretical perspective; a detailed examination of errors and updates on small timescales in response to specific movements and viewpoints would constrain models of the angular path integration circuit and its interaction with visual updates. Such data could also clarify tuning curve deformation and anticipation variability, specifically to what extent variability and conflicting data in those can be explained by external factors constant across cells (movement, behavioural state) and how much by differences between cells. Recordings in darkness and specific attention to the properties of non-HD cells would also be of interest.

A speculative approach would be to combine properties found in slices with those found extracellularly. In a slice preparation, it would be much more feasible to find connected pairs of cells between HD areas, of which the membrane properties and process morphology could then be studied in detail. Gold et al. (2006) show that on a hippocampal data set with simultaneous intracellular and extracellular recordings, features of the extracellularly recorded waveform correlate with the presence of specific membrane currents. In this way, it might be possible to identify different classes of cells in HD areas in slice (there are also other open questions which could be addressed in slice experiments, discussed in Chapter 8). For instance, Taube (1993) found two different neuron types recording from PoS in a slice preparation, the synaptic connectivity of which could be correlated with extracellular recordings if those allow separation of those same types.

A novel approach which has had some success in the place cell literature recently (e.g. Vazdarjanova and Guzowski 2004) is the use of immediate-early-gene (IEG) techniques, which rely on immuno-histochemical identification of activity-dependent gene expression, yielding individual cell resolution of recent activity at multiple time points (for a review, see Guzowski et al. 2005). Comparison of the activation patterns in HD areas during spatial behaviours with different sampling of the directional range (e.g. animal still vs. animal moving passively vs. running on linear track vs. running on circular track) could contribute some quantitative information on the relative numbers of cells likely to be involved in the encoding of angular velocity and direction; however, testing specific ideas in this way will require considerable ingenuity.

Chapter 4

Theories of navigation and the role of head direction information

Navigation, the "planning and execution of a goal-directed path" (Gallistel 1990), is an ability fundamental to the survival of many organisms, with many of those displaying remarkable proficiency: ants and bees can make a direct return ("beeline") to the home nest after long and tortuous outward paths (Collett and Collett 2002), while rats can learn to solve complex mazes under extreme sensory deprivation (Carr and Watson 1908). For humans, too, navigation is important, from finding one's way to work in the morning (especially if your usual route is blocked), to London taxi drivers whose work it is to find their way (Maguire et al. 2003) and marine or aerospace pilots who have to operate in cue-impoverished environments (Hutchins 1995; Gillingham and Previc 1996). Easily amenable to systematic behavioural study, navigation has been studied extensively, in rats specifically since the beginning of the 20th century. It has been of great interest, not just to the neuroethology community, but to neuroscience in general, to find out about how animals navigate; one reason for this is that many of the paradigms used to study other areas of neuroscience (e.g. learning and memory) often rely on tasks that require the animal to navigate (e.g. the Morris water maze, introduced in more detail below). Spatial tasks are a productive way of "asking animals questions" and the interpretation of such experiments will then involve assumptions about how animals are solving the task, i.e. how they are navigating. Insights from animal navigation have also been applied to navigating robots (Trullier et al. 1997), sometimes even with commercial success as in the case of robot vacuum cleaners (cited in Morris 2006).

However, the study of navigation does not need to be content with a mere supporting role, for at least two very good reasons. First, there is evidence that some navigation behaviours expressed by animals and humans require representations beyond simple stimulus-response

(Hull 1943) or other associative learning methods (Chamizo 2003). For instance, the ability to make a straight return to a home location after an outward path in a novel environment requires a specifically spatial representation of the direction of the home location[1]. Even if a sequence of landmarks were available that could be chained in a sequence by associative learning (as some computer models of navigation do successfully), such information would not be sufficient for a direct return path. Thus, studying navigation can provide insight in specifically spatial aspects of brain function which may not be accessible in other domains.

The second reason concerns the ubiquity or generality of space and its relationship to the brain. There is a realisation that the processing of continuous, temporally sequenced information, such as the encoding of trajectories in space, could be fundamental to, or at least similar to other brain functions, such as episodic memory[2]. This suggestion of a link between spatial representations and episodic memory originates from two classic observations: First, reports on patient H.M., who after bilateral hippocampal lesions could no longer remember new information (like the names of his caregivers, or what he had for breakfast in the morning) although he could learn some new skills (Scoville and Milner 1957; Corkin 1968)[3]. Second, the discovery of neurons tuned for place ("place cells", discussed in section 2.1) in the rodent hippocampus (O'Keefe and Dostrovsky 1971). These two findings inspired the influential *cognitive map* theory (O'Keefe and Nadel 1978) of the hippocampus, which contends that the hippocampus essentially stores maps of environments, "within which the items and events of an organism's experience are located and interrelated." (O'Keefe and Nadel, p. 1). In this framework (and its extensions and derivatives, notably Redish 1999), such maps can be used for navigation, but are also important for memory. Specifically, recent proposals have suggested that episodic memory recall may depend on the re-instantiation of the map or "context" where the original episode was encoded (Redish 1999; Burgess et al. 2001; Howard et al. 2005; Wills et al. 2005; Kentros 2006), which would also require recall of a reference direction provided by the head direction system (Burgess et al. 2001). Recording studies are starting to explore possible similarities in the way episodic and spatial memories are encoded (Buzsáki 2005; Dragoi and Buzsáki 2006). For instance, Dragoi and Buzsáki (2006), extending earlier work by Skaggs et al. (1996) and O'Keefe and Recce (1993), show that when a rat traverses a sequence of overlapping place fields, the relative locations of these fields are represented in precise temporal correlations of their firing during a single period of the theta rhythm (about 1/8th of a second). This "sequence compression" provides a way for plasticity mechanisms such as spike-timing dependent plasticity (which require firing patterns on very short timescales, Markram et al. 1997; Bi and Poo 1998) to bind together an episode

[1] The details of this ability, "path integration", and details on aspects of spatial representations are discussed in more detail later in this chapter.

[2] The recollection of events (Tulving 1972).

[3] Details of different types of memory and their anatomical and neural basis are beyond the scope of this chapter, see e.g. Cohen and Eichenbaum (1993) for an extensive review.

which actually occurred over a more extended period. Replay of such sequences, both during wakefulness and sleep (Skaggs and McNaughton 1996; Nádasdy et al. 1999; Foster and Wilson 2006) could serve to consolidate them to permanent memory, compatible with standard consolidation models of episodic memory (reviewed in Squire et al. 2004). As noted by Suzuki (2006), such indirect evidence is still some way from showing the neural correlate of episodic memory, but at least mechanisms such as these have some of the characteristics required. Interestingly, the co-localisation of spatial firing correlates and lesion effects on memory seen for the hippocampus in humans appears to extend to the head direction system (Aggleton and Brown 1999), although as is the case for place cells, it is not yet clear whether this link is the result of the loss of spatial firing cells specifically (Aggleton 2005). A recent study in head direction cells showed that they share at least some of the hippocampal dynamics implicated in sequence encoding (Yu et al. 2006), although difficulties in obtaining the large numbers of simultaneously recorded cells necessary for these types of analysis have precluded more detailed examination.

The above studies illustrate an important advantage of studying the neural basis of navigation. Because we understand the mathematics of space, i.e. how to quantify directions, locations the relationships between them, this provides a framework and a metric with which to interpret neural activity (Redish 1999). It allows us to note that place cells with nearby firing fields fire in particular temporal relationships, an effect not exhibited in cells with spatially distant fields. It allows us to distinguish a coherent representation, indicating a specific location, from ambiguous representations or random noise. In the case of the head direction system, it allows us to observe the amount of drift of the system and relate that to behavioural observations in the same spatial frame.

This chapter will first provide a general overview of different types of navigation, focusing on what representations are needed to learn and execute different strategies. Anticipating the experimental chapters that follow, particular emphasis will be placed on path integration and the role of the head direction system in navigation.

4.1 A taxonomy of navigation

What are the strategies available to an animal trying to get from A to B? Several general taxonomies of navigation have been proposed (O'Keefe and Nadel 1978; Schöne 1984; Gallistel 1990; Redish 1999), with the one provided here largely being an amalgam of these, with the addition of an attempted classification of different strategies based on what kinds of representations they require. Like previous taxonomies, the most obvious distinction is based on whether external information from the animal's environment is used. Even if no external information is used, information derived from the animal's own movement (e.g. vestibular) can still provide spatial information. External information is taken to

include everything that is included in the sensory input of an animal at a given time; this is conventionally referred to as "local view", even though it can include non-visual stimuli as well. Both "internal" and "external" navigation categories encompass a range of different specific strategies, from simple and inflexible (e.g. a fixed sequence of motor commands, or "praxic" navigation) to a complex, flexible interaction of subsystems allowing the animal to infer its own location relative to a goal from local view information and plan the shortest route to it ("locale" navigation).

An important point about classification of navigation is that separating out different strategies does not mean that animals will use one strategy exclusively on a journey from A to B: they are likely to switch flexibly between strategies and combine them even within a single journey. For instance, bees initially use path integration to get close to where there hive is, and then look for landmarks that indicate its precise location (Gallistel 1990). For rats, this is demonstrated in a study by Maaswinkel and Whishaw (1999), who trained blindfolded rats to fetch food from the centre of a circular table before returning to a starting location on the perimeter to eat. When the rat was in the fixed centre of the table, the experimenters rotated the rest of the table 90°. On the initial leg of their return trip (but already on the rotated part of the table), rats initially headed towards the original location of where there refuge had been, but as they approached they deviated to the refuge's new location, indicating a mid-journey change of strategy. A further notable point is that by definition, an essential ingredient of navigation is that the animal has access to some kind of representation of its goal. This can range from simply some way of recognising the goal location when it sees or otherwise senses it, to knowing its location on a "map". If an animal is lost, this can be because it does not know where it is, or because it does not know where the goal is, or because it does not care about finding the goal. How goals are encoded is addressed in several network and robot models of navigation (e.g. Redish and Touretzky 1998, Strösslin et al. 2005) and more recently also experimentally (Hok et al. 2005; see Poucet et al. 2004 for a review on goal encoding).

Returning to the taxonomy of navigation, within the broad categories of "internal" or "external" navigation, there are strategies of varying complexity, as noted above. In addition, at least at the extremes of this scale, some strategies must require a representation of space, while others could, at least in principle, be successfully implemented without any concept of space. Execution of a fixed motor program, for instance, does not need a spatial representation: it just needs a sequence of movements to be carried out. The planning of a shortcut, in contrast, probably requires a spatial representation[4], a map, perhaps. In many cases in between, what is required will depends on the exact implementation of the strategy. For instance, if the goal location is indicated by a cue, as in the cued Morris water maze, where the animal is released into a pool of opaque water with an invisible

[4]Under appropriate conditions, at least: not if the agent can see the goal.

escape platform underneath a cue[5], all the animal needs is to do is to orient to the cue and swim towards it. This could be achieved by a representation of egocentric bearing relative to the cue (Figure 2.1 on page 6), such that the animal can change its heading until it is heading straight for the cue (in addition to, of course, knowing that the cue in fact indicates the goal). Alternatively, orienting could potentially rely on local view recognition (template matching, in its simplest form, additional processing like size invariance could make the process more flexible): the animal could rotate on the spot until its view matched a representation of the cue, which would not be a truly spatial representation.

What, then, *does* constitute a spatial representation? Gallistel (1990) discusses a concept relevant to this question, that of *isomorphism*[6]. Applied to space, this means that a spatial representation (e.g. of place) must not merely have some arbitrary correspondence to space (e.g. different places being assigned a unique representation), but the representation must allow for operations (i.e. computations, transforms) performed on them, the outcome of which then again has some correspondence with actual space. For instance, an animal's ability to take a straight path to a home base after arbitrary outward paths in the absence of any cues must ultimately rely on a representational process that is isomorphic with vector addition (an operation which allows the "homing vector" to be updated as the animal moves). Note that this does not make any claims about how the necessary processing might be implemented, analogous to the computational level of Marr (1982)'s classic "levels of description". Spatial representations can vary from simple to complex, in terms of what kinds of operations they allow; if an animal was unable to do vector addition but could do scalar addition, it could estimate the exact location of its home base as long as it walked in a straight line.

A critical distinction in the navigation domain is that between *egocentric* and *allocentric* spatial representations. Egocentric representations of the world depend on the local view of the animal, as illustrated in Figure 2.1. For instance, as an animal changes its head direction, the egocentric bearing of a given object will change with it. In contrast, allocentric representations are relative to a constant reference direction, that does not depend on the location or orientation of the animal. Allocentric encoding of an array of objects is potentially more efficient than storing all pairwise relations between them ($O(n)$ against $O(n^2)$), and allocentric representations allow inferences to be drawn that are unavailable or at best extremely inefficient to achieve with egocentric methods (McNaughton et al. 1991).

If the goal is to ask what animals must be representing in order to do particular behaviours, we have to be mindful of the fact that how animals ultimately actually navigate in specific

[5] Such as a cardboard toilet roll covered in alternating strips of black and white electrical tape, hanging from some flexible steel wire, in use in the Morris lab until recently.

[6] In fact, Gallistel's term is *functional isomorphism*, with the "functional" indicating that the animal uses the isomorphic representation for behaviour rather than it arising as an unused correlate of it.

cases requires carefully controlled experiments to distinguish between strategies. However, if this is done correctly, knowing what animals must be representing can be a powerful guiding principle in search of the neural basis of the behaviour those representations support.

With that in mind, a possible taxonomy of navigation is the following:

Random navigation. When an animal does not know where it is, and can sense nothing that provides any information (which can be either spatial information that constrains the animal's location, or something that triggers an association), it will have to move randomly and hope the situation improves (Redish 1999). Smart animals will combine this with other strategies to ensure efficient exploration of space, i.e. without going down the same blind alley twice. This situation commonly occurs in experiments when an animal is introduced to a novel environment it knows nothing about. It can also occur when the animal knows where it is, but not where the goal is, as in some water maze tasks.

"External egocentric" navigation. This is navigation based on external cues which have a known relationship to the goal which does not require allocentric knowledge to exploit; in some cases, it requires no spatial knowledge at all. In either case, the cue and the goal of course have some spatial relationship in the world, but this does not mean the animal necessarily needs spatial knowledge to take advantage of the cue. For instance, the following of walls and odour trails, and well as gradient navigation, are instances of this (called "guidances" by O'Keefe and Nadel). This behaviour is essentially a stimulus-response strategy, and no spatial representations are needed to explain it.

A slightly more complex variant of this class of navigational strategy is if the animal can see the goal itself, or something trivially related to the goal, e.g. the beacon in the cued version of the Morris water maze. In this case, all the animal needs to do is orient towards the cue and move towards it. Navigating towards such directly perceptible cues or beacons is known as "taxon navigation" (O'Keefe and Nadel 1978; Schöne 1984; Redish 1999). Advanced versions of this strategy would involve chaining together sequences of beacons ("route navigation" in O'Keefe and Nadel): walk to the church, look for the red house, walk there, spot the oak tree, and so on. Instead of locomoting *towards* something, it is also possible for a cue to point the way, e.g. walk in the direction the bus took off in. Taxon strategies can be learned using simple stimulus-response models (Hull 1943) and temporal-difference learning algorithms to bridge temporal gaps (Sutton and Barto 1998).

Does orienting towards a stimulus require a spatial representation? As mentioned above, it it possible to imagine a strategy that is purely based on local view: if the cue or its surroundings have some asymmetry, an animal might learn how the cue looks when looking directly at it. Position on the retina might also be sufficient (given a constant eye and head position relative to the body). Certainly, a representation of egocentric bearing relative to

the cue would be useful for this ability. Interestingly, this is exactly what is provided by the superior colliculus (Droulez and Berthoz 1991; Trappenberg 2002). Animals appear to be using this information for orienting: lesions of the superior colliculus do not impair visual discrimination, but prevent orientation towards stimuli (Dean and Redgrave 1984; Carman and Schneider 1992). There is, however, some indication that animals with such lesions can still orient towards stimuli (Midgley and Tees 1986; Durmer and Rosenquist 2001), perhaps with a strategy like the one outlined above. Parietal cortex is also thought to be involved in orienting movements (reviewed in Redish 1999).

Dorsal striatum is also thought to be involved in taxon navigation, as indicated by lesion studies of navigation to cued vs. hidden goals. For instance, rats with dorsal striatum lesions can learn a water maze reference memory task (platform always in the same place) as well as control animals, but are impaired on a cued version of the task when the platform is moved to a new location on every trial (Packard and McGaugh 1992). So, they appear to be able to go to an allocentrically defined place, but not to use taxon navigation to go to a moving goal.

"Internal egocentric" navigation. This is a "praxic" strategy, involving the execution of fixed motor commands. If the animal is always released at the same location and in the same orientation, it can simply execute a constant sequence of movements that lead it to the platform. Such strategies do not require spatial representations. Of course, a fixed sequence of movements corresponds to some displacement in space, but such a sequence doesn't allow, for instance, for the return to a starting point after an arbitrary sequence of movements (path integration, discussed below). Early experiments using complex mazes (e.g. Watson 1907) suggest that rats were using praxic strategies to solve them: when a corridor was shortened by the experimenters, rats ran full tilt into the wall. Some more recently popular experimental paradigms, such as T-maze alternation, can also be solved using a praxic strategy.

"Internal allocentric" navigation. This type of navigation relies on a mapping of praxic commands to an allocentric spatial representation, allowing the animal to make a direct return to a home base after a complex outward path in the absence of cues, an ability referred to as *path integration*, discussed in detail in the next section. Returning by following an odour trail back, or navigating to a cue indicating the home base would be taxon navigation, but behavioural experiments have provided convincing evidence that rodents are able to do this without using external cues. As mentioned above, this ability requires some mechanism of continuously updating at least one's directional heading (a "homing vector") relative to the home base. This is an allocentric representation which does not need to be related to any external cues, unlike the next class of strategies; the reference point or direction can in principle be set to any location the animal desires.

Animals are able to return to a home base even on their first experience in an environment, indicating that no environment-specific representations need to be learned (Wallace and Whishaw 2003). Instead, once a mapping of movements to displacement and rotation is learned (which according to a proposal by Hahnloser (2003) could work based on visual supervision and local learning rules), it appears to be generally applicable.

"External allocentric" navigation. This would be a navigational strategy that relies on allocentric spatial representations, built with the use of external cues and/or used to navigate in combination with cues[7]. For instance, O'Keefe and Nadel (1978) suggest that animals automatically build an allocentric representation ("cognitive map") of environments, encoding the locations of objects and relevant places and their relationships in a spatial framework. A key feature of such a spatial representation is that it is extremely flexible: for instance, it could support the planning of arbitrary routes from the animal's current location to a goal in the face of changes or obstacles (given an appropriate planning mechanism). Because it is independent of the animal's (egocentric) viewpoint, the animal can efficiently determine its position in the environment at any time (self-localise, given sufficient external cues). O'Keefe and Nadel called navigation based on such maps "locale navigation", and proposed the hippocampus as its anatomical instantiation[8]. Indeed, the theory has received a lot of support from the combination of the effects of hippocampal lesions, which impair performance on most versions of allocentric place navigation tasks, and the presence of place cells in the hippocampus. However, this is also not direct evidence that rats use maps to navigate (place cells might simply be a spatial reflection of a more general encoding mechanism, e.g. Eichenbaum et al. 1999). For the hippocampus in particular, it is clear that lesions of it impair more than locale navigation (comprehensively reviewed in Andersen et al. 2006). This might be because its spatial abilities, in particular the ability to select the correct map, are fundamental to many non-navigational behaviours (Redish 1999) but it complicates the interpretation of lesion experiments with respect to what we can conclude about navigation.

Do rats use map-like constructs for navigation? As noted above in the case of taxon navigation, in many cases, it is not unambiguously clear whether particular strategies that make use of external cues rely on spatial representations or not. However, a large body of evidence across different tasks makes it very likely and commonly accepted that rats do build and use allocentric spatial representations of the environment. Whether such representations take the form of a *cognitive map* (Tolman 1948; O'Keefe and Nadel 1978; Gallistel 1990; Redish 1999; Andersen et al. 2006) or consist of simpler and more

[7] The fact that path integration probably also relies on some learning process requiring external (visual) information is different because that happens only once for all environments, whereas maps of environments have to be learned for each new environment.

[8] The issue of what aspects of spatial tasks the hippocampus is and not required for is beyond the scope of this thesis; suffice it to say that most experiments have supported the notion that the hippocampus is needed for allocentric navigation tasks. Extended reviews can be found in Redish (1999) and Andersen et al. (2006).

elementary mechanisms remains the subject of debate (reviewed in Morris 2006); here I will focus on the behavioural evidence that rats build and use spatial representations for navigation, without getting into the details of whether spatial learning is configural or elemental, associative or non-associative (reviewed in Mackintosh 2002 and associated special journal issue).

The original experiments that inspired Tolman's proposal of "cognitive maps in rats and men" (Tolman 1948), and their refinements and variations added over the years, remain among the most compelling suggestions that rats use allocentric representations of environments to navigate. The first piece of evidence is that rats of rats planning shortcuts through previously unexplored areas (Tolman et al. 1946a). In terms of locale navigation, this would require a representation of where the rat wants to go relative to its current location, and some sort of spatial computation to determine the direct route between the two points, precisely the sort of computation that could be efficiently implemented using a map. The alternative explanation that this behaviour is actually achieved by using landmarks or features of the environment associated with relevant locations, however, cannot be ruled out. Indeed, experiments in humans suggest that humans only use shortcuts based on landmarks (Foo et al. 2005), which could be consistent with several later failures to replicate the Tolman et al. result convincingly in rodents (Muir and Taube 2004). In principle, shortcut behaviour could also be achieved by path integration, if the reference point (goal) of the path integrator is set appropriately.

The second category of results that nicely fits the cognitive map theory is a broad range of evidence that rats can quickly learn to navigate to specific places not obviously associated with any particular cue. In Tolman et al. (1946b), rats learned to navigate to a single rewarded arm of a plus maze, regardless of which arm the rats were starting from[9]. Using the radial arm maze (Olton and Samuelson 1976) and the Morris water maze (Morris 1981), rats can be trained on conceptually similar tasks, with the water maze in particular offering additional control over the cues available to the rat, as well as high motivation levels. The classic task that suggests animals have access to allocentric spatial representations of their environment is the one-trial hidden platform delayed-matching-to-place task in the Morris water maze (Steele and Morris 1999). In this task, the animal is released at some point in a featureless, opaque pool which has a hidden escape platform somewhere. The room the pool is in contains various fixed cues and landmarks. The first time the animal is released into the pool it has no information about where the platform is and must use random navigation to find it (even though it might know where it is in the room, which is will typically have been pre-exposed to). Then after some intertrial interval, the animal is released from a different place in the pool, and the main result is that they can reliably

[9]Thus excluding a praxic strategy, but they could theoretically be using an elaborate taxon strategy, see below.

swim to the platform[10].

How does the animal know where the platform is? One possibility is that animals know at least the platform's allocentric bearing and distance relative to one or more landmarks, perhaps even the landmark's position on a cognitive map; these possibilities would require the animal has access to allocentric direction and/or place as provided by the HD and place systems. These are all spatial representations. Alternatively, it is possible to imagine a non-spatial strategy, such as trying to match specific properties of local view (Leonard and McNaughton 1990), but this would likely be inefficient and appears inconsistent with rats' apparent ability to swim directly to the platform at very different approach angles. Nevertheless, alternatives along these lines has not been put to rest entirely; there are studies suggesting that the ability to find the platform when starting from a new location depends on the rat having explored that part of the pool previously (Sutherland et al. 1987; Whishaw 1991), and the learning theory community continues to explore such associative rather than "mapping" strategies (reviewed in Chamizo 2003). It is also clear that with extended (or specialised) training, rats can learn allocentric place tasks without a hippocampus (Morris et al. 1990; Day et al. 1999).

A final observation that was original to Tolman (1948)'s cognitive map theory relates to latent learning (learning without any explicit reinforcement). Tolman exposed rats which were neither hungry nor thirsty to a Y-maze with food at the end of one arm and water at the end of the other. Animals were then either made hungry or thirsty and returned to the maze; hungry animals chose the food arm, while thirsty animals chose the water arm. However, this is more a statement about the automatic recording of information rather than about the nature of the representations used.

A relatively recent observation is that rats notice when an object has moved or is absent in relation to other objects (Save et al. 1992a, Save et al. 1992b), as evidenced by their tendency to explore the moved object or the place of the absent object more. Morris (2006) interprets this as evidence as consistent with the cognitive map theory. The evidence is certainly suggestive, but again it is possible to imagine associative strategies that could detect such changes, as discussed above, although they would seem likely to be inefficient, both in storage and use.

Perhaps the most convincing evidence of external navigation requiring a true allocentric (directional) representation involves experiments where the animal has to search for reward at a fixed bearing relative to a single circularly symmetric landmark (Collett et al. 1986; Biegler and Morris 1996; Roberts and Pearce 1998). Critically, because animals learn to search at the correct location even when the landmark is moved from trial to trial, this cannot be explained by associative learning of local view information. Thus, it appears to

[10] Or to the location where the platform used to be, in the case of a probe trial, which rules out that animals can sense the platform by removing it and recording where animals search for it.

at least require an allocentric head direction signal, or some uncontrolled directional cue like a temperature gradient. The former possibility is supported by a lesion study of the head direction system (Wilton et al. 2001), discussed in section 4.3, as well as observations that disorientation of the rat prior to the start of a trial causes a disruption in performance (Biegler and Morris, personal communication, cited in Redish 1999). It has been argued that rats do not appear to use locale navigation on this task, as hippocampal lesions do not affect performance (Pearce et al. 1998). This is another example of that it can be difficult to distinguish a cognitive mapping strategy from a "heading vector strategy" sufficient for this particular task without very specific control experiments.

Thus, although locale navigation or "cognitive maps" are consistent with a large body of evidence (a lot of it not discussed here), direct unambiguous evidence that rats use such representations to navigate is lacking. This does not mean that it is not the theory most consistent with the data (I believe it is, despite its problems); it just means that we do not know for sure whether classic locale navigation behaviours, such as water maze tasks really depend on cognitive maps. For the purposes of this thesis, it does seem the case that rats at least use allocentric spatial representations, both in path integration tasks and navigating to places indicated by landmarks. Also, even if we assume that rats can use maps, this does not imply that when they lose this ability (e.g. by lesions of the hippocampus of the head direction system) that no alternative strategies are available. In an elegant demonstration of this "multiple navigation systems" idea, Packard and McGaugh (1996) found that as training on a T-maze task progressed, rats switched from a hippocampal-dependent place strategy to a dorsal striatum (caudate)-dependent response strategy. Similar results have been found in related studies (e.g. McDonald and White 1994; Yin and Knowlton 2004), suggesting that there are multiple independent systems with different characteristics that can control behaviour, with dorsal striatum thought to be involved in slowly learned, "habitual" behaviours, while hippocampal-dependent behaviour tends to be learned quickly and flexibly.

Would locale navigation, in principle, require a head direction signal? The building of allocentric maps probably does, because it requires the integration of information across different viewpoints into a single framework. More generally, the idea that path integration (which requires a directional signal) lies at the basis of cognitive mapping has been proposed theoretically (O'Keefe and Nadel 1978; Gallistel 1990; McNaughton et al. 1996; McNaughton et al. 2006) and is supported by experiments (Biegler and Morris 1993; Knierim et al. 1995) and simulations (Samsonovich and McNaughton 1997; Foster et al. 2000). Does using a map once it is built require a HD signal? A number of proposals suggest that this need not necessasrily be the case. For instance, simulations by Foster et al. (2000) show that "chains" of place cells leading to goals can be learned by a standard temporal difference learning algorithm. Alternatively, a population of goal cells, located

downstream of a place map and receiving strong input when the rat receives reward, could use one-shot Hebbian learning to associate places with rewards. Generic methods such as gradient ascent (on the degree of overlap between the stored goal representation and the animal's location) could then be used to find the goal (Burgess and O'Keefe 1996). Such proposals are consistent with the observation that lesions of the HD system typically lead to very mild deficits on allocentric navigation tasks compared to hippocampal lesions (discussed below), although as mentioned above, this could be due to other hippocampal contributions beyond mapping. However, it might be noted that these navigation schemes rely on the map being consistently aligned in the encoding (when the rat received reward) and retrieval (when the rat decides to navigate towards the previously encountered reward site) phases; that is to say, the same place cells need to be active in the same place. Combined recording and lesion studies suggest that correct map alignment might be mediated by the HD system (section 4.3).

Returning to a general perspective, it would appear that the only tasks where we are relatively sure an allocentric head direction signal is important is path integration in the absence of any landmarks, and navigation to a fixed place relative to a moving, symmetric landmark. If our goal is to investigate the contribution of the head direction system to navigation, this might be a good place to start, and indeed this is the approach taken in the experimental section of this thesis. Section 4.2, below, will review the path integration literature in detail, while section 4.3 discusses the effects of lesions of the HD system in general.

Disorientation

For some of the above strategies, it doesn't actually matter where A (the current location) is when you are trying to get from A to B (the goal), e.g. if you can see B. However, other strategies, like path integration and locale navigation, require some representation of the relationship between A and B. As mentioned earlier, navigation errors then can come from an incorrect representation of the goal, or an incorrect representation of current location (or both). The last problem is usually referred to as *spatial disorientation* (Clark and Graybiel 1955). In the human aviation literature, three types of disorientation have been distinguished (Gillingham and Previc 1996): Type I disorientation refers to a mismatch between the agent's represented location A' and the actual location A without the agent being aware of this, i.e. you think you are somewhere else than where you actually are. Type II disorientation refers to the case where the agent has no sufficiently good representation of current location but is *aware* of this, while Type III disorientation is the case where the subject is physically incapacitated from having a good current location representation, e.g. by continued fast rotation causing dizziness. These distinctions are shown in Figure 4.1.

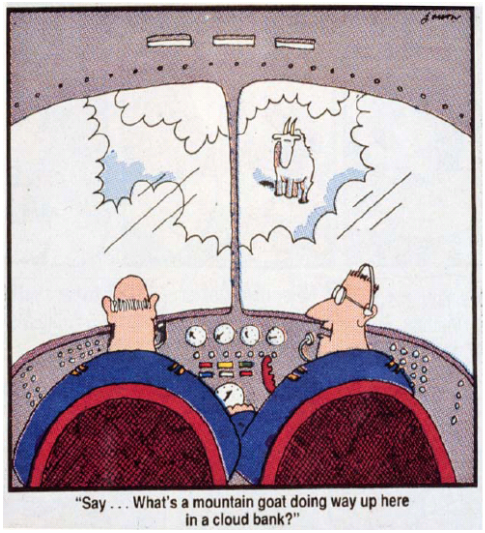

Figure 4.1: Spatial disorientation. If these Type I disoriented pilots are able to draw the correct conclusion from the evidence in front of them, they will become Type II disoriented (perhaps even un-disoriented with appropriate navigational aids or external cues), hopefully in time to avoid disaster (an extreme case of Type III disorientation). (Copyright Gary Larson / The Far Side)

4.2 Path integration

In the most literal sense, path integration is the maintenance of a representation of one's position relative to some point based on small sections of "path" taken. Mathematically, it involves integrating velocity (i.e. directed speed, v at angle θ) over some small time interval dt and adding the result to a running estimate of position (x, y). In two dimensions, mathematically ideal path integration corresponds to

$$\frac{dx}{dt} = v\cos\theta, \quad \frac{dy}{dt} = v\sin\theta \tag{4.1}$$

A key point is that when the term "path integration" is used in the navigation domain, it refers to this integration process happening based on internal cues only, i.e. without reference to the external world. This process is sometimes also called "dead reckoning" (from deduced, or *ded* reckoning, according to Bowditch 1977), and is still used in some marine navigation settings (Hutchins 1995). Confusingly, in the animal navigation literature, the term path integration is also used to mean animals' ability to return to a home site without using external cues, i.e. referring to a behaviour relying on path integration rather than the process underlying it. *Angular* path integration is a special case which just tracks allocentric bearing and not position.

The first documented suggestion that animals might be capable of using a process that amounts to path integration to navigate seems to be a discussion in *Nature* between Charles

Darwin and Alfred Wallace in 1873 (cited in Redish 1999), where Wallace suggested animals find their way back to a home site using sequences of smells, while Darwin argued they must be using path integration. For rodents specifically, some early experiments prompted investigators to speculate that rats appeared to possess an internal "sense of direction". For instance, Watson (1907) reports that rats can run a complex ("Hampton Court") maze apparently without touching the walls, running into the walls when a particular arm was shortened (Carr and Watson 1908), suggesting that animals may be using path integration[11]. In the classic "sunburst maze" experiment in Tolman (1948), rats were trained to find reward at a location only accessible through a non-direct route of a single open maze arm. When this maze arm was closed off and replaced with several possible alternative arms, rats chose the arm leading directly to the goal. A different experiment was carried out by Douglas (1966), who wanted to find out how rats were able to alternate arm choice on a T-maze, a spontaneous behaviour. When alternate trials were given on separate but similar T-mazes in different rooms, Douglas found that when the mazes were oriented the same way, alternation remained intact, but when the mazes were not parallel, performance dropped to chance levels. This prompted Douglas to suggest that rats were not simply making egocentric choices; instead, they must somehow navigate to a place or to a direction.

These early experiments were not explicitly designed to test path integration, and the lack of appropriate controls precludes a strong interpretation of evidence for path integration (e.g. in the Tolman experiment, the goal was also indicated by a light). Meanwhile, Barlow (1964) suggested that animals may be able to path integrate using vestibular information as the source of the update signal, but it was not until Mittelstaedt and Mittelstaedt (1980) that this idea was tested directly in rodents[12]. Mittelstaedt and Mittelstaedt (1980) hid the pups of female desert mice away from the nest (located on the edge of a circular environment), on a central platform that could be rotated independently of the rest of the environment. The mother would search for her pups and, once found, make a direct return to the nest. Critically, when the platform was rotated slowly (below the vestibular threshold), the mother returned to a location matching the rotation. This indicates she was not using olfactory or other external cues on the non-rotated part of the apparatus to plot her return, although the possibility that she may have been using a cue on the rotated platform has not been explicitly ruled out. When the central platform with the animal was rotated above the vestibular threshold, she was able to compensate for this rotation, suggesting that vestibular information is critical to the animal's homing performance. Later experiments showed that rodents (hamsters, in this experiment) could also home to a starting location after a passive outward journey (Etienne et al. 1986), further supporting the idea that path integration is based on vestibular information.

[11] Although they could in principle have been using motor programs instead.

[12] for humans and dogs, there were some experiments from the golden age of cybernetics, reviewed in Beritashvili 1965.

More recently, path integration has also been shown in rats. In a series of experiments using a large circular table, Whishaw and colleagues similarly showed that rats were able to make straight returns to a home site. Early experiments included controls showing that rats could do this even when blindfolded or when the apparatus (not including the rat) was rotated (Whishaw and Tomie 1997; Whishaw and Maaswinkel 1998; Maaswinkel et al. 1999; Whishaw et al. 2001). Although these do not explicitly control for the possibility that rats were using some distal (extramaze) cues to guide their returns (e.g. by rotating the rat as in the Mittelstaedt and Mittelstaedt experiment), observing what happens when rats are started rats from novel location in light provides some indirect evidence. In light, rats return to their old location; in darkness, rats return to the new location, indicating that if cues are available to guide rats to the old location, they use them, but in darkness, these do not appear to be available (Whishaw and Tomie 1997). Further experiments showed that rats could also home accurately during their initial experience in an environment, and that return journeys were "temporally paced", i.e. that rats reached maximum velocity about halfway on the way back, and did not "bump into" the home base (Wallace and Whishaw 2003). Alyan and McNaughton (1999) used a similar homing task on a circular table, in addition to a task similar to the Tolman sunburst maze, obtaining good path integration performance (but see the discussion below on the effect of hippocampal lesions).

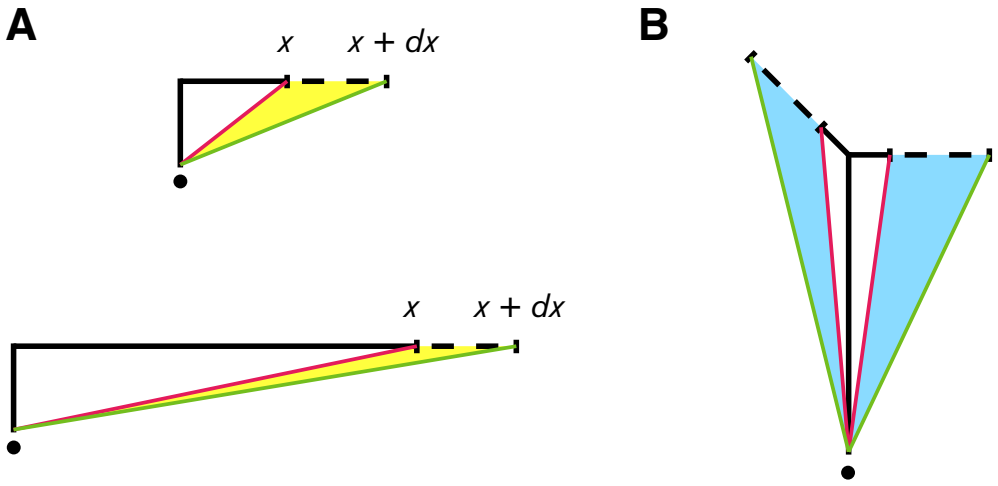

Figure 4.2: The problem of path integration. **A**: When moving the same distance dx in the same direction, the bearing change of a home location (black dot) depends on position relative to the home location. It is large in the top example (close to home) and small in the bottom example (far from home). **B**: The home bearing change also depends on heading direction. Thus, to maintain an accurate representation of the home direction requires a representation of heading direction and distance to home.

What is required for successful path integration (in the sense of the ability to return to some starting point)? In principle, if the goal can be recognised (i.e. a representation of the distance to the goal is not necessary[13]) storing (angular) bearing to the goal, a "homing

[13] Although this will become problematic when the goal is missed.

vector", is sufficient. However, as illustrated in Figure 4.2 on the preceding page, updating this vector when moving requires knowledge of the distance to the goal and current heading direction. The homing vector can be stored allocentrically (such that it is independent of which way the rat is facing) or egocentrically (relative to which way it is facing), but in both cases, updating the homing vector requires a representation of the rat's current heading (Benhamou and Séguinot 1995), as provided by the head direction system. It is notable that strictly speaking, the head direction system does not actually provide heading direction as such; rats can and sometimes do move in ways other than the way its head is pointing, it is not known whether path integration processes take this into account. However, path integration doesn't have to be perfect (as in equation 4.1) in order to be useful, and various "weaker" forms of can be imagined, perhaps in combination with other strategies (e.g. taxon navigation using odour trails or familiar landmarks when getting close to the goal). Indeed, in a study of whether golden hamsters did mathematically perfect path integration, Séguinot et al. (1993) found systematic path integration errors which depended on the outward path taken. One reason for this may be to increase the chance that a returning animal finds its own outward odour trail by returning at an angle that is too sharp rather than too shallow (Séguinot et al. 1998). For some simple situations, "full" path integration is not necessary, like for the task used in Chapters 5 and 6, where rats fetch food from the centre of a circular environment.

Anatomical basis

The place correlates of the hippocampus provide a natural possibility for the anatomical instantiation of the path integrator (McNaughton et al. 1996). An alternative proposal (Redish and Touretzky 1997) proposed the path integrator resides in the subiculum-medial entorhinal cortex loop, external to the hippocampus. Early experiments of the Whishaw group showed that fimbria-fornix lesions impaired path integration (Whishaw and Tomie 1997; Whishaw and Maaswinkel 1998), which they interpreted as evidence for the involvement of the hippocampal formation in path integration. However, as noted by Alyan and McNaughton (1999), fornix transections also disconnect the head direction system from the hippocampal formation (the ADN-PoS pathway) so leave open the possibility that the hippocampus proper (the dentate gyrus and CA subfields) is not needed for path integration. Investigating this possibility, Alyan and McNaughton (1999) found that hippocampal lesions did not impair path integration on the two tasks they examined, while the Whishaw group, now also doing hippocampal lesions, found a clear impairment (Maaswinkel et al. 1999; Wallace and Whishaw 2003). The reasons for this discrepancy have not been resolved; in principle, it is possible that animals are not actually path integrating in the tasks in the Alyan and McNaughton study, or that the impairment observed in the Whishaw studies is not due to a path integration deficit, but this would

need to be clarified with further study. It is worth noting that in the blindfolded, arena-rotated task in Maaswinkel et al. (1999), lesioned animals still had a significant directional preference, raising the possibility that on a different task with lower control performance levels no lesion effect might be discernible.

