

**Exploring how spatial learning can affect the firing of
place cells and head direction cells: the influence of
changes in landmark configuration and the
development of goal-directed spatial behaviour.**

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Abstract

Rats learn to navigate to a specific location faster in a familiar environment (Keith and Mcvety 1988). It has been proposed that place learning does not require specific reward signals, but rather, that it occurs automatically. One of the strongest pieces of evidence for the automatic nature of place learning comes from the observation that place and head direction cells reference their receptive fields to prominent landmarks in an environment without needing a reward signal (O'Keefe and Conway 1978; Taube et al. 1990b). It has also been proposed that an allocentric representation of an environment would be bound to the landmarks with the greatest relative stability to guide its orientation (O'Keefe and Nadel 1978). The first two parts of this thesis explore whether place and head direction cells automatically use the most coherent landmarks for orientation. Head direction cells have been shown to orient their preferred firing directions coherently when being exposed to conflicting landmarks in an environment (Yoganarasimha et al. 2006). A model of head direction cells was thus used to explore the necessary mechanisms required to implement an allocentric system that selects landmarks based on their relative stability. We found that the simple addition of Hebbian projections combined with units representing the orientation of landmarks to the head direction cell system is sufficient for the system to exhibit such a capacity. We then recorded both entorhinal head direction cells and CA1 place cells and at the same time subjected the rats to repeated experiences of landmark conflicts. During the conflicts a subset of landmarks always maintained a fixed relative relationship with each other. We found that the visual landmarks retained their ability to control the place and head direction cells even after repeated experience of conflict and that the simultaneously recorded place cells exhibited coherent representations between conflicts. However, the 'stable landmarks' did not show significantly greater control over the place and head direction cells when comparing to the unstable landmarks. This argues against the hypothesis that the relative stability between landmarks is encoded automatically. We did observe a trend that, with more conflict experience, the 'stable landmarks' appeared to exert greater control over the cells.

The last part of the thesis explores whether goal sensitive cells (Ainge et al. 2007a) discovered from CA1 of hippocampus are developed due to familiarity with the environment or from the demands for rats to perform a win-stay behaviour. We used the same win-stay task as in Ainge et al. and found that there were few or no goal sensitive cells on the first day of training. Subsequent development of goal sensitive activity correlated significantly with the rat's performance during the learning phase of the task. The correlation provides support to the hypothesis that the development of goal sensitive cells is associated to the learning of the win-stay task though it does not rule out the possibility that these goal sensitive cells are developed due to the accumulated experience on the maze.

In summary, this thesis explores what kind of spatial information is encoded by place and

head direction cells and finds that relative stability between landmarks without a reward signal is not automatically encoded. On the other hand, when additional information is required to solve a task, CA1 place cells adapt their spatial code to provide the necessary information to guide successful navigation.

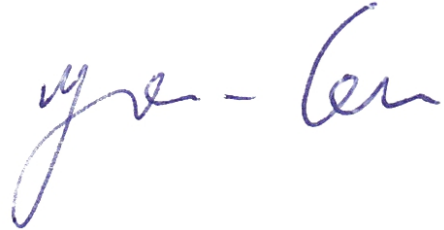
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Declaration

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.

A handwritten signature in blue ink, appearing to read 'Yen-Chen' followed by a stylized flourish.

(Yen-Chen Steven Huang)

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List of Abbreviations

ADN	Anterodorsal thalamic nuclei
AHV	Angular head velocity
AMN	Anteromedial thalamic nuclei
ATN	Anterior thalamic nuclei
AVN	Anteroventral thalamic nuclei
C.I.	Confidence interval
DMS	Delayed match-to-sample
DNMS	Delayed nonmatch-to-sample
DTN	Dorsal tegmental nuclei
EC	Entorhinal cortex
HD	Head direction
LDN	Laterodorsal thalamic nuclei
LMN	Lateral mammillary nuclei
PFD	Preferred firing direction
PoS	Postsubiculum
RSPL	Retrosplenial cortex
SC	Superior colliculus