However, in support of the Whishaw group result that path integration depends on the hippocampus proper, recordings of HD cells indicate that they are unstable in the dark after hippocampal lesions (Golob and Taube 1999). As noted by Sargolini et al. (2006), the presence of place, direction, and velocity information in the firing of medial entorhinal (MEC) cells would in principle be sufficient for path integration. At present, it is not clear whether these cells depend on an intact hippocampus to generate these firing patterns; another possibility is that this information is required to pass through the hippocampus in order to be used for navigation. Lesions of the MEC impair spatial memory and acquisition of a water maze task requiring allocentric information (Steffenach et al. 2005), but the exact relationship between MEC and the hippocampus in spatial memory remains to be determined.

Remarkably, the role of the head direction system in path integration has only been addressed recently (Frohardt et al. 2006). Similar to previous path integration experiments, rats were trained to forage for food hidden in one of several wells on a central platform, returning to a fixed starting location which was not visually distinguishable from other locations. Two types of testing trials were run: one where rats were blindfolded (and presumably using path integration) and one where rats had full view of the environment (a large white cue card on the curtains surrounding the apparatus). Frohardt et al. (2006) then lesioned DTN in one group of animals, and ADN in another. Interestingly, for both lesion groups, they found an impairment in homing performance, but this was the case equally for the visual and blindfolded versions on the task. Thus, although they found evidence for the involvement of these areas in navigation, this effect was not specific to path integration. In their visual task, it is possible that the only salient cue containing directional information is a cue card on the curtain surrounding the apparatus, such that rats were not able to use a simple taxon navigation strategy (i.e. their cued task may have required an allocentric strategy). If this is the case, it is not so surprising that rats were also impaired on the visual task; it would have been informative to have a control task which both lesion groups were able to do well in order to aid interpretation of these results. As it is, there is no evidence that the observed deficits are in fact navigational and not mnemonic or even more nonspecific. A further interesting finding is that the performance of the DTN-lesioned animals was much worse than that of the ADN-lesioned group. This suggests that there is a way for information upstream from ADN to be used for navigation, although this need not necessarily be the HD signal.

Lesions of the vestibular system impair path integration (Wallace et al. 2002); however,

this doesn't distinguish between whether that is due to loss of coherent place cell activity (Stackman et al. 2002; Russell et al. 2003), head direction cell activity (Stackman and Taube 1997), or both.

4.3 The role of the head direction system in navigation

Apart from the path integration experiments discussed above, there are a number of other behavioural experiments which provide evidence that rodents have access to an allothetic directional signal. As discussed in section 4.1, gerbils (Collett et al. 1986) and rats (Roberts and Pearce 1998) can learn to search at a constant allocentric bearing relative to a single cylindrical landmark. This could be achieved by using some other uncontrolled landmark as a reference, but the fact that animals don't appear to be able to do this when they are disoriented prior to the task (Biegler and Morris, personal communication, cited in Redish 1999) suggests they rely on a directional signal.

Lesions and behaviour

Apart from the path integration experiment discussed in the preceding section, there are a number of studies which have looked at the more general effects of lesions of limbic areas containing head direction cells. Several of these studies did not selectively lesion the HD-cell-containing nucleus, but would damage all anterior thalamic nuclei (ATN, consisting of the anteroventral (AV), anteromedial (AM), and anterodorsal (AD) nuclei, with only the latter containing HD cells) or the all mammillary bodies (MB, of which only the lateral nuclei contain HD cells). As noted by Aggleton (2005), a null result from such studies (i.e. that the animal is still able to do something) is useful in that it tells us HD cells in that area are not needed for that task (assuming there was no sparing in the HD area). ATN lesions do not impair an animal's ability to turn left or right depending on the identity of a visually presented cue, i.e. egocentric conditional discrimination (Sziklas and Petrides 2004). ATN lesions also leave an animal's ability to always turn the same way on a T-maze intact (Aggleton et al. 1996; Warburton et al. 1997), suggesting that the ATN are not required for egocentric spatial decisions. For MB lesions, a similar result is obtained, that egocentric discrimination tasks appear unaffected (Aggleton et al. 1991; Sziklas and Petrides 2000).

Although a positive result of such "omnibus" lesions (i.e. a lesion group impairment) leaves open the contribution of HD cells versus other, non-HD areas and cells, lesions of ATN, and MB consistently impair performance on a variety of spatial tasks. MB lesions result in anterograde deficits on T-maze alternation (Rosenstock et al. 1977; Aggleton et al. 1990; Aggleton et al. 1995), reference and working memory tasks in the Morris water maze (Sutherland and Rodriguez 1989; Santín et al. 1999; Vann and Aggleton 2003) and delayed

non-matching to place (Saravis et al. 1990). Further studies supported the idea that these deficits appear to be specific to tasks requiring allocentric processing. For instance, Neave et al. (1997) found that MB-lesioned animals were much slower than controls in learning a plus-maze task where they were rewarded for going to the same location regardless of where they were started from, but they were unimpaired in a version where they merely always had to turn the same way. Similarly, Vann and Aggleton (2003) found that MB-lesioned animals did not use an allocentric strategy to solve a radial arm task (as control animals did) but instead relied on local maze cues, as distinguished by rotating the maze relative to the room.

For ATN lesions, the results are broadly similar: anterograde deficits have been found on T-maze alternation (Aggleton et al. 1995; Aggleton et al. 1996; Warburton et al. 1997; Warburton et al. 1999), reference memory and working memory tasks in the water maze (Sutherland and Rodriguez 1989; Warburton and Aggleton 1999; van Groen et al. 2002a) and radial arm maze (Byatt and Dalrymple-Alford 1996). Comparisons of allocentric and egocentric task variations indicate that these deficits are specific to allocentric tasks. For instance, Sziklas and Petrides (1999) found that ATN-lesioned rats were impaired on a conditional object-in-place task (reward given only if a particular object appeared in a particular place), while they could learn to turn left or right in response to a particular object as well as controls. Similarly, ATN-lesioned animals were impaired in an allocentric, but not the egocentric T-maze alternation task (Warburton et al. 1997)[14]. Thus, the effects of ATN lesions, like that of MB lesions, appear to be specific to allocentric spatial processing.

Unlike the case of MB lesions, however, lesions of specific nuclei within the ATN have also been studied. Remarkably, the different sub-nuclei (AD, AM and AV) appear to be making a complementary, non-redundant contribution. A number of studies using T-maze alternation, a radial arm maze and the water maze respectively found that even though lesions of AD (usually combined with AV) resulted in a (mild) deficit, so did lesions of AM, with the greatest deficits seen in combined lesions (Aggleton et al. 1996; Byatt and Dalrymple-Alford 1996; van Groen et al. 2002a). This suggests that head direction information does not play a role of special importance (over that of adjacent areas) in these tasks, with their contributions to task performance similar and non-redundant (additive). If any impairments are due to loss of the HD signal at all, it seems unlikely that this would result in a deficit of similar magnitude when compared to lesions of adjacent areas. A possible conclusion with respect to the HD system appears to be that these tasks (and in particular, including possible compensatory strategies after surgery) do not require a head direction signal, even though they explicitly rely on allocentric cues. In support of this interpretation, Aggleton et al. (1996) found that animals with AD/AV lesions are still able

[14] Surprisingly, their impairment was worse than that of a fornix-lesioned group, suggesting the possibility that not all of the output from the ATN goes through the hippocampal formation, or the availability of different compensatory strategies.

to learn an allocentric T-maze alternation task; initial, transient deficits might then reflect the loss of the HD signal.

Two lesion studies which have targeted specific HD nuclei (AD/LD: Wilton et al. 2001, LMN: Vann 2005) provide additional evidence for the idea that the HD signal is not necessary for performance on a range of allocentric tasks. Vann (2005) found that LMN-lesioned animals were only transiently impaired on a water maze working memory task, and T-maze alternation was normal, confirming that successful task acquisition probably does not depend on the HD signal[15]. Surprisingly, Wilton et al. (2001) found a deficit on the same T-maze alternation task, which suggests that that deficit cannot be due to loss of the HD signal in AD; after all, those HD cells are expected to lose their directional properties following LMN lesions (Blair et al. 1998). This deficit might reflect a contribution from LD instead, consistent with reports that LD lesions have mild effects on radial arm maze (Mizumori et al. 1994) and water maze tasks (van Groen et al. 2002b).

Importantly, Wilton et al. (2001) found that AD/LD lesioned rats were impaired on a task which requires the rat to navigate to a place at a fixed bearing and distance from a moving cylindrical landmark in the water maze, as in the Roberts and Pearce (1998) study. The authors point out that hippocampal lesions do not result in an impairment on this task (Pearce et al. 1998), suggesting that rats are not solving this task using locale navigation. A useful addition to support the requirement of an allocentric HD signal for this task would be to test the effects of disorientation on a version of this task with a cue-poor environment; an even more useful addition would be to record the HD signal as rats perform this task.

It is worth noting that several studies found impairments of lesions including HD cell areas on tasks unlikely to require such information (Parker and Gaffan 1997; Wolff et al. 2006). In the Wolff et al. study, rats with lesions of the ATN were impaired in learning odour sequences relative to controls, but they were normal in recognising odours. Such evidence confirms the involvement of these areas in more general, non-spatial processing.

For MEC and PoS, nonspecific lesions remain difficult to interpret because of the known role of the hippocampus and the subiculum in allocentric spatial tasks (Morris et al. 1982; Morris et al. 1990). However, two specific studies (Taube et al. (1992) for PoS, and Steffenach et al. (2005) for dorsolateral MEC) found allocentric spatial memory deficits when tested in the water maze, although both lesions slowed rather than abolished new learning, indicating that alternative strategies not requiring a directional signal may have been available, or the impairment was not due to loss of the HD signal but to something else.

[15] Unless the HD signal in DTN is not affected by LMN lesions, which would be surprising, and the signal can "get out" (i.e. be used ultimately for navigation) through a non-LMN pathway, which would be doubly surprising.

In summary, although there are many studies which find a specific deficit in allocentric processing after lesions of areas containing HD cells, it seems unlikely that this deficit is attributable to the loss of the allocentric directional signal provided by the HD system. This is because (a) different subnuclei in the ATN and MB appear to combine additively, and (b) lesions of specific HD sub-nuclei only have mild or transient effects on some allocentric tasks. For most of these tasks, it is unclear what strategies animals were using; recent attempts to test more specific tasks which are thought to require a HD signal do find an effect of HD system lesions, although in the case of the "path integration" task of Frohardt et al. (2006), the result is hard to interpret.

HD cell recordings and behaviour

Another, complementary, approach in identifying the role of the HD system in navigation and behaviour is to record from HD cell activity and look for correlations with behaviour. If rats rely on the HD signal for directional orientation, there must be a correspondence at some level between the HD signal and spatial decisions. A specific version of such a **neural compass hypothesis** can be stated as follows: given a suitably encoded goal in a given reference frame, rats can use a head direction signal relative to that frame's reference direction (as provided by the HD system) to navigate to the goal without using external cues. This hypothesis predicts that assuming the rat is using its neural compass, the *orientation of the HD system relative to the reference direction* (as can be measured by recording the PFD from HD cells[16]), directly predicts the rat's spatial behaviour. Type I disorientation in this framework would correspond to the situation where the activity packet drifts relative to the reference direction (so this is equivalent to the reference direction drifting, but this would seem to be a relatively unnatural alternative), and the rat's initial choice of goal would be off by the amount of drift. What would happen in the case of Type II disorientation, where the rat is aware of something being amiss, is harder to predict, as this might trigger a change in strategy where the animal decides to ignore the HD signal in favour of trying to use cues in the environment.

To what extent is this hypothesis supported by unit recording data? One approach, pioneered by Mizumori and Williams (1993), is to induce a non-specific degrading of the HD signal (loss or instability of directional firing) and correlate this with performance on a spatial navigation task. Mizumori and Williams recorded from LDN HD cells and found that in darkness, these cells had unstable PFDs and in some cases hardly any directional firing at all. Because rats performed worse on a radial arm maze task under these same darkness conditions, they speculated that this could be because the directional signal was less stable, consistent with the neural compass hypothesis. Because this is purely correlational

[16] Assuming the reference direction stays constant, which is most likely *not* the case in at least some HD recording experiments. This will be discussed in detail below.

evidence, however, it leaves open the alternative explanation that the HD signal and task performance are both affected by the available visual cues. This possibility is supported by the observation that LDN HD cells appear particularly affected by darkness conditions when compared to ADN or PoS HD cells, which can maintain directional firing in darkness over extended periods of time (section 2.3) and would presumably be available to the animal in this experiment.

This type of correlational evidence is similar to that obtained from a study by Dudchenko and Taube (1997), except that these authors attempted to link the specific orientation of the HD system to navigational decisions. Like Mizumori and Williams, they used a radial arm maze, this time within a curtained enclosure that had a prominent cue card. Rats were trained to select a rewarded maze arm, which was always at the same orientation relative to the cue card. Next, they rotated the cue card (in the absence of the rat, either 90° or 180°), which in agreement with previous studies usually (but not always) resulted in a corresponding rotation of the HD cells' PFD. Dudchenko and Taube found that this PFD rotation was typically accompanied by the rat choosing the corresponding maze arm, i.e. the relationship between the cue, HD cell PFD, and behavioural choice remained intact. In (rare) cases where the HD cell PFD did not rotate with the cue, rats made incorrect responses; the authors also report a small number of instances where a HD cell had the usual PFD relative to the cue card, yet the rat made an incorrect choice.

Dudchenko and Taube interpret these results as a correlation between the HD signal and navigational decisions. However, as noted by these authors, the same caveat as in the Mizumori and Williams study applies: there is a possibility that a common factor (the cue) was influencing the rats' navigational decisions and HD system independently. Indeed, similar studies on allocentric maze tasks (see the previous section) suggest that rats might not rely on a HD signal to solve this task (although disorientation impairs learning on this task, Dudchenko et al. 1997).

In addition and related to the correlational evidence issue, it is important to note that even though this experiment correlates a directional measure of navigation performance with the directional orientation of the HD system, the cue rotation manipulation does not manipulate the HD system's orientation relative to a constant reference direction; it manipulates the reference direction itself. Thus, this is not a case where rats are Type I disoriented and the HD system's orientation has drifted relative to the reference direction – the task here is simply to decide on the correct reference direction to use (the cue) that reliably predicts the goal. Nevertheless, both the Mizumori and Williams and the Dudchenko and Taube study are consistent with the neural compass hypothesis, although the observation that rats can be wrong, even though the HD signal is stable, emphasises the point that a stable compass is not enough for consistent performance: rats can decide to ignore the signal (perhaps for motivational/attentional reasons), or might have a goal

encoding problem. This idea is supported by evidence from Muir and Taube (2004) showed that rats maintained a stable directional signal but made varying choices on a variant of Tolman's (1948) sunburst maze task.

The issue of a change in reference direction vis-á-vis Type I disorientation is also relevant to the next experiment, the results of which appear to threaten the neural compass hypothesis. Golob et al. (2001) trained rats to go to a particular corner in a square box (again with surrounding curtains containing a cue card) to find food reward. They introduced rats to a rectangular box instead of the original square box, which, consistent with previous results (Golob and Taube 1997), caused a large PFD shift. Despite this, rats were still able to go to the rewarded corner, apparently inconsistent with the neural compass hypothesis. There are two possible explanations here that can reconcile this finding with it: First, it may simply be the case that rats don't need the directional signal to solve this task, and different sets of cues are controlling the orientation of the HD signal and the rats' behaviour. Second, the HD system has switched reference direction; it is using different maps for the square and the rectangular box, leaving open the possibility of whether or not it then uses the directional signal[17].

In support of the second possibility, complete hippocampal remapping was found when, in a similar place cell experiment (Jeffery et al. 2003), the recording box was changed from black to white. Despite this remapping, rats could retrieve a food reward in the white box nearly as well as in the black box. Interestingly, Jeffery et al. (2003) also show that acquisition of this task is dependent on an intact hippocampus, suggesting that even though the hippocampus remaps, this information is still needed to perform the task[18]. Hence, this result is essentially the same as that of the Golob et al. study, with the addition that acquisition of this task requires the hippocampus. As Jeffery et al. suggest, it indicates that the goal location (and other information required for task performance) is represented outside the hippocampus, yet this does mean that the hippocampus itself isn't needed. Taken together, these two studies suggest the HD and place systems could contribute task-relevant information which can change depending on reference frame. In terms of the neural compass hypothesis, this implies the rat isn't *just* using the directional or place signal for navigational decisions; the compass is only useful when combined with the other information that makes up a reference frame, specifically the reference direction and the goal location.

This interpretation does bring attention to the issue of why these systems remap: in both experiments, optimal generalisation performance from one environment to the other would

[17] If rats use the directional signal for this task in the remapping case, the clear prediction would be that if the system remaps (reorients) immediately when entering the rectangle for the first time, the rat will not know where the food is without looking at the original map or having some sort of conversion method, because the goal is only encoded on the old map.

[18] An alternative possibility is that the hippocampus is merely required for acquisition of the task.

be achieved by simply keeping the same reference frame, avoiding having to re-learn the goal location. This idea is formalised in a proposal by Fuhs (2006), who takes a Bayesian approach to which reference frame to select. This can be thought of as a pattern completion/pattern separation issue, where the question of whether to treat and environment as the same as a previous one or as different will depend on the resulting predictive power of behaviourally relevant factors in that environment. In terms of this approach, the observed remapping suggests that in general, it is beneficial for rats to treat these environments as separate, although that may not have been borne out in this particular experiment. Additionally, the capacity to maintain the same reference direction across all environments is likely limited by angular path integration capabilities, although with enough exposure, rats can learn to use a single reference direction for multiple environments (Dudchenko and Zinyuk 2005), so it is possible that with enough experience, rats will adopt the same reference frame for the two boxes.

Returning to the Golob et al. experiment, it is clear that the authors' interpretation of the HD signal being inconsistent with behaviour is true only in the most simple sense, specifically it disregards the possibility that the HD signal acts in a more general system capable of switching between reference frames. Hence, the PFD shift between the square and the rectangular box should not be interpreted as a Type I disorientation, as a reflection of the animal perceiving his orientation with respect to the laboratory frame having changed. A compelling demonstration of that such reorientation or remapping of the HD system does not reflect an angular path integration deficit (i.e. Type I disorientation) comes from the multiple-box experiment of Dudchenko and Zinyuk (2005). As discussed earlier, if a rat is independently introduced to environments "A" and "C", such that the HD system is oriented differently in the two boxes, and then walks from A to C, the HD system will shift from the A orientation to the C orientation. Because the system does not shift when the animal walks from A to novel environment "B", this cannot be due to an angular path integration deficit, but has a straightforward interpretation in terms of reference frames.

In the light of the above discussion, it is clear that when the aim is to link the head direction signal to behaviour, the possibility of switching reference frames is a potential confound in interpreting such experiments. A potential way forward, then, is to record the HD signal on a task which does not involve different reference frames, with path integration (Section 4.2) a prime candidate because it additionally requires a directional signal, at least under the right conditions, where rats cannot "cheat" by using external cues or motor programs. In a preliminary study, this is what Frohardt and colleagues (Frohardt et al. 2002, reviewed in Dudchenko et al. 2005) attempted to do. They developed a task similar using the food-carrying paradigm of Whishaw and colleagues (Whishaw et al. 1990; Whishaw and Tomie 1997), where rats were trained to retrieve food pellets, returning to a fixed refuge at the perimeter of a circular environment to eat. Head direction cell activity was recorded as

rats performed this task in four conditions: light (where the refuge and its relationship to the curtains with cue card could be observed), dark (lights off), blindfold (rats blindfolded), and rotation (path integration apparatus including refuge rotated 180°). The main result Frohardt et al. (2002) found was that rats were generally very good at returning to the refuge, coinciding with the HD system's orientation being stable. Occasionally a rat would make a wrong choice without a corresponding change in its HD system (which would remain stable), consistent with previous results and associated distraction/goal problem interpretation (see above). Interestingly they do not report the reverse case, where the HD system orientation changes but performance is unaffected, which suggests that rats can indeed not solve this task without reference to their HD system. This was the case for all conditions except the rotation condition, where reference shifts were observed. Typically, the HD system shifted 180°, along with the apparatus and refuge, with homing performance intact. However, in a number of sessions the HD system shifted by some different amount. In those cases, the rat did *not* make the correct return response. This result can be interpreted as failure to retrieve/select the correct reference direction whilst maintaining the same behavioural choice relative to the (incorrect) reference direction, and does suggest that rats were relying on the HD signal to guide their choice in this case. Once rats corrected their errors, the reference direction did not change, consistent with the interpretation that these errors were not due to a path integration deficit or Type I disorientation, but rather of a mismatch between the reference direction and the goal direction, which may or may not be a property of the head direction system[19].

In conclusion, recording experiments have provided evidence which is consistent with the neural compass hypothesis proposed here, although some authors have interpreted the same evidence as inconsistent with a simpler version of such a hypothesis. However, a truly convincing experiment in support of the neural compass hypothesis, where the behavioural effects of Type I disorientation (i.e. HD system drift) are measured, without confounding reference direction changes, and on a task that requires the HD system as backed up by a lesion study, remains to be done. The experimental content of this thesis, as laid out in the next two chapters, constitute an attempt to do this.

[19]This is an open question – presently we only know that the hippocampus probably inherits the reference direction from the HD system, using the simple ring model discussed in the previous chapter of how this is chosen in the HD system, but this doesn't address goal memory.

Part II

Experiments

Chapter 5

Effects of head direction system lesions on a path integration task

5.1 Background and rationale

The rodent head direction (HD) system contains cells maximally active when the animal's head is facing that cell's preferred firing direction in the horizontal plane, irrespective of location or ongoing behaviours (Taube et al. 1990a, reviewed in Chapter 2). Different cells have different preferred directions, evenly covering the directional space to form a "neural compass" representing the animal's current head direction in allocentric space (Johnson et al. 2005). From when these cells were first discovered, their potential role in spatial navigation was appreciated (Taube et al. 1990b; Gallistel 1990; McNaughton et al. 1991). A representation of directional heading[1] is fundamental to path integration, a form of navigation most strikingly expressed as animals' ability to make a direct return to a starting point or "nest" after complex outward journeys to different locations, apparently using idiothetic (self-motion) cues only (in rodents: Mittelstaedt and Mittelstaedt 1980; Etienne et al. 1986; Wallace and Whishaw 2003, reviewed in Chapter 4). This ability has been shown in many organisms, notably in ants, bees, birds, and mammals including rodents, dogs, and humans (reviewed in Biegler 2000; Jeffery and Etienne 2004). Furthermore, path integration is thought to be the basis for cognitive mapping, the construction of allocentric, metric maps of environments that support locale (map-based) navigation (O'Keefe and Nadel 1978; Gallistel 1990; Redish 1999).

The idea that rats rely on the head direction system to navigate can be stated more precisely as follows: given a suitably encoded goal in a given reference frame, rats can use a head direction signal relative to that frame's reference direction (as provided by the HD system) to navigate to the goal. This is the "neural compass hypothesis" (section 4.3). Note that this

[1] Which is not the same as head direction, but it's a start...

hypothesis does not state that rats *will* use their HD system to navigate; other strategies could be available that it may prefer to use. With this important caveat in mind, this hypothesis makes two main predictions, both with the same qualification, that *on navigation tasks which require a representation of head direction*, (1) lesions or other disruptions of the HD system should devastate performance, and (2) the state of the HD representation should correlate with the rat's navigational decisions. The aim of this chapter and the next is to test these predictions.

What tasks require a head direction representation? To say that this is any task on which HD-lesioned rats are impaired[2] relies on several assumptions[3]: it would be preferable to have independent criterion. One can never be entirely sure, but a good candidate would be a task which theoretically requires head direction, in combination with appropriate controls to rule out alternative methods of "cheating" that might not require a head direction signal.

As discussed in the previous chapter, prediction (1) has been addressed in two previous studies, and largely been confirmed. Wilton et al. (2001) trained rats to search at a fixed angle and distance relative to a circularly symmetric landmark moved between trials (Collett et al. 1986; Roberts and Pearce 1998; Pearce et al. 1998), and found rats with lesions to the anterodorsal (AD) and laterodorsal (LD) thalamic nuclei to be impaired[4]. Beyond a probe trial where distal cues were obscured by a curtain, the authors did not do any control tasks to assess the contribution of the HD system independently of the lesion; for instance, they did not disorient the animals before the curtain probe trial.

Frohardt et al. (2006) used a version of the Whishaw path integration task (Whishaw and Tomie 1997) where blindfolded rats returned to a home base after retrieving food pellets from a circular arena. They found that both rats with ADN lesions and rats with DTN lesions were impaired on this task; however, both groups were almost equally impaired when they were not blindfolded, and Frohardt et al. did not include a version of the task which lesioned rats were able to do as well as controls. Thus, the nature of the deficit could potentially be more general than a loss of the HD signal, particularly for the DTN-lesioned group; for ADN lesions, other studies using similar navigation tasks (such as the Wilton et al. experiment, above) suggest that the impairment is likely to be related to the HD system, although the ADN-lesioned deficit in Frohardt et al. was relatively small.

Several studies by Taube and colleagues are relevant to prediction (2) (Dudchenko and Taube 1997; Golob et al. 2001; Muir and Taube 2004). These have yielded results that are interpreted as inconclusive or even incompatible with a role for the HD system in

[2] This type of argument is sometimes used for the role of the hippocampus in relation to allocentric navigation tasks: "*x* is an allocentric navigation task because hippocampus-lesioned rats are impaired on it".

[3] Such as that lesions of HD areas affect the HD system exclusively, which seems unlikely given the lesion evidence of HD areas reviewed in Chapter 4.3.

[4] Rats with lesions of all anterior thalamic nuclei were previously shown to be unimpaired on a cued version of the water maze (Sutherland and Rodriguez 1989).

navigation (reviewed in Muir and Taube 2002; Dudchenko et al. 2005). In section 4.3 on page 67 I argue that these results can potentially be explained by taking a number of factors into account that are incorporated in the neural compass hypothesis. Specifically, in the Golob et al. study, rats may not require a HD signal to solve the task. Alternatively, they might require a HD signal, but change reference frames. In the Muir and Taube study rats might not have a suitable goal representation. The studies that have supported the involvement of the HD system in navigation (the Dudchenko et al. study and Mizumori and Williams 1993) only offer correlational evidence sensitive to alternative explanations without a role for the HD system. Preliminary results by Frohardt et al. (2002), who recorded HD activity on the path integration task described above, appear more consistent with prediction (2), although as argued in section 4.3, they do not offer strong evidence in direct support of it (they do not test the effects of Type I disorientation).

A test of the neural compass hypothesis, which sidesteps potential confounds or alternative explanations in previous studies relevant to prediction (2), could restore faith in the idea that the HD system can be used for navigation. The existing lesion evidence in support of prediction (1) does not have recording evidence to support it. This chapter provides evidence that on a task with independent controls for the use of head direction information (a path integration task), rats with lesions of the lateral mammillary nuclei (LMN, a critical node in the HD network, see section 2.2) are impaired on the path integration, but not the cued version, supporting prediction (1). The next chapter provides recording evidence supporting prediction (2).

As reviewed in Jeffery and Etienne (2004), showing animals are path integrating is difficult due to their ability to flexibly switch strategies (Maaswinkel and Whishaw 1999) and the large number of possible alternative cues/strategies available. We aim to do this by *manipulating* rats' sense of direction, following Mittelstaedt and Mittelstaedt (1980), who rotated subjects (female desert mice retrieving pups) below the vestibular threshold before they made a return journey. They found that subjects were wrong by whatever amount they had been rotated, suggesting that subjects were not relying on cues in the stable external world to get home and were presumably path integrating. By doing this experiment in rats (using appetitive rather than "progenitive" reinforcement) we aim to to show that they are path integrating, to test whether lesions of the HD system impair their ability to do so, and exploit the rotation manipulation to see if (either naturally-occurring or rotation-elicited) changes in HD signal correlate with behaviour (Chapter 6).

Why lesion LMN and not another HD area? As reviewed in section 2.2, LMN is the first area in the HD circuit which contains a substantial population of HD cells (see Figure 2.4 for a schematic of HD system circuitry). LMN lesions are known to abolish directional firing the anterodorsal thalamic nucleus (ADN), which is downstream from it (Blair et al. 1998; Blair et al. 1999). ADN lesions, in turn, lead to loss of directional firing in postsubicular

HD cells (Goodridge and Taube 1997). No lesion data is presently available on the effects of postsubiculum (PoS) lesions on entorhinal (EC) HD cells, but the anatomical pathway from PoS to EC (Caballero-Bleda and Witter 1993), as well as the effects of PoS lesions on hippocampal place cells (Calton et al. 2003) suggest that PoS may be important for EC HD activity. Hence, bilateral LMN lesions likely knock out most, if not all, of HD activity downstream of it. Network models of the HD system strongly suggest that the generation and updating of the HD signal requires a recurrent loop, for which that between LMN and DTN presently seems the only candidate (section 3.1.2). Thus, it is likely that LMN lesions abolish the small amount of HD activity in DTN as well.

5.2 Methods

We developed a behavioural task which would allow us to show that rats are using idiothetic information exclusively to solve a spatial navigation problem. Following Mittelstaedt and Mittelstaedt (1980), the overall strategy is to observe the effects of manipulating their "sense of direction" on behaviour. We used a homing task, where rats are trained to leave a home base (the location of which was varied on a trial-to-trial basis) to retrieve food chunks from the centre an open field and return to the home base. Rats could be confined to the centre of the open field to (a) allow an experimenter to clean the apparatus of cues which could guide homing, and (b) allow rats to be rotated slowly by an electric motor. The rats' response this rotation allows us to distinguish whether they are using stable external cues or an internal sense to return home. If rats are using external cues, they should not be affected by rotation, since the cues have not moved relative to the home location. If they are using an internal sense (and the rotation is such that it cannot be compensated for) they should be affected. In the case where they are fully unaware of being rotated, their choice of return should correspond to the rotation. This idea is illustrated in Figure 5.1 on the following page.

5.2.1 Subjects

Twenty naïve adult male Lister Hooded rats, weighing approximately 225g at the start of the experiment, were housed in cages of 4 in an animal room on a 12 hour light/dark cycle. All testing was carried out during the light phase of the cycle. From the first day of training, animals were food-deprived to between approximately 85%-90% of their free feeding weight and were maintained on this diet throughout the protocol, a two-week recovery period following surgery excepted. Rats were allowed ad-libitum access to water. From one week prior to training, rats were handled daily. Compliance was ensured with national (Animals [Scientific Procedures] Act, 1986) and international (European Communities Council Directive of 24 November 1986 [86/609/EEC]) legislation governing

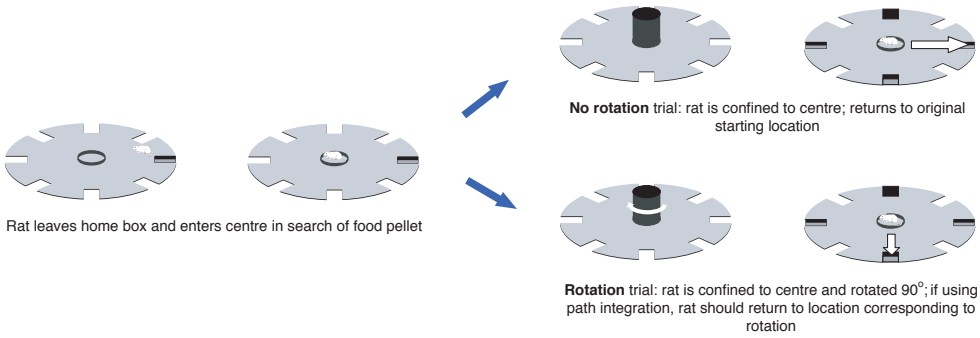

Figure 5.1: Design for a homing experiment where idiothetic (i.e. self-movement, or cues internal to the animal) and allothetic (i.e. cues external to the animal) strategies can be dissociated. Rats were trained to fetch food chunks from the centre of a circular table, returning to a home box (at a trial-unique location, "east" in this example) to eat. On "no rotation" trials, rats were confined to the centre for 60 s before making their return journey. On "rotation" trials, rats were rotated 90° during confinement. If they are navigating using external cues, their response should be unaffected; in contrast, idiothetic strategies should be sensitive to rotation (provided it is slow and smooth enough), and the rats' choice of return should be affected accordingly. Before the rat is allowed to return, the table surface is cleaned and new home boxes are inserted at 90° intervals.

the maintenance of laboratory animals and their use in scientific experiments.

5.2.2 Apparatus

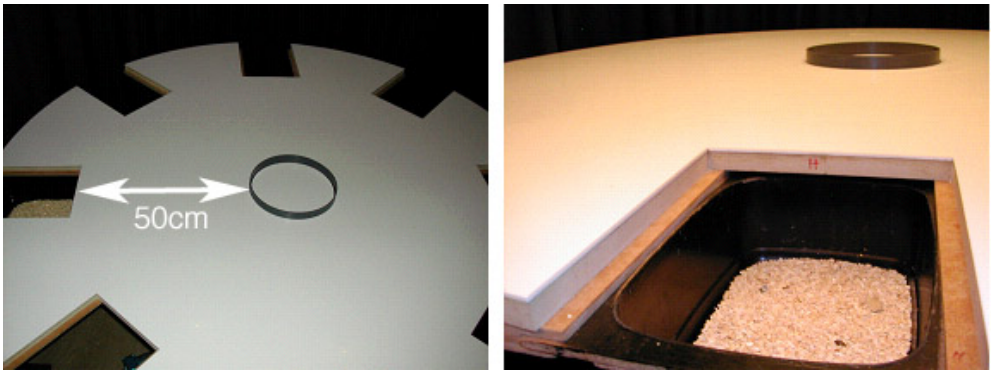

Figure 5.2: Experimental apparatus. A circular table 185 cm in diameter was covered with a single sheet of white acrylic (left). 8 evenly-spaced cutaway bays could accommodate removable plastic home boxes (right). A central platform, together with a surrounding plastic tube which could be raised and lowered from the adjacent room, could be rotated by a geared-down stepping motor. The apparatus was surrounded by thick ceiling-to-floor curtains.

The experimental apparatus, a modified Barnes maze (Barnes 1979), was a large white circular table 185 cm in diameter, with 8 start locations (rectangular cut-away bays) spaced evenly around the perimeter (Figure 5.2). The table surface, designed to minimise surface imperfections and be easy to clean, was cut from a single sheet of smooth, opaque white

acrylic (Altuglas International) mounted on a MDF base[5]. Black plastic home boxes (30 x 25 x 9cm) lined with sawdust could be placed securely into any of the start locations, such that rats could climb out onto the table and back into the box. In the centre of the table, a grey plastic tube (25cm in diameter) could be raised and lowered electronically from the adjoining control room (this took about 2.8 seconds to raise or lower). The tube contained a central platform, level with the table surface and of the same material, which together with the tube could be rotated (independently from the table surface) by a geared-down stepping motor (Astrosyn, UK, model SST0040, step size 1.8° and gearbox ratio 50:1, for an effective step size of 0.036°) controlled from the adjacent room. The table was surrounded by floor-to-ceiling black curtains to minimise extramaze visual cues, and white noise (from a speaker positioned centrally above the apparatus) at 65dB was used to mask auditory cues. The curtains could be opened at four different locations to allow the experimenter to enter and exit the curtained enclosure at different points. The apparatus was lit from overhead by 4 DC lights and a monochrome video camera (Panasonic) was positioned above the centre of the table so that all behaviour could observed from the control room and recorded for reference and offline analysis.

5.2.3 Experimental protocol

In general, the experimental protocol (represented schematically in Figure 5.3 on the next page) was organised into four stages: training, pre-surgery testing, surgery, and post-surgery testing. The aim of pre-surgery testing was to show that rats can home to a trial-unique starting location, and do so by path integration rather than by relying on external cues. Post-surgery testing would then address whether that ability depended on an intact head direction system. First, however, rats needed training in order to be able to perform the homing task successfully.

Training

Training consisted of two stages, "fetching" and "raising". The aim of the first ("fetching") was to get rats to retrieve food chunks from the centre of the apparatus and take them to their starting (or "home") location to eat. The food chunks ("Wotsits", Walkers, Leceister, UK) were cheese-flavoured, baked corn puffs low in nutritional value[6] cut up to approx. 5-10mm in length and 500mg in weight. As central-place foragers, rats naturally prefer to eat sufficiently large chunks of food in sheltered or perceived safe places rather than in a relatively exposed open field (Whishaw et al. 1990). Rats received 20-minute training

[5] The table surface and base rested on ball bearings mounted on a steel frame, allowing the table to be rotated by an experimenter, but this feature was not used for the experiments reported here.

[6] But not low in taste: the author consumed an estimated 1.2kg of Wotsits over the course of this experiment.

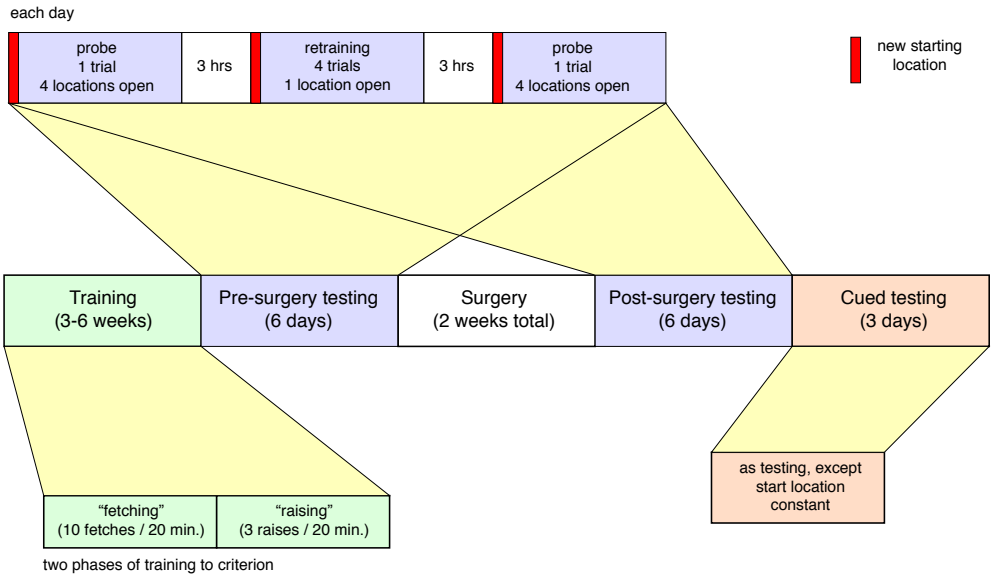

Figure 5.3: Experiment timeline. Rats were trained to a procedural criterion (of achieving three 60-second tube confinements or "raises") before testing began. During testing, rats received three sessions per day over 6 days: two "probe" sessions, with four locations available (containing a home box) for a single return after confinement, and one "retraining" session, where rats were given multiple raises with only one location containing a home box. Starting locations were varied between sessions. A cued version of the task was run after post-surgery testing, using the same probe-retraining-probe protocol, but always starting from the same location, and with several cues added to the apparatus and surrounding curtains.

sessions on alternate days, which were repeated until they successfully fetched at least 10 pellets per session for two consecutive sessions.

Individual training sessions started with a habituation/disorientation procedure, designed to (a) prevent the rat from carrying a sense of direction into the experiment, and (b) encourage the rat to become accustomed to its "home" box, a black plastic container lined with sawdust, which could be plugged into the apparatus. This procedure consisted of the rat being placed into a clean home box inside an opaque, covered holding box (30 x 40 x 22cm) located in the control room adjacent to the main experiment room. After 4 minutes (during which the rat was given a single "reminder" food pellet, the apparatus cleaned, its surface rotated to a new pseudorandom orientation, and a food pellet placed in its centre) the experimenter carried the holding box into the experiment room and inside the curtained enclosure, and walked around the apparatus three times. Next, the holding box was placed on top of the tube mechanism of the apparatus, which allowed the holding box to be rotated 90° (direction chosen pseudorandomly for each session) over 60 seconds. Finally, the home box containing the rat was taken out of the holding box and plugged into a pseudorandomly chosen starting location, starting the training session.

During a training session, the experimenter monitored the rats' behaviour from the adjacent

control room on a video monitor. When a rat fetched a food pellet from the centre of the apparatus, the experimenter entered the curtained enclosure containing the apparatus from one of the four entry points to place a new food pellet. Some rats would occasionally attempt to eat a food pellet at a location other than their home box (usually in the centre); this was discouraged by taking the food pellet away from the rat and placing it and the rat back into the home box, after which rats quickly learned to discontinue this behaviour. Some rats were initially reluctant to leave the home box; for those rats, outward excursions were encouraged by placing food pellets close to the home box.

Once a rat met the fetching stage criterion of at least 10 fetches per session for two consecutive sessions (this took less than two weeks for all but two rats), it was moved on to the second stage of training, "raising". The goal of this stage was to get rats used to being confined to the tube in the centre of the apparatus before returning to their home box. The training protocol was similar to "fetching" (20-minute sessions on alternate days), albeit with the addition of several shaping techniques. To encourage rats to enter the tube completely (rather than just reaching into it with their snout or entering it with their front paws only) such that it could be raised, on some fetches a food pellet was only dropped once the rat entered the tube with all four of its paws. As rats became more comfortable entering the tube, the tube was raised briefly on some fetches, the frequency and duration of such "raises" gradually increasing. During raises later in training, the experimenter started cleaning the apparatus (a cloth wet with lemon-scented Fairy liquid solution) and replacing the start box with a clean one. To encourage rats to return to their home box after the tube was lowered, an additional food pellet was dropped into the tube just before lowering. Still, some rats tended to stay in the centre after the tube was lowered; as before, this behaviour was discouraged by increasing the white noise level temporarily and/or taking their food away. Once rats tolerated three 60-second raises in a 20-minute session and appeared motivated to leave the tube once lowered, they were ready for testing.

Whilst all rats were initially reluctant to enter the tube again once confronted with a raise, some learned to tolerate raising quicker than others. Due to time constraints, the 8 worst affected rats were excluded from the experiment. Note that this selection was not based on how well rats were performing in terms of returning to the correct (home) location: this is a procedural criterion selecting those rats who tolerated tube-raising the best independently of homing accuracy. The 12 remaining rats reached the three-raise criterion within four weeks of "raising" training, at which point rats proceeded to testing.

Testing

The testing protocol, from which pre-surgery data was taken, consisted of six days of three sessions per day for each rat (Figure 5.3). Each session was preceded by the habituation/disorientation procedure described above, and starting locations for each session were

randomly generated. Each day contained two "probe" sessions with a "retraining" session in between, with the sessions at least three hours apart[7]. A probe session, designed to provide minimal cues to the rat as to the location of its home, consisted of the rat fetching 3 pellets from the tube centre. When a rat entered to fetch the 4th pellet, the tube was raised, confining it to the centre of the apparatus. During this confinement period, the home box was replaced by a clean one, and three additional home boxes were inserted into the apparatus at 90° intervals relative to the original home location. Also, the apparatus surface as well as the top edge of the raised tube were cleaned with a cloth wet with Fairy liquid solution. Before the tube was lowered and rats could make their return choice, a food pellet was dropped into the tube for rats to carry home. Once rats made their return choice, defined as their snout being above one of the possible starting locations (which need not necessarily contain a home box), their choice was noted down and they were removed from the apparatus. A probe session could be a "no rotation" (no rotation of the tube during confinement) or a "rotation" session (90° clockwise or counterclockwise rotation of the tube): over 6 days, rats received 4 sessions of each type for a total of 12 per rat.

During probe sessions, rats received no particular reinforcement for choosing to return to their original home location instead of to one of the other open boxes, and thus may learn to search randomly for an open box. "Retraining" sessions were designed to encourage rats to return to the correct home location. Retraining sessions are similar to "no rotation" probe sessions, except that no additional home boxes were inserted (i.e. only the original box was replaced), and the tube was never rotated. Additionally, instead of the rat being removed after the first raise, the rat was allowed to keep retrieving pellets until four raises had been achieved, or the 20 minutes were up, whichever came first[8].

Surgery and post-operative testing

Surgical methods are described in the following section; post-surgery testing was identical to the pre-surgery testing described above.

Cued testing

After post-surgery testing, the apparatus was changed from a cue-deprived configuration to containing many cues. The aim of this was to make it as easy as possible for the rats to find their home location whilst keeping the protocol the same, as a control experiment. Strips of tape and velcro were attached at several positions on the apparatus surface and

[7] Six subjects, 4 lesion rats and 2 control rats, did not receive retraining sessions pre-surgery. Their pre-surgery performance was not different from rats which did receive pre-surgery retraining sessions.

[8] On all retraining sessions except one, rats achieved at least three raises, indicating they could perform the procedural aspects of the task well. The one session in which a rat failed to achieve three raises resulted in that rat being relegated to the "training" part of the protocol, until he met the raising criterion and testing was resumed.

two intramaze cues were placed on the table; one next to the home location, which was kept constant throughout cued testing. Cues were also hung on the curtains surrounding the apparatus, and at one entry point the curtains were opened to reveal a slit covering about 20° of arc. Cued testing using this arrangement was carried out for three days in the standard probe-retraining-probe arrangement, except that the starting locations were always the same and probe sessions were never rotation sessions.

5.2.4 Surgical and histological methods

Animals were randomly assigned to one of two groups: a lesion group which were given bilateral excitotoxic lesions of the lateral mammillary nuclei (LMN) (n = 7) and a sham control group which had dura pierced but received no lesion (n = 5). Lesions were made with ibotenic acid (Sigma) dissolved in phosphate buffered saline (pH 7.4) at 10mg/ml. Anaesthesia was induced and maintained using halothane (Merial Animal Health, UK) and animals were positioned in a stereotaxic frame (Kopf Instruments, Tujunga, CA). Bilateral craniotomy was carried out at the target site to expose the dura above the LMN. The skull was levelled by adjusting the nose cone such that bregma and lambda were at the same DV level. A blunt 1l syringe (Hamilton) attached to the frame by a stereotaxic arm (Kopf) was lowered at an angle of 10° (with the tip pointing towards the rat's tail), aimed at the following coordinates relative to bregma: AP -4.5 mm, ML $\pm$ 1.0 mm, DV -9.2 mm (DV coordinate measured from dura). A single injection (0.4 μl) of ibotenic acid was made into each hemisphere over 6 minutes, beginning 5 minutes after the syringe was lowered. After completion of the ibotenic acid injections (or piercing of dura for sham animals), gelatine sponge (Johnson & Johnson, UK) was placed over areas where bone had been removed and a subcuticular stitching technique used to close the skin over the top of the skull. Animals were placed back in their group cages immediately after surgery. Analgesia was administered in oral form (Large Animal Rimadyl, Pfizer, UK) in the animals' water supply. This analgesic solution was freely available to all animals from 24 hours pre-surgery until 48 hours post-surgery. Behavioural testing commenced after a 14 day postoperative recovery period.

At the end of testing all animals were terminally anaesthetised with sodium pentobarbitol (Euthatal, Merial Animal Health, UK) and then perfused intracardially with 0.9% saline followed by 4% formalin. The brains were removed and stored in formalin for a minimum of 24 hours. Coronal 30μm sections were cut on a cryostat with every fifth section recovered for histological analysis. These recovered sections were mounted on gelatine subbed slides, stained with 0.1% cresyl violet acetate and coverslipped using DPX. The extent of the lesions was then assessed by examining each section under a microscope (Wild M420, Switzerland), transferring each image to a computer using a slide scanner (Epson F-3200) at 3200 dpi, and computing lesioned and spared areas using NIH ImageJ.

5.2.5 Data analysis

On all probe and retraining sessions (pre-surgery testing, post-surgery testing, and cued testing) the rats' first home box location choice after lowering the tube was recorded. A choice was defined as the rat (viewed from above on the video monitor) "checking out" or "visiting" a cutaway home box bay in the apparatus[9]. Thus, first choice data is in 45° steps, where 0° is used to refer to the original home location, and positive numbers indicate the counterclockwise direction.

To measure rats' homing performance, two measures were used: first, the ratio of first choices correct and total number of trials (where correct is defined as either the original location on a non-rotation trial and the rotated location on a rotation trial). Standard analysis of variance and associated post-hoc tests were performed on this data. Second, a "homing vector" was constructed by taking the vector mean of individual return choices, i.e. each individual return choice contributes a vector of length 1 in the direction of the choice relative to the home location, and the sum of these choices is then divided by the number of choices to yield a mean homing vector. This homing vector, conventionally indicated as r, contains two independent quantities of interest: firstly its direction, which indicates the rats' mean homing direction, and secondly its length $|r|$, which is a measure of homing strength. A mean vector length of 1 indicates rats always made the same response; a mean vector length of 0 indicates they had no preferred homing direction at all (although this doesn't mean their responses were uniformly distributed: they might go one way half the time and the opposite way the other half of the time). A correction to $|r|$ was applied because data were spaced with 45° intervals (Batschelet 1981). Rayleigh's test for uniformity, which takes $|r|$ and the number of data points as input, was used to test whether rats had a significant homing preference against responses not being distinguishable from randomness (Batschelet 1981). Confidence intervals for the mean homing direction (which are related to the circular variance $1-|r|$) were computed (Fisher 1993) and used to establish whether homing directions deviated from a reference direction (e.g. the home location at 0°) or to compare conditions (e.g. non-rotated and rotated). To test whether two response distributions were different, Watson's Y_r (due to Watson (1983) and described in Fisher (1993) p. 115-117) was used, which tests for a common mean direction. Its values distribute as χ^2, with $df = 1$ for the two-sample comparisons made here. Different formulae are used depending on sample size and the relative dispersions in the samples compared (Fisher 1993).

[9] In the absence of digitised traces, there is some degree of subjectivity inherent in judging this. However, only in rare cases were rats' choices potentially ambiguous (e.g. a rat walking closely past a location without appearing to check it out), so any biases as a result of this are likely to be minimal.

5.3 Results

We developed a homing task designed to test rats' ability to return to a home location using path integration. Rats (n = 12) were trained to fetch food pellets from the centre of a circular open field, returning to a trial-unique home location (a removable "home box") to eat. On probe trials, rats could be confined to the centre (by raising a cylindrical tube 25 cm in diameter) for 60 seconds, while the table was cleaned, the home box replaced, and three additional home boxes inserted at 90° intervals relative to the original home location. On rotation trials, the centre was additionally rotated 90° clockwise or counterclockwise during confinement. After tube lowering, the rats' first choice of return location was recorded. If rats are relying on idiothetic cues to guide behaviour, they should be affected by rotation; if they are using stable environment cues, they should not be affected by it.

5.3.1 Pre-lesion performance

The first question of interest is whether rats are able to return to their starting location after being confined to the tube for 60 seconds. We plotted circular histograms of the first location rats chose to return to after lowering of the tube. First choice data for non-rotation probe trials, i.e. with 4 boxes open and a trial-unique starting location, are shown in the top panel of Figure 5.4 on the following page. The starting location, defined as 0°, is indicated with a black dot, with all trials aligned to this location. For both control (n = 5) and lesion (n = 7) groups, responses were biased towards a single mean homing direction (Rayleigh test for uniformity, control: $r = 0.49$; $p < 0.001$, lesion: $r = 0.41$; $p = 0.001$, combined: $r = 0.44$; $p < 0.001$). Homing directions were consistent with a true homing angle of 0° (mean $\pm$99% confidence interval, control: $5.5° \pm 41.3°$, lesion: $8.0° \pm 33.8°$, combined: $6.9° \pm 25.3°$)[10]. Thus, rats are able to return to a trial-unique correct starting location after confinement.

How did rotation of the tube during confinement affect the rats' behaviour? Histograms for first return choices on rotation trials are shown in the bottom panel of Figure 5.4 on the next page, with the clockwise trials rotated 180° to be comparable with the counterclockwise trials. All trials are aligned to the same starting location at 0°, indicated by the black dot, as before. Although for the control group the most popular choice was the 90° rotated location (matching the tube rotation), choices could not be distinguished from randomness (Rayleigh test: $r = 0.20$; $p = 0.20$). However, when grouped together with the lesion group (which on its own did differ from randomness, Rayleigh test: $r = 0.38$; $p < 0.001$), choices were significantly biased towards a direction consistent with population mean of 90° (homing direction $78.2° \pm 35.3°$, Rayleigh test: $r = 0.31$; $p < 0.001$). Although the hypothesis of a

[10] When including retraining trials (with only 1 box open) in addition to probe trials, results were similar (Rayleigh test, control: $r = 0.43$; $p < 0.001$, lesion: $r = 0.46$; $p < 0.001$, mean homing directions $-6.0° \pm 22.9°$ and $20.6° \pm 21.0°$ for both groups respectively).

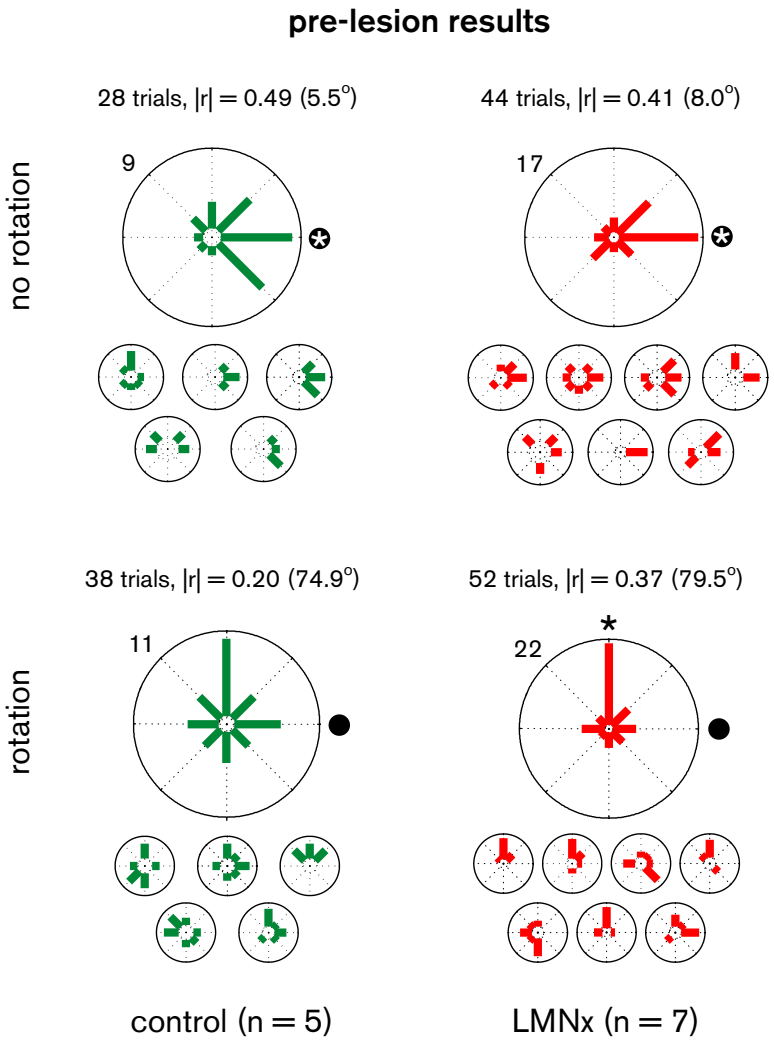

Figure 5.4: Rats can successfully return to a trial-unique starting location after confinement, and rotations shift their return choice. **Top**: Circular histograms of the first location rats chose to return to on no-rotation probe trials. All trials are aligned to the same starting location, indicated by the black dot at 0˚. The small histograms correspond to individual subjects, which are summed to make a joint histogram for each group (control: green, left column; lesion: red, right column). Stars indicate the presence of a significant homing direction (Rayleigh test, $p < 0.05$) consistent with a homing direction of 0˚ (99% confidence intervals). The total number of trials, $|r|$ values and mean homing directions are given above each histogram; the scale for each histogram is indicated by the number at the 135˚ location. Both groups home significantly to the home location of 0˚. **Bottom**: Homing performance on rotation probe trials, using the same layout as the top panel. Trials are aligned to the same starting location (black dot), and rotated to the counterclockwise direction to allow clockwise and counterclockwise trials to be combined. The lesion rats home to the 90˚ location, and although the control rats alone do not home to the 90˚ location significantly, they do choose it most frequently.

common mean direction between the non-rotation and rotation probe trials could not be rejected for the control group alone (Watson's Y_r, control: $Y_r = 3.2, p = 0.074$), it could be for the lesion group as well as for both groups together (lesion: $Y_r = 14.9, p < 0.001$, both: $Y_r = 17.6, p < 0.001$). Thus, rats were affected by the rotation, tending to return to the location corresponding to the rotation.

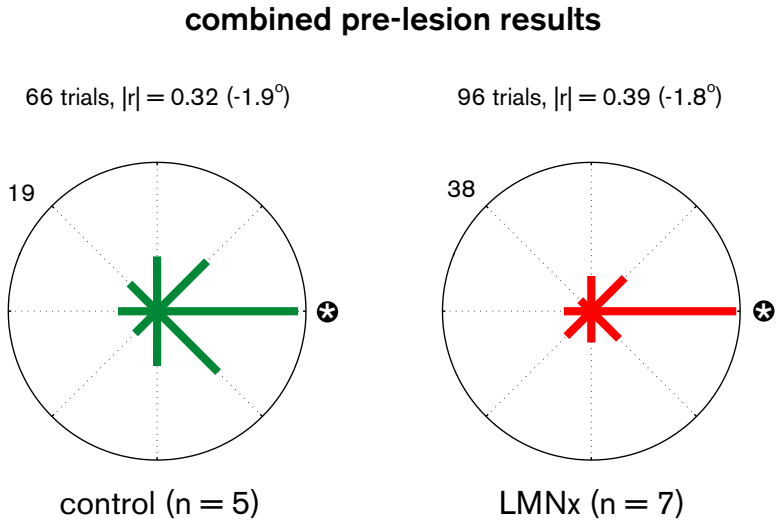

Figure 5.5: Combined return choice histograms for both rotation and non-rotation trials confirm that both groups display robust homing. Unlike the previous figure, trials are aligned to the correct *r*eturn location at 0° (indicated by the black dot) to obtain a representation of overall homing performance. Stars indicate significant homing direction.

By combining rotation and non-rotation probe trials, we can obtain an overall homing performance measure for both control and lesion groups; this is shown in Figure 5.5. Both groups home significantly (Rayleigh test, control: $r = 0.32$; $p = 0.001$, lesion: $r = 0.39$; $p < 0.001$) and in the correct direction (control: $-1.9° \pm 41.3°$, lesion: $-1.8° \pm 24.7°$). None of the no rotation, rotation, or combined mean homing directions were different between the control and lesion groups.

Hence, before surgery, rats return to their starting location when not rotated and to the 90° rotated location when rotated (with the control rats alone not homing significantly when rotated, but a similar pattern of results). Because their return location is affected by the rotation, this suggests that they are not relying on stable external cues to guide their behaviour, and are probably path integrating (see Discussion).

5.3.2 Post-lesion performance

Lesion group rats received bilateral ibotenic acid lesions of the lateral mammillary nuclei (LMN), while control rats received sham surgery (dura pierced). After two weeks' recovery, both groups were tested using the same protocol as used pre-surgery.

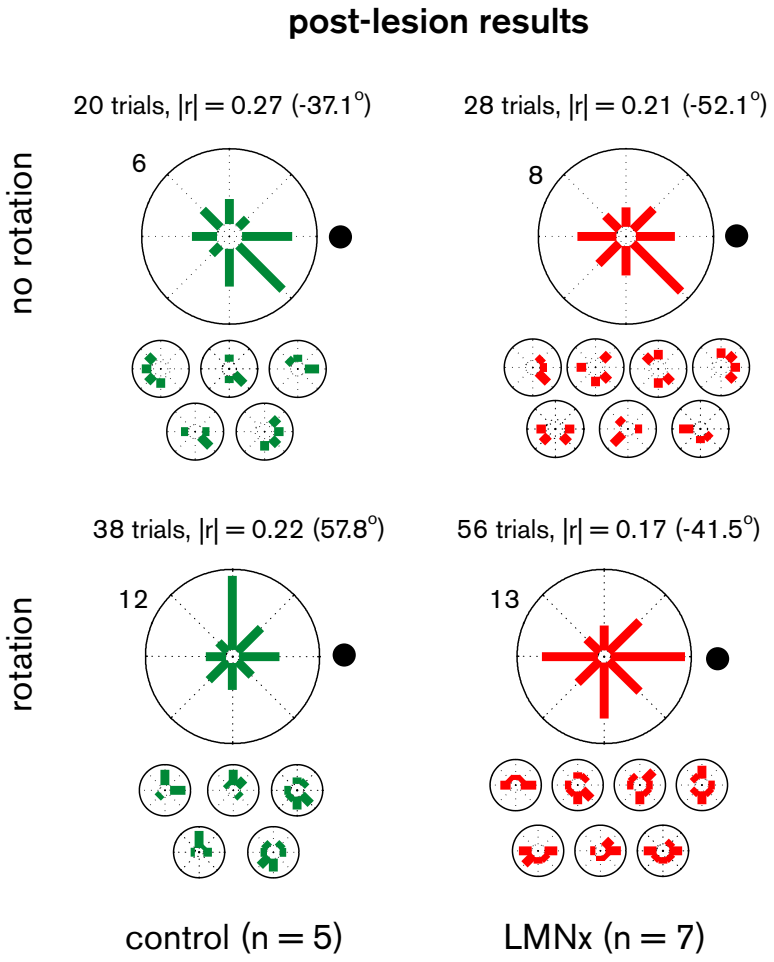

Figure 5.6: Post-lesion homing performance on probe trials, figure layout as Figure 5.4. **Top**: First choice circular histograms for non-rotation probe trials, with neither group showing significant homing. **Bottom**: Idem, for rotation trials. However, when non-rotation and rotation trials are combined, control rats but not lesion rats home significantly (see Figure 5.7 and main text).

Figure 5.6 shows circular histograms of the rats' first choices after surgery, again for probe trials only. When considering non-rotation and rotation probe trials separately, neither group showed a significant tendency to home (control no rotation (Fig. 5.6, top left): Rayleigh test: $r = 0.27$; $p = 0.25$, control rotation (Fig. 5.6, bottom left): $r = 0.22$; $p = 0.15$, lesion no rotation (Fig. 5.6, top right): $r = 0.21$; $p = 0.29$, lesion rotation (Fig. 5.6, bottom right): $r = 0.18$; $p = 0.17$). However, when combining non-rotation and rotation trials, the control group displayed a significant homing direction (Top left panel on Fig. 5.7 on the following page, $-34.1^\circ \pm 68.4^\circ$, $r = 0.24$; $p = 0.037$), while the lesion group did not (Fig. 5.7 (top right), $r = 0.15$; $p = 0.16$). This difference became more pronounced when including trials from the retraining sessions, with the control group homing (Fig. 5.7 (bottom left), mean direction $-0.8^\circ \pm 38.4^\circ$, $r = 0.21$; $p = 0.001$) and the lesion group displaying almost entirely unbiased choices (Fig. 5.7 (bottom right) $r = 0.04$; $p = 0.65$). Thus, there is

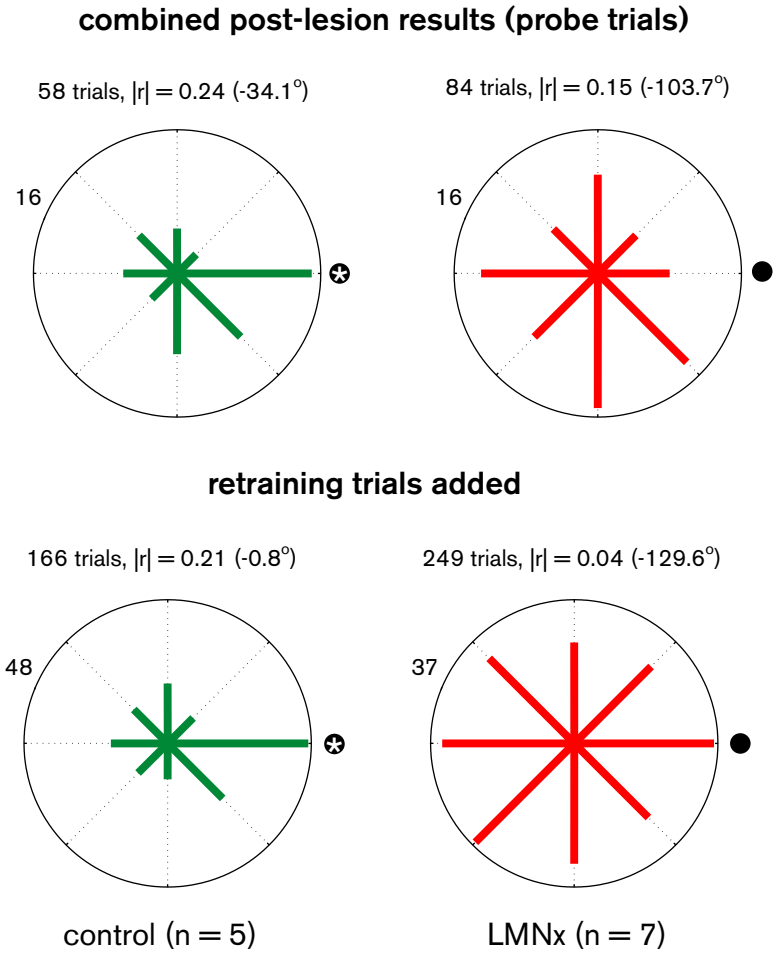

Figure 5.7: Control, but not lesioned animals, home significantly after surgery. **Top**: When non-rotation and rotation trials are combined, the control group, but not the lesion group, homes significantly. **Bottom**: When retraining trials are added, the difference between control and lesion groups becomes more marked, with the lesion group displaying almost random homing behaviour ($|r|$ near zero).

evidence of a homing impairment in the LMN-lesioned rats.

Is this impairment of the lesion group due to a general deficit unrelated to head direction or path integration, such as motivational, motor or memory impairments? To address this question, we modified the apparatus to maximise the allocentric spatial cues available to the rats by adding cues to the environment (Methods) and always started rats from the same location (but in the same probe-retraining-probe protocol, with 4 boxes opened during probes). Due to time constraints, this experiment was only run with 3 subjects per condition; circular histograms of first choices are shown in Figure 5.8. Both groups displayed strong homing towards the starting location (control, Fig. 5.8a, top: mean homing direction $-2.9^{\circ} \pm 19.9^{\circ}$, Rayleigh test: $r = 0.85$; $p < 0.001$, lesion, Fig. 5.8b, top: $-22.7^{\circ} \pm 38.6^{\circ}$. $r = 0.56$; $p = 0.002$) with no significant difference in mean homing direction between them

($Y_r = 1.4, p = 0.23$). Adding retraining trials to the analysis resulted in a (weakly) significant mean homing direction difference ($Y_r = 4.1, p = 0.043$, Fig. 5.8, bottom), with the controls' mean homing direction closer to 0° than the lesion group.

From the relatively high performance of both groups in the cued task, it is clear that procedural or general issues such as motivation or motor skills were not the cause of the lesion group impairment on the path integration (i.e. non-cued) task. This suggests a deficit specific to path integration.

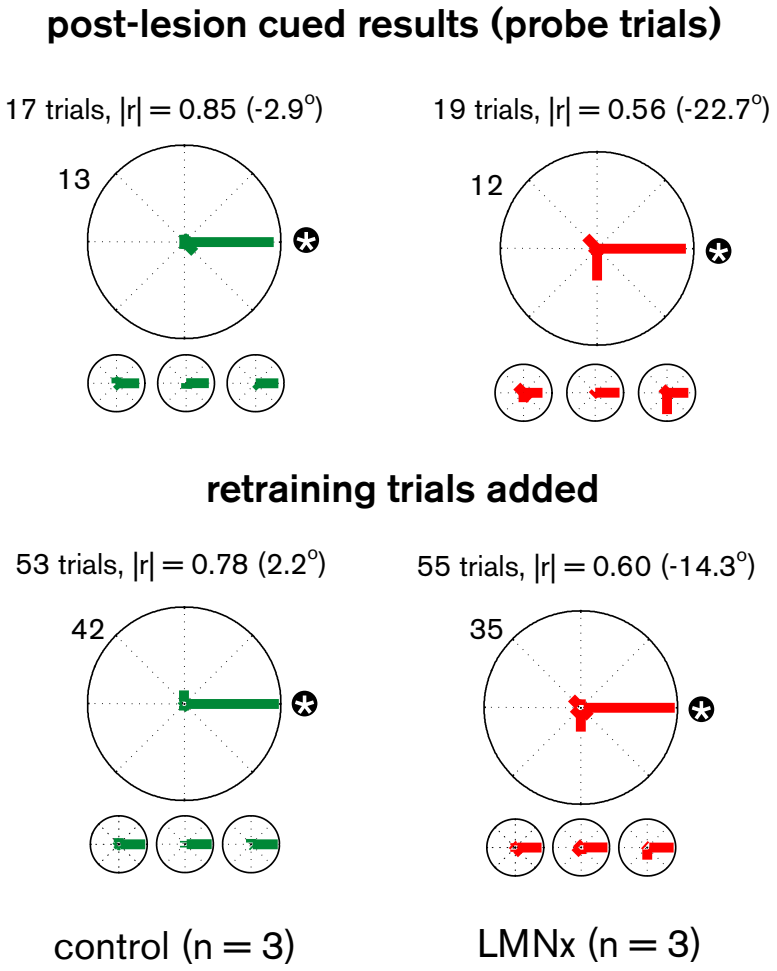

Figure 5.8: Post-lesion, both control (left column) and lesion (right column) groups perform well on a cued version of the task. **Top**: First choice circular histograms, probe trials only. **Bottom**: Idem, with retraining trials added. Both groups home significantly to the starting location in both cases, and with accuracy higher than in the non-cued (path integration) task.

A different way of viewing the results is to consider the number of correct choices made, where a correct choice is defined as returning to the original starting location (non-rotation trial) or the location corresponding to the rotation (rotation trial). In this way, homing performance can be expressed as a single number (proportion of correct responses over all

trials from some group/condition), and standard statistical techniques applied. Combined homing performance (both no-rotation and rotation trials) on probe trials is show in in Figure 5.9, with a more detailed view in Figure 5.10 on the following page.

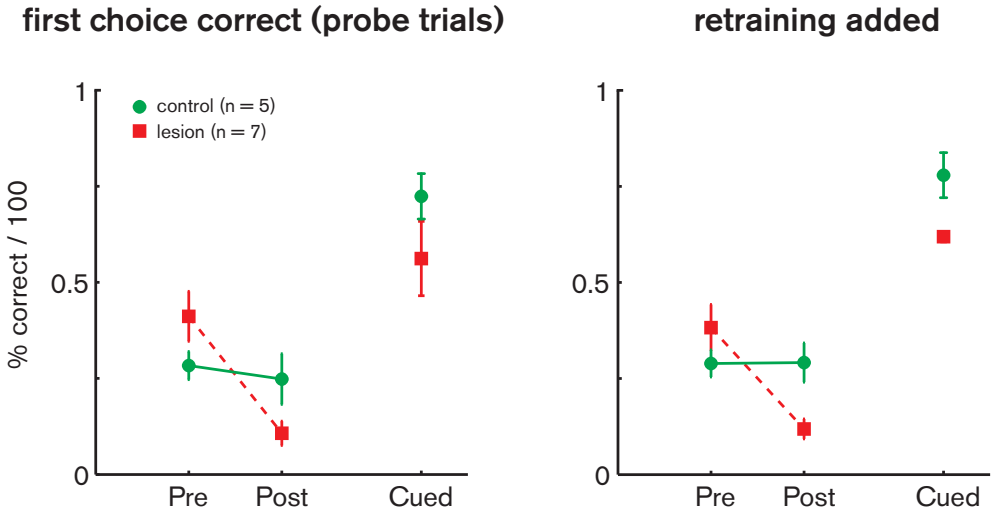

Figure 5.9: When considering the fraction of correct first choices, lesioned rats, but not control rats, are impaired after surgery. Bar graphs show the mean (±S.E.M.) fraction of first choices correct for probe trials only (left) and probe and retraining trials combined (right), for control (green, left column) and lesion (red, right column) groups. Lesion rats perform significantly worse after surgery on the path integration, but not the cued task, compared to control rats (see main text). On the cued task, each group contained three rats only.

Analogous to considering the homing vector length r in the circular statistics of the rats' return choices, we can ask whether as a group, subjects perform above chance (1/8 correct). Using probe trials only and aggregating non-rotation and rotation trials, control and lesion groups performed above chance pre-surgery (Student's one-sample t-test, control: $t_{(1)} = 3.71$; $p = 0.021$, lesion: $t_{(1)} = 3.40$; $p = 0.014$). Post-surgery, control group performance was not strictly distinguishable from chance ($t_{(1)} = 2.53$; $p = 0.065$) with the lesioned group clearly impaired ($t_{(1)} = -0.88$; $p = 0.411$). When additionally considering retraining trials, however, the control group performance was also different from chance ($t_{(1)} = 3.44$; $p = 0.026$) without changing the other results. On the cued task, both groups performed above chance.

To assess the influence of the various task variables on homing performance, a three-factor analysis of variance (ANOVA) was run on the first choice data, with group (control or lesion), condition (pre- or post-surgery) and rotation (no rotation or rotation) as factors. Using probe trials only, this analysis revealed a main effect of condition ($F_{(1,6)} = 9.43$; $p = 0.004$) and an interaction effect of condition $\times$ group ($F_{(1,6)} = 5.93$; $p = 0.019$), with no other significant effects found. This is consistent with LMN lesions, but not sham lesions, reducing performance. To confirm this, pairwise comparisons were performed. Combining no-

rotation and rotation probe trials, there was no performance difference between control and lesion groups before surgery (two-sample unpaired Student's t-test: $t_{(10)} = -1.21$; $p = 0.253$, $\chi^2 = 2.59$; df $= 3$; $p = 0.459$). After surgery, there was a significant difference between groups ($t_{(10)} = 2.75$; $p = 0.021$, $\chi^2 = 10.87$; df $= 3$; $p = 0.012$), with the control group's performance unaffected by surgery (paired Student's t-test: $t_{(4)} = 0.19$; $p = 0.856$, $\chi^2 = 0.07$; df $= 3$; $p = 0.996$) and the lesion group getting worse ($t_{(6)} = 4.46$; $p = 0.004$, $\chi^2 = 23.69$; df $= 3$; $p < 0.001$). Adding retraining trials to the analysis did not change the qualitative pattern of results (but made it more obvious).

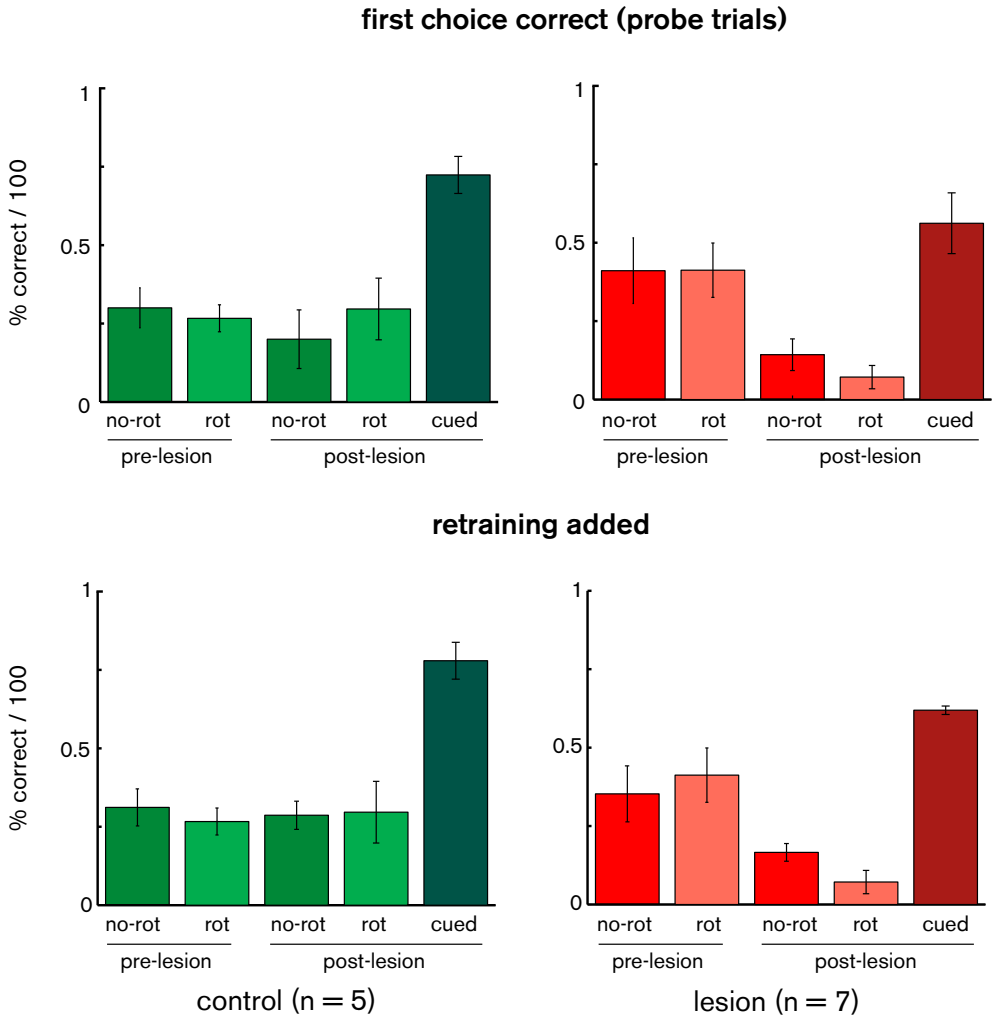

Figure 5.10: When considering the fraction of correct first choices, lesioned rats, but not control rats, are impaired after surgery. Bar graphs show the mean (±S.E.M.) fraction of first choices correct for probe trials only (top) and probe and retraining trials combined (bottom), for control (green, left column) and lesion (red, right column) groups. Label abbreviations: no-rot, no rotation trials; rot, rotation trials. Lesion rats perform significantly worse after surgery on the path integration, but not the cued task, compared to control rats (see main text). On the cued task, each group contained three rats only.

On the cued task, control and lesion groups did not differ when considering probe trials only

($t_{(4)} = 0.97$; $p = 0.385$, $\chi^2 = 0.63$; df $= 1$; $p = 0.429$), with adding retraining trials resulting in a hint of a difference ($t_{(4)} = 2.04$; $p = 0.11$, $\chi^2 = 3.07$; df $= 1$; $p = 0.08$). A two-factor ANOVA on the post-surgery results, with group (lesion or control) and task (rotation, no rotation, and cued) as factors, revealed significant main effects of both, but no significant interaction between them.