Part I

Review

Chapter 1

Rodent navigation, disambiguation and use of landmarks

1.1 Introduction

Study of spatial navigation has always been an important approach to understanding the cognitive capacity of animals. With their ease of observation and close relation to natural behaviour, behavioural tasks employed to test rodent cognition often relate to their ability to achieve a navigation goal. After earlier exploration of rodent navigation capacity, more recent studies focused on understanding how different structures of the brain guide navigation and the integration between sensory information and internal states such as motivation. A reductionist approach such as lesioning or inactivating specific structures of the brain while observing the resultant deficit in navigation is often employed in understanding the respective role of each structure. The advances of single unit recording technology provide a complementary approach to investigate potential information and computation carried out by each structure. Despite not being able to establish a link between the observed neural activities and its direct contribution to behaviour, unit recording experiments allow direct observation of underlying neural activity in normal rats. This observation allows hypotheses of the basic computation characteristics in the brain to be proposed. The use of unit recording techniques is particularly prevalent in navigation studies due to the discovery of many different populations of neurons whose firing rates are strongly modulated by specific attributes in navigation such as rat's orientation or location in the environment. O'Keefe and Nadel (1978) proposed that spatial navigation differs from associative learning because information is automatically encoded in spatial navigation whereas associative learning requires a re-enforcement signal. Single unit recording techniques allow us to observe the encoded information either without or before engaging the rat in learning specific tasks, which could shed light into what spatial information is encoded automatically and whether such information prelude behavioural manifestation of learning.

This thesis aims at exploring how novel information of the surrounding environment get incorporated into the cell representation in the brain. By using single unit recording techniques to monitor the activity of place and head direction cells over multiple days and manipulating the surrounding environment in a controlled manner, I am able to study both the short term and long term responses of these cells to environmental changes and how the activity of these cells evolve with learning. Chapters 1–3 constitute the first part of this thesis, which summarises relevant background literature. The second part of the thesis, which includes Chapters 4–6, reports the results from a simulation experiment and two single unit recording experiments. Chapter 1 reviews literature of animal navigation with most attention on rodent studies. The purpose of the chapter is to briefly introduce different types of navigation behaviours and their specific characteristics. Chapter 2 reviews the contribution of different structures in the brain to spatial navigation, especially those that contain spatially modulated neurons to provide contrasts to results obtained from single unit recording studies. Chapter 3 reviews the single unit recording literature with particular attention to experiments that record neurons with either location or orientation modulation. The chapter addresses what spatial information is encoded in different structures, how it flows between structures and how external environments influence the firing properties of the neurons. Chapter 4 presents a computational model of head direction cells that attempts to simulate how head direction cell systems resolve conflicting landmark information from the environment. The model uses Hebbian learning projections to allow introduced landmark conflicts to be resolved. Chapter 5 presents an experiment investigating how CA1 place cells resolve repeated conflicts between distal landmarks when some subsets of the landmarks maintain stable relative relationship with each other. Chapter 6 presents an experiment that explores the development of so called 'goal sensitive cells' that fire differentially on the overlapping parts of running trajectories depending on the final destination. These cells are typically developed when rats have to run through a common path to reach several possible goal destinations and the reward is only given when the correct goal is chosen, usually following a win-stay or a win-shift rule. We explored how the development of goal sensitivity is related to the learning of a win-stay task by monitoring the activities of CA1 pyramidal cells over the course of fourteen days while the rats were learning a win-stay task on a double Y-maze. Finally, chapter 7 includes general discussions and conclusions of the thesis as well as possible future directions.

1.2 Navigation strategies

Navigation is part of almost everyone's life. We move from home to work through complex road systems, trying to take shortcuts or avoid traffic to minimise travel time. This seemingly easy task encapsulates many aspects of cognitive function. For example, navigating along a

familiar route requires recollection of the learnt route from memory and using external landmarks to correct for accumulated errors during navigation. Taking shortcuts requires a mental representation of present and goal locations and the ability to compute alternative, more efficient routes without physically experiencing them. Many animals possess navigation systems with amazing capacities. Migratory birds are able to utilise genetically coded information to navigate through a novel route in winter without prior experience (Berthold et al. 1992). Ants utilise both path integration and external landmarks for route following or homing (Hölldobler 1971; Merkle and Wehner 2008; Wehner et al. 1996; Wehner and Srinivasan 1981), whereas bees use visual cues to guide navigation (Collett and Collett 2002) and communicate the direction and distance of goals using symbolic dances (von Frisch 1974). Lab rats, one of the most studied animals, have also been shown to be able to navigate using the configuration of external landmarks (Morris 1981) or by path integration (Etienne and Jeffery 2004). Despite the availability of augmentation devices such as maps or GPS, human also possesses strong navigation skills. As an example, taxi drivers in London are able to plan and drive through complex routes in the city without the aid of assistive devices (Maguire et al. 1997). On top of that, humans uniquely employ advanced symbolic and language skills to aid navigation. Verbal communication of spatial knowledge and the use of symbolic representations of space (e.g. maps) are common. However, many navigation strategies employed by animals are also applicable to humans (Hamilton et al. 2002; Shrager et al. 2008). As many experiments, including those in this thesis, use lab rats as subjects, this review will focus on navigation strategies commonly employed by rats.

As rats constantly move around and interact with the surrounding environment, the spectrum of navigation behaviours is almost infinite. In order to decipher common mechanisms underlying navigation and simplify comparison between experiments, many authors have attempted to classify navigation behaviours under several broad categories (O'Keefe and Nadel 1978; Redish 1999; Trullier et al. 1997; Wang and Spelke 2002). These categories aim at summarising the information and/or computation required to execute navigation strategies. Experiments can then be designed to test these hypotheses in an attempt to decipher the common mechanisms underlying animal navigations. Here I describe a navigation taxonomy adapted from Redish (1999). Evidence supporting the existence of each navigation mechanism will also be briefly discussed.

Exploration. Cognitive psychology defines navigation as 'to plan and to perform a goal-directed path that leads from a point A to a point B, the goal (Gallistel 1990). However, in some situations animals do not have a explicit goal in mind. This can be due to an animal having insufficient information to decide its goal, such as entering a novel environment for the first time (Redish 1999). Or the animal simply is following its natural tendency to explore novelty in an environment (Ennaceur and Delacour 1988). One can question whether ani-

mals actively encode the surrounding environment under spontaneous exploratory behaviour though the novel object recognition task demonstrates that rats do encode previously visited objects, locations or contexts when exploring the environment spontaneously (Eacott and Norman 2004). Additional evidence comes from the study of latent learning where it is shown that prior exploration of a given environment without any re-enforcement signals such as rewards does facilitate subsequent task acquisition in the environment (see Thistlethwaite 1951 for a review). A more recent example used the water maze spatial reference memory paradigm and demonstrated that rats with prior exposure to the water maze room (by placing them on the escape platform without swimming) performed better than naive rats in locating the escape platform (Keith and Mcvety 1988). This phenomenon is used to support the hypothesis that spatial learning is uniquely different from associative learning as it does not require a reinforcement signal to encode the surrounding environment. On the other hand, research groups that support the associative memory paradigm argue that correctly locating previously experienced landmarks can itself serve as the reinforcement signal to guide learning (Prados and Redhead 2002).

Praxic navigation. Under praxic navigation (Redish 1999), animals execute a sequence of actions predetermined at the beginning of the navigation to complete the task. Such navigation strategies are capable to guide behaviours that only require to move from a fixed starting point to a fixed end point repeatedly or to execute a fixed motor sequence such as running straight and then turn left to complete the task. The strategy can be implemented simply by executing a fixed sequence of motor commands without having any knowledge of the surrounding environment. On the other hand, successful navigations require the correct motor sequence to be chosen to complete the task. Some early animal experiments demonstrated that rats use praxic strategies to guide navigation (Watson 1907) by showing that when a rat is well-trained on a complex maze, shortening a corridor caused the rat to run into the wall, which showed that the rat navigated the maze by executing a fixed motor sequence. The strategy can also be used to navigate some of the popular mazes such as T-maze or double Y-maze frequently used in more recent experiments. A recent experiment where the rats had to navigate in the dark from a fixed starting point to the fixed escape platform inside a water maze demonstrated that those rats could eventually learn to reach the platform via direct routes (Moghaddam and Bures 1996), which was most likely completed by a praxic navigation strategy.

Taxon navigation. Taxon navigation (O'Keefe and Nadel 1978; Redish 1999) refers to navigation strategies that utilise external landmarks to guide navigation in a way that does not require spatial knowledge of the environment or the relationships between the external landmarks and the goal destination. For example, strategies such as following olfactory trails or physical barriers of an environment (e.g. a river bank), do not require any spatial knowledge of the environment and can still guide animals to the correct goals (Hölldobler 1971). Alter-

natively, animals can associate the location of a visual landmark to the target destination. For example, rats swim toward the escape platform based on the location of the visual landmark in the cue-navigation version of the water maze task (McGauran et al. 2004; Morris et al. 1982). This purely associative learning can be acquired using stimulus response mechanisms and does not require a representation of the whole environment nor the ability to keep track of the animal's present location in the environment. More complicated navigation can be achieved by combining multiple taxon strategies such that animals move from one intermediate waypoint to another based on local views of the environment.