5.3.3 Behavioural observations

Lesion effects

In two lesion group rats (0812 and 0817) a remarkable locomotion behaviour was observed 1-3 h after completion of surgery. When moving around in their cage, they appeared to move in a clockwise direction only for prolonged periods, even when they seemed alert otherwise. Most lesion rats displayed "chewing" behaviour as they were recovering from the effects of anaesthesia, where they would move their jaws without appearing to open them or chew on anything in particular. This is consistent with observations of LMN-lesioned rats of a different strain (S.D. Vann, personal communication). By the following day, these effects were no longer visible, and lesion and control rats appeared indistinguishable in general locomotion, grooming, eating behaviours, and alertness levels (although this wasn't explicitly tested). On the homing task, however, several lesioned rats, but none of the control rats, had a tendency to move around the perimeter of the table in a single direction, in search of the home location (thigmotaxis). This was especially apparent when such a rat happened to initially miss the correct box by 45° or less, yet proceeded to search all around the perimeter of the apparatus in the wrong direction, to finally find the home box which could have been reached by moving a small distance the other way (Figure 5.11 on the next page).

Behaviour on the task

For all rats, it seemed clear from their behaviour that they were not using olfactory or visual cues to detect locations with a home box present. Rats often investigated locations without a box present (pausing briefly and peering their snout over the edge of the table into a home box location) just as they appeared to do for locations that did have a home box present. There are also many observations of rats just missing the correct location by a small distance, and then turning the wrong way. Accordingly, in terms of choices, rats did not prefer the $\pm 90°$ locations (i.e. those containing boxes) over the average of the $\pm 45°$ and $\pm 135°$ locations (lesion and control groups combined, $\chi^2 = 1.96$; df $= 1$; $p = 0.16$) on probe trials with four boxes present.

When the tube was lowered after confinement, rats did not typically immediately start their return journey. They tended to first step outside the cylinder, rear and/or move around near

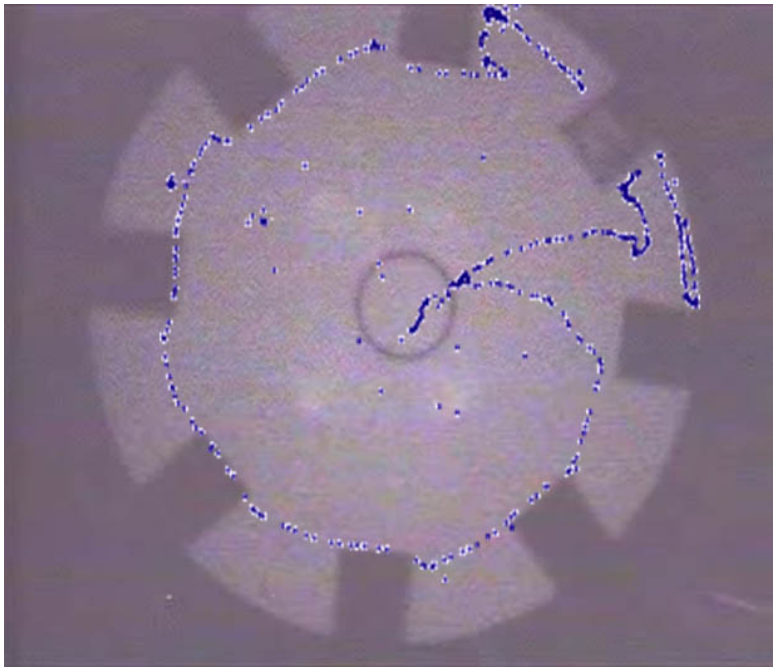

Figure 5.11: Thigmotaxic behaviour in a LMN-lesioned rat. On this trial, on which the tube was not raised, the rat's home box is in the north-west. After exploring the edge of the apparatus (to the south of the home box) briefly, the rat fetched a food chunk from the center, returning to the 45° clockwise location, and proceecing to go clockwise all around the apparatus until finally finding the original home box (which is not replaced by a new one on "fetch" trials such as this one, nor is the table cleaned). The rat's position is indicated by the blue dots, estimated by background substraction and thresholding of the video stream from the overhead camera.

the centre for a couple of seconds, before making a relatively straight and fast, apparently purposeful, return journey. Nevertheless, some rats appeared more motivated than others to return to a home box, with some frantically scurrying from location to location until a box was found, and others appearing more leisurely, taking time to investigate the curtains from outside a home box before entering one. Rats did not appear to be attracted to particular locations (in the room reference frame) more than others (it is conceivable that some directional cue might influence their homing behaviour); their allocentric choices (i.e. in stable "room space") on probe trials across groups did not differ from randomness (Rayleigh test: $r = 0.05$; $p = 0.63$). No changes in performance with time within 6-day testing blocks were apparent from plotting the number of correct choices for each session across days.

5.3.4 Histology

Figure 5.12 on page 103 shows example cresyl violet-stained brain slices for a representative control (left) and lesion (right) group rat. The lesion subject shown had bilateral damage to the lateral mammillary nuclei (LMN), although some sparing was apparent (green arrows). For the control subject, the right LMN is indicated with yellow arrows, on slices at roughly

the same place on the anterior-posterior axis.

In general, the extent of the lesions, which was never complete, seemed to fall in two groups: four animals (0813, 0817, 0818, 0819) had extensive damage to the LMN, with some characteristic dark-stained cell bodies remaining in one or two slices only (as in subject 0813 shown in Figure 5.12 on page 103). The other three animals still had visible damage to the LMN, but either more sparing was evident (0810, 0816) or the recovered sections did not cover the extent of where the LMN could be expected (0815) so the possibilty of sparing could not be ruled out. No post-lesion performance difference was apparent between these groups of animals: for instance, in terms of first choice, the two worst animals were 10 and 17, and the two best 16 and 18 (i.e. one from each group).

5.4 Conclusions and discussion

We developed a homing task in which rats are able to return to a trial-unique starting location after spending 60 seconds in confinement before their return journey. When rats are rotated slowly during confinement, they shift their return choice to the location corresponding to the rotation, suggesting that rats use (angular) path integration to solve the task. Rats with bilateral lesions of the lateral mammillary nuclei (LMN) were impaired on this task compared to sham-operated controls. As lesioned rats performed as well as controls on a cued version of the task, this impairment appears specific to path integration and not due to general (motor, motivational) factors. However, it is possible that the HD system contributes to cued task performance as well (see *Effect of lesions*, below).

5.4.1 How are rats solving the task?

In order to interpret the effects of lesions and the recording study in the next chapter, it is of interest to ensure that rats were solving the task by relying on idiothetic cues only. The confinement allowed us to rotate the rats slowly, in order to establish how they were finding their way home. Rats were affected by the rotation, homing to the rotated location instead of the original location. This suggests they were not relying on cues on the stable part of the apparatus or in the room: they were not solving the task allocentrically, but either relying on some purely internal strategy (a motor program or path integration) or using a cue on the inside of the rotating tube. In the current experimental design, these alternatives cannot be distinguished directly. However, the possibility that rats were using a motor program seems unlikely, given their tendency to move around vigorously and seemingly at random, in search of the food pellet, when confined to the tube; for an illustration of this (using rats tracked with infrared lights) see Figure 6.3 on page 115 and subsequent figures in the next chapter.

Despite our efforts to eliminate asymmetries from the apparatus, the alternative of rats relying on a cue inside the rotating enclosure is more difficult to exclude[11]. It is possible that either the inside of the confinement tube or the central platform contain some asymmetry, a beacon rats can use find their way home by taxon navigation, or even that rats leave a cue by entering the centre (perhaps an odour trace), which they can then use to orient themselves later. To minimise the latter possibility, the top edge of the tube was cleaned during confinement. Additionally, rats tended to move at least their heads out of the tube upon it being lowered (usually step out of it entirely), then usually pausing, looking up and around, often changing direction before deciding on a homing course.

Furthermore, in previous work using a similar task and apparatus (Dudchenko and Bruce 2005) it was found that even when cues were added to the inside of the tube (i.e. cues which were both stable and salient, presumably stronger than the cues we are concerned with here), rats still did not use them for homing. More generally, in several homing studies rats are reported to favour path integration over olfactory cues emanating from the home box, e.g. when they are wrong, they will search around where they think their home should be (e.g. Maaswinkel and Whishaw 1999; Cooper et al. 2001). But this might depend on rats' confidence in their internal sense, so might not necessarily apply.

In the next chapter, we show that even when rats are not rotated, their head direction cells show drifts in their preferred direction during confinement. This indicates they are not being stabilised by or anchored to cues within the tube; moreover, in those cases, rats follow their HD system and not putative cues in the tube, which they would be expected to use if available (Maaswinkel and Whishaw 1999). Taken together, these observations suggests rats are likely path integrating rather than using cues inside the tube.

5.4.2 Effect of lesions

Rats with LMN lesions were impaired on the task, both in terms of first choice correct and homing vector strength. Critically, on a cued version of the task, lesioned rats performed very well (above pre-lesion performance on the non-cued task). This indicates that there is no general motor, memory, or motivational impairment limiting performance on the non-cued task. In principle, the lesion group impairment could be due to starting from different locations (the cued task was run from a constant starting location across trials). However, given that rats do not appear to be solving the task by navigating based on allocentric cues (they are affected by the tube rotation) this seems unlikely. The remaining explanation is that LMN lesions impair (angular) path integration.

On the cued task, there was a hint of difference between groups that could potentially

[11] This is a weakness of even the most convincing demonstrations of path integration in the literature, including Mittelstaedt and Mittelstaedt (1980) and Wallace and Whishaw (2003).

reflect a genuine difference because of small animal numbers. This and the fact that the ANOVA did not yield a significant interaction between the non-cued and cued versions of the task and lesion/control factors could be consistent with a recent report of the effects of other areas containing head direction cells on spatial task with visual cues available (Frohardt et al. 2006). These data suggest that HD cells may contribute to, but are not necessary for, at least some cued spatial behaviours. For instance, because cued data were taken right from the rats' first experience in the cued environment, lesioned rats might not have had access to flexible (e.g. map-based) learning methods of control rats; such differences in the strategy used might also explain the significant but still better-than-chance performance of HD-lesioned rats on cued tasks.

In all lesioned animals damage to the LMN was apparent, with no discernible performance difference between "extensive" and "limited" lesion size groups. In this respect, it is notable that theoretical models of the head-direction system postulate a highly tuned continuous attractor network architecture, which would be expected to be sensitive to disruptions. (Of course, equally, various homeostatic and compensatory mechanisms might be expected to exist in a biological system; however, this situation is qualitatively different from areas which have a feedforward input-output arrangement where any spared cells are likely to be unaffected by damage elsewhere.) Thus, it is conceivable that a relatively limited amount of damage to this network is sufficient to cause the system to fail. In line with this idea, Blair et al. (1998) reported loss of ADN directional firing after electrolytic LMN lesions made with small recording electrodes, which in at least one clear case left over half of LMN intact in both hemispheres. However, more definitive lesion evidence with complete and selective destruction of LMN would be informative, perhaps using a neuronal nuclear antigen such as NeuN.

As reviewed in section 4.3, previous lesion studies have generally lesioned the entire mammillary bodies (MB) and not selectively lesioned LMN. However, one experiment where LMN was selectively lesioned (Vann 2005) reported transient impairments on a working memory water maze task, with no explicit path integration or "homing vector" (Wilton et al. 2001) task tested. Such transient impairments might reflect a loss of the systems necessary for fast, flexible learning on tasks where slower, compensatory strategies are available. In the results from the present experiment, there was no evidence of lesion animals improving perfomance over days, but of course it was puposely set up to require a HD signal. In a task similar to the present experiment, Frohardt et al. (2006) reported mild effects of ADN lesions, and substantial deficits of DTN lesions, on both a cued and a path integration version of a homing task. However, their cued task was different from the cued task in the current experiment: in their version, a single cue card on the curtains surrounding the apparatus was the only intentional directional cue, whereas in the present experiment, an array of cues was available, including one directly next to the goal. As noted

before, the lack of a control task which their HD-lesioned animals are able to do precludes a strong interpretation of their results, although the fact that Frohardt et al. find impairments on the path integration task is consistent with the present results, with the cued impairment possibly due to their cued task also requiring a HD signal, or at least not being as easily solved by taxon navigation as the cued task in the present experiment.

5.4.3 Comparison with related behavioural tasks

The most convincing path integration studies in mammals have used rotation or displacement manipulations, upon which the present study is based (Mittelstaedt and Mittelstaedt 1980; Etienne et al. 1986). Path integration studies in rats (Alyan and McNaughton 1999; Wallace and Whishaw 2003; Shettleworth and Sutton 2005) have not previously used such a manipulation, although the Whishaw group experiments in particular include other evidence that rats are capable of path integration (section 4.2). In comparison with lesion studies using tasks thought to require a sense of direction (Wilton et al. 2001; Frohardt et al. 2006) the rotation feature of our design is a strength, both in providing explicit evidence that rats are path integrating, and when combined with recording data (Chapter 6). One undesirable side effect of the confinement required for the rotation manipulation is that it makes the task more difficult, which could explain the relatively low $|r|$ values (low homing performance; rats do not make the correct first choice over half the time) compared to similar tasks. Several factors could contribute to this effect. First, the fact that there is a delay of at least a minute, and the associated distraction of a moving tube, may make it more difficult to remember the task or the location of the goal in comparison to the uninterrupted, short journeys used in some other tasks. Second, because rats spend time confined in the centre (and frequently eat food chunks there), this might reduce their natural tendency to return to the home location. However, the cued task results suggest that these factors are not do not impair rats' ability to remember *that* they would like to return home, some representation of the goal, and their motivation to do so. Thus, the most likely explanation for the relatively low performance on path integration trials appears to be that it is hard to path integrate accurately on this task. The observed drifts in the head direction system, even when the rat is not rotated, described in the next chapter support this interpretation.

On the first version of the task (Dudchenko and Bruce 2005) rats were not affected by the rotation manipulation, indicating they had access to stable, external cues. The exact reasons for this are unclear, but it is possible that this resulted from protocol differences (the rats in this previous experiment were trained for a longer time period) which gave rats more time to learn about cues in the room. The present experiment was done in a different room, potentially with different cue availability. For the second version of the task (not reported here), a new maze was built and placed in a new room. The rotations

now had some effect, but rats appeared to be able to return to previous starting locations, indicating that they had access to external cues. Also, rotations were by achieved by a hand-driven mechanism and tended to have a low success rate in rotating HD cell preferred firing directions. In the current version, as described here, apart from a new maze and a new room, the introduction of the disorientation protocol seemed to make a difference. Using this same apparatus and a similar protocol, similar results (homing strengths of around 0.4 and successful rotations) were obtained with a previous batch of 6 rats (results not shown).

The task protocol itself went through several stages of development. During collection of the results reported here, some changes were made. Half the subjects (2 control, 4 lesion) were initially trained to dig for food in a sand pot located in the centre of the maze. After it became apparent that this discouraged rats from entering the tube so that it could be raised, this was abandoned in favour of just having loose food chunks in the centre.

5.4.4 Implications

The present results provide evidence for the specific involvement of the head direction (HD) system in a path integration task, supporting a key prediction of the neural compass hypothesis by providing a causal link between the HD system and path integration. Such of the involvement of the HD system opens up the possibility of testing the second (correlational) prediction of the neural compass hypothesis (Chapter 6) using this same task. With sufficient support, this hypothesis provides a way to reconcile previous, apparently conflicting, evidence of HD cell recordings, HD system lesions and navigational decisions. Showing that the conceptually simple, unambiguous case of navigation by path integration depends on the HD system provides a starting point for comparing to tasks where the results are less clear cut. The involvement of the HD system in path integration is also relevant to theories and experiments involving the construction of allocentric spatial representations; if path integration is the basis of cognitive mapping, disruptions of the HD system may have different effects either before or after acquisition of such a task, a prediction that can be tested experimentally.

The present experiment could be improved in a number of ways. First and foremost, it would be desirable to develop the surgical and histological methods such that the exact location and extent of the lesions can be confirmed. We aim to do this by using NeuN immunocytochemistry, which would allow only nuclei of healthy intact neurons to be stained. Behaviorally, a protocol where each individual animal completes a sufficient amount of trials in order to establish whether individuals are homing significantly or not would be helpful, for instance in correlating individual performance with lesion size and/or location. In terms of providing additional evidence that rats are solving the task by path integration, a control task that cannot be solved by local cues inside the tube would be

useful. This could perhaps be done by rotating the centre one full revolution during confinement, such that if rats are using local cues they are still aligned with the home location and performance would be unaffected. Since the rotation will affect any idiothetic navigation strategy (because of vestibular adaptation), these alternatives could potentially be dissociated. Finally, a way of tracking animals such that their movements can be digitised reliably and accurately, ideally in combination with synchronised timestamps of when the tube was raised and lowered, would allow unbiased and more detailed analysis of their behaviour and homing perfomance. Measures such as the length of the path taken from the centre to the correct box, or the latency to make a choice, would help in further characterisation of lesion deficits.

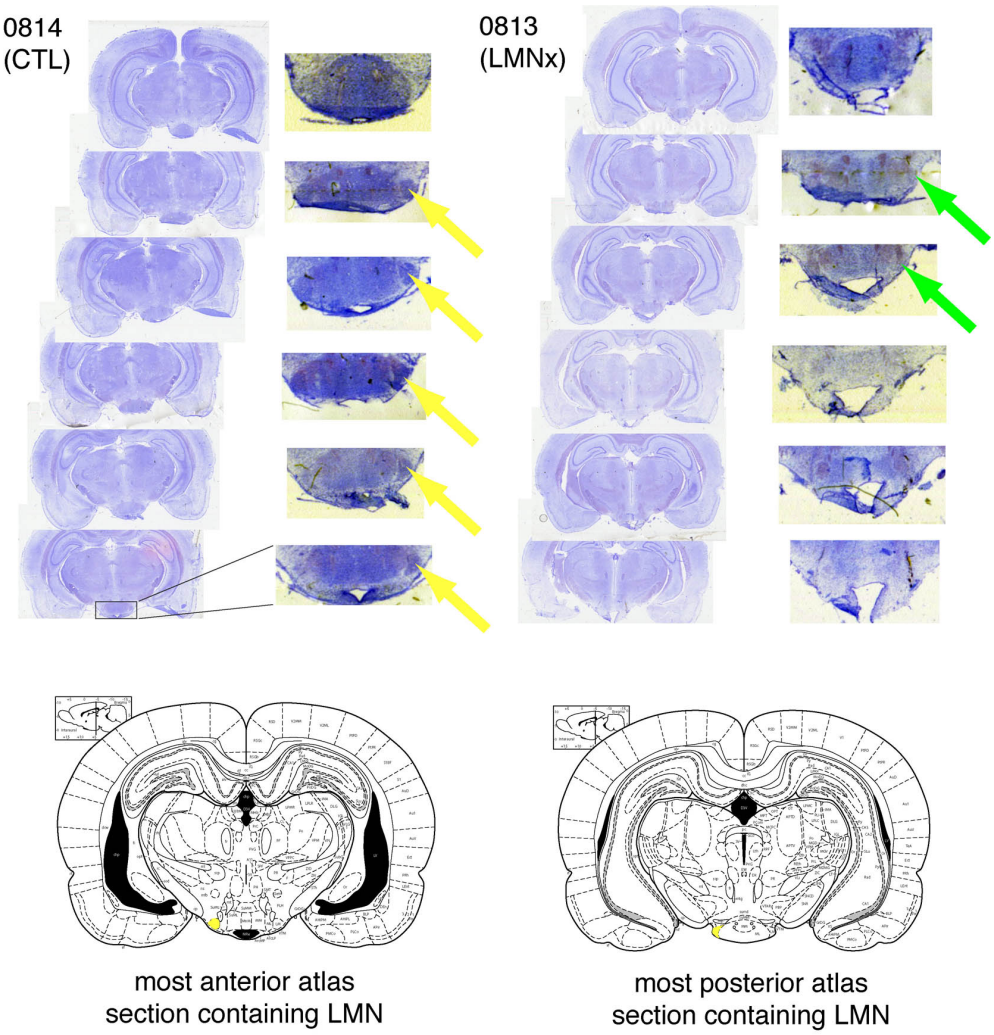

Figure 5.12: Top: representative cresyl-violet stained brain sections for a control (**left**) and lesion group (**right**) subject. Yellow arrows indicate the intact (right) lateral mammillary nucleus (LMN) in the control subject, largely absent in the lesion animal. Green arrows indicate areas where some sparing is discernible. No lesion animal had a complete bilateral LMN lesion, although for all animals damage was apparent, roughly dividing into four with "extensive" damage (among which this example) and three with "limited" damage (see main text). **Bottom**: diagrammatic representation of the most rostral (left) and caudal (right) brain slices containing LMN tissue (indicated in yellow). Reproduced from Paxinos and Watson (1998).

Chapter 6

Recording of head direction cell activity during path integration

6.1 Background and rationale

As reviewed in earlier chapters, the rodent head direction (HD) system is thought to provide rats with a "neural compass" useful for spatial information processing and navigation (Taube et al. 1990b; McNaughton et al. 1991; Redish 1999). In support of this idea, there is some evidence that lesions specific to areas containing HD cells result in impairments on a number of spatial tasks (Wilton et al. 2001; Frohardt et al. 2006; Chapter 5, this thesis). If we attribute such deficits to the loss of the direction signal provided by the HD system, we would expect that during these behaviours, there is a relationship between what is represented in the HD system on the one hand, and rats' spatial decisions on the other. However, both in the case of the HD system and for "place cells" in the hippocampus (O'Keefe and Dostrovsky 1971), experiments testing this prediction have yielded inconclusive results. This experiment and underlying ideas are aimed at clearing the confusion.

A straightforward form of the neural compass hypothesis ("simple neural compass hypothesis") would predict a perfect correspondence between any shifts (or absence thereof) in the HD signal[1] and rats' navigational choice: for the task described in Chapter 5, this idea is illustrated in Figure 6.1. Dudchenko and Taube (1997) obtained exactly this result; when they trained rats to select a radial maze arm at a constant angle relative to a prominent directional cue, they found that when this cue was rotated, HD cells changed their preferred direction accordingly, and rats chose a new arm corresponding to the change. As pointed out by these authors, such a correlation is consistent with the neural compass hypothesis,

[1] A HD system shift, i.e. the same population of HD cells being active when the rat is facing a different direction, manifests itself as a preferred firing direction shift on the single cell level, see Figure 6.1 on page 106 for an illustration.

but it does not provide much evidence that the change in behaviour was caused by the HD shift. In particular, it is possible that rotation of the cue influenced both the HD system and the rats' behaviour independently, without there being a direct link between the HD system and the rats' spatial decisions. It is also not clear whether rats actually required an intact HD system to do this task (as could be tested with a lesion study). Similar results have been obtained for place cells; for instance, O'Keefe and Speakman (1987) found that when rats made errors on a spatial memory task, the place fields were often "misplaced", such that the place representation in the start box was predictive of the rats' subsequent performance.

So far so good for the simple neural compass hypothesis. However, more recent studies have complicated this picture. Golob et al. (2001) trained rats to go to a particular corner of a square box. When they then changed the shape of the box to rectangular, rats would still go to this same corner, but their head direction cells showed large shifts in preferred firing direction. As Golob et al. note, such a dissociation, where a spatial behaviour is unaffected by a HD signal shift, is inconsistent with the neural compass hypothesis. Muir and Taube (2004) found the opposite dissociation, that despite the HD signal being stable over many sessions, the rats' performance on a version of (Tolman 1948)'s sunburst maze task was erratic and unrelated to the (stable) HD signal.

In section 4.3 I argue that these results can be integrated into an updated neural compass hypothesis, which takes a number of factors into account. First, a rat can choose to ignore its HD signal for behaviour, perhaps when it can solve a given task by other (e.g. taxon navigation) methods. Second, a stable HD signal alone is not enough for accurate performance on a spatial task that requires it. It also requires the goal to be encoded in relation to the reference HD direction, sufficient motivation, and possibly other knowledge. Third, analogous to "remapping" in the hippocampus, where different environments have independent representations, the HD system operates in multiple reference frames: it can dynamically change its reference direction. The first two factors can explain the Muir et al. result, and the third can account for the PFD changes seen in the Golob et al. study.

Thus, an updated hypothesis about the role of the HD system in spatial behaviour is the following: given a suitably encoded goal in a given reference frame, rats can use a head direction signal relative to that frame's reference direction (as provided by the HD system) to navigate to the goal without using external cues (**neural compass hypothesis**). As noted above, to say that rats *can* use the HD signal is not to say that they *will* under all circumstances. Thus, a test of this hypothesis requires a task where performance depends on the integrity of the HD system. The homing task described in the previous chapter, where rats spend a minute in confinement to get a food reward before returning to a trial-unique starting location, fulfills these criteria. This task also allows the testing of a critical prediction of the neural compass hypothesis: the orientation of the HD system relative to

the reference direction should directly predict the rat's spatial behaviour. As discussed in section 4.3, both in the Golob et al. study and in preliminary data from a task on which HD-lesioned rats are impaired (Frohardt et al. 2002; Frohardt et al. 2006), shifts in reference direction are observed. Such shifts make it difficult to observe drifts relative to the reference direction. Strong support for the neural compass hypothesis would come from observing the relationship between the HD signal and behaviour during Type I disorientation, that is, when there is a mismatch between the rat's perceived orientation and its actual orientation, without the rat being aware of it. In this case, there is no shift in reference orientation, just drift in the HD system's representation of directional heading. If the rat is using this to navigate, drifts should correlate with navigational choices. As in previous experiments (e.g. Mittelstaedt and Mittelstaedt 1980) the apparatus described in the previous chapter allows us to induce Type I disorientation in rats by rotating them below the vestibular threshold: this is shown schematically in Figure 6.1. In the experiment described in this chapter, activity from HD cells is recorded as rats perform the path integration task described in Chapter 5, where we observe the effects of both spontaneous and rotation-induced drifts in the HD system on their homing performance.

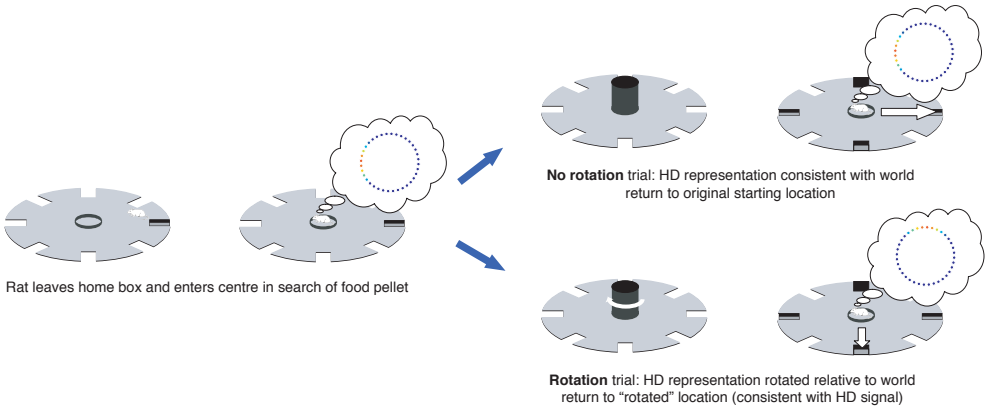

Figure 6.1: Schematic of the expected effects of confinement on the head direction (HD) signal and behaviour, on the path integration task described in Chapter 5. HD cells are laid out such that their preferred firing direction corresponds to their angular location on the ring, with lighter shading indicating activity. Hence, the "west" cells are active when the rat is facing west (**left**). When the tube is not rotated (**top right**), this same population of HD cells is active when the rat faces west after confinement; the HD system remains consistent with respect to the world (and the rat should be able to find its home location). However, if the rat is rotated without its HD system being updated (e.g. because it is too slow to be detected), the relationship between the HD signal and the world is disrupted (**lower right**). As the rat is facing west, the "north" cells are now active. If, as before, the rat makes his return choice based on the HD signal, he will now choose the 90° rotated box. When recording from a single HD cell, such a shift in the HD system will manifest itself as a shift in the preferred firing direction of the cell.

6.2 Methods

Rats (n = 3)[2] were implanted with recording electrodes to allow recording of head direction (HD) cell activity as rats performed the path integration task described in Chapter 5. We sought to determine whether rats exhibited changes in the head direction signal as a result of confinement and/or rotation, and whether any such changes correlated with the rats' choice of return journey.

6.2.1 Subjects

Three adult male Lister Hooded rats, weighing between 250-300g prior to recording electrode implant surgery, were housed in individual cages in an animal room on a 12 hour light/dark cycle. All testing was carried out during the light phase of the cycle. After a 1-week recovery period following surgery, animals were food-deprived to between approximately 85%-90% of their free feeding weight and were maintained on this diet. Rats were allowed ad-libitum access to water. From one week prior to surgery, rats were handled daily. Compliance was ensured with national (Animals [Scientific Procedures] Act, 1986) and international (European Communities Council Directive of 24 November 1986 [86/609/EEC]) legislation governing the maintenance of laboratory animals and their use in scientific experiments.

6.2.2 Electrodes and surgery

Recording assemblies, built with a modified tripod design (Kubie 1984), contained 4 tetrodes of Formvar-coated 25μm NiCr wire (California Fine Wire, Grover Beach, CA). Tetrodes were threaded through a 27Ga thin-wall stainless steel cannula, with the recording tip extending 2-3 mm beyond the cannula at one end, and individual wires affixed to the pins of a MillMax plug (MillMax, Oyster Bay, NY) at the other. Together with three screws (80 threads per inch) secured into tapped Amphenol sockets (Wallingford, CT), the plug and cannula with tetrodes were made into a single advanceable unit using dental acrylic. The recording tip of the assembly was coated in paraffin (polyethylene glycol, Sigma) to prevent the tetrodes from bending during surgery.

Anaesthesia was induced and maintained using halothane (Merial Animal Health, UK) as rats were placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA), and bilaterally implanted with recording electrodes. After craniotomy, dura was pierced and electrodes were lowered to the target site (rat 6225: anterodorsal thalamic nucleus, coordinates AP

[2] Over two years, I performed electrode implant surgery on 31 animals intended for use on this experiment, three of which yielded HD cell recordings, one of which (6225) yielded data shown here. The other two rats from which data were collected (0304 and 4322) were implanted by JAA and RFL, colleagues in the lab, respectively. Rat 4322 was previously trained to run a T-maze alternation task in a different room.

-1.8 mm, ML ± 1.3 mm, DV -3.9 mm relative to bregma; rat 0304: postsubiculum, AP -7.0, ML ± 2.8, DV -1.7 mm; rat 4322: hippocampal CA1, AP 3.5, ML ± 2.5, DV -1.5 mm). Electrode assemblies were affixed to the skull using small screws (Fine Science Tools) and dental acrylic. Each assembly was connected to a skull screw using copper wire, allowing the animal to be grounded through the recording system. Analgesia was administered in oral form (Large Animal Rimadyl, Pfizer, UK) in the animals' water supply. This analgesic solution was freely available to all animals from 24 hours pre-surgery until 48 hours post-surgery. Rats were allowed 1 week recovery time before screening for cells began.

At the end of the experiment animals were terminally anaesthetised with sodium pentobarbitol (Euthatal, Merial Animal Health, UK). Small electrolytic lesions were made on the electrode tips (electrode positive, using a 9V battery for 10 sec.) and animals were perfused intracardially with 0.9% saline followed by 4% formalin. The brains were removed and stored in Formalin for a minimum of 24 hours. Brains were then placed in a solution of 2% potassium ferrocyanide made from 10% formalin in saline for 24 h. Coronal 30μm sections were cut on a cryostat with every fifth section recovered for histological analysis. These recovered sections were mounted on gelatine subbed slides, stained with 0.1% cresyl violet acetate and coverslipped using DPX. The location of the electrode tips was then assessed by examining each section under a microscope (Wild M420, Switzerland). For display purposes, images of selected sections were transferred to a computer using a slide scanner (Epson F-3200) at 3200 dpi.

6.2.3 Recording electronics

After post-surgical recovery rats were screened for unit activity using an Axona (St. Albans, UK) 32-channel recording system equipped with a two-spot tracking system as rats sat on a paper towel-lined dish 25 cm in diameter. Each electrode assembly was connected to a recording headstage, one of which contained two clusters of infrared light-emitting diodes (LEDs), one small (2 LEDs) and one large (4 LEDs), 6 cm apart. The output of a monochrome CCD camera (Panasonic, 50Hz frame rate) mounted overhead fed into a two-spot tracking system which outputs time-stamped positions of the largest and second-largest cluster of pixels exceeding an adjustable luminance threshold. These points usually correspond to the small and large LED clusters on the headstage, with the position of the rat defined as the average and the head direction as the angle between the these two points.

Neuronal activity was amplified through unity gain buffer amplifier chips on the headstages, relayed through a flexible tether connected to a ceiling-mounted commutator, amplified 1000-fold, and band-pass filtered between 600 and 6000Hz. The amplified signals were digitised at 50KHz, further amplified (10-30 times) and displayed on a personal computer

monitor. Signals were monitored visually for unit activity above noise and background activity levels, and custom analysis software was used to plot the firing characteristics of putative cells[3]. When directional firing was found, the recording protocol began (see below). When no suitable units were found, the electrodes were advanced 20-80 μm and the screening procedure repeated no less than 6 hours later. During recording sessions, tracking data was recorded continuously at 50Hz, and neural data stored when any signal channel exceeded an amplitude threshold defined by the experimenter: for every such event, 1 ms of neural activity (from 0.2 ms before to 0.8 ms after when threshold was reached) was timestamped and stored for the four channels on the corresponding tetrode.

6.2.4 Experimental protocol

Recording sessions

Once a unit with directional firing was identified, a baseline recording session (for use in assessing recording stability) on the screening dish was collected before the experimental session on the apparatus (described in Section 5.2.2) commenced. The screening dish was located outside the curtained enclosure containing the apparatus, with the experimenter and recording equipment in the adjoining room (Figure 6.2a). After the baseline session, the rat was placed in an opaque holding box and transported by the experimenter into the curtained apparatus enclosure whilst remaining plugged in to the recording system[4]. Then the disorientation procedure and testing protocol (probe trials described in section 5.2.3, "testing") began. Rats were allowed to fetch a few food chunks from the centre of the apparatus, returning to a home box to eat. After a couple of such "fetches", when the rat next entered the centre, a tube was raised to confine the rat to the centre for 60 seconds. During this time, the apparatus was cleaned, the home box replaced with a clean one, and three additional boxes inserted at 90° intervals. In some ("rotation") trials, the tube was rotated 90° over 60 seconds. After the rat made a return to one of the home boxes, at least 5 minutes of data was collected before it was returned to the holding box, to be put back on the screening dish for another baseline session. This sequence was repeated for as long as recording stability could be maintained and rats remained interested in performing the task.

[3]During a typical screening session, 4-8 minutes of data was collected for this analysis, which used an automatic clustering algorithm (KlustaKwik, K. Harris) to identify putative units. For clusters exceeding a directional selectivity statistic (Watson's U^2, Batchelet 1981), directional and place tuning curves were plotted. This procedure served to increase the chances of identifying units that may have been missed by visual monitoring alone, and to confirm suspected directionality.

[4]This was made possible by attaching the commutator to an upside-down wooden toy ambulance which could be moved along linear track mounted on the ceiling (Jamie Ainge and Livia de Hoz).

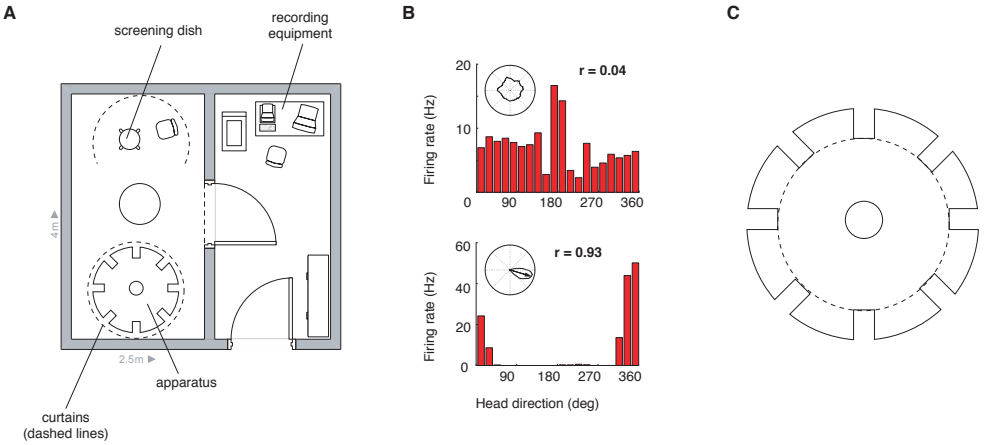

Figure 6.2: A: Recording room layout. Screening sessions and pre-recording baseline sessions were collected from the screening dish (top left). The rat was then transported in an opaque container into the curtained enclosure containing the apparatus (bottom left) where the disorientation procedure began, followed by the actual recording session. During recording sessions, the experimenter monitored the rat's progress from the desk in the adjacent room (top left) returning to the apparatus either to place food chunks or to clean the apparatus and replace home boxes during confinement. **B**: Illustration of the tuning curve length measure *r*, which is low for a cell without directional tuning (top) and high for a clear head direction cell (bottom). **C**: To compute the rat's choice of return after confinement, the angle between where it touched the dashed line and the middle of its starting location was taken.

Training

Unlike the protocol described in Chapter 5, rats did not receive controlled training to criterion. At the time of the recording sessions reported here, rats had varying degrees of experience with the experimental apparatus. Rats 6225 and 0304 were experienced subjects who would complete a session (i.e. make a couple of fetches, tolerate a tube raise, and make a return choice) within 10 minutes. Rat 4322 only had two habituation sessions on the apparatus and at the time of recording would not enter the centre of the apparatus voluntarily on all sessions except the first one. On those sessions, the rat was gently picked up and slowly placed in the raised tube, whereupon the trial proceeded as normal, the rat apparently motivated to return to the home box.

6.2.5 Data analysis

It was of interest to determine whether neural activity recorded from head direction (HD) cells shifted in preferred firing direction following confinement (Figure 6.1), and whether such shifts correlated with spatial behaviour (the rats' chosen return).

Unit isolation

All of the data acquired during baseline and recording sessions were analysed off-line. Using the timestamped neural data, single units (putative cells) were isolated based on the relative amplitudes of signals recorded simultaneously from a tetrode. Additional waveform characteristics, particularly energy[5], were also used for isolation. Waveform characteristics were plotted as a scatter plot of one of the channels versus another. Individual units formed clusters of points on such scatter plots, the boundaries of these plots were manually defined using the MClust cluster cutting package (A.D. Redish, University of Minnesota)[6]. Isolation quality of clusters was quantified using L-Ratio and Isolation Distance (Schmitzer-Torbert et al. 2005). L-Ratio reflects the extent to which spikes not in a cluster are close to its centre, indicating the likelihood of a Type II error (i.e. leaving out a spike waveform that is in fact part of the cluster). Isolation Distance is the distance of the nth closest spike not in the cluster (of size n) to the centre of the cluster, and reflects the probability of a Type I error (i.e. including spikes in a cluster that are not actually part of it). Because these measures can be unreliable for recordings close to the recording threshold, isolation quality was also rated on a subjective scale of 1 (very well isolated) to 5 (poorly isolated), based on the size of the waveforms relative to background and on the closeness and degree of potential overlap between neighbouring clusters. These ratings were made independent of the firing properties of the cell or its behaviour on the task. For each cluster, interspike interval histograms, auto-correlograms, and plots of spike amplitude on each channel over time were generated and inspected for suspicious activity.

Inclusion criteria

Isolated units were assessed for inclusion in the analysis based on how coherently they expressed a single preferred firing direction (PFD, i.e. to what extent they behaved like a "classical" head direction cell with a Gaussian or triangular tuning curve). It is possible for cell firing to contain information about head direction without having a clear single PFD (e.g. Johnson et al. 2005), but for the purposes of this experiment we were interested in observing PFD changes in single cells. For each recording session, spikes from a cell were separated into "pre-confinement" and "post-confinement" segments. For each segment, a directional tuning curve was constructed by summing spikes and time spent for each angular bin of direction θ_i (bins were 1° wide); firing rates F_i were obtained by dividing number of spikes by amount of time spent for each bin. A measure of the cell's directional consistency was obtained by computing the "tuning vector length" r of the vector mean of these bins weighted by their firing rates:

[5] Energy is the sum of squares of each waveform sample (L2 norm).

[6] A file format conversion program that allowed Axona system files to be read by MClust (and other clustering programs) was written by the author.

$$C = \frac{1}{\sum_{i=1}^{n} F_i} \sum_{i=1}^{n} F_i \cos\theta_i, \quad S = \frac{1}{\sum_{i=1}^{n} F_i} \sum_{i=1}^{n} F_i \sin\theta_i, \quad r^2 = C^2 + S^2 \tag{6.1}$$

This measure, the length of the circular mean or population vector of the cell's directional tuning curve, expresses how coherently a cell expresses a single PFD: a cell not tuned for direction or a directional cell with opposing bimodal PFDs would have r approaching 0, while a well-isolated head direction cell can exceed 0.9 (illustrated in panel B of 6.2 on page 110). If a cell had a tuning vector length $r \geq 0.3$ for both pre- and post-confinement segments as well as the pre- and post-recording baseline sessions, it was included for analysis. For all cells included this r value was sufficient to be indicative of a nonrandom distribution of firing rate along the directional range (Rayleigh test for uniformity); factors contributing to low r values include poor cell isolation, suboptimal tracking quality, and preferred direction drifts over time. It seems likely some of the cells recorded are not "classic" head direction cells (Taube et al. 1990a; Taube 1995), but since they were stable and had a significant single directional preference, they were considered relevant and included in the current analysis. The tuning curves shown in Figures 6.3–6.10 plot the firing rates against the corresponding bin's direction θ_i in polar coordinates, after smoothing by taking the circular mean of a 11-bin window around each bin (i.e. $G_i = \frac{1}{11}\sum_{i-5}^{i+5} F_i$, where i wraps around from 359 to 0 and vice versa and G_i are the smoothed firing rates).

Preferred firing directions

Cell PFDs were computed for pre- and post-confinement using Equation 6.1 and extracting the direction of the vector resultant:

$$\bar{\theta} = \begin{cases} \tan^{-1}(S/C) & (\mathrm{S} > 0, \mathrm{C} < 0) \\ \tan^{-1}(S/C) + \pi & (\mathrm{C} < 0) \\ \tan^{-1}(S/C) + 2\pi & (\mathrm{S} < 0, \mathrm{C} > 0) \end{cases}$$

This method for determining PFDs, although different from previously reported methods which involve fitting a triangle or a Gaussian to the cell's tuning curve (Taube et al. 1990a; Blair et al. 1997), yields comparable results to the Gaussian fit method for cells that have approximately Gaussian tuning curves, but makes no assumptions about tuning curve shape. This has the effect of being more accurate in cases where the tuning curve isn't strictly Gaussian, but is also noisier, since "stray" spikes are able to influence the PFD instead of being excluded by the fitting process. Because the sliding window tuning curve analysis (below) relies on computing tuning curves based on limited data where often tuning curves were incomplete and definitely not Gaussian, this method was preferred.

Comparison of the pre- and post-confinement PFDs is sensitive to PFD shifts over time. To ensure that PFDs were obtained when the cell had a stable PFD, fine-timescale PFDs

were plotted as a function of time by computing the PFD in a sliding window of 240s in length. This enabled visual inspection and selection of appropriate time intervals to reflect the cell's true PFD as close before and after confinement as possible. As an indication of how coherent each data point indicated a single PFD, 90% confidence intervals around the mean were computed (Fisher 1993)[7]. Note that tight PFD confidence intervals do not always indicate an accurate estimate of the cell's true PFD: in particular, limited directional sampling can bias the PFD estimate, for instance when the rat faces a constant direction at the "tail" of a given cell's directional tuning curve throughout the PFD estimation window. Furthermore, when there is a genuine PFD change, the time course over which this is reflected in PFD window analysis depends additionally on the width of the window and the relative spike counts from the old and new PFDs. Because of these limitations, conclusions based on this analysis require careful examination of the circumstances for individual cases.

Behavioural responses

The rat's choice of return post-confinement was defined as the crossing point of the rat's path with an imaginary circle, concentric with the table and covering the innermost point of the home box bays (Figure 6.2 on page 110). This method is more accurate than merely recording the choice of home box as in the behavioural experiment, enabled by the tracking system.

6.3 Results

Neural activity from head direction (HD) cells was recorded as rats (n = 3) performed the path integration task introduced in Chapter 5. A total of 11 sessions which yielded at least one cell which met the inclusion criteria (*Methods*) were recorded. Most cells were recorded for several sessions; the total number of cells is estimated at 8, although no explicit effort was made to keep track of cell identity across sessions. Cells were recorded from the anterior thalamic nucleus (1 cell), the postsubiculum (5 cells) and the CA1 region of the hippocampus[8] (2 cells).

It was of interest to determine first, whether confinement and/or rotation during a foraging trip caused a shift in the preferred firing direction (PFD) of HD cells, and second, whether any such shift was related to the rats' behaviour, specifically where they chose to return to after confinement. To assess this, HD cell activity was recorded first as rats fetched food

[7] As noted before, this measure is directly related to the mean tuning vector length *r* introduced above, but confidence intervals preserve units of degrees for convenient plotting on the same axes as the preferred direction.

[8] Although relatively rare, several reports of HD recordings have been noted in this area, for instance by Ranck Jr. (2005), Leutgeb et al. (2000), and P.A. Dudchenko (personal communication). It is possible these recordings were in fact from the axons of HD cells in entorhinal cortex.

chunks without the tube being raised, and compared to activity recorded post-confinement. Results from individual sessions are shown in Figures 6.3-6.11, with panel A indicating the rat's path on the apparatus before (red) and after confinement (blue). When available, the rat's inward and return paths to and from the centre tube are plotted in a thicker line. Taking Figure 6.3 on the next page as an example, panel A shows that before confinement, the rat's home box was located in the northwest (as can be seen from the high path density there, also indicated by the red dot). After confinement (and 90° counterclockwise rotation in this case), the rat took the thick blue path from the centre, corresponding to a choice of 78° (indicated by the blue dot; positive numbers are counterclockwise), apparently ending up in the home box in the southwest, as suggested by the position sampling density there.

Panel B shows the tuning curves of two head direction cells recorded during this session, with one row for each cell (this layout is maintained through panels B-D). Tuning curves are plotted in polar coordinates, showing firing rate against the direction in which the rat pointed its head. The red tuning curve corresponds to pre-confinement, and the blue curve to post-confinement. Arrows indicate the preferred firing direction associated with each tuning curve (for clarity only plotted if the tuning vector length $r > 0.5$, see *Methods*). In this example, the two cells shifted their preferred directions by 83° and 86° respectively, consistent with previous reports on head direction cells maintaining their relative firing directions (Taube et al. 1990b; Knierim et al. 1998; Yoganarasimha et al. 2006).

To provide a view of the cells' preferred directions on a finer timescale, their preferred directions were plotted over time by computing PFDs using a sliding window around each time point (see *Methods*). Panel C shows the preferred direction over time in dark green, along with 90% confidence intervals in light green, overlaid on the rat's head direction over time (small black points) and individual spikes (purple points). The shaded yellow area indicates the time of confinement; in this example, pre- and post-confinement data were collected in separate files, hence the absence of data during confinement. From observing the green data points indicating preferred direction, is is apparent that at least before confinement, both cells had stable preferred directions, which (consistent with the tuning curve shifts in panel B) shifted coherently after confinement. Towards the end of the graph there appears to be a clockwise shift in preferred direction starting for both cells; as indicated by the blue line above each graph, this was not included in the tuning curve and preferred direction analysis in panel B.

Panel D shows the interspike interval histogram (note logarithmic scale) and the autocorrelogram on two different timescales for each cell. Such data can give an indication of isolation quality ("unbiological" spiking patterns such as activity within the refractory period or at 50Hz intervals are signs of poor isolation), and frequency modulation can give clues about cell type. In this case, the top cell (which is well-isolated) has a relatively clean refractory period compared to the bottom cell which is contaminated by some noise spikes.

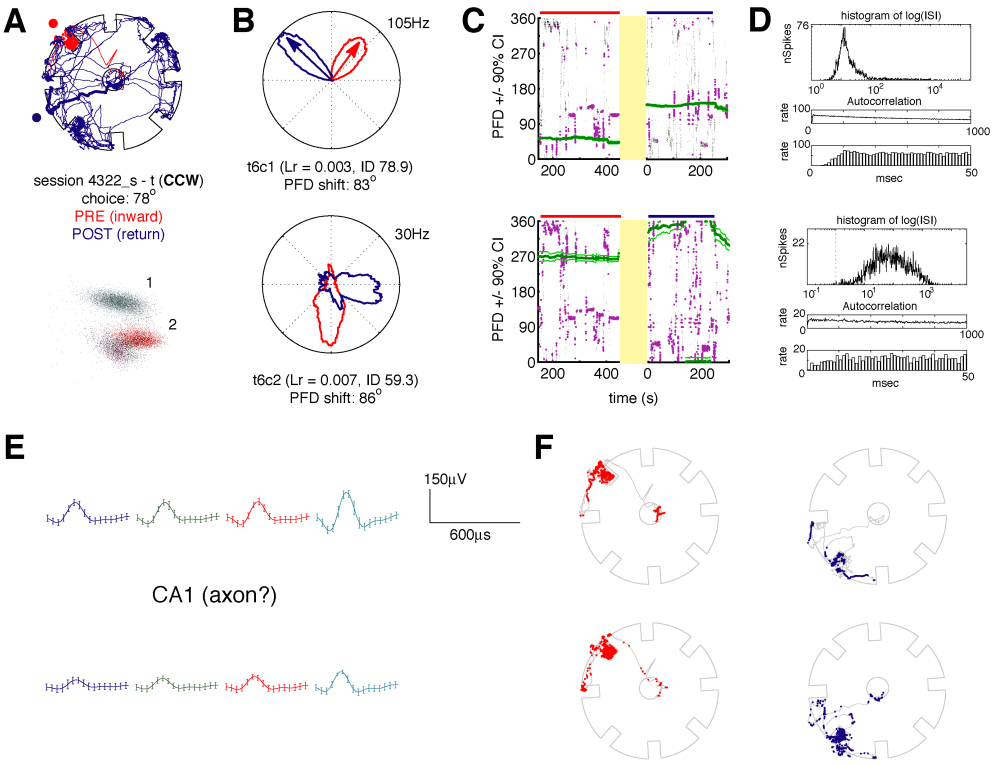

Figure 6.3: Slow rotation of the rat accompanied by a corresponding change in the preferred firing direction (PFD) of two simultaneously recorded head direction (HD) cells, and in the rat's return choice. **A,top**: The rat started from the northwest location (red dot, red lines indicate pre-confinement position), and after 90˚ CCW rotation, returned to 78˚ (blue dot, thick blue line indicates initial return). Post-confinement position sampling is indicated in thin blue. **Bottom**: sample cluster plot in energy space of neural activity recorded during this session. **B**: Tuning curves of head direction cells recorded during this session (clusters 1 and 2, one for each row), with the pre-confinement tuning curve in red and the post-confinement tuning curve in blue. For the two cells respectively, preferred firing directions shifted 83˚ and 86˚, in close agreement with the rotation and behavioural choice. Tuning curves are computed over the period indicated by the lines of corresponding colour in panel **C**, with the position sampling in panel **A** restricted to the same period. **C**: Cell preferred firing directions (dark green dots, 90% confidence intervals in light green) are stable pre- and post-confinement (confinement period indicated in pale yellow). Purple dots indicate spikes, small black dots head direction tracking samples. Coloured bars indicate the time window over which the position and tuning curves in previous panels are computed. **D**: Interspike interval histograms (top) and autocorrelograms (bottom) on two different time scales, confirming good isolation for cluster 1 and marginal isolation for cluster 2. (A scatterplot of the energies of waveforms recorded from three tetrode channels is shown in the bottom left of the figure.) **E**: average waveforms ($\pm$ SD) on each of the four tetrode channels, one row per cluster. **F**: Raw spike positions (coloured dots) plotted on top of the rat's position (grey line).

There is no theta-rhythm modulation apparent.

6.3.1 Head direction signal shifts induced by confinement

The above example (Figure 6.3) showed a session in which a 90° counterclockwise rotation of the tube during confinement induced a matching PFD shift (83° and 86°) in two HD cells. Figure 6.4 on the following page shows the effects of a clockwise rotation (from a different rat) on three simultaneously recorded HD cells. All three cells showed tuning curve rotation in the corresponding direction, although none rotated by a full -90° (range: -28 to -82°, mean -58°). (This inconsistency could be due to poor isolation quality combined with low firing rate in all three units.) This "underrotation" of the tuning curves was accompanied by an "overrotation" of the rat's return choice of -122°. Note that unlike the previous session, this session was recorded in a single data file, with data during confinement included. The time course of the PFD shifts as shown in panel C appears to suggest that PFDs shifted *after* confinement; however, this is probably a result of using a 240s-wide time window, and does not reflect the real time course of the shift accurately (see section 6.2.5 on page 112 for details).

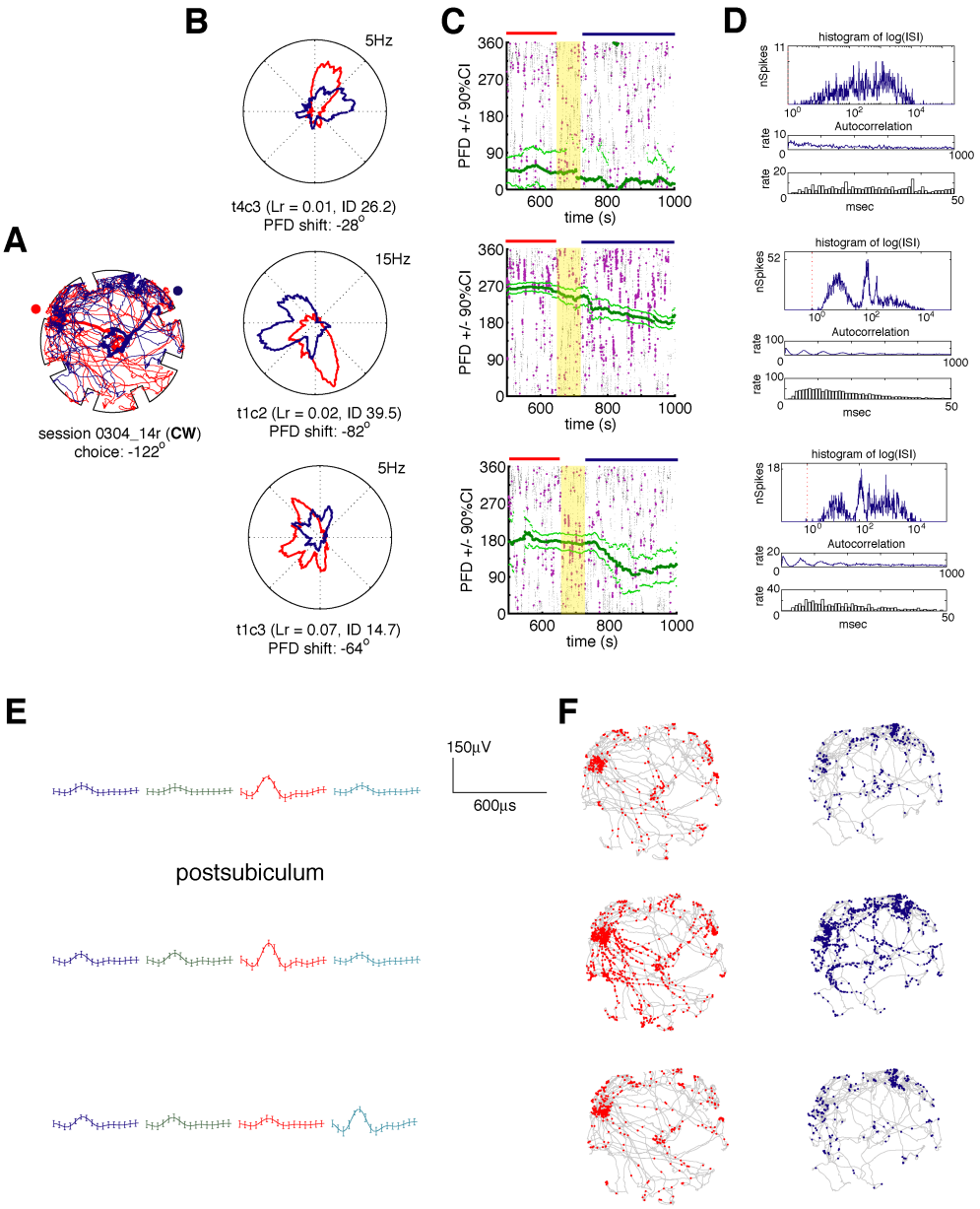

Figure 6.4: Another slow rotation, clockwise this time, of a different rat, accompanied by a (more or less) corresponding change in the preferred firing direction (PFD) of three simultaneously recorded postsubicular cells with directional tuning. Figure layout as in Figure 6.3 on page 115; the cluster on the first row is from a different tetrode than the other two, which are on the same tetrode.

In the previous two examples, rotation resulted in PFD shifts. However, rotation was not necessary to induce PFD shifts: in several cases, confinement without rotation resulted in "spontaneous" PFD changes, as in Figure 6.5 on the following page. In this case, two HD cells shifted their PFDs by 53° and 63°, with the rat making a corresponding choice to 48°. Another example of this is shown in Figure 6.6 on page 119, where despite the tube not being rotated, two HD cells shifted by 36° and 88°, with the rat accordingly choosing 42°.

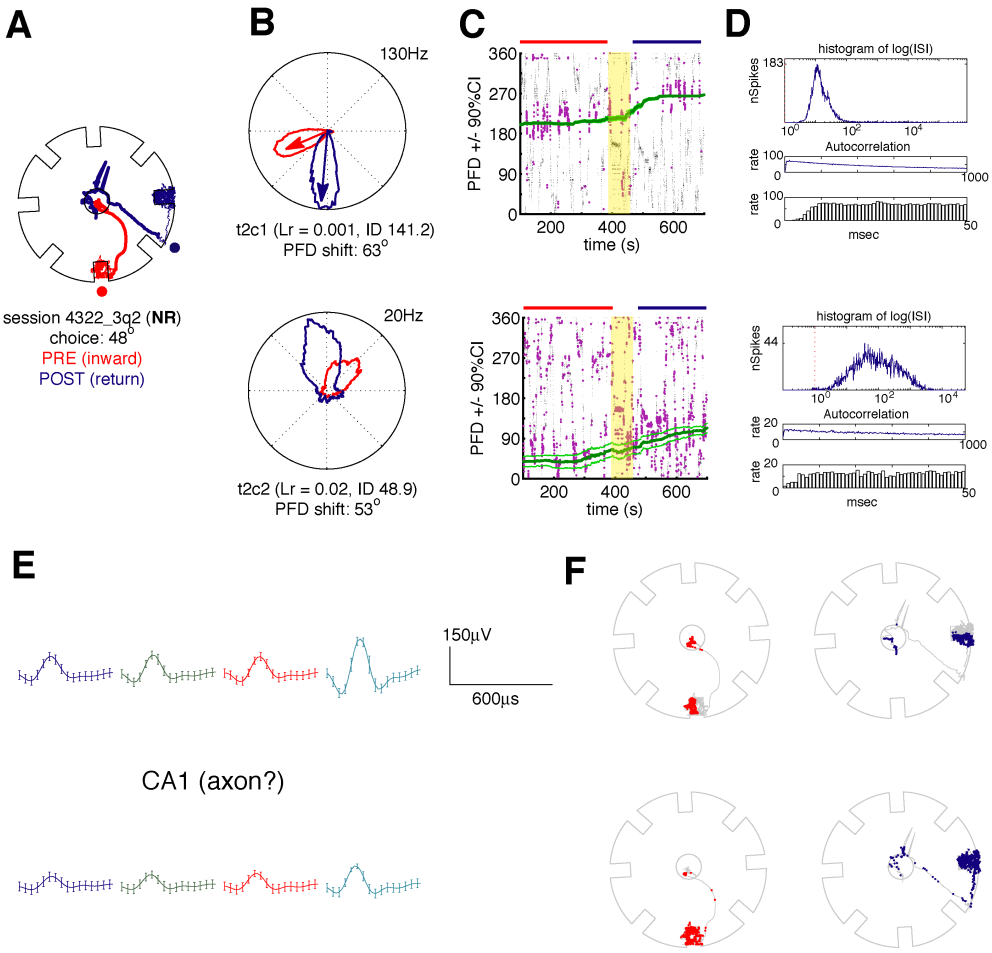

Figure 6.5: An example of spontaneous PFD drift during a non-rotation session. The rotation of the cells matched the rat's behavioural choice in this case.

PFD shifts during non-rotation confinement appeared to fall on a continuum from large (as in the previous examples) to small: Figure 6.7 on page 120 shows an example of two HD cells showing small or nonexistent PFD shifts during confinement (-32° and -3°), with the rat accordingly returning to the original location relatively accurately (-19°). Figure 6.8 on page 120, from a different rat, also shows a small shift combined with an accurate (albeit circuitous) return.

6.3.2 Head direction signal shifts in relation to behaviour

All 6 previous example sessions showed some degree of correlation between PFD shift (either spontaneous or rotation-induced) and choice of return. However, this was not always the case. Figure 6.9 on page 121 shows a non-rotation confinement session where two HD cells (one of which with good isolation quality) shifted their PFDs the *opposite* way from the rat's behavioural choice.

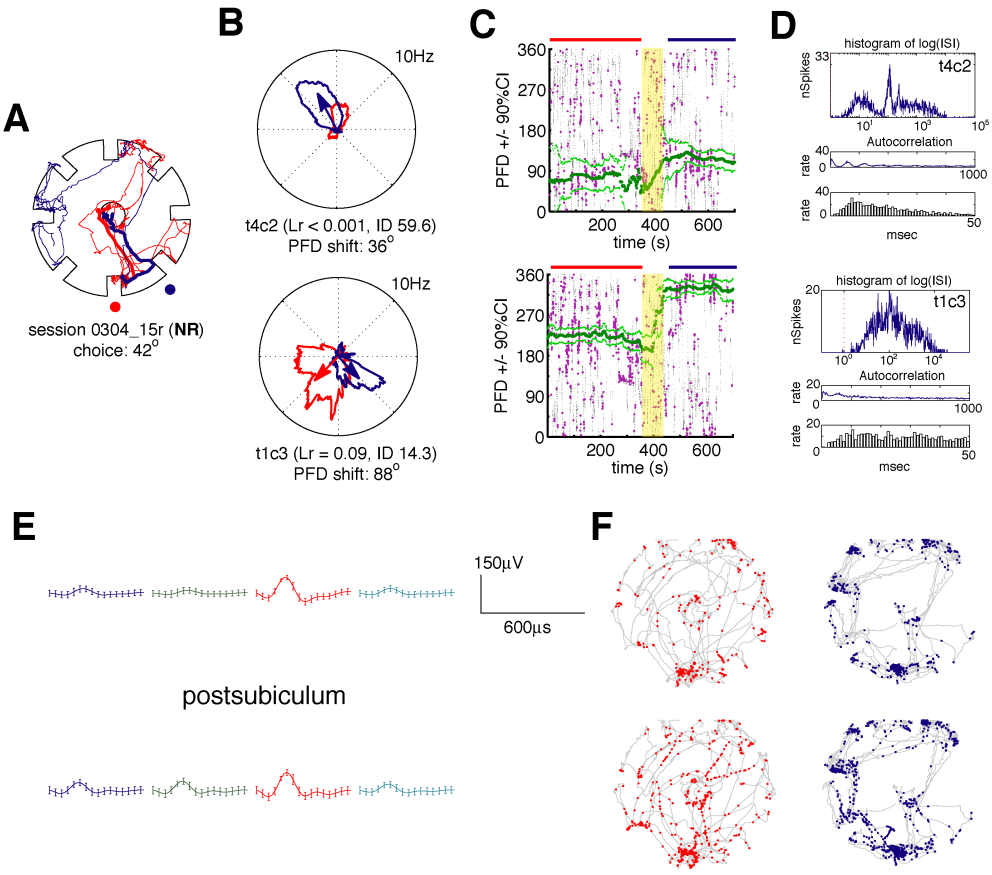

Figure 6.6: Another example of spontaneous PFD drift during a non-rotation session.

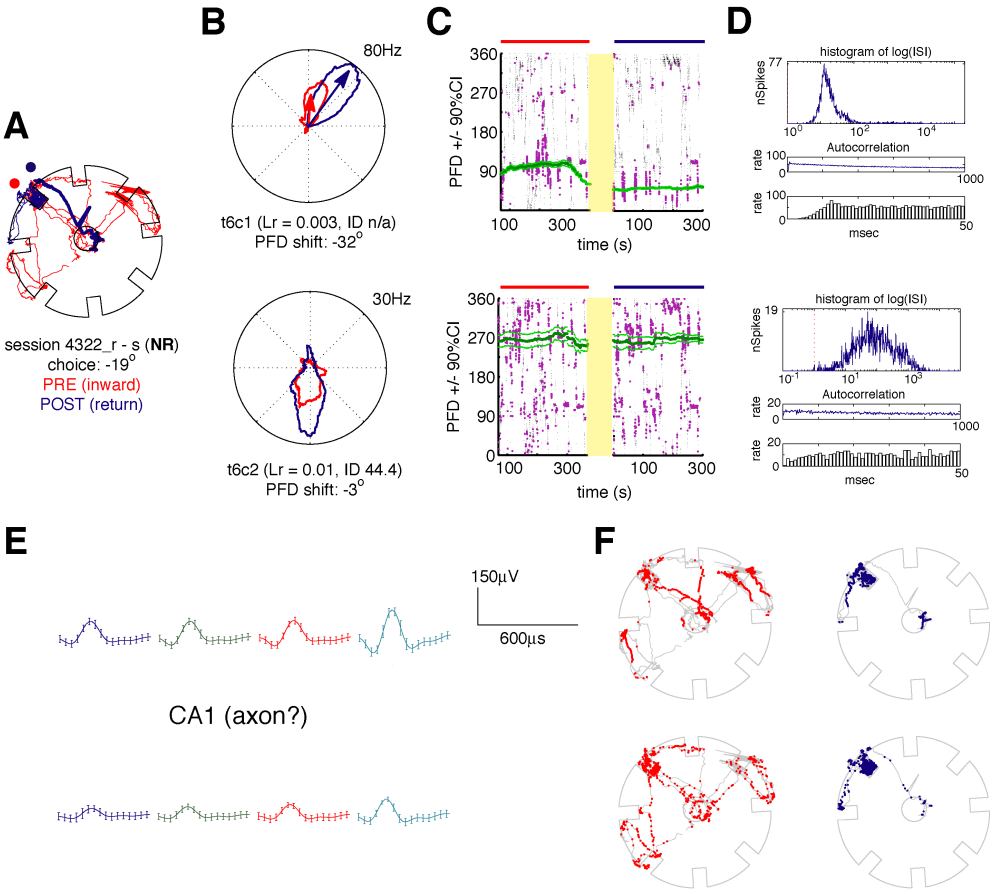

Figure 6.7: A session with small PFD drift during a non-rotation session, accompanied by accurate return.

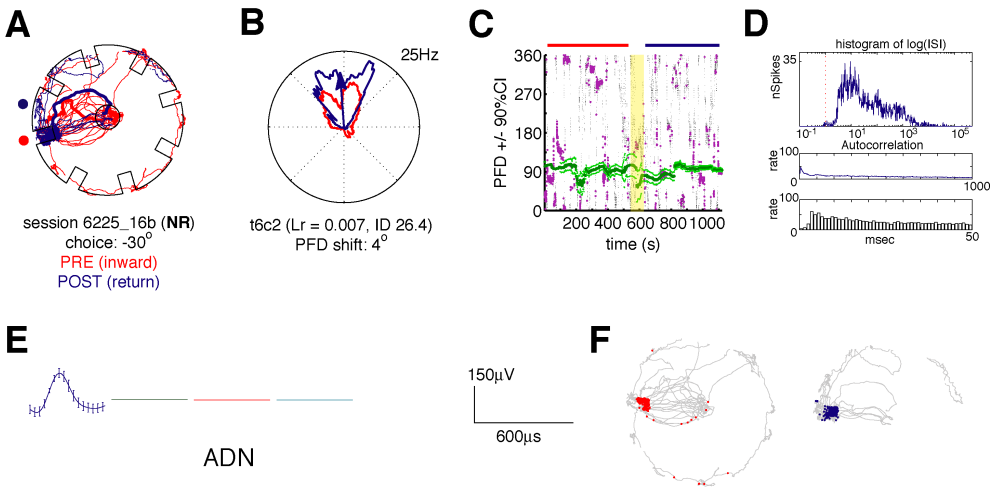

Figure 6.8: Another small PFD drift during a non-rotation session accompanied by accurate return.

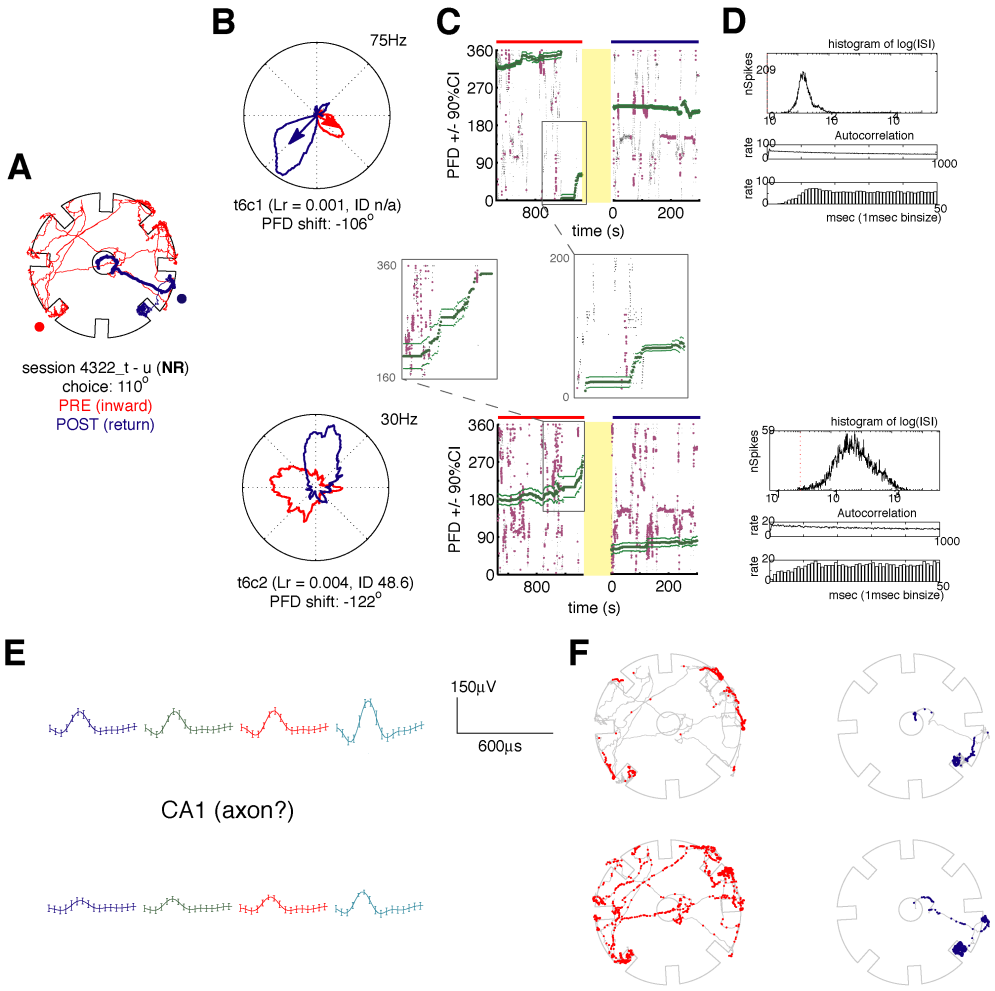

Figure 6.9: Apparent mismatch no rotation session, where HD cells seemed to shift preferred directions one way, yet the rat chose to return the opposite way. **A**: Position tracking indicates the rat choosing to return to 110°. **B**: Tuning curves shifted by the opposite amount (-106° and -122° for the two cells respectively), however, this might be obscuring some fine-timescale changes. **C**: Sliding window analysis reveals a possible preferred firing direction shift just before confinement. The two inset plots show a magnified view of the 100s before confinement, using a smaller time window (120s instead of the 240s used for the main panels). If instead of computing pre-confinement tuning curves over the time indicated by the coloured bars (as in panel **B**), preferred firing directions are estimated from this analysis, return choice and HD signal shift are in agreement (see main text). **D-F** as before.

However, this may be a case where the temporal resolution of average tuning curve analysis does not reflect fast-timescale changes that may be relevant. Observe how at the end of the pre-confinement PFD plot in panel B, both cells seem to change their preferred directions suddenly (counterclockwise/positive). The insets show the same data zoomed in and plotted with a smaller window size (120 s) for added resolution. There seems to be a lack of head direction samples (small black dots), but the inset for cell 1 (top) shows spikes in the middle of the inset where none were fired when the animal sampled the same HD at the

beginning of the inset, suggesting a possible PFD shift. Since the pre- and post-confinement data were collected in separate data files and analysed separately, this could not have been due to post-confinement spikes being included in the pre-confinement data PFD plot. If we were to take the PFD estimate from just the final window sample point (75° and and 270° for the two cells respectively) the resulting PFD shifts are 150° and 156° (instead of -106° and -122°), much closer to the behavioural choice of 110°.

Another possible mismatch session is shown in Figure 6.10, where during a non-rotation session, the rat chose to return 50° clockwise, with two HD cells shifting a similar amount counterclockwise. It is notable that both cells exhibit some drift in preferred direction, with for cell 2 in particular the initial change around confinement time being in the negative (clockwise) direction, consistent with behaviour.

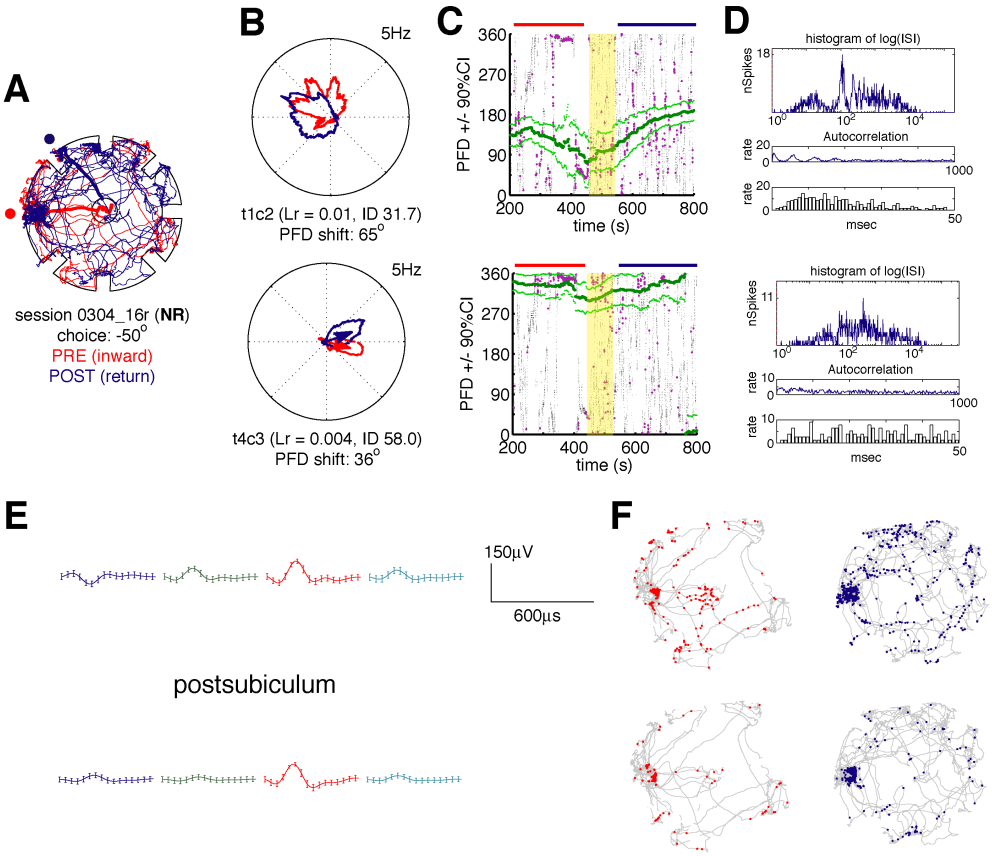

Figure 6.10: A slightly more convincing mismatch session, where after no rotation confinement the rat returns clockwise, but two simultaneously recorded cells change their PFDs in the opposite direction (see main text).

The final mismatch session is shown in Figure 6.11 on the following page, and again, there are some factors possibly precluding straightforward interpretation of an apparent clockwise PFD shift (-94°) coupled with clockwise behaviour (52°). Pre-confinement, directional sampling was largely limited to the preferred firing direction, and post-confinement,

the cell's mean firing rate was reduced by about 75%. Two other cells were recorded simultaneously (one of which with very good isolation, ID > 200, L-ratio $< 10^{-5}$) and although these cells didn't meet the criteria for inclusion due to not being directional enough, their "preferred directions" rotated clockwise coherently (107° and 106°) which would suggest a smaller mismatch between PFD shift and behaviour than the cell shown here indicates.

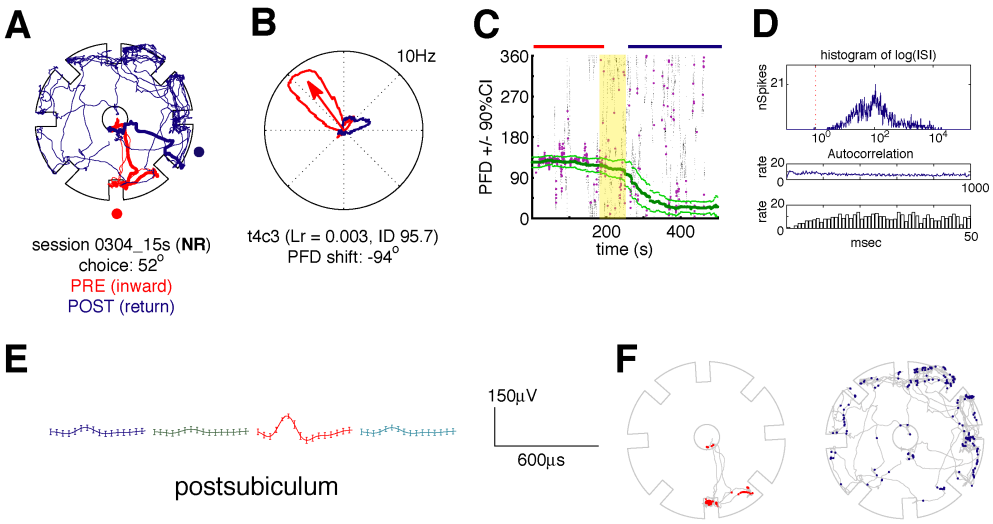

Figure 6.11: Final mismatch session.

Summarising across all sessions, Figure 6.12 on the next page shows the rat's choice of return plotted against changes in cell PFDs, for the data from all the above sessions plus a non-rotation session with non-rotating behaviour and cells not shown separately (0304_16s). The ambiguous session in Figure 6.9 is indicated in its two possible positions, with the other mismatch sessions also labelled. The dotted line indicates $x = y$, where behavioural choice and cell PFD change are equal. Each data point has three further dimensions apart from its position on the plot. *Colour* indicates *which rat* the cell was recorded from; each *session* has a unique *shape*, and their *size* is proportional to *tuning vector length*. So, the three small five-pointed blue stars on the left of the plot are cells recorded simultaneously from rat 0304, and which are not as well tuned for direction as most other cells.