Path integration. A well-known navigation strategy is called dead-reckoning, which was first proposed in animals by Darwin (1873) and refers to the ability to keep a 'true course to a particular spot' while exploring the often complex surrounding environment. This ability has also been demonstrated in rodents under conditions in which no external information is available (Etienne et al. 1986; Mittelstaedt and Mittelstaedt 1980; Séguinot et al. 1993). Under these sensory deprived conditions animals rely upon self motion generated signals such as linear and angular velocity information (Wallace et al. 2002) or proprioceptive information (Etienne et al. 1988) to guide navigation. This ability is generally referred as path integration and is commonly observed in many animals including humans (Etienne and Jeffery 2004). Path integration, especially in insects, is sometimes also computed from visual inputs (Wehner and Menzel 1990). Here we choose a definition of path integration as navigating based on integrating self motion generated information to update one's location or orientation continuously. This definition makes a better distinction between navigation strategies that require external landmarks and those that don't. Animals using path integration need to update their locations relative to a reference point in the environment based on these self motion signals. For example, to compute a homing vector while exploring, the animal, at the least, needs to update its orientation with respect to the homing beacon continuously based on self motion signals such as angular head velocity information from the vestibular system. Due to the continuous update requirement, it is generally assumed that a path integration system requires a continuous representation of self location, which can then be associated to a certain reference point such as the location of home to guide navigation. The use of self motion information ensures that path integration does not require the availability of external sensory inputs nor prior experience of an environment (Wallace and Whishaw 2003). On the other hand, the accuracy of path integration without visual input is often poor (Loomis et al. 2001, 1993; Séguinot et al. 1993). It has even been suggested that humans could not reliably path integrate in a cue deprived environment (Foo et al. 2005), which emphasises the importance of using external sensory information to calibrate the path integrator.

Locale navigation. The last category encompasses navigation strategies that rely on the ability of animals to construct a mental representation of the surrounding environment, i.e. a

cognitive map (O'Keefe and Nadel 1978; Tolman 1948). This mental map encodes relationships between landmarks as well as the animal's present location within the environment. Such a map enables the application of many flexible navigation strategies. For example, it allows the animals to plan shortcuts between two destinations without prior experience of the route. This is slightly different from a path integration based shortcuts as the cognitive map does not just keep track of the relationship between the animal's present location and the goal and hence allows the planning of shortcuts based on prior experiences instead of just a homing vector (Tolman 1948). An animal that has developed a cognitive map of an environment can thus plan the shortest route to a desired destination when being placed at anywhere in the environment. As a cognitive map encodes relationships between landmarks in the environment, it is also able to use multiple landmarks to provide greater accuracy in guiding navigation, which is an improvement over taxon navigation where objects of the environment can only be used to guide navigation in a non-spatial manner. Several experiments support the hypothesis that animals can use the relationships between landmarks and goals for navigation. One of the well-known experiments is the demonstration of spatial reference memory described in Morris (1981). The authors used the water maze, which consisted of a circular, featureless pool of water with a submerged escape platform that could not be seen from water surface, to test spatial reference memory. Rats were dropped into the pool and needed to find the escape platform to complete the experiment. Several visually distinct landmarks were provided in the room containing the pool that could be used to guide navigation. However, there was no visual landmarks that directly indicated the position of the escape platform. The rats thus could not simply use a taxon strategy to find the escape platform. The authors showed that, after learning how to reach the escape platform from a starting point in the pool, the rats could quickly find the platform even when they were dropped into the pool at a novel location, suggesting that they had learnt the platform location with respect to the environment landmarks, thus demonstrated spatial reference memory in rats. In addition, Steele and Morris (1999) showed that continuous training in the same water maze environment allowed one trial learning of the new position of the escape platform in a delayed matching to place (DMP) task, in which the main difference from the reference memory task is that the location of the escape platform changes everyday and thus rats need to relearn the platform location everyday. The result supports the idea that rats form a cognitive map of the environment which is referenced to the visual landmarks. This allows the position of the escape platform to be quickly associated with the cognitive map and thus enables the rat to perform one trial learning. This is somehow similar to the latent learning phenomenon described briefly before which demonstrated that prior exposure to an environment, despite lack of any motivation signal, facilitated the subsequent acquisition of navigation tasks in the same environment (Thistlethwaite 1951).