When the ambiguous data point is excluded, there is a significant positive correlation between cell PFD shift and behavioural choice: T-linear circular correlation (Fisher 1993), $r = 0.46$; $p = 0.001$, this correlation increases slightly when it is corrected and included, and decreases when it is included in its non-corrected form. Accordingly, in the plot, most data points lie on or close to the dashed line. A different measure quantifying the relationship between PFD shift and choice can be obtained by comparing the distribution of differences between PFD shift and behaviour to the level expected if the two were independent, i.e. 90° different on average. The observed average difference (43.3° ± 9.4°, ambiguous

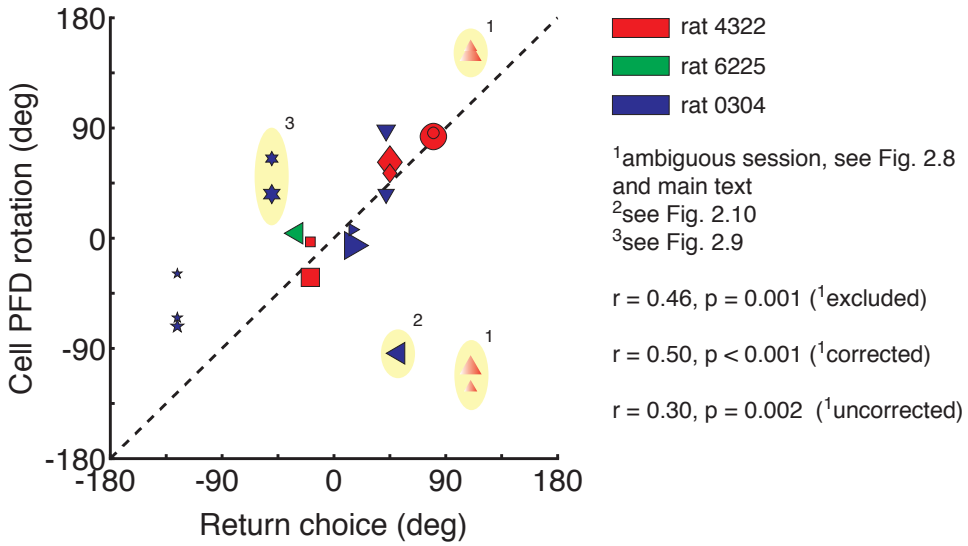

Figure 6.12: Head direction (HD) cell preferred firing direction (PFD) shifts correlate with behaviour on the path integration task. Shown is a scatterplot of the angular point on the apparatus rats chose to return to after confinement, against shift in preferred direction of recorded HD cells, for all recording sessions. Each point corresponds to a recording of a single HD cell during a single session. Each data point has three further dimensions apart from its position on the plot: colour indicates which rat the cell was recorded from, different shapes correspond to different recording sessions, and size is proportional to tuning vector length (larger shape indicates better tuning). The dashed line indicates $x = y$; PFD shifts are significantly correlated with behavioural choice: T-linear circular correlation, $\rho_T = 0.46$; $p = 0.001$ when the ambiguous data point (1) is excluded (see main text). Other mismatch sessions (indicated by numbers) are included.

data point removed) is significantly below this chance level (Student's one-sample t-test: $t_{(16)} = -4.9$; $p = 0.001$). Including the uncorrected ambiguous data does not affect this result ($t_{(18)} = -3.17$; $p = 0.005$). Thus, even in this limited data set, there is evidence of a link between the HD signal and the rats' behaviour.

6.3.3 Histology

Figure 6.13 on the following page shows electrode tracks for the subjects in this experiment. The exact position of the electrode tips could not be ascertained in animals 0304 and 6225, especially in the ADN animal (6225) whose electrode assembly unfortunately detached prematurely. However, the cannula/electrode track (just visible above the AD/LD border) appears to be headed for AD/LD. It is possible that this cell was actually recorded from the laterodorsal thalamus. In the PoS animal (0304), the electrodes appear a little more lateral than where the atlas places PoS; however, apart from the cells shown in the results, an unambiguous, "classic" HD cell was also recorded from this animal some days earlier (although not on the path integration experiment), suggesting that the electrodes were really in PoS. The electrodes in rat 4322 were located near the cell layer of hippocampal

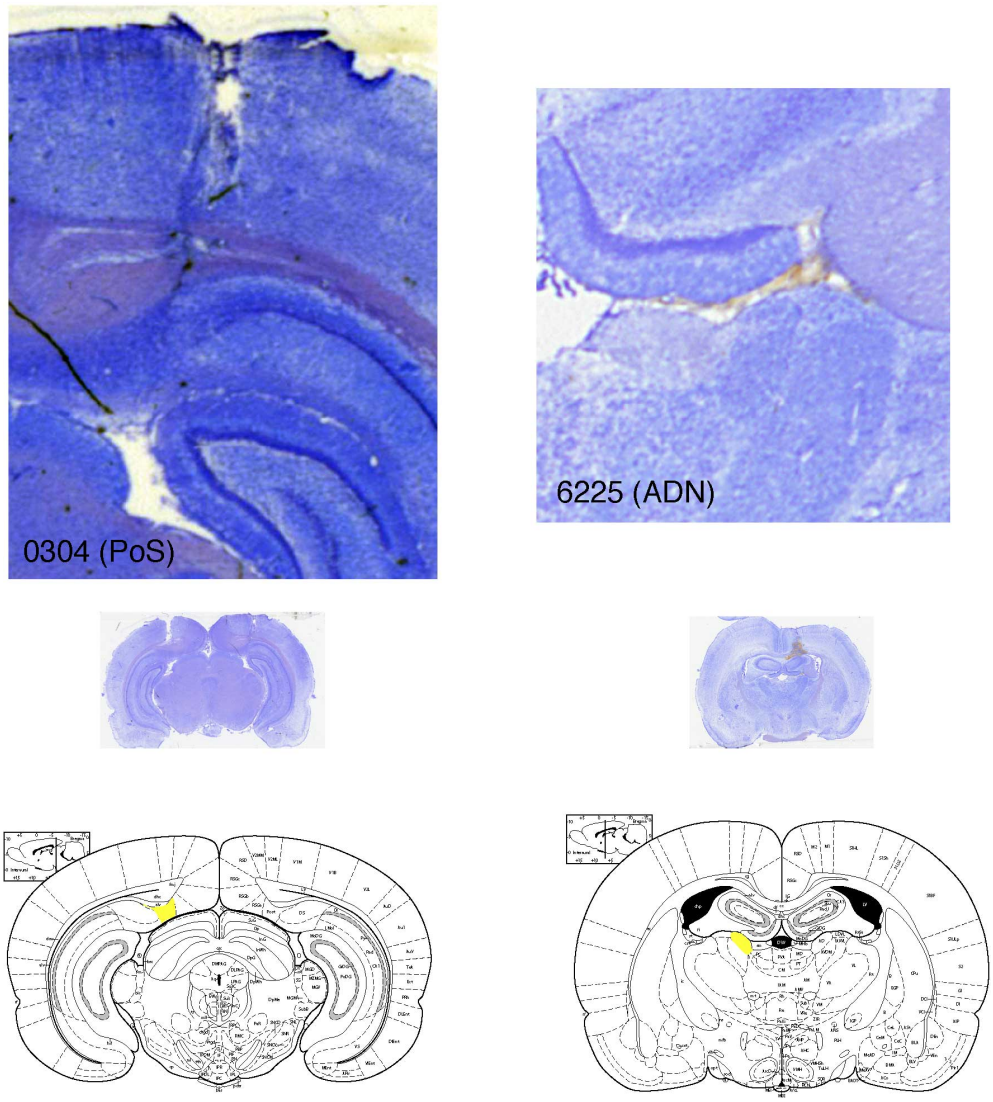

Figure 6.13: Cresyl-violet stained brain sections for rat 0304 (left) with electrodes targeting the postsubiculum (PoS), and rat 6225 (right) with electrodes targeting the anterior thalamic nuclei (ADN). The exact position of the electrode tips could not be ascertained, especially in the ADN animal whose electrode assembly unfortunately detached prematurely. However, the cannula/electrode track, just visible above the AD/LD (laterodorsal thalamic nucleus) border, appears to be headed for AD/LD. In the PoS animal, the electrodes appear a little more lateral than where the atlas places PoS; however, apart from the cells shown in the results, an unambiguous, "classic" HD cell was also recorded from this animal some days earlier (although unfortunately not on the path integration experiment). On the diagrammatic brain slices (bottom, reproduced from Paxinos and Watson 1998) PoS (left) and AD (right) are indicated in yellow.

field CA1 (not shown).

6.4 Conclusions and discussion

We show that on a path integration task which requires an intact head direction system, rats' return journeys (after an outbound journey to a central point on the apparatus) are correlated with shifts in their head direction (HD) signal, on a trial-to-trial basis. This suggests that, consistent with the lesion study results from Chapter 5, rats are using the directional signal provided by the HD system to guide their return journey.

If this is the case, HD system shifts would be expected to precede the rats' behavioural choice, rather than behaviour causing a corresponding shift in the HD signal. Ideally, this would be verified by reconstructing the HD representation (from many simultaneously recorded cells) on a sub-second timescale, as in Brown et al. (1998) and Johnson et al. (2005). With current data from only 1-3 cells recorded simultaneously, this is usually not feasible. However, in the present data, rats do not appear to reset their HD signal based on their behavio-spatial choices or cues in the environment. For instance, in Figure 6.5 on page 118, the rat eventually returns to the home box at 90° relative to his starting location, treating this new location as "home"; yet, two HD cells recorded do not "snap" to this new location, rotating by less (53° and 63°). Similarly, in Figure 6.6 on page 119, the rat returns to its original home location, yet his HD cells maintain a shifted preferred direction. These and other examples strongly suggest that, under task circumstances, rats maintain an internal sense of direction independently from potential directional cues, and that their choices are guided by this sense of direction rather than the other way around.

Related to this issue of what comes first, the HD shift or the choice of return journey, is the question of how rats are solving the task; as discussed in Chapter 5, it is possible rats are not path integrating but relying on a cue inside the tube instead. The recording data indicate that HD cells do not appear to be anchored to any such cues, as shown in several examples where the HD signal has shifted coherently during non-rotation trials (e.g. Fig. 6.4 on page 117). By itself, this does not mean rats were not using cues (as implied by the dissociation between HD signal and behaviour in Golob et al. 2001); however, since rats' return choice seemed to match the drift in their HD signal, this suggests they were not relying on any cues to guide behaviour, at least in those trials. Even in cases where the recording data indicated a potential mismatch between HD signal and behaviour, rats didn't return to a location consistent with the (0° or 90°) rotation of the tube. Rats are thought to rely on idiothetic information when external cues are not available (e.g. Maaswinkel and Whishaw 1999); the present data are consistent with this. As to what is happening during mismatch sessions, it is possible that rats are not motivated to return home (perhaps attracted by a sound or "cue" somewhere) and thus simply not engaging their HD signal to

guide behaviour; or perhaps the rat "knows" its HD signal is no longer reliable (rats appear to make decisions regarding mismatches of internal vs. external cues, e.g. Knierim et al. 1998). The question of how such "switching" might occur is interesting – is it a modulation in the HD system itself (a global decrease in firing rate perhaps, of which there may be an anectodal hint in the current data), or in some downstream integrative decision area? The present data are not sufficient to observe any systematic changes in the head direction signal.

Are the shifts in the HD signal observed here the result of slow drifts, presumably due to accumulating path integration error, or of fast "remapping", due to the rat changing maps or reference frames? Again, a good way of distinguishing this would be to observe changes in the HD signal on a fine timescale by reconstruction techniques based on the activity of many cells. Even in the absence of such analysis, the present data seem to favour drift over remapping, based on several observations. In a number of clear cases (e.g. Figures 6.7 and 6.8), the HD signal does not change substantially during or after confinement. In animal 4322, shifts were observed in both an earlier and a later session; in contrast, a remapping process would be more consistent with differing PFD shifts on every trial. This lack of a within-subject consistent PFD shift is compatible with the apparent absence of directional cues (as supported by the rotations inducing matching cell and behaviour changes), which could trigger or align new maps. This leaves the possibility that the shifts are due to path intgeration error. This is supported by the observation that rats tended to move around vigorously dusing confinement (as can be seen from the tracking data), not only precluding the use of simple motor/praxic strategies but presumably encouraging path integration errors. Fine-timescale reconstruction is a possible way of relating HD system drifts to specific head movements (for a detailed proposal in this regard, see Chapter 7).

The behaviour of the HD cells recorded here, where they tended to shift coherently, is consistent with previous reports (Taube et al. 1990a; Knierim et al. 1998; Yoganarasimha et al. 2006). In the current data this tends to be noisier for less well isolated cells, as expected, but no clear counter-examples are seen, and for the best-isolated cells (rat 4322) shifts are always consistent. Each of the three rats in this experiment had the recording electrodes in a different area, and while on fine timescales differences might be apparent (and would even be informative), HD cells in different areas are thought to behave in the same coherent way on broader timescales (e.g. in terms of responding to cue rotations in the same way, Knierim et al. 1998), and no differences were apparent from this (small) sample.

Comparison with related studies

In a preliminary report, Frohardt et al. (2002) recorded from HD cells during a similar task, where rats fetched food from a circular environment, returning to a home base to eat. The main difference with the task described here is that these authors do not compare the state of the HD system within a single excursion. Instead of having a mechanism to induce Type I disorientation within a journey as in the "rotation" sessions in the present experiment, in their rotation sessions the animal's starting location is changed. In one such session, Frohardt et al. report an example of a correlation between the resulting shift in PFD and the rats' behaviour (compared to non-rotation sessions): on the first (standard session), the rat returned 75° clockwise relative to a HD cell's PFD. On the subsequent rotation session, the cell's PFD rotated by 120°, but the rat's return choice relative to this cell's PFD remained constant. While this is consistent with a role for the HD system in behaviour, it does not distinguish between the possibilities of a change in *reference* direction, or the HD system drifting relative to a constant reference direction. In the present experiment, the within-journey design makes it likely there is no shift in reference direction, as supported by sessions where PFDs did not drift significantly. The Frohardt et al. study also does not provide explicit evidence that rats are path integrating or need their HD system specifically to do the task.

A possible difference between the subjects in this experiment and those in the lesion experiment in the previous chapter is that these rats were relatively inexperienced on this task. It has been suggested that for studying path integration, it is probably an advantage to have unexperienced rats (Wallace and Whishaw 2003), since they are less likely to have picked up on stable cues and would be more likely to rely on idiothetic navigation strategies. Although in the experiment in the previous chapter we observed no change in the rats' behaviour or strategy over time, it is possible that the present subjects' relative unfamiliarity with the environment contributed to the coupling between the HD signal and behaviour. The small number of "mismatch" sessions observed is a reminder that the HD signal is not the only factor, even in behaviours that rely on it: rats can choose to ignore it, or may have forgotten where the goal is. Overall, however, the present results provide evidence that on a path integration task, rats rely on the HD system to find their way home, supporting the neural compass hypothesis.

Future directions

Apart from providing more data to strengthen the evidence for HD system involvement in path integration, further experiments could address the dynamics of the HD signal on a fine timescale. This would allow confirmation of that changes in the signal are really slow, gradual drift rather than "episodic" reference shifts. It would also provide direct

evidence that drifts in the signal precede navigational choices rather than follow them. It would also be helpful to confirm that in the Frohardt et al. study, HD cells are unable to maintain a stable PFD *between* sessions, which would indicate that there are no stable cues it is anchoring itself to, which could be used for navigation.

More generally, evidence for the requirement of the HD system in path integration suggests questions of how the HD signal itself might interact with related representations. For instance, path integration might be a useful restricted case where the relationship of the HD signal with goal memory could be studied. The involvement of the hippocampal formation in path integration is still an unresolved question; a better understanding of the involvement of entorhinal cortex in path integration and the dynamic properties of its cells during such tasks will be useful in resolving this issue.

Part III

Modelling

Chapter 7

Modelling anticipation in the HD system

7.1 Rationale

As reviewed in earlier chapters, the rodent head-direction (HD) system (Ranck Jr. 1984; Sharp et al. 2001; Wiener and Taube 2005) is a striking example of a "cognitive" representation without a direct sensory correlate. A given HD cell is maximally active when the animal's head is facing that cell's preferred firing direction in the horizontal plane, irrespective of location or ongoing behaviours (Taube et al. 1990a). Different cells have different preferred directions, evenly covering the directional space to form a "neural compass" representing the animal's current head direction (Johnson et al. 2005). The compass can be updated by visual inputs, yet it persists in darkness (Mizumori and Williams 1993; Chen et al. 1994). The HD system is thought to be a critical component for several forms of spatial navigation (reviewed in Chapter 4).

When viewed as a sensory system, HD cells would be expected to encode with some delay. However, in several brain areas HD activity correlates best with future head direction, anticipating the animal's HD by anticipatory time intervals (ATIs) of up to 75 ms (Blair et al. 1997; Stackman and Taube 1998, note erratum).

These ATIs are highly variable: Blair et al. (1997) report that ATIs of the same HD cell recorded during multiple recording sessions can differ by as much as 50 ms. Estimates of the mean ATI can differ by 25-30 ms between different studies (Blair et al. 1998; Stackman and Taube 1998), including studies from the same group (Taube and Muller 1998; Bassett et al. 2005). Finally, a recent report (Bassett et al. 2005) showed an ATI increase of 40 ms when rats were passively rotated compared to freely moving. Understanding how these ATIs are generated helps constrain network models of the HD system, but presently

their origin is not well understood. Previous theoretical models exploring the mechanisms underlying HD anticipation (Goodridge and Touretzky 2000; Xie et al. 2002) rely on deformations of the "hill of activity" in a population of HD cells (reviewed in section 3.2). Such deformations occur as a side effect of the update mechanism necessary to move the hill of activity (angular path integration), and cannot account for the above variations in ATI. Additionally, they fall short of generating the long ATIs observed in the lateral mammillary nuclei (LMN). Simulations reported in Goodridge and Touretzky (2000) only resulted in 30 ms of anticipation in the single most favourable case, while mean experimental values range up to 67 ms (Stackman and Taube 1998).

In this modelling study we present a novel hypothesis for the generation of anticipation in the HD system. Like previous models (McNaughton et al. 1991; Redish et al. 1996; Song and Wang 2005), we assume that the HD system integrates angular head velocity (AHV) from the vestibular system. However, we consider the firing dynamics of vestibular neurons, such that instead of being updated by a perfect vestibular AHV signal, the HD system effectively receives a high-pass filtered version of that signal (right panel in Figure 3.3 on page 43). This filter incorporates the effects of vestibular spike rate adaptation and post-inhibitory rebound firing (Sekirnjak and du Lac 2002) to generate HD anticipation. Spike rate adaptation, illustrated in Figure 7.1 on page 134, refers to a neuron gradually reducing its firing rate to a steady value in response to a constant input. Post-inhibitory rebound (illustrated in the same figure) is a transient burst of activity following release from inhibition.

We show that for physiological amounts of vestibular adaptation and rebound, the model generates realistic ATIs on a large set of rat tracking data. Critically, the resulting anticipation depends on the statistics of the input head movement pattern, thus providing an explanation for the observed ATI variability. In support of our hypothesis, we show that the ATIs generated by the model are strongly correlated with experimental values on the same head movement patterns.

7.2 Methods

Ring attractor network model

Our model of the HD system uses a "ring" attractor network of nonlinear units with generic rate-based dynamics, similar to previous models (Skaggs et al. 1995; Redish et al. 1996; Zhang 1996; Trappenberg 2002). However, the critical component of the model lies in the dynamics of the input signal to this network (described in *Input dynamics*, below) Figure 7.1a shows a schematic of the complete model, of which the ring attractor network is the last processing stage. It is designed to integrate angular head velocity input to yield a persistent representation of head direction. Briefly, the network units (representing populations

of neurons) are placed on a ring, where angular position on the ring corresponds to the unit's preferred firing direction. A rotationally symmetric matrix of recurrent weights is constructed so that a Gaussian-shaped activity packet, or attractor state, persists in the network, even in the absence of input (Amari 1977). The packet is stable at any position along the ring, and its position corresponds to the head direction encoded by the network. The packet is moved around the ring by external inputs, through addition of an asymmetric component to the weight matrix proportional to the magnitude of the input (Zhang 1996).

Following Stringer et al. (2002), the activity level $u(t)$ of unit i in the HD ring is modelled by

$$\tau \frac{du_i(t)}{dt} = -u_i(t) + \sum_j w_{ij}(t) F(u_j(t))$$

where τ is the time-constant of the unit and the activation function F is a sigmoid

$$F(u) = 1/(1+e^{-\beta u})$$

with a slope denoted by β.

The weight matrix w of the recurrent connections in the network consists of a constant symmetric component w^s, and two variable asymmetric components, corresponding to left (clockwise) and right (counterclockwise) turns respectively.

$$w(t) = w^s + \gamma[v_l(t) w_l^a + v_r(t) w_r^a] \tag{7.1}$$

The symmetric weights matrix w^s implements a standard local excitation and global inhibition connectivity. The strength of the recurrent excitation depends on the angular difference between the preferred directions of the units:

$$w_{i,j}^s = w_E \, e^{\frac{-d_{ij}^2}{2\sigma^2}} - w_I \tag{7.2}$$

where d_{ij} is the angular difference between the preferred firing directions of the units i, j, σ denotes the width of the Gaussian weight profile, and w_E and w_I determine the strength of the excitation and inhibition respectively. These are chosen such that the network has a stable attractor state.

The asymmetric components in Eq.(7.1) are obtained by multiplying the asymmetric weight profiles $w_{\{l,r\}}^a$ with the activity of the vestibular inputs $v_{\{l,r\}}$ and a constant gain (scaling) factor γ (see section *Input dynamics*).

For the asymmetric weights $w_{\{l,r\}}^a$ we use the derivative of the symmetric weights given by Eq.(7.2), as in previous models (Zhang 1996; Stringer et al. 2002):

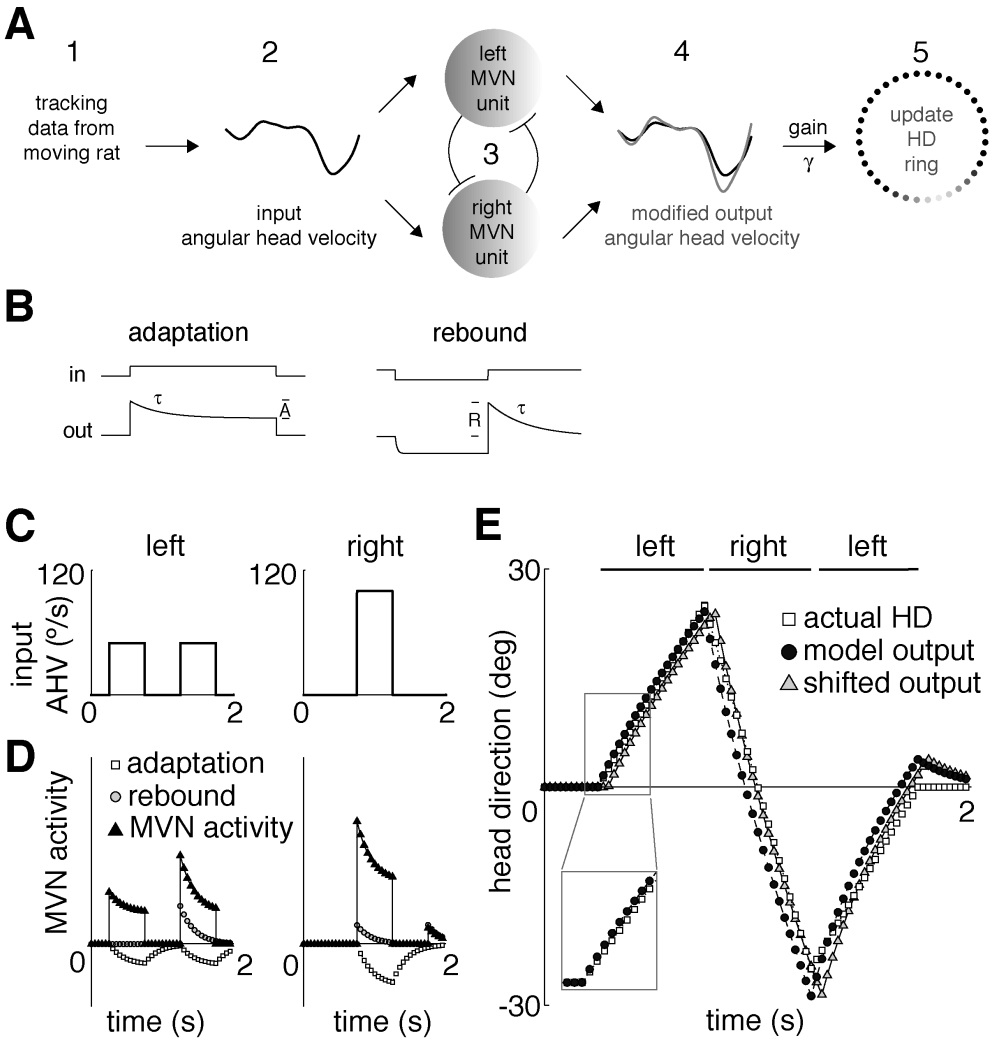

Figure 7.1: Adaptation and rebound generate anticipation in the model, illustrated here with an artificial angular head velocity (AHV) input pattern. **A**: Schematic model layout. Tracking data from freely moving rats (1) yields an AHV input pattern (2), which is split up into its left (clockwise) and right (counterclockwise) components. The two AHV components are the input to corresponding cross-inhibiting medial vestibular nucleus units (3), which filter the signal by means of adaptation and post-inhibitory rebound (**B**). The filtered signal from the MVN units (4, dark grey line; black line is the original input signal) is used to update a ring attractor network representing head direction (5). The gain γ controls how much the HD network is updated in response to input, and is chosen to minimise tracking error (*Methods*). **B**: Schematic representation of adaptation and rebound in response to a step input. Adaptation and rebound are parameterised by their respective strengths (A, R) and time constants τ. **C**: Example artificial "left-right-left" input AHV profile. **D**: Adaptation (open squares) and rebound (grey circles) currents are added to the AHV input pattern to yield the net activity (black triangles) of the MVN neurons, which update the head direction (HD) module. The second "left" pulse results in a bigger response than the identical first one, due to rebound generated by the right input. **D**: Model output. Note how during the initial stage of a turn, the model output (black circles) is updated faster than the actual HD (open squares). To find the resulting anticipatory time interval (ATI), the model output is shifted in time until the error with respect to actual HD is minimal (but non-zero). In this example, the output was shifted by 48 ms (grey triangles).

$$(w_l^a)_{ij} = \frac{d_{ij}}{\sigma^2} e^{\frac{-d_{ij}^2}{2\sigma^2}}$$

for the left-turning weights and $w_r^a = -w_l^a$ for the right-turning weights.

In summary, rotation of HD is effectively implemented through a modulation of the weights. We chose this simple implementation because the details of the update mechanism are not relevant for this study and the actual biological mechanism is not known, although more detailed, biologically plausible, update mechanisms have been suggested (Compte et al. 2000; Goodridge and Touretzky 2000; Boucheny et al. 2005; Song and Wang 2005).

Table 7.1 shows the parameters used for all simulations presented.

Input dynamics

The core of the model describes how the input units that update the HD representation respond to the angular head velocity $\omega(t)$ to be tracked by the model. The angular head velocity signal is split up into 'left' and 'right' components, which feed into cross-inhibiting 'left' (v^l) and 'right' (v^r) units, consistent with vestibular system physiology (Shimazu and Precht 1966; Markham et al. 1978). These units correspond to a population of angular head velocity-sensitive neurons afferent to the HD system (see *Discussion*). The firing properties of the input units are augmented with adaptation and rebound firing, as described in medial vestibular nucleus (MVN) neurons by Sekirnjak and du Lac (2002); for clarity, we refer to the input units as "MVN units". This arrangement is shown schematically in Figure 7.1a. MVN unit activity equals the angular head velocity, minus an adaptation current (I_A), plus a rebound current (I_R), as follows:

$$\begin{aligned} v^r(t) &= [\omega^r(t) - I_A^r(t) + I_R^r(t) - v^l(t)]_+ \\ v^l(t) &= [\omega^l(t) - I_A^l(t) + I_R^l(t) - v^r(t)]_+ \end{aligned}$$

The last term describes vestibular cross-inhibition from the contralateral MVN unit. The angular velocity inputs $\omega^r(t)$ (and $\omega^l(t)$) are simply the right (left) components of the input angular velocity signal, i.e. $\omega^r(t) = [\omega(t)]_+$, and $\omega^l(t) = [-\omega(t)]_+$, where $[x]_+ = \max(x, 0)$.

Prolonged activation of a MVN unit activates an adaptive current, I_A, illustrated in Figure 7.1b. The adaptive current is linear in the angular head velocity input, and is modelled with a first order differential equation. For the left unit:

$$\tau_A \frac{dI_A^l}{dt} = -I_A^l + A\omega^l(t) \tag{7.3}$$

and similar for the right unit. The parameter τ_A describes the time-constant of the adaptation build-up, and the parameter A denotes the adaptation strength. The adaptation current was chosen to depend on the input rather than the activity of the unit itself to allow straightforward interpretation of the parameter A as a fraction of the input, in line with Sekirnjak and du Lac (2002). This does not change the qualitative features of the model. A parameter value $A = 0$ corresponds to no adaptation and $A = 0.4$ to a steady state firing rate of 60% of initial activity.

The post-inhibitory rebound currents I_R^l (and I_R^r, illustrated in Fig. 7.1b) build up due to cross-inhibition from the contralateral side. The rebound current has a time constant τ_R and a net rebound gain factor R, which combines the strength of the contralateral inhibition and amount of rebound of the MVN unit.

$$\tau_R \frac{I_R^l}{dt} = -I_R^l + R\omega^r(t) \tag{7.4}$$

and vice versa for I_R^r. Thus, $R = 0.2$ means that when the left input ceases to be active after a long time of activity ($t \gg \tau_R$), the right MVN unit rebounds with an initial activity level of 20% of the left input. For shorter rotation times, the rebound current is less. In Figure 7.1 the adaptation and rebound currents are shown for a simple velocity profile.

Choice of parameters

For all simulations, we used $A = R = 0.4$ and $\tau_A = \tau_R = 200$ms, unless stated otherwise. $A = 0.4$ corresponds to a strongly adapting MVN neuron in Sekirnjak and du Lac (2002). The time constants were extracted from a single-exponential fit to the published data. The physiological value of R is more difficult to estimate using currently available data, since it depends on both the characteristics of the MVN neuron and on the strength of the cross-inhibition it receives.

To assess the effect of the simplifications and parameter choices of our input implementation, we also simulated the MVN units v using the two conductance-based spiking MVN neuron models described in Sekirnjak and du Lac (2002). Although we were unable to exactly reproduce background firing rate of the reported model, the rate dynamics matched closely those reported there. To accommodate these neuron models into our HD network, the 'left' model neuron received excitatory input current proportional to ω^l and inhibitory input proportional to ω^r (and vice versa for the otherwise identical 'right' model neuron). The neurons' spiking output was convolved with a Gaussian of 100 ms standard deviation to serve as input v to our rate model. As the precise proportionality between angular head velocity and input current is not known, we have chosen values which make use of the full dynamic range of the neurons: we used $100\,nA\,s/deg$ (i.e. the instantaneous net input

Symbol	Parameter	Value
τ	single unit time constant	10 ms
τ_A	input adaptation current time constant	200 ms
τ_R	input rebound current time constant	200 ms
dt	simulation time step	1 ms
N	number of neurons in ring	100
β	activation function slope	0.07
w_E	recurrent weights scale factor	15
σ	recurrent weight profile width	21.6°
w_I	recurrent weights global inhibition level	9
A	MVN unit adaptation	0.4
R	MVN unit rebound	0.4

Table 7.1: Model parameters used for the results presented, unless stated otherwise.

current to the neuron is 100 nanoampères per unit angular velocity, which is in degrees per second) for excitation and $1000\,nA\,s/deg$ for inhibition. This corresponds to strong inhibition and thus strong rebound; hence, the rebound simulation results should be viewed as an upper bound on how much anticipation this mechanism generates.

Computing anticipatory time intervals

The head direction encoded by the model is extracted using a linear population vector read-out (the vector sum of the preferred firing directions of the model cells weighted by their firing rate, Georgopoulos et al. 1983). In order to accurately track angular head velocity input, the gain γ needs to be set. The gain determines by how much the HD representation is updated in response to a given input. An incorrect gain value leads to build-up of error in the head direction representation over time, and can lead to artifactual anticipation or lag. For each HD input profile (e.g. a 60-second segment of tracking data (see below), or an artificial step pattern) the optimal gain is found by minimising the error between the model's population vector output and the time-shifted actual head direction. The error is defined as the summed absolute difference per second between input pattern and decoded model output; using a sum of squares error yielded comparable results on a representative subset of the data. Both gain and time shift were varied to minimise the error; the time shift corresponding to the minimal error output is the anticipatory time interval (ATI) for that pattern. To assess the effect of computing the gain for each input separately, we also ran the model on the set of tracking data with a fixed gain value (the mean of the gains previously obtained for each of the input patterns separately using the error-minimising procedure described above). Mean ATI values obtained this way did not differ significantly from the values reported, although both tracking errors and ATI

variability were higher. In general, different head movement patterns require a different value for γ in order to minimise error. For step patterns, the optimal value can be calculated analytically (see *Step Input* in section 7.5 on page 155).

Using the model's population vector output to compute ATIs is much more precise than the single-cell based method used in the experimental literature, because all units in the model are accessible. In order to obtain the ATI of single cells, the time shift which maximised the mutual information between the cell's activity and the HD input was calculated, as was done for HD recording data (Taube and Muller 1998).

Poisson head direction cell simulation

To assess the anticipation variability that can be expected from spiking variability alone (Figure 7.3c), we used the fact that head direction cell firing is thought to be approximately Poisson-distributed (Blair et al. 1998). We simulated a Poisson head direction cell where the probability of a spike at each simulation time step (1 ms) was defined by a Gaussian tuning curve ($\sigma = 21^{\circ}$) for direction, with the mean $+/-5$ degrees different for clockwise vs. counterclockwise turns respectively, in order to generate anticipation. The cell has a 100 Hz peak firing rate, 20 Hz mean firing rate, and 40 ms of anticipation on average. The simulation used a 0.1 Hz sinusoidal directional profile 8 minutes in length, covering the entire directional range. For comparison with the experimental data from Blair et al. (1997) we used their method for computing ATIs in this simulation: two tuning curves for clockwise and counterclockwise turns were constructed, and the HD cell spikes were shifted in time until the two curves overlap (Blair and Sharp 1995). This simulation variability value was compared to an experimental estimate: this was obtained by taking the standard deviation of all ATI values reported in Table 1 in Blair et al. (1997), which contains recording sessions from 33 HD cells, many of which were recorded for several identical sessions. Thus, the experimental value shown in Figure 7.3c contains both between- and within-cell variability.

Tracking data

In order to provide the model with realistic inputs, rat HD tracking data was used. Tracking data were obtained from adult male Long-Evans rats (n = 3) running a plus maze approximately 1.8m in diameter during the Neural Systems & Behavior summer course at the Marine Biological Laboratory, Woods Hole, MA. A colour camera mounted overhead sampled the LED pattern of a HS-54 recording headstage (Neuralynx, Tucson, AZ) and a 10 cm long boom attached to the rats' head at 30Hz, as described in Yoganarasimha et al. (2006). The effect of missing samples was minimised first by only accepting recording sessions where at least 90% of the tracking samples were sufficient to determine instantaneous

HD at the sampling points, and second by extracting angular head velocity from pairs of consecutive non-missing samples only, and using those to reconstruct a continuous HD profile. In other words, only angular head velocity information known to sampling precision was used. This procedure left 2 hours and 22 minutes of usable data.

Because rat head direction movements are sampled with finite precision and at too coarse a timescale to be used as model inputs directly, we approximated the rat's true HD profile by fitting three different cubic splines to each dataset: a spline which is forced to pass through all sampled points (natural or variational spline; no smoothing), as well as a 'weak' and a 'strong' smoothing spline (MATLAB Spline Toolbox function *spaps*, tolerances 0.001 and 0.002 respectively), which need not pass through every sample but are constrained by an error function instead. The type of smoothing/interpolation applied to the data slightly affects the absolute ATIs reported here but not the qualitative pattern of the results. All simulations are done on the weakly smoothed data.

We randomly selected 100 2-second and 30 non-overlapping 60-second long segments that had a mean absolute angular velocity between 45 deg/s and 1000 deg/s. The same set of 60-second segments was used for all tracking data simulations, except for the spiking models from Sekirnjak and du Lac (2002), for which the 2-second set was used to reduce simulation time. For the artificial data simulations, the step input patterns were 6 seconds long: 1 second of constant input followed by 5 seconds of rest. The sinusoidal input patterns were 10 seconds long, the ATI was computed over the last 5 seconds to eliminate the effects of initial transients.

Experimental anticipation data

To compare the model's predictions directly to experimental HD cell data, we used two recording data sets from two different behavioural tasks. The first set is a subset of the data described in Yoganarasimha et al. (2006). Rats ran on an elevated circular track while HD cell activity from the anterodorsal thalamic nucleus (ADN) was recorded and their head movements tracked. We used the 'baseline' sessions, where apparatus and cues are always in the same, stable configuration. The second set is of rats foraging for randomly scattered chocolate sprinkles in a walled square box with a prominent polarising cue card, using the same recording procedure. This experiment is similar to recording conditions in previously reported HD anticipation data. A smoothing spline was fitted to the tracking data as above, after application of a simple swap detection algorithm to correct for erroneous samples (which can occur when part of the LED array on the headstage is obscured temporarily).

The first 'circular track' dataset included 12 3-to-6 minute long recording sessions from a total of two animals, the second 'square box' set consisted of 9 9-to-12 minute long sessions from three animals (one of which also contributed to the circle dataset). In one animal in

the square box data set, the recording electrode was identified as being in the anteroventral thalamus (in the border region between the AV and VA nuclei). Data from this animal did not appear different in its firing or anticipation properties and was therefore included. Every recording session was split up into 60-second segments, such that segment 1 for that session was the first 60 seconds, segment 2 the second 60 seconds, and so on. The anticipatory time interval (ATI) for each segment was then computed using the mutual information method described in Taube and Muller (1998). Segments less than 45 seconds long, or containing less than 400 spikes from a HD cell, were rejected. For comparison with model output, when multiple cells were recorded simultaneously during a segment, the experimental ATI was taken to be the mean of individual cells' ATIs. ATIs for complete recording sessions were obtained by averaging across the segments of that session.

7.3 Results

We implement a single-layer continuous "ring" attractor network model of the rodent head direction (HD) system, similar to previous models (Redish et al. 1996; Zhang 1996; Goodridge and Touretzky 2000; Stringer et al. 2002; Xie et al. 2002; Boucheny et al. 2005; Song and Wang 2005). This type of model has a continuum of stable states in which a subset of HD cells or "activity packet", representing the animal's current directional heading, is persistently active. In order to track the animal's movement, the position of the packet needs to be updated. In contrast to earlier models and in accordance with physiology, we incorporate spike rate adaptation and post-inhibitory rebound of medial vestibular nucleus (MVN) neurons (Sekirnjak and du Lac 2002, Fig. 7.1b) into the update mechanism. MVN neurons are thought to provide the vestibular input to the HD system (Stackman and Taube 1997). As a result, the input signal integrated by the model HD network is a modified version of the actual angular head velocity. Following vestibular anatomy (Shimazu and Precht 1966; Markham et al. 1978), the model contains "left" and "right" input units, whose activity provides the update signal for the HD "ring". These units, representing populations of MVN neurons, increase their activity during a left and a right turn respectively. They adapt in response to constant input and cross-inhibit each other, resulting in post-inhibitory rebound when a turn stops and inhibition is released. Adaptation and rebound are characterised by their strengths (A, R) and time constants (τ_A, τ_R); we fitted these to the data in Sekirnjak and du Lac (2002) (*Methods*). A schematic diagram of the model layout is shown in Figure 7.1a.

The effect of MVN adaptation and rebound on our model HD system is illustrated in Figure 7.1c-e, where a model rat moves its head in an artificial left-right-left pattern. The angular head velocity input to be tracked by the model is first split up into "left" (clockwise) and "right" (counterclockwise) components (Fig. 7.1c). This input is then modified by adaptation (Fig. 7.1d, open squares) and rebound currents (Fig. 7.1d, grey circles) to

yield the net MVN activity (Fig. 7.1d, black triangles). Specifically, the left MVN unit responds to the constant leftward input and adapts, while rebound current builds up in the right MVN unit. The rebound becomes active once left movement stops (releasing cross-inhibition), coinciding with the start of the right turn. The right MVN response to the right turn is boosted by the rebound current. Meanwhile, as the right unit adapts, rebound builds up in the left MVN unit. This rebound then boosts the response to the following left turn: compare the response to the two identical turns in the left MVN unit. The second response is larger due to the rebound current generated by the intervening right turn.

The net activity of the left and right MVN units described above moves the HD representation in the corresponding direction, allowing the system to track a given input pattern. Exactly how much the HD activity packet moves in response to MVN activity is determined by a fixed gain parameter γ, which is chosen to minimise tracking error (*Methods*). For our example, the model's resulting HD representation can be seen in Figure 7.1e. As the movement stimulus comes on, the model output (black circles) initially updates faster than the actual HD (open squares). When the stimulus changes direction, rebound provides an additional update boost. These mechanisms effectively implement a high-pass filter or angular acceleration component (Zhang 1996; Song and Wang 2005, also see the Appendix) which results in anticipation: the model output precedes the actual HD in time. To calculate by how much the model anticipates, the model output is shifted in time to minimise the error with respect to the actual HD (*Methods*). The time shift corresponding to the minimal error (gray triangles in Fig. 7.1e) is the model's anticipatory time interval (ATI). For this example, the model's ATI was 48 ms.

Anticipation on artificial input patterns

To characterise the model's behaviour further, we first present simple artificial angular head velocity (AHV) patterns to the model. On step inputs of constant AHV (Fig. 7.2a), adaptation (+A-R) and rebound (-A+R) both generate anticipation. When adaptation and rebound are combined (+A+R), the resulting anticipatory time interval (ATI) is larger than the sum of the two separately. The ATIs shown here can be derived analytically: the theoretical values (+A+R: 133 ms, +A-R: 66 ms, -A+R: 40 ms, -A-R: 0 ms) are derived in section 7.5 on page 155 and match the simulations well.

For sinusoidal input patterns (Fig. 7.2b) there is a strong effect of input signal frequency on anticipation. Some intuition about this result comes from the observation that anticipation results from a transient boost at the start of the input signal. Because this boost doesn't happen instantaneously it will only generate anticipation if the direction of the boost is consistent with the subsequent signal; if the signal changes too fast, the boost will be in the wrong direction and will not constitute anticipation. Comparing the model's ATI

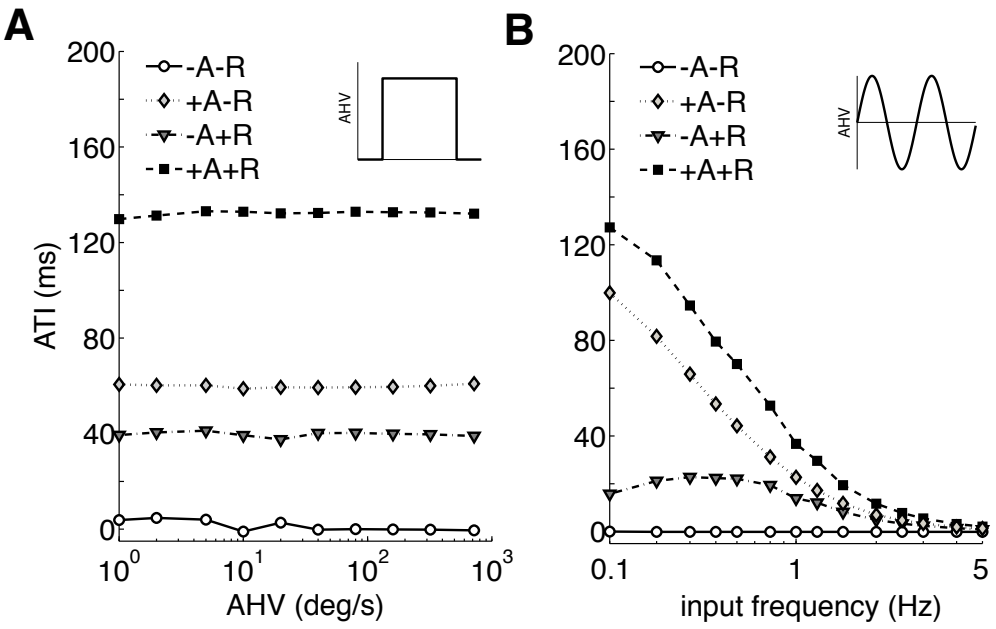

Figure 7.2: Anticipation in the model depends on input frequency, but not on input magnitude. **A**: Anticipatory time interval (ATI) as a function of angular head velocity (AHV) using a step input. Adaptation (A) and rebound (R) can both generate anticipation independently (+A-R/grey diamonds and -A+R/grey triangles respectively), and add supralinearly (+A+R/black squares). **B**: ATI as a function of frequency of a sinusoidal input. Higher input frequencies result in less anticipation. At low frequencies, adaptation generates more anticipation than rebound. For analytical results supporting these simulations, see section 7.5 on page 155. Parameters in *Methods*.

on sinusoidal inputs at low frequencies to that on step inputs, adaptation makes an even bigger contribution to anticipation than rebound. This occurs because at low frequencies, rebound decays before it becomes active; at higher frequencies, like adaptation, it becomes ineffective because the signal changes too quickly. The theory provided in section 7.5 on page 155 provides a good description of the simulation results, but is limited to the case where adaptation and rebound strength are equal ($A = R$).

Anticipation on realistic input patterns

Simulations on artificial input patterns show that in the model, anticipation depends on the frequency of the input. Do behaving rats move their heads at frequencies capable of supporting the experimentally observed amounts of anticipation, for realistic parameters of the model? To address this question, we ran the model on 30 1-minute long input patterns, selected randomly from a large corpus of rat tracking data (*Methods*). The resulting anticipatory time intervals (ATIs) are plotted in Figure 7.3a, for different values of adaptation and rebound. As expected, the ATI values on the tracking data are lower than the ATIs in response to step patterns (Fig. 7.2a), because of higher-frequency components present in real rat head movements. The mean adaptation value found experimentally appears to lie between 0.2 and 0.3 (Sekirnjak and du Lac 2002); the value for rebound is more difficult to estimate, because it does not depend solely on the intrinsic firing properties of the neuron, but also on the strength of vestibular cross-inhibition. For the ATI in the most anticipatory head direction area, the lateral mammillary nuclei, values of 39 and 67 ms have been reported (Blair et al. 1998; Stackman and Taube 1998). Hence, even if rebound were completely absent the model can still account for a substantial part of the observed anticipation.

An obvious concern is that the results reported here depend on simplifications in the model MVN neurons. To assess this, we used the spiking neuron models provided by Sekirnjak and du Lac (2002) as inputs to our HD network (*Methods*), again using actual tracking data as inputs. A literal implementation of these spiking neurons coupled to our HD network yielded comparable ATIs (Fig. 7.3b), indicating that the anticipation is robust and does not depend on details or simplifications in our model.

In generating anticipation, the model necessarily introduces tracking error, as illustrated in Figure 7.1. Perhaps the parameters of MVN neurons are optimised for generating anticipation and/or reducing tracking error. In section 7.5 on page 155, we show that for step profiles, tracking error is minimal when adaptation and rebound have equal strength. On the realistic tracking data set, the error per unit anticipation is minimal when adaptation and rebound are matched, and about 0.2 (Fig. 7.3d). Sekirnjak and du Lac (2002) found that adaptation and rebound of a given cell were strongly correlated, suggesting that MVN cells

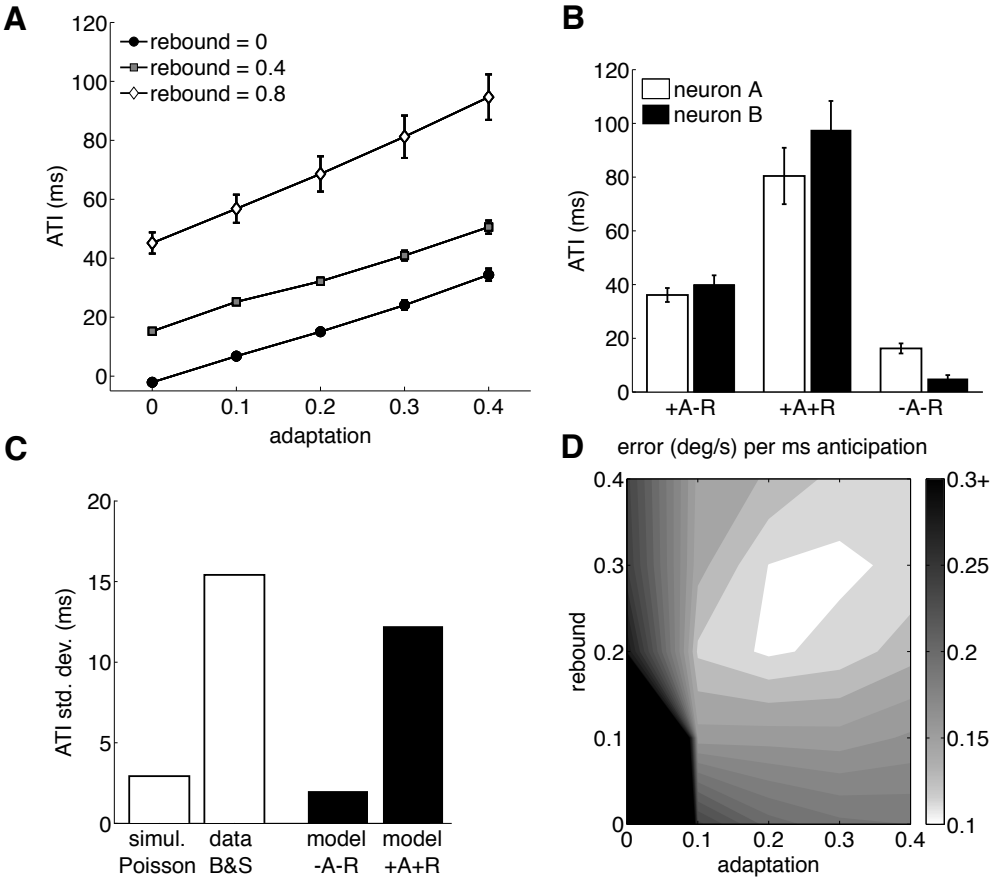

Figure 7.3: The model produces realistic levels of anticipation using rat tracking data input. **A**: Mean anticipatory time intervals (ATIs, +/- SEM) for different values of adaptation and rebound, simulated over a set of 30 60-second long tracking segments. Experimental estimates for the mean ATI are 39-67 ms. **B**: Mean ATIs (+/- SEM) using the conductance-based vestibular neuron models (their neurons A and B) from Sekirnjak and du Lac (2002), simulated using 100 2-second tracking segments. The resulting ATIs for adaptation only (+A-R) and both adaptation and rebound (+A+R) are a good match with the results in panel A. **C**: Adaptation and rebound can account for the experimentally observed ATI variability. Shown is the ATI standard deviation for a simulated HD cell with Poisson spiking, along with the experimentally observed value (white bars, experimental value calculated from the data in Blair *et al.* 1997). In the model, adaptation and rebound result in a level of variability approaching the experimental value (black bars). **D**: Matching adaptation and rebound values reduces error. Shown is a contour plot of tracking error divided by ATI on the set of 60-second tracking segments, where white corresponds to small error and black to large error.

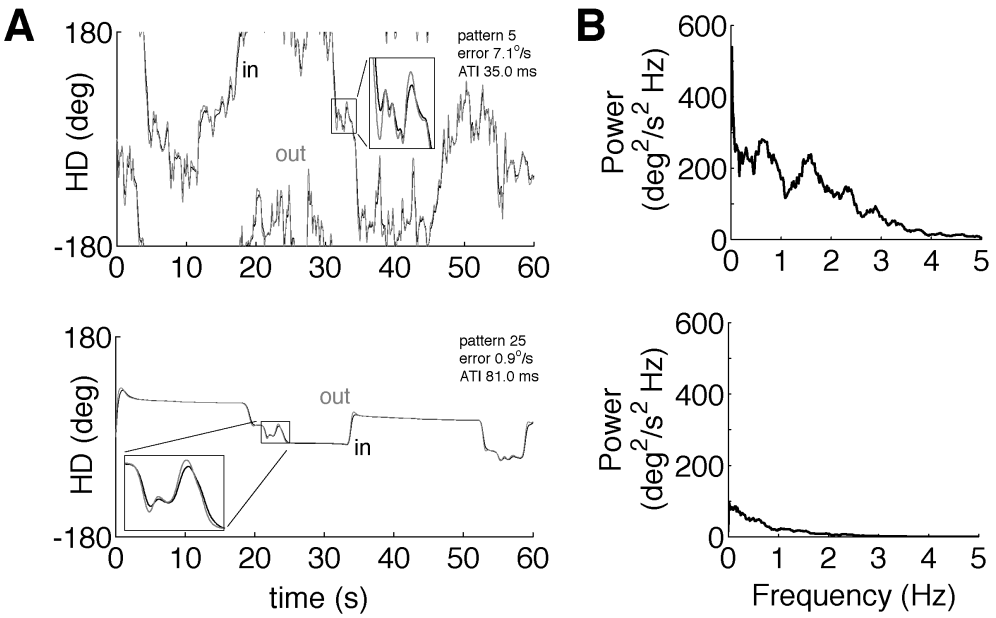

Figure 7.4: Differences in the statistics of tracking data input result in different anticipatory time intervals (ATIs). **A**: Input patterns resulting in the lowest (top) and highest (bottom) ATIs. The input is shown in black with the model output overlaid in grey; the (top) high-ATI pattern contains strong high-frequency components compared to the (bottom) low-ATI pattern. **B**: Angular head velocity power spectrum for the five lowest ATI patterns (top) and the five highest ATI patterns (bottom). Low ATI patterns (top) have higher power at higher frequencies (note the peak at 1.5 Hz and the presence of $>$3 Hz components) than high ATI patterns (bottom).

may be tuned to produce anticipation at the lowest possible tracking error. Additionally, we found that the tracking error depends on the time constant of adaptation and rebound. The error per unit anticipation was minimal for a time constant of about 175 ms when tested on the tracking data (not shown), matching the physiological time constants of adaptation and rebound (Sekirnjak and du Lac 2002).

Between-session anticipation variability

Using realistic data, the model produces anticipatory time intervals (ATIs) comparable to those observed experimentally. However, a salient aspect of the experimental data is its high variability. To what extent does the model capture this? Without adaptation and rebound, the model yields little ATI variability. When adaptation and rebound are included, the ATI variability increases to experimentally observed levels (Fig. 7.3c, black bars), as different input patterns result in different amounts of anticipation. The reason is that the dynamics of adaptation and rebound interact with the statistics of the input pattern, as shown by the frequency-dependence of Figure 7.2 and section 7.5 on page 155. For realistic data, this idea is illustrated in Figure 7.4a, where the input patterns generating the least (top) and most (bottom) anticipation are shown. As evidenced by their respective power spectra (Fig. 7.4b), the low anticipation pattern has more power in higher frequencies than the high anticipation pattern. The high power, low anticipation pattern is relatively difficult to track (average tracking error of 7.1 deg/s compared to 0.9 deg/s for the low power pattern). Although in the limit, no error results in no anticipation, not all errors necessarily result in more anticipation. For instance, the large overshoots in the model output (as apparent in the magnified inset of the high power pattern), a side effect of the mechanism that generates anticipation, contribute little to ATIs but generate substantial tracking error. Apart from differences in frequency content, the rat in the low power pattern held its head direction constant for long periods; while this does not affect ATIs directly, in the dataset it tended to be the case that low frequency head movements were accompanied by stationary periods. This illustrates that rats exhibit a range of movement patterns, which in the model can result in different ATIs.

HD cell spike trains are inherently variable: where examined, HD cell firing is reported to be approximately Poisson (Blair et al. 1998). This irregularity of firing could contribute to ATI variability. To quantify this, we simulated a Poisson HD cell on a 8-minute long sinusoidal input pattern (*Methods*). Over multiple repetitions using the same input, the variability in the ATI of this model cell was much smaller than the experimentally observed variability (Fig. 7.3c, white bars; experimental value obtained from the data in Table 1 of Blair et al. 1997). Thus, the experimental variability cannot be explained simply by spike timing variability.

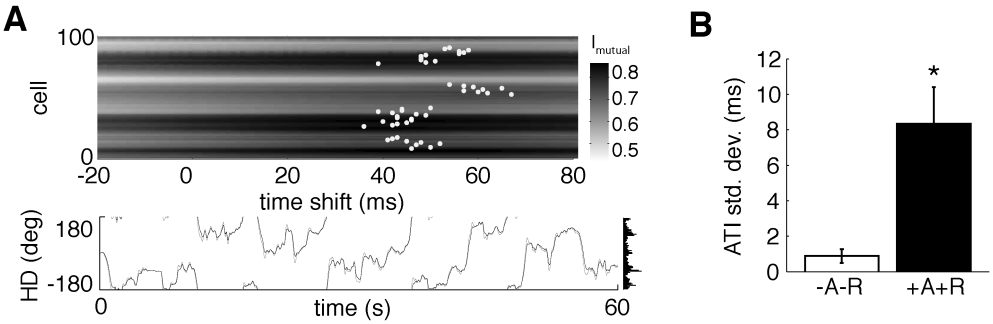

Figure 7.5: Adaptation and rebound can explain different anticipatory time intervals (ATIs) of simultaneously recorded head direction cells. **A**: ATIs of individual units in the ring attractor (top) when tracking an example head direction profile (bottom). Units are indexed from 1 to 100 according to their preferred firing directions (location in the ring) spanning the directional range. ATIs are computed as the peak of the mutual information between that cell's activity and head direction over a range of time shifts. The shaded area shows the mutual information as a function of time shift, with the location of the white circle indicating the maximum information, and thus the ATI, for that unit. Only units with sufficient sampling ($> 5\%$ of time spent in the cell's directional range) are shown. In this example, ATIs of "simultaneously recorded" individual units range from 37 to 67 ms. **B**: Average standard deviation of within-session ATIs over 30 patterns without (white bar) and with adaptation and rebound (black bar). Adaptation and rebound cause increased within-session ATI variability.

Within-session anticipation variability

We have shown that the model provides a possible explanation for the observed between-session variability in HD cell anticipation by exploiting differences in the angular head velocity input. However, it is also known that there is substantial within-session variability between simultaneously recorded HD cells (up to 30ms, Blair et al. 1997). To address this issue, we computed anticipatory time intervals (ATIs) for the units in the model individually (*Methods*). An example of this is shown in Figure 7.5a: the white dots indicate the ATIs of the individual units, superposed on their mutual information content with respect to the head direction input as a function of time shift. Individual unit ATIs for this example range from 37-67 ms; the differences are due to the fact that each cell has a limited tuning curve, and "sees" a different part of the input pattern. As has been shown before, different input patterns lead to different amounts of anticipation. When averaged over the complete tracking data set, the model with adaptation and rebound results in significantly more within-session variability than the model without (Fig. 7.5b, ANOVA $F(1,29) = 12.75$, $p < 0.001$).

Comparison with experimental data

To test the idea that differences in angular head velocity input contribute to HD anticipation directly, we used two recording data sets from different behavioural tasks. In both sets, activity from HD cells in the anterior thalamus was recorded from freely moving rats as their head movements were tracked (*Methods)*. In the first data set, rats ran clockwise on a elevated circular track (12 sessions total from 2 rats, of 3-6 minutes in length each; data from Yoganarasimha et al. 2006). The second set consists of data from rats foraging for randomly scattered food pellets in a square box enclosure (9 sessions total from 3 rats, 9-12 minutes in length each).

We compared the model's predicted ATI to the experimental value on a session-by-session basis. For each session, we computed the experimental anticipatory time interval (ATI, see *Methods*) and the ATI predicted by the model from the rat's head movements during that session. (Note: Experimental ATI values are sensitive to the exact timestamping and synchronisation of video and neural data. While we have made every effort to ensure that the values reported here are as close to the real value as possible, small inaccuracies in the absolute values reported here may still be present.) Figure 7.6a shows scatterplots of the model and experimental ATIs for both data sets (top: circular track, bottom: square box), where each data point corresponds to one recording session. On both data sets, the model and experimental ATIs are strongly correlated (Pearson product-moment correlation, circular track: $r = 0.79$, $p = 0.002$, square box: $r = 0.92$, $p < 0.001$), indicating that the model explains over 60% and over 80% of the experimental ATI variance on the two data

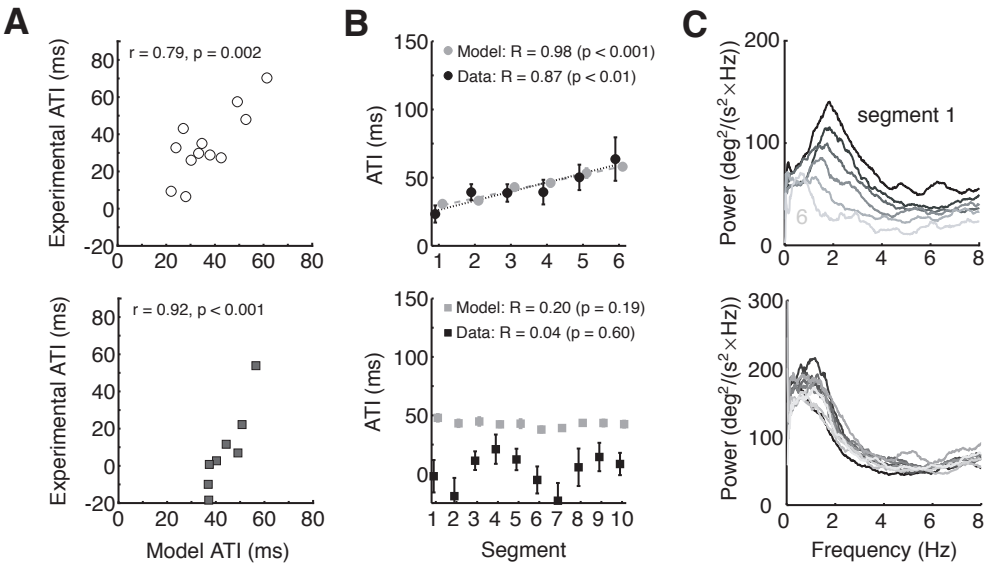

Figure 7.6: The model explains a substantial, significant amount of experimental anticipation variability. **A**: Scatterplots of model against experimental ATIs across two data sets (*top*: circular track, *bottom*: square box). Each data point corresponds to one recording session. For both sets, the model and experimental values are significantly correlated. Statistics shown are Pearson's product-moment correlation coefficient r and associated significance level p. **B**: The model accounts for systematic within-session changes in ATI on the circular track data set *top*. Recording sessions are split up into 60-second segments and the average ATI +/- SEM per segment plotted. For both data and model (linear regression statistics shown), there is a significant increase in ATI as the session progresses. *Bottom*: On the square box data set, there is no (linear) within-session effect on ATI (*left*) in either the model or experimental values. On this data set the model overestimates the ATI (see main text). **C**: On the circular track data, the increase in ATI over segments is accompanied by a corresponding change in the head movement power spectrum (*top*). Shown are average angular head velocity power spectra for each segment, with the top (dark) line corresponding to the first segment, and the bottom (light) line to the last. Note that with increasing segment, there is less power overall and the peak shifts to lower frequencies. *Bottom*: On the square box data set, the power spectra for the segments do not differ systematically. Parameters used: $A = 0.3$, $R = 0.4$.

sets respectively.

To illustrate how the model accounts for the data, we looked at within-session ATI differences. Recording sessions were split up in 1-minute long segments (with segment 1 the first minute of a session, segment 2 the second, and so on) and ATIs computed for each segment separately. Starting with the circular track data set, we then plotted the average experimental and model ATIs for each segment (Fig. 7.6b, top). Both the experimental and model data show a significant increase in anticipation with segment (linear regression, model: R = 0.98, F = 198.6, $p < 0.001$, data: R = 0.87, F = 26.2, $p < 0.01$): the HD cells anticipated more as the recording sessions progressed. The model explains this increase by changes in the frequency content of rat's head movements. Average power spectra for each segment are shown in Figure 7.6c (top); the darkest line corresponds to the first segment, with the line for each subsequent segment coloured progressively lighter. The first segment (top black line) has higher overall power and a peak at a higher frequency than the last segment (bottom, light grey line). As in Figure 7.2b and 7.4, higher frequency components result in less anticipation in the model and in the recording data.

In contrast, the square box data set did not show an effect of segment on ATI for either model or experimental data (Figure 7.6b, bottom; linear regression, model: R = 0.2, F = 2.0, $p = 0.19$; data: R = 0.04, F = 1.3, $p = 0.60$). Consistent with this, the average power spectra per segment (Fig. 7.6, bottom) do not show a clear progression as in the circular track data set. As Figures 7.6a and b (bottom) illustrate, the model overestimates the experimentally observed ATI on the square box data set. The fact that the model does not always reproduce the exact ATI values is not surprising. Apart from ignoring various delays and filters present in a biological system, the model implements a simplified view of AHV input signal processing. In modelling MVN adaptation and rebound with a single exponential, it does not include contributions from mechanisms with different time constants (e.g. adaptation in the vestibular apparatus itself). Such contributions would respond to different components of the head movement power spectrum, potentially contributing differences between different data sets not seen in the current implementation. Also, several experimental factors beyond the scope of the model may affect absolute ATI values, including the use of different subjects for the two data sets, or the walls of the square box environment restricting head movements artificially (e.g. the rat spends much time searching for food pellets along the walls or in the corners, and thus does not have the freedom to move its head in all directions). In our view, the fact that the model can account for much of the experimentally observed anticipation variance on both data sets without tuning of parameters is more compelling than if we had fit the parameters to the anticipation data without physiological justification.

7.4 Conclusions and discussion

We provide a novel hypothesis on how anticipation is generated in the head direction (HD) system. Following the *in vitro* firing properties of medial vestibular nucleus (MVN) neurons, which are thought to provide angular head velocity (AHV) information to the HD system, we incorporate physiological levels of adaptation and rebound firing in our model. When run on a corpus of rat tracking data, the model produces realistic anticipation without further parameter tuning. Critically, the model provides an explanation for the substantial anticipation variability: the statistics of the rat's head movements interact with the high-pass filtering generated by adaptation and rebound, such that movement patterns with high frequency components result in lower anticipation than lower frequency movements. When compared directly against experimental recording data from two different behavioural tasks, the model accounts for 60%-80% of the experimentally observed variance.

Despite the high correlation between the model and the experimental ATI values on both data sets independently, it is notable that while the absolute values match well on the circular track data set, experimental ATIs in the square box are lower than expected. Intuitively, it seems likely that foraging for randomly scattered pellets would be more unpredictable than running on a circular track; however, no such differences were apparent in the rats' head movements that served as inputs to the model. It is possible that the square data set actually contains high frequency components which are filtered out by the smoothing procedure; however, inspection of the head movement power spectra for the two datasets did not reveal any such difference. At may be that limitations in the tracking system (30Hz sampling frequency and limited angular resolution) contribute to this difference. An alternative possibility is that because HD activity was recorded from ADN, there are influences of other HD areas, notably postsubiculum (PoS) and retrosplenial cortex (Rsp) on these HD cells which may differ between the two data sets. In support of this idea, lesions of PoS are known to increase ATIs in ADN (Goodridge and Taube 1997), which suggests that if PoS and/or Rsp, which receive inputs from visual areas (section 2.2) might contributes differentially in walled (square box) and open (circular track) environments. Ideally, data recorded in darkness would be used to eliminate the contribution of visual inputs.

Origin of the HD update signal

Several lines of evidence indicate that the MVN are a likely origin of vestibular inputs to the HD system (for a review, see Brown et al. 2002). Anatomically, the MVN project to the dorsal tegmental nuclei of Gudden (DTN), through the nucleus prepositus hyperglossi (nPH) and possibly also directly (Brown et al. 2005; Hayakawa and Zyo 1985; Liu et al. 1984). DTN, in turn, is reciprocally connected with the lateral mammillary nuclei (LMN) (Gonzalo-Ruiz et al. 1992). Both these areas contain AHV as well as HD cells, and cause

loss of downstream directional firing when lesioned (Sharp et al. 2001; Blair et al. 1998; Bassett and Taube 2001a). Similarly, bilateral lesions of the vestibular apparatus itself abolish directional activity in HD areas (Stackman and Taube 1997). Recording studies (albeit to our knowledge not in rats) have shown that semicircular canal-dependent MVN neuronal activity contains angular head velocity information (e.g. Melvill Jones and Milsum 1971; Fuchs and Kimm 1975 and many others). If the vestibular AHV signal is responsible for updating the HD system, its properties will be relevant to models of the HD system.

To assess the effects of vestibular dynamics on the HD system, and anticipation specifically, we based our model on the intrinsic firing properties of MVN neurons (Sekirnjak and du Lac 2002) as reported in rat brain slices. In recordings from intact animals, the MVN response is reported to have a phase lead relative to a sinusoidal AHV input (Melvill Jones and Milsum 1971; Fuchs and Kimm 1975), which decreases and even lags with increasing frequency (Kaufman et al. 2000). This pattern is consistent with our model. Although it is possible that these dynamics result from the properties of vestibular afferents (e.g. Fernandez and Goldberg 1971) rather than, or in addition to, intrinsic MVN firing properties, our implementation captures the relevant dynamics. In principle, the present model and the results reported only depend on the HD input signal being a filtered AHV signal, the mechanisms for which need not necessarily be implemented in the MVN. AHV neurons have also been found in the DTN (Bassett and Taube 2001b; Sharp et al. 2001), and have been reported to exhibit complex activity before, during and after head turns (Sharp et al. 2001). Fine-timescale analysis of DTN and MVN AHV-sensitive neurons in rats, for instance during a controlled head movement paradigm (Bassett et al. 2005; Zugaro et al. 2001), would address whether these neurons could support anticipatory firing, as the model suggests.

Visual input and tracking error

In the model, the HD system updates using vestibular information exclusively. Rats can use visual information to update their HD representation (Taube et al. 1990b), and a brief view of familiar landmarks improves homing performance in hamsters (Etienne et al. 2000). The influence of visual inputs on HD anticipation has not been addressed experimentally: for instance, no anticipation data have been reported for animals navigating in darkness. If a visual update involves setting the represented HD to the animal's true HD, the model's ability to anticipate is limited by the frequency of such updates. In the present model, a noticeable reduction in anticipation is only seen at update frequencies of more than 1Hz (data not shown), suggesting that visual fixes affect anticipation only marginally. A complete model of the HD system would include visual inputs, which are not included in the present model. However, the present model is compatible with such inputs, which have been modelled in previous studies (e.g. Song and Wang 2005 and others) and have

been left out for simplicity.

In contrast to earlier models, our model explicitly displays tracking error, resulting from the same adaptation and rebound mechanisms that generate anticipation. This error could contribute to the drift of head direction cell preferred firing directions observed in darkness (Goodridge et al. 1998; Knierim et al. 1998; Mizumori and Williams 1993). The model tracking error is determined precisely by the angular head velocity input, potentially consistent with systematic path integration errors found behaviourally (which depend on the outward path taken, Séguinot et al. 1993). A potentially related observation is that when animals walk into a novel environment, as in e.g. Taube and Burton (1995) and Dudchenko and Zinyuk (2005), small shifts in HD cell preferred directions are observed. It might be expected that in the absence of sufficiently strong visual input (as encountered in a novel environment where visual inputs have not yet had time to associate with HD cells using plasticity mechanisms), the HD system experiences drift before being stabilised by visual inputs. Interestingly, Dudchenko and Zinyuk (2005) found that this shift, although small on average (about 20°), was biased in the clockwise direction. Such a systematic shift would not be expected if the PFD change was the result of novel visual inputs; instead, it might arise from an imperfect angular head velocity update signal to the HD system, as suggested here. Comparisons of the rats' head movements and the resulting PFD shifts could shed light on this issue.

Relation to previous models

Several previous models have suggested a generic angular acceleration component to account for anticipation in the head direction (HD) system (Zhang 1996; Song and Wang 2005), the origin and neural implementation of which is unclear: the current model contains a physiologically plausible implementation of this idea. Other models have used offset connections between HD areas to generate anticipation (Redish et al. 1996; Goodridge and Touretzky 2000), for which there is some indirect experimental evidence (Blair et al. 1997). However, simulations of the offset scenario could only account for 30 ms of anticipation (Goodridge and Touretzky 2000) in the most favourable case, while mean anticipatory time intervals of 67 ms have been reported (Stackman and Taube 1998). Offset connections and afferent anticipation/rebound are not mutually exclusive, and it is possible both contribute to anticipation: the input dynamics of the current model could be combined with an additional offset layer. Like offset connections, our model provides a way for the HD signal to anticipate yet still be sensory; this contrasts with earlier interpretations where anticipation was interpreted as evidence against the HD signal being sensory (e.g. Taube and Muller 1998).

Apart from providing additional anticipation, the current model differs from the offset con-

nection explanation in two important respects. First, the time constants of the mechanisms generating anticipation in the offset model are necessarily fast, on the order of the synaptic and membrane time constants (5-20 ms). This implies that any frequency-dependence of anticipation will only become apparent at very high frequencies. In the current model with its slow (200 ms) dynamics, the effect of different input is clearly seen using naturally occurring variations in rat tracking data, and can explain much of the experimentally observed ATI variability. Second, since the offset connection scheme generates anticipation in the receiving layer only, it predicts there should be a population of non-anticipating HD cells afferent to LMN, where the highest ATIs have been found. In the original proposal (Redish et al. 1996), this population was placed in the postsubiculum (PoS), whose HD cells do not anticipate, and PoS sends a projection to LMN. However, a subsequent lesion study showed that PoS lesions left anticipation intact (Goodridge and Taube 1997). This result does not doom the offset connection hypothesis, as long another non-anticipating population (in DTN perhaps) can provide the required connections to LMN. In contrast, the current model supports the view that those HD cells closest to the source of the angular head velocity signal should anticipate most, with ATIs decreasing as the signal is propagated.

The current model uses a simplified, "generic" ring attractor network, which does not attempt to reproduce the experimentally observed cell types and anatomical realisations. This is done intentionally; the present results do not depend on this simplified architecture, and similar results can be obtained by incorporating the input dynamics of the present model into a more biologically plausible ring attractor model in the literature (e.g. Song and Wang 2005).

Implications

Our results suggest it would be informative to examine to what extent previously reported differences in anticipation can be explained by differences in head movements. Bassett et al. (2005) report that during passive movement (rats rotated by an experimenter), head direction cells anticipated significantly more than when the rats could move their heads freely. As suggested by these authors, it seems likely that the active and passive movement conditions had very different movement frequency spectra; thus, it is possible that the difference in anticipation can be explained by a mechanism like the present model.

The mechanism proposed here provides an explanation of HD anticipation which does not require specialised neural circuitry, but instead results from head movements interacting with the properties of the vestibular system, which supports many other functions as well. More generally, we show that the statistics of the input signal to a system can inform and constrain putative neural mechanisms needed to account for the system's properties.

7.5 Analytical derivations

To gain a deeper understanding of the model's behaviour and its precise dependence on the parameters, we study the anticipation analytically for two simple input profiles: a single step stimulus and a sinusoidal input. In these cases we obtain explicit expressions for both the ATI and its associated error.

Step input

First we consider an angular head velocity profile that consists of a single turn over a certain angle. The input angular velocity has a step profile

$$\omega(t) = \omega_0 \quad (0 < t < T)$$

and $\omega(t) = 0$ otherwise. The actual angle of the head θ_0 is the integral of $\omega(t)$ and is given by $\theta_0(t) = \omega_0 t$, for $0 < t < T$, and $\theta_0(t > T) = \omega_0 T$, where without loss of generality we set $\theta_0(0) = 0$.

The input to the head-direction integrator is not the pure velocity signal, but one which is altered due to adaptation and rebound firing. Due to adaptation the velocity input during the turn (given by Eq. 7.3 in the main text) becomes

$$v(t) = \omega_0(1 - A + Ae^{-t/\tau_A}) \quad (0 < t < T)$$

During the rotation the rebound current of the contra-unit builds up to a value $\omega_0 R(1 - e^{-t/\tau_R})$. When the rotation stops, the velocity input (from Eq. 7.4, main text) therefore behaves as

$$v(t) = -\omega_0 R(1 - e^{-T/\tau_R})e^{(T-t)/\tau_R} \quad (t > T)$$

Unlike our full simulation we ignore subsequent dynamics and processing of the integrator in what follows. Instead we assume that the velocity integrator integrates the input signal v perfectly with a gain γ. The estimated head direction angle follows from integrating the input,

$$\begin{aligned} \theta(t) &= \gamma\omega_0[(1-A)t + A\tau_A(1 - e^{-t/\tau_A})] \quad (\text{for } 0 < t < T) \\ &= \gamma\omega_0\{(1-A)T + A\tau_A[1 - e^{-T/\tau_A}] - R\tau_R(1 - e^{-T/\tau_R})[1 - e^{(T-t)/\tau_R}]\} \quad (\text{for } t > T). \end{aligned}$$

The gain of the integrator is set such that when the integrator has equilibrated, the estimated and actual angle are the same, $\lim_{t\to\infty} \theta(t) = \omega_0 T$. This leads to

$$\gamma = \frac{1}{1 - A + A\tau_A/T(1 - e^{-T/\tau_A}) - R\tau_R/T(1 - e^{-T/\tau_R})}.$$

In the limit $T \gg \tau_A, \tau_R$ and when $A = R$ and $\tau_A = \tau_R$, the gain equals $1/(1-A)$.

Calculation of the ATI

The angular profile $\theta(t)$ will show anticipation w.r.t. the true angle $\theta_0(t)$. To determine the amount of anticipation, we shift the true profile with an amount δt to minimise the error $E(\delta t) \equiv \int_{-\infty}^{\infty}[\theta_0(t+\delta t)-\theta(t)]^2\,dt$. The ATI corresponds to the shift for which the error is minimal, that is $t_{ATI} = \arg\min E(\delta t)$. This minimisation can be performed in the limit $T \gg \tau_A, \tau_R$. The resulting anticipation is

$$t_{ATI} = \frac{1}{2(1-A)}(A\tau_A + R\tau_R) + O(1/T),$$

where $O(1/T)$ denotes correction terms of the order τ_A/T and τ_R/T, that disappear as T increases. We see that both rebound and adaptation contribute to the ATI. Each contribution is proportional to its time constant. In the limit when $A, R \ll 1$, adaptation and rebound contribute equally to the ATI for these simple profiles.

Minimal error

Given that both adaptation and rebound contribute to the ATI, one can wonder how to best choose their contribution. This can be evaluated by calculating the remaining error with the optimally shifted profile, i.e. $E(t_{ATI})$. This yields

$$E(t_{ATI}) = \frac{\omega_0^2}{12(1-A)^2}[A\tau_A - R\tau_R]^2 T + \ldots \tag{7.5}$$

Importantly, the leading contribution to the error is proportional in the step duration T, and hence diverges for long steps. In order to reduce the error for a given ATI, adaptation and rebound should be matched such that, $A\tau_A = R\tau_R$. When matched, the leading term disappears and the sub-leading terms in $E(t_{ATI})$, indicated by the ellipsis in Eq. (7.5), become important. Assuming $A = R$ and $\tau_a = \tau_R$, this term is $E(t_{ATI}) = \frac{1}{3(1-A)^3}\omega_0^2(A\tau_A)^2[3\tau_a + 2A\tau_A]$. To obtain a certain ATI one can still choose between a long time constant (τ_A, τ_R) or a large strength (A, R). This expression shows that for the step profiles, it is somewhat better to choose a short time constant, as then the first term in the brackets disappears, reducing the error.

In summary, adaptation and rebound contribute to the ATI, and in order to minimise error both should be equally strong.

Periodic input

The effect of adaptation and rebound for more general profiles is complicated. However, in the special case that $R = A$ and $\tau \equiv \tau_R = \tau_A$ the combined effect of adaptation and rebound can be described as a high-pass linear filter. This filter kernel is

$$\kappa(t) = \delta(t) - \frac{A}{1-A}\frac{1}{\tau}e^{-t/\tau},$$

which captures both the transient overshoot when the velocity comes on, and the undershoot from rebound when it turns off. To investigate how the model ATI depends on the properties of periodic input patterns, we consider the simplified case of identical adaptation and rebound. The head direction velocity is $\omega(t) = \omega_0 \exp(2\pi i f t)$. We convolve the input signal with the kernel:

$$\begin{aligned}\omega^*(t) &= \int_{-\infty}^{t} \left[\delta(t-t') - \frac{A}{\tau(1-A)} e^{-(t-t')/\tau}\right] \omega_0 e^{2\pi i f t'} dt' \\ &= \frac{1}{1-A}\left[\frac{1-2A+4\pi^2(1-A)f^2\tau^2+2\pi i A f\tau}{1+4\pi^2 f^2\tau^2}\right]\omega(t)\end{aligned}$$

From this the phase shift $\Delta\phi$ follows as

$$\begin{aligned}\Delta\phi &= atan\left(\frac{Im(\omega^*(0))}{Re(\omega^*(0))}\right) \\ &= atan\left(\frac{2\pi A f\tau}{1-2A+4\pi^2(1-A)f^2\tau^2}\right)\end{aligned}$$

For small anticipation ($\phi \ll 1$) the time shift of the convolved signal's ATI is

$$t_{ATI} = \frac{\Delta\phi}{2\pi f} = \frac{A\tau}{1-2A+4\pi^2(1-A)f^2\tau^2} \tag{7.6}$$

The above expression shows that for low input frequencies f, the ATI increases linearly with τ, in accordance with the step input results. At higher frequency, however, the ATI decreases again. This decrease is faster in the case of large τ. The maximum ATI occurs for $1/\tau = 2\pi f\sqrt{1-A}/\sqrt{1-2A}$, with an ATI of $t_{ATI} = \frac{1}{2(1-A)}A\tau$. Thus, a fast time constant gives a small amount of anticipation which is less affected by fast-changing input, whereas a slow time constant gives a lot of anticipation at slow frequencies, falling off rapidly (to below fast τ levels) as input frequency increases.

Chapter 8

Adaptation, depression and anticipation in head direction circuits

The rodent head-direction (HD) system contains cells that have approximately Gaussian tuning curves for direction in the horizontal plane. It is thought to integrate self-motion (angular head velocity) information from the vestibular system to maintain an accurate heading representation when external cues are unavailable. As reviewed in earlier sections (2.5 on page 27 and 3.2 on page 41), HD cells anticipate the animal's actual HD: when an anticipating HD cell spike train is shifted with respect to the animal's HD, their cross-correlation or mutual information will be highest when the spike train is shifted some amount into the future (Blair et al. 1997; Taube and Muller 1998).

8.1 Rationale

The previous chapter investigated modulation of the angular head velocity "update signal" as a possible source of anticipation in a model with a single population of head direction (HD) cells. However, a salient feature of the HD system is that HD cells are found in many brain areas, with at least several appearing to be connected in a simple feedforward manner where HD activity in one brain area depends on the integrity of the previous node in the chain (reviewed in section 2.2). This suggests that a vestibular-derived angular head velocity update signal is propagated through the HD system, an idea supported by the observation that HD cells in areas closest to the vestibular system appear to anticipate most: 39/67 ms for the lateral mammillary nuclei (LMN), 25 ms for the anterodorsal thalamic nuclei (ADN), and -5 ms for the postsubiculum (PoS, Figure 8.1 on the next page).

Using simulations, Redish et al. (1996) showed that offset connections between layers of HD cells could generate anticipation. In such a scheme, a HD cell with preferred firing

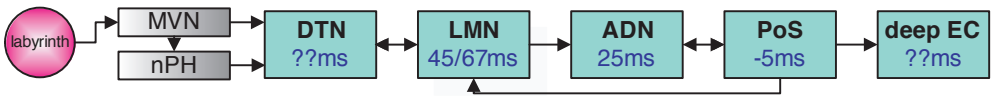

Figure 8.1: Anticipation decreases as the head direction (HD) signal is further from the vestibular apparatus (labyrinth). Shown is a diagram of different anticipatory time intervals (ATIs) in different head direction areas. Arrows indicate anatomical connections, with only the main connections and brain areas shown. HD cells are found in the areas coloured green; however, no reliable data for dorsal tegmental nucleus (DTN) and entorhinal cortex (EC) HD cells are available. Abbreviations: MVN, medial vestibular nuclei; NPH, nucleus prepositus hypoglossi; LMN, lateral mammillary nuclei; ADN, anterodorsal thalamic nuclei; PoS, postsubiculum.

direction (PFD) ϕ_i receives two offset inputs, one which is active during clockwise turns and originates from a HD cell with PFD $\phi_i - d$, and one from a HD cell with PFD $\phi_i + d$ which is active during counterclockwise turns. The amount of anticipation in the receiving cell layer is then proportional to the offset d.

Tuning curve deformations in the anterodorsal thalamic nucleus (ADN) provide indirect experimental evidence for offset connections (Blair et al. 1997). However, simulations showed that even the largest deformations could only account for 30ms of anticipation (Goodridge and Touretzky 2000). HD cells in the lateral mammillary nuclei (LMN) deform less (Blair et al. 1998) but anticipatory time intervals of up to 95ms have been reported (Stackman and Taube 1998). Similarly, in a more anatomically plausible proposal, Song and Wang (2005) report about 25ms of anticipation in LMN when using a perfect angular head velocity update signal. This raises the question of how anticipation in LMN is generated. In the previous chapter, possible contributions from the angular head velocity signal were explored; in this chapter, contributions from the firing properties of HD cells and the synapses between them are examined.

In particular, we investigate whether spike frequency adaptation and depressing synapses[1] in HD circuits can cause anticipation. Spike frequency adaptation in single neurons, and synaptic depression between pairs of neurons, is known to advance the phase of sinusoidal inputs (Fuhrmann et al. 2002; Sekirnjak and du Lac 2002; Puccini et al. 2006) but how it affects a population-coded variable like HD, and how it interacts with attractor dynamics in such a system, is presently unknown. We consider several scenarios where we incorporate these concepts into models of the HD system. We ask whether adaptation in HD cells that constitute the HD ring attractor network leads to anticipation. Next, we consider a case where the attractor units themselves do not adapt, but instead project to a "follower" layer which does not have attractor dynamics but consists of adapting units, as well as the case

[1] Analogous to spike frequency adaptation, synaptic depression refers to a decrease in the rate of neurotransmitter release in response to a constant stimulus.

where the synapses between the attractor network and a follower layer are depressing. We also asked what the effects of propagating the HD signal through several layers are in the absence of any adaptation or depression machinery.

8.2 Model 1: Adapting attractor units

To investigate the effects of adaptation in HD cells, we constructed a "ring attractor" network of nonlinear rate-based units capable of angular path integration, similar to previous models (Stringer et al. 2002; Redish et al. 1996; Skaggs et al. 1995). We implemented a standard firing rate model for the units r_i in the ring, as presented in the previous chapter (section 7.2 on page 132), albeit with the addition of an adaptation current:

$$\tau \frac{du_i(t)}{dt} = -u_i(t) + \sum_j W_{ij}(t) r_j(t) \tag{8.1}$$

$$r_i(t) = [F(u_i(t)) - I_i^A(t)]_+ \tag{8.2}$$

where $\tau = 10$ms is the time-constant of the unit, F is a sigmoidal activation function $F(u) = 1/(1+e^{-\beta u})$ with slope $\beta = 0.07$, and W is the recurrent weight matrix (described below). The adaptation current I^A obeys

$$\tau_A \frac{dI_i^A(t)}{dt} = -I_i^A(t) + g r_i(t) \tag{8.3}$$

This current grows and decays with a time-constant τ_A to a maximum of g times the unit's activity $r(t)$.

As in the preceding chapter, to achieve stable attractor "bump" states, the weight matrix W consists firstly of a constant symmetric component W^s:

$$W_{ij}^s = w_E e^{-d_{ij}^2/2\sigma^2} - w_I$$

where d_{ij} is the smallest angular difference between the preferred firing directions of the unit i and j; unit i has a preferred firing direction $\phi_i = \frac{2\pi i}{N}$, and $N = 100$ is the number of units in the ring. $\sigma = 6$ is the width of the Gaussian weight profile in units, $w_E = 15$ the strength of excitation, and $w_I = 20$ describes constant global inhibition.

To move the bump, two time-dependent asymmetric components are added to the weight matrix by multiplying two asymmetric weight profiles $w_{\{l,r\}}^a$ with their associated angular head velocity inputs $v_{\{l,r\}}$ and a constant gain factor γ, to yield

$$W(t) = W^s + \gamma[v_l(t)W_l^a + v_r(t)W_r^a]$$

The asymmetric weights are simply the derivative of the symmetric weights:

$$(W_l^a)_{ij} = \frac{d_{ij}}{\sigma^2} e^{\frac{-d_{ij}^2}{2\sigma^2}}$$

with $W_r^a = -W_l^a$. As in the previous chapter, the gain γ was calibrated such that the summed error between the input and the model's linear population vector output was minimal. The calibration process allowed for time-shifts between input and output, such that anticipation or lag did not contribute to the error. The time-shift minimising the error was taken to be the model's anticipatory time interval, or amount of anticipation, for that pattern, where positive values correspond to anticipation.

In all simulations, an integration time constant of 0.1 ms was used, and the simulation was allowed to reach a stable state before the presentation of any input.

Adapting HD cells in a ring attractor

Endowing the units in the network with a spike rate adaptation current had a number of effects. Firstly, for the symmetric weights used, while the network was stable at 15% adaptation (i.e. $g = 0.85$) with a time constant (τ_A) of 150 ms, both more or slower adaptation resulted in instability. (The relationship between the strength of the symmetric weights and the amount of permissible adaptation is treated in detail in Hansel and Sompolinsky 1998). Secondly, the adaptation increases the gain of the integrator, i.e. the same asymmetric modulation of the weight matrix now causes a larger shift of the activity bump. An intuitive explanation for this effect is that cells directly adjacent to, but not yet part of the activity bump, have not yet adapted and are therefore relatively excitable. This same idea explains the third effect: once the activity bump is moving, adaptation causes an additional asymmetry in the network, which persists with a very long time constant when modulation of the asymmetric weights has ceased. This manifests itself as inertia in the moving bump (Hansel and Sompolinsky 1998): once input is stopped, the bump keeps moving in its previous direction, because the cells on the unadapted side (where the bump is going) are more easily activated than the ones on the adapted side (where the bump came from). The amount of drift depends on the adaptation current strength and the adaptation time constant; see Figure 8.2 on the next page (left) for an example.

We examined the model using both step inputs and periodic inputs of different frequencies, and for different recurrent weight and global inhibition strengths. In a systematic parameter search no combination of adaptation strength and adaptation time constant resulted in

anticipation. On the contrary, the adaptation-generated inertia resulted in lag (Figure 8.2, middle and right).

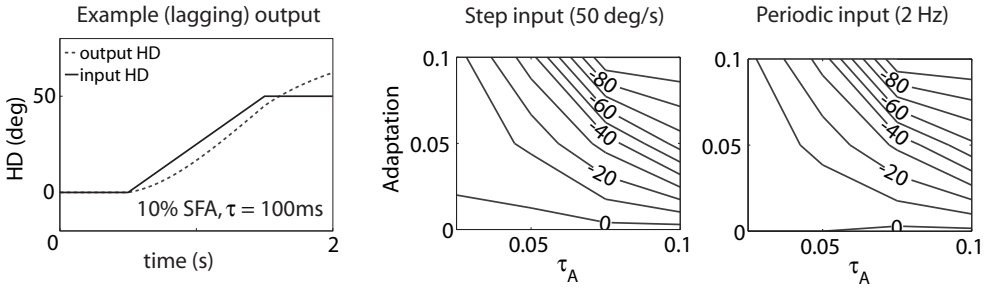

Figure 8.2: Adaptation of HD cells within an attractor does not lead to anticipation. **Left**: Example model output (dashed line) in response to a constant step input (solid line) for an attractor network with adapting units (10% adaptation, time constant 100ms). The output is time-lagged with respect to the input and drifts with a long time constant after input has ceased. **Middle**: Contour plot of the optimal time shift between the model input and output on a step input (contour labels, in ms) as a function of adaptation strength (abscissa) and time constant (ordinate). Step input was 50 deg/s for 1 s. Negative numbers indicate lag. **Right**: As before, but for 2 Hz periodic input with average angular head velocity of 50 deg/s during 1 s.

8.3 Model 2: Adapting follower layer

We now consider the case where an attractor-integrator network without spike rate adaptation projects to another layer of HD cells, without attractor dynamics, but with spike rate adaptation.

Analytical results

This scenario lends itself to analytical treatment if we assume that we have linear rate neurons with adaptation that can be described as

$$\begin{aligned} r(t) &= in(t) - gCa(t) \\ \tau_A \frac{dCa(t)}{dt} &= -Ca(t) + r(t) \end{aligned}$$

where $r(t)$ is the firing rate of the neuron (or a population), $in(t)$ is its input (for instance from the attractor network), g is the adaptation strength, $Ca(t)$ is the calcium concentration in the cell, which decays with a time constant τ_A and builds up during activity. The first equation implies that the neuron dynamics (from membrane and synaptic time constant) is much faster than the calcium dynamics, so that the firing rate is an instantaneous reflection of the input. Under this approximation the rate obeys

$$\tau\frac{dr(t)}{dt} = -(1+g)r(t) + in(t) + \tau\frac{d\,in(t)}{dt}$$

In other words the neuron is responsive to both the input and its derivative, hence the adaptation acts as a filter enhancing high frequencies. In a ring of these neurons (and corresponding inputs), the input signal for neuron i is modelled as $in_i(t) = A[1+\cos(\phi_i - \phi(t))]$, where $\phi(t) = \omega t$ describes the constant rotation of the input and ϕ_i the preferred direction of each neuron.

Integration and removing onset transients yields

$$r_i(t) = \frac{A}{1+g} + A\frac{(1+g+\tau^2\omega^2)\cos(\phi_i - \omega t) + g\tau\omega\sin(\phi_i - \omega t)}{(1+g)^2+\tau^2\omega^2}$$

From this we extract the population vector of the neural population response by weighting the directions by the neuron's activity

$$\mathbf{p}(t) = \frac{1}{N}\sum_i^N \begin{pmatrix} \cos\phi_i \\ \sin\phi_i \end{pmatrix} r_i(t)$$

In the limit when $N \gg 1$ the sum becomes an integral yielding

$$\mathbf{p}(t) = \frac{A}{(1+g)^2+\tau^2\omega^2}\begin{pmatrix} (1+g+\tau^2\omega^2)\cos\omega t - g\tau\omega\sin\omega t \\ (1+g+\tau^2\omega^2)\sin\omega t + g\tau\omega\cos\omega t \end{pmatrix}$$

The angle of the population vector is extracted by $\theta = \arctan\frac{p_y(t)}{p_x(t)}$. The anticipation angle can be extracted by considering $t = 0$, to yield $\Delta\theta = \arctan\frac{g\tau\omega}{1+g+\tau^2\omega^2}$. The anticipatory time interval is then $t_{ATI} = \Delta\theta/\omega$. For small g, and $\omega \ll 1/\tau$ this behaves as $t_{ATI} \approx g\tau$, and strong reduction of anticipation time occurs when $\omega > 1/\tau$. This result is similar to that obtained analytically for the system in the previous chapter; one difference lies in the implementation of the adaptation current, which is different in the previous chapter in order to match the *in vitro* data (section 7.2 on page 132).

Simulation results

We simulated the follower-layer scenario using step and periodic inputs. We again simulated an attractor layer, but this time without adaptation. The attractor projects (with one-to-one connectivity) to a follower layer without attractor dynamics, but with adaptation. Thus, the first layer dynamics are as in the single-layer setup above (Equations 8.1, 8.2 and 8.3) with $g = 1$, corresponding to no adaptation. Each unit in this layer was connected in a

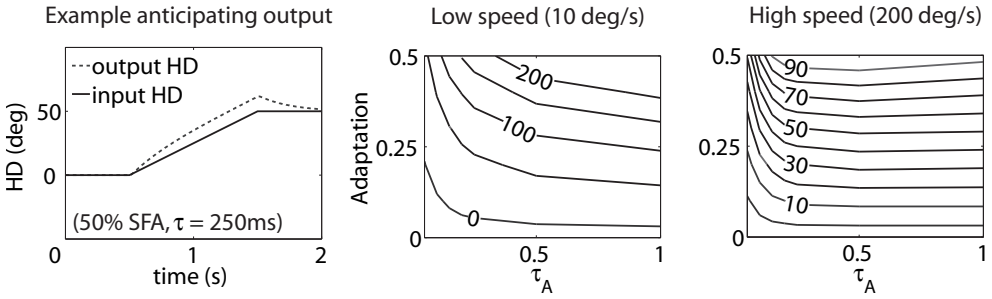

Figure 8.3: Spike frequency adaptation in a non-attractor follower layer generates anticipation. **Left**: Example model output (dashed line) in response to a constant step input (solid line) for 50% adaptation (time-constant 250ms) in the follower layer. **Middle**: Contour plot of anticipation (in ms, contour labels) for a slow step input. **Right**: Contour plot for a fast step input. In agreement with the analytic results, anticipation is reduced for faster inputs.

one-to-one fashion to the next layer with a synaptic weight w_{ff}, such that the activity r of unit i in the N-th layer ($N \geq 2$) was as follows:

$$\tau \frac{du_i^N}{dt} = -u_i^N + w_{\text{ff}} F(u_i^{N-1}) \tag{8.4}$$

$$r_i(t) = [F(u_i(t)) - I_i^A(t)]_+ \tag{8.5}$$

Where the adaptation current I^A is as in Equation 8.3. Note that this layer does not contain recurrent connections. In this case, we simulate only one follower layer; Equation 8.4 is given in its N-layer form for later simulations.

In agreement with the analytic results, but in contrast with the adapting attractor case, the output was anticipatory: see Figure 8.3 (left) for an example. Stronger (faster) inputs resulted in less anticipation for step inputs (Figure 8.3, middle and right). For periodic inputs, anticipation was particularly sensitive to input frequency: the middle (low frequency) and right (high frequency) panels in Figure 8.4 were generated with sinusoids of the same average angular velocity, but at high frequency only very fast adaptation results in a (small) amount of anticipation.

Adding symmetric recurrent connections to the follower layer decreased the amount of anticipation (Figure 8.4, bottom left). These connections were identical to those used in the attractor layer, except here we varied their strength:

$$\tau \frac{du_i^N}{dt} = -u_i^N + w_{\text{ff}} F(u_i^{N-1}) + \kappa \sum_j w_{ij}^s F(u_j^N)$$

The parameter κ sets the strength of the attractor dynamics in these layers; for a stable "bump" in the absence of external input a strength of 15 is needed. The result that such attractor dynamics reduce anticipation is consistent with previous results (Eq. 5 in Ben-Yishai et al. 1995) and can be intuitively understood as contributing inertia.

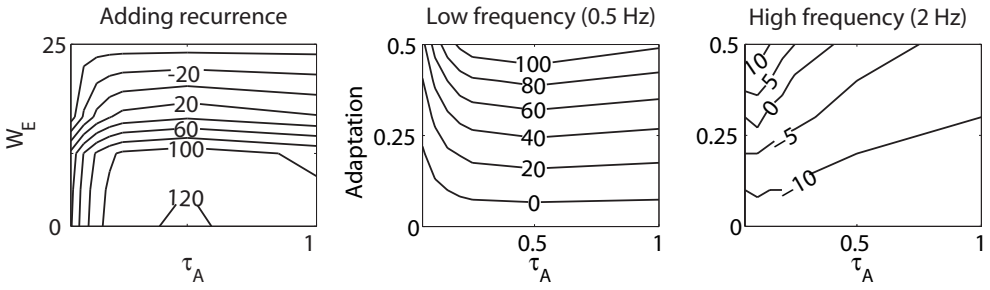

Figure 8.4: Properties of anticipation in a follower layer. **Left**: Anticipation is reduced by adding symmetric recurrent weights (of strength W_E, abscissa) in the follower layer. **Middle**: Contour plots of anticipation (in ms, labels on contour lines) for slow (0.5 Hz) and fast (2 Hz, **right**) periodic input. Higher frequency input patterns result in reduction of anticipation.

8.4 Model 3: Depressing synapses between layers

Next, we consider the case where two layers of HD cells are connected by depressing synapses. As in Model 2, the first layer contains attractor dynamics implemented by a symmetric recurrent weight matrix, as well as an asymmetric weight update mechanism allowing it to track AHV input. The second layer does not contain recurrent connections and passively receives feedforward input from the first layer, with the addition of an activity-dependent "release probability" $P_{rel}(t)$ (Tsodyks et al. 1998):

$$\tau \frac{du_i^N}{dt} = -u_i^N + w_{\text{ff}} P_{rel}(t) F(u_i^{N-1}) \tag{8.6}$$

where

$$\tau_{depr} \frac{dP_{rel}(t)}{dt} = P_0 - [1 + \tau_{depr} r(t)(1-f)] P_{rel}(t) \tag{8.7}$$

Because the release probability depends on the presynaptic firing rate, which are modelled on a range from 0 to 1, these were scaled to a 0–50 range, corresponding to the presynaptic HD cells having a 50Hz peak firing rate[2]. The results are similar to those for adapting following units. For an example step and periodic pattern, the network's output is shown in the top panel of Figure 8.5 on the following page. The output shows clear anticipation, which

[2] Additionally, Equation 8.7 is an approximation only valid for Poisson presynaptic activity $r(t)$.

depends on the strength of the depression f and its time constant τ_{depr} (Figure 8.5, bottom left), with stronger depression and longer time constants resulting in more anticipation. There is also a weak effect of the (unadapted) strength of the feedforward connections between the layers. Intuitively, the effect that depressing feedforward connections lead to anticipation can be understood in the same way as the case of adapting units in the follower layer: when the activity bump starts moving, the bump in the follower layer is boosted by the relative excitability of the cells adjacent to the bump. When the attractor layer bump stops moving, the follower layer does not keep moving like the adapting attractor layer case, but is constrained to location of the bump in the attractor layer, leading to "perfect" anticipation: only when the bump is moving does the follower layer lead the attractor layer; when it is still, the follower layer is set to be identical to the attractor layer.

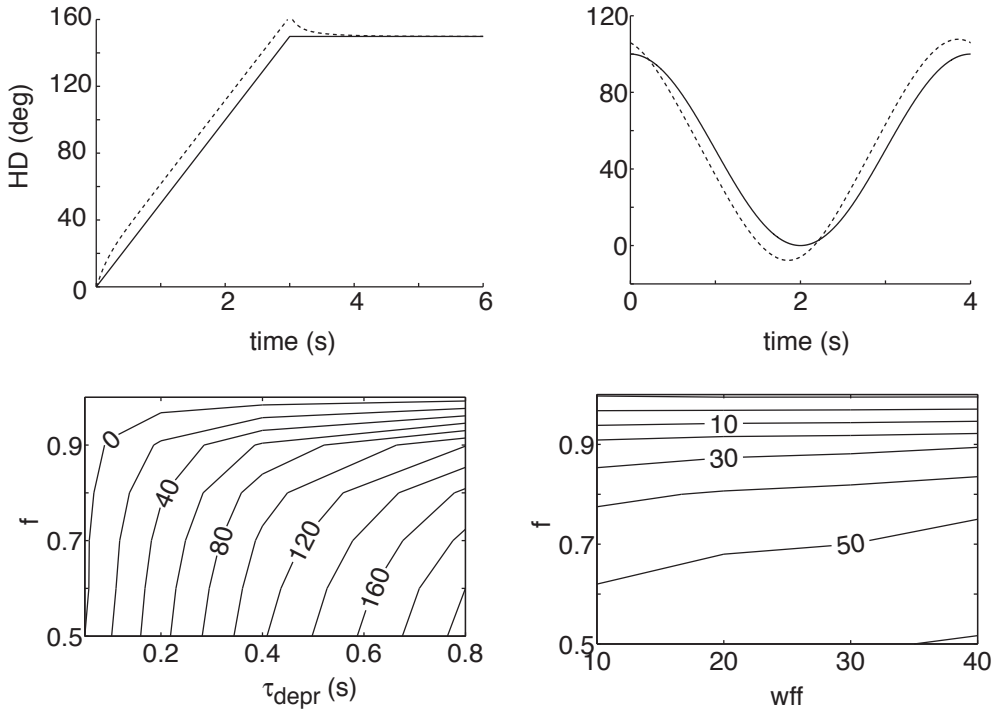

Figure 8.5: Depressing synapses between an attractor layer and a follower layer of HD cells result in anticipation in the follower layer. **Top left**: Example of the model output corresponding to perfect integration of a step input (solid line), and the follower layer output (dashed line). **Top right**: idem for a periodic input. **Bottom left**: The amount of anticipation (contour labels in ms) increases with the amount of depression (f) and the depression time constant (τ_{depr}). **Bottom right**: Anticipation depends weakly on the strength of the feedforward connections (w_{ff}, $\tau_{depr} = 0.2$).

However, analogous to the adapting follower layer case, the time constant τ_{depr} in the boost provided by the depression causes the amount of anticipation to be dependent on the frequency of the stimulus. This is illustrated in Figure 8.6 on the next page, where high-frequency inputs result in less anticipation than low-frequency inputs. It is still the case that more depression and a longer depression time constant result in more anticipation,

but the effect of frequency is clear from comparing the top panels (left: high frequency, right: low frequency).

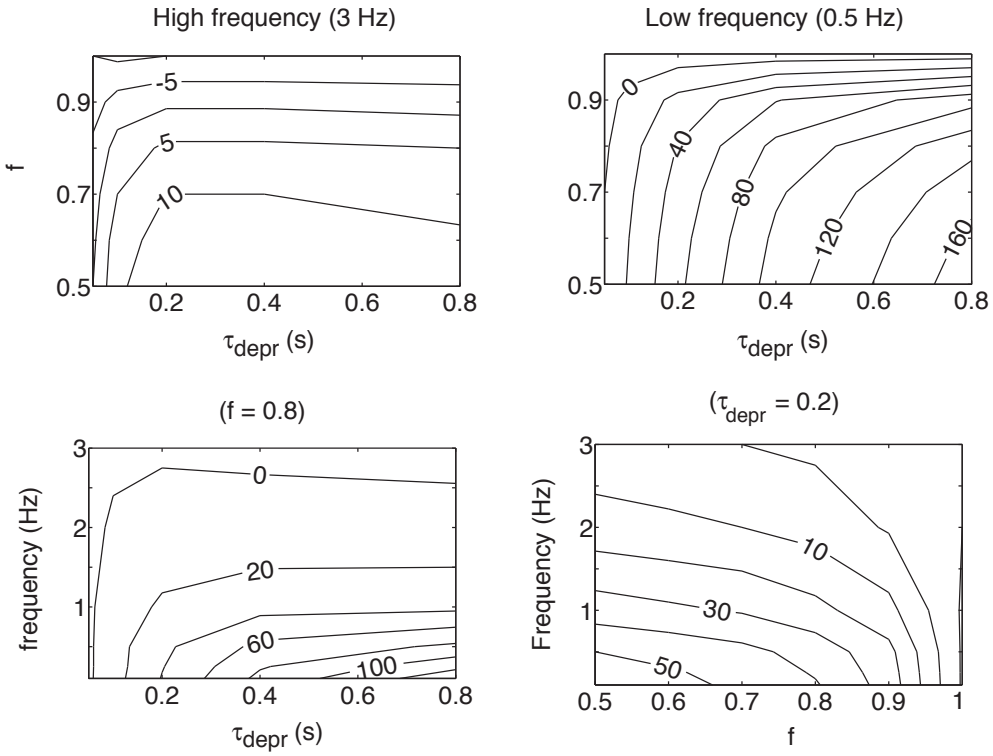

Figure 8.6: On periodic inputs, the amount of anticipation generated in the follower layer by depressing synapses depends strongly on the frequency of the input signal. However, for all but the fastest frequencies (see bottom left panel) it is still the case that more depression (f) and a longer time constant (τ_{depr}) result in more anticipation.

Thus, we show that although adaptation within an attractor layer of HD cells does not result in anticipation, adaptation in a follower layer without attractor dynamics does generate anticipation. In this case, the time constant of the adaptation results in the amount of anticipation being frequency-dependent. Using depressing synapses to the follower layer gives similar results.

8.5 Filtering through propagation

Next, we asked how the ATI and tracking error behave when the HD is propagated through four layers of non-adapting units using non-depressing synapses. In this case, each layer adds additional latency to the HD signal, counteracting the anticipation in the first layer. For these simulations, we used the model in the previous chapter and the dataset containing 100 2-second patterns of rat tracking data to generate anticipation in the first layer. This signal was then propagated through four successive follower layers (Equation 8.4 on page 164), in which the strength of symmetric recurrent connections was varied.

The amount of delay that results in this scenario depends on the ratio of the feedforward and recurrent connections; with stronger recurrent connections the network resists change increasing the delay (Ben-Yishai et al. 1995). As shown in Figure 8.7 (left), long delays between layers can be generated by weak feedforward projections and attractor dynamics in follower layers. Apart from these two factors, the amount of lag between layers is additionally determined by the time constant of the units in the layer (results not shown). In the absence of recurrent connections, the minimum lag that each layer contributes is equal to the this unit time constant (10 ms in this case).

The "sluggishness" of each layer low-pass filters the HD signal. It thereby counteracts the high-pass filtering (achieved by adaptation and rebound in the medial vestibular nuclei model of the previous chapter) of the signal that results in anticipation. As a result, propagation through layers not only reduces the ATI, but also reduces the distortion caused by the anticipation. Filtering of the signal as it propagates results in improved tracking performance compared to the first layer for all but the most conservative amounts of adaptation and input, Fig. 8.7 centre. Interestingly, when optimising the gain for lowest errors in the fourth layer (instead of in the first as in previous simulations), mild adaptation and rebound can actually improve absolute tracking performance over no adaptation and rebound (Figure 8.7, right).

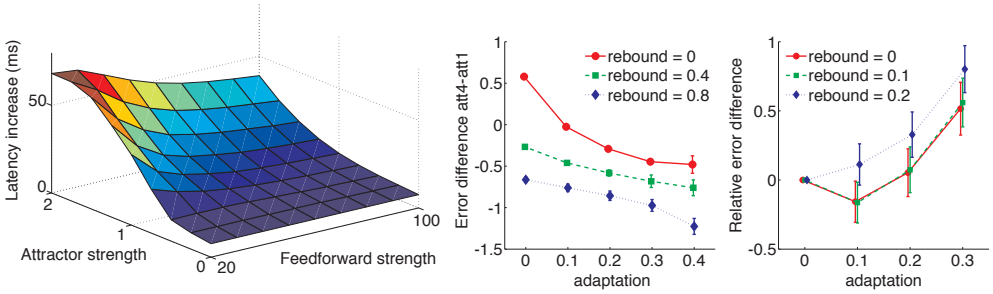

Figure 8.7: Effects of propagating the HD signal through 4 layers. **Left**: latency increase per layer as a function of attractor strength in each subsequent layer and strength of the feedforward connections between layers. **Middle**: Difference in tracking error between the decoded output of the fourth and first layers. Negative values indicate better tracking in the fourth layer. **Right**: Error differences in the fourth layer compared to no adaptation and no rebound when the model gain is optimised for error in the fourth layer. Negative values indicate better tracking than no adaptation/no rebound.

8.6 Conclusions and discussion

We have shown that adaptation in head direction (HD) cells within an attractor capable of integrating realistic angular velocity inputs with minimal error does not lead to anticipation. In contrast, spike rate adaptation in HD cells *can* generate anticipation when they passively receive input from another HD population, with depressing synapses between layers

yielding similar results. Hence, if the system contains a ring attractor without adaptation, followed by a follower network with strong adaptation, a net anticipation of HD can result, but only in the second layer. This anticipation is strongly dependent on input frequency, because the input interacts with the time constant of the adaptation (or depression), similar to the model in the previous chapter. Although we have not run the models presented on this chapter on the experimental data set that would allow comparison to the experimental ATI values, the present models are expected to yield similar results, since both models rely on the inertia of a single time constant in the anticipation mechanism for their frequency-dependence.

However, there is an important difference between the models presented here and that from the previous chapter. The model proposed in the previous chapter predicts that because anticipation is the result of a modulation of the angular head velocity input signal, the first[3] area containing HD cells should be the most anticipatory, with subsequent areas being less anticipatory as a result of factors contributing to lag as in the present simulations. In contrast, in the present models, anticipation is generated in a layer that depends on propagation of the HD signal from a previous layer. Thus, a critical piece of evidence that would distinguish between these two proposals, is to find the ATI of DTN HD cells. If it is less than that of LMN cells, there could be a contribution of adaptation in HD cells or depressing synapses providing input to them. If it is more than that of LMN cells, adaptation must be generated earlier, potentially in high-pass filtering of the angular head velocity signal. As with offset connections between layers, these mechanisms are mutually compatible, so it is possible the actual situation will not be so clear-cut and could reflect a contribution from all these sources.

For the proposals in this chapter, it is notable that no adaptation in HD cells has been reported, at least when recorded from freely moving rats (Taube and Muller 1998). However, it is possible that there is adaptation present, but that its presence is obscured by the fact that in a moving animal, a given HD cell is never "switched on" instantly from completely silent to fully active. As the animal moves its head, a given HD cell will first fire slowly, starting from the tail of its tuning curve before peak firing is reached. Detailed examinations of HD cell spike trains as a rat turns through its tuning curve might in principle help resolve this, although it could be difficult to distinguish the effect of adaptation from that of other sources contributing to anticipation in this way. Another possible method would be to test for adaptation and depression in anaesthetised or slice preparations, although as previously noted, the identification of the relevant cells will be an obstacle.

In the simulations and analysis presented here, a biologically implausible recurrent weight matrix was used in the first attractor layer, whose strengths are updated instantly in response to angular head velocity input. The same result could be achieved by more detailed circuits

[3] First in the sense that all downstream HD areas depend on its integrity.

which do not violate biological constraints (see section 3.1.2 for a review); confirmation that adaptation in depression in those detailed circuits yield similar results to those obtained here is work in progress.

Chapter 9

Conclusions, discussion, and future directions

The main experimental contributions of the present work provide support for two critical predictions of the **neural compass hypothesis**, which states that given a suitably encoded goal in a given reference frame, rats can use a head direction signal relative to that frame's reference direction (as provided by the HD system) to navigate to the goal. It predicts that on navigation tasks which require a representation of head direction, (1) lesions or other disruptions of the HD system should devastate performance, and (2) the state of the HD representation should correlate with the rat's navigational decisions. In support of these predictions, it is shown that:

- Rats can be trained on an (angular) path integration task which, unlike previous such experiments in rats, has an explicit slow rotation manipulation to rule out the use of diffuse distal cues. When rats are slowly rotated during excursions away from their home base, they do not return to their original home location, but a location corresponding to the rotation.
- On this task, rats with lesions to the lateral mammillary nuclei (LMN), which is a critical node in the head direction cell network, are impaired relative to unlesioned controls. On a cued version of the task, however, there is no difference between the two groups, suggesting that the lesion deficit is (angular) path integration-specific.
- Recordings of head direction cells as rats perform the (angular) path integration task are consistent with the hypothesis that rats rely on the head direction signal to perform this task. Specifically, there is a significant correlation between the rats' choice of return and shifts in the head direction signal.

The neural compass hypothesis can account for a number of previous results which have examined the issue of the behavioural relevance of the HD system, and have been interpreted as conflicting. The present results offer a clean start for studies addressing this question, by showing that in a case unconfounded by the influence of cues and reference direction shifts, there is a clear relationship between the HD system and behaviour. Although correlations between the state of the HD system and behaviour have been shown previously, those result could have been obtained from behaviour and the HD system having been influenced by a common factor, and it thus does not provide strong evidence for a direct relationship between the two. Because the task used here depends on an intact HD system as shown by the lesion study, and rats appear to be using a sense of direction as shown by the rotation manipulation, we offer causal (lesion) evidence in addition to correlational (recording) evidence on the same task.

How the HD system interacts with goal encoding, and with behaviour in more complex cases, for instance in the construction and use of map-like constructs, will require further study, are interesting questions for further study, which are on firmer ground because of the present result that the HD system appears to be used for path integration.

In the theoretical part of this thesis, a number of novel proposals to account for anticipation in the head direction system are outlined, implemented, and directly compared to experimental data. Existing proposals for the generation of anticipation cannot account for any variability in anticipation, which as experimentally observed takes various forms: variability in anticipatory time intervals (ATIs) when the same HD cell is recorded for multiple sessions, variability between simultaneously recorded HD cells, differences in estimates of the mean ATI between and within different laboratories, and an increase in ATI when animals are passively rotated when compared to freely moving.

The main modelling result is that all these manifestations of ATI variability can potentially be understood as the result of a single mechanism, that of the statistics of the rat's head movements interacting with the anticipation mechanism. In the first proposal, it is shown that high-pass filtering of the vestibular-derived angular head velocity signal updating the HD system can generate anticipation. This filtering could be achieved by taking the membrane properties of neurons in the medial vestibular nucleus (MVN) into account, which is thought to provide input to the HD system. In this model, the time constants of spike rate adaptation and post-inhibitory rebound cause high-frequency head movements to result in less anticipation than low-frequency head movements. This prediction was confirmed by running the model on a large experimental data set, where high correlations (of 0.6-0.9 across 21 recording sessions) of the model and experimental ATIs were found. We also outline ways in which a similar result could be obtained by different mechanisms, which rely on spike rate adaptation and/or depressing synapses in HD circuits themselves. These possibilities can be distinguished with current recording methods.

There are two main implications of the result that ATIs are dependent on the frequency of head movements. First, it has methodological consequences. For instance, Bassett et al. (2005) show that when rats are rotated passively, higher ATIs are observed compared to when they are freely moving. Before conclusions are drawn about the mechanisms that might be responsible for this difference, it would be worth finding out if the difference is related to the frequency content of the head movements on both conditions. Another example is the apparent inconsistency of ADN receiving offset inputs from LMN, yet being less anticipatory. The hypothesis that this is due to inputs from PoS to ADN could be tested by PoS lesions and measuring the ATI in ADN, which would then be expected to be higher than in LMN. However, unless the head movement frequencies are approximately matched between this group and the group where the LMN ATI value is taken from, this comparison could lead to wrong conclusions. Given that average ATI estimates between labs vary 30ms, this is not an unlikely scenario.

The second implication is that the frequency-dependence of ATIs provides a constraint on network models of the HD system. The simulations in the modelling chapters suggest that in principle, an anticipation-generating mechanism with a relatively long time constant is sufficient for this result. Whether this is implemented in filtering of the input signal or in the properties of units and connections in HD circuits could be addressed in experimental studies. An imperfect update signal is consistent with systematic path integration errors and HD PFD drifts when entering novel environments observed experimentally, and could potentially be observed by recording from a number of HD cells simultaneously as to allow reconstruction of the encoded signal at fine timescales. Such an approach would also be useful to resolve some details of the path integration experiment; specifically, to rule out remapping and to confirm that a shift in the HD system precedes, not lags, the rat's navigational choices.

More generally, the modelling studies presented here illustrate the point that using a large data set of actual rat behaviour can give insights into sources of variability in experimental data associated with it. One question the present results do not explicitly address is what HD anticipation might be *for*. While the experimental results indicate that the HD system is a useful neural compass and not an epiphenomenon, the same cannot yet be said for anticipation.

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