1.3 Does the cognitive map exist?

Among the four navigation strategies discussed above, the existence of locale navigation in animals has been heavily discussed (Bennett 1996; Mackintosh 2002). The main issue is that implementing a cognitive map system is more complicated than other navigation systems and, despite the obvious benefit of having a map-like mental representation of the environment, there are often simpler solutions to solve navigation tasks that are proposed to require cognitive maps. Here I will address several issues of the existence of the cognitive maps in animals.

As described above, the ability of animals to make shortcuts is described by Tolman (1948) as evidence supporting the existence of cognitive maps. Since then, alternative interpretation of the results that do not require a cognitive map has been voiced. One suggestion is that the shortcut can be guided instead by animals recognising local views of the previously visited goal. For example, Muir and Taube (2004) showed that removing the light source at the goal box reduced the number of rats taking direct shortcuts on a sunburst maze compared to the original report (Tolman et al. 1946). Similarly, Chapuis and Scardigli (1993) showed that hamsters' ability to take shortcuts in a wheel is dependent on the presence of distal cues in the environment. However, this result emphasises more of the inadequacy of path integration to guide navigation of shortcut than a definitive evidence against the existence of cognitive maps. This leads to a second issue when interpreting shortcut ability as evidence supporting cognitive map based navigation. As discussed earlier, the ability to take shortcuts (i.e. choose a shorter 'homing' route) is also considered to be a supporting evidence for path integration. Several research groups correctly pointed out that many papers examining shortcuts are in fact assessing the animal's ability to path integrate (Bennett 1996; Foo et al. 2005). As will be discussed in more detail in section 1.4, path integration, despite being computationally inefficient, does not necessarily require an internal representation of space to calculate spatial relationships between landmarks or locations in the environment. Thus evidence supporting the existence of a path integrator in animals does not automatically imply the existence of cognitive maps. On the other hand, if animals possess a mental representation of the surrounding environment, then this representation should always remain coherent to maintain a unique mapping between the mental map and the external world. Under this argument, the strongest evidence that supports the existence of cognitive maps perhaps comes from the observation that rats possess a head direction cell system that appears to always encode a single head direction (Yoganarasimha et al. 2006), even when conflicts between external landmarks are introduced. This part of the literature will be discussed in more details at chapter 3.

O'Keefe and Nadel (1978) proposed that spatial learning of the environment is fundamentally different from associative learning and hence cognitive maps should integrate all of the information in the environment. Based on this hypothesis, phenomena such as blocking or overshadowing should not occur in the spatial domain. However, whether blocking or over-

shadowing exists in the spatial domain is controversial with evidence supporting each side of the argument. On the one hand, Fenton et al. (1994) demonstrated that adding two new landmarks to a room with two familiar landmarks, and the subsequent removal of the two familiar landmarks did not affect the rat's ability to locate the hidden platform in a water maze, which suggests that the novel landmarks were successfully integrated even in the presence of two familiar landmarks. The experiment also demonstrated that a subset of the four landmarks used in the experiment is adequate to guide navigation. On the other hand, several experiments did demonstrate blocking and overshadowing between landmarks (Chamizo 2003; Chamizo et al. 1985; Redhead et al. 1997), especially between subsets of landmarks with different distances from the rat (e.g. proximal vs. distal landmarks). In particular, Biegler and Morris (1999) specifically tested and confirmed that the added novel landmarks were explored by the rat, but still failed to contribute to locating the reward site, suggesting blocking in the spatial domain. In general, it appears that blocking in the spatial domain is less clear cut than in the traditional Pavlovian conditioning experiments and animals often seem to more or less learn about all of the available landmarks (Mackintosh 2002).

One of the main arguments that navigation based on a cognitive map can be distinguished from taxon navigation is that cognitive maps allow the spatial relationship between landmarks and goals to be exploited (Collett et al. 1986; Hamilton et al. 2009; Morris 1981; Pearce et al. 1998; Steele and Morris 1999) instead of the purely associative learning guiding taxon navigation (O'Keefe and Nadel 1978; Tolman 1948). However, critics argue that such experimental observations do not necessarily support the existence of a cognitive map as these behaviours can simply be guided by some kind of local view based taxon navigation. Several experiments aimed at addressing this showed that changing the local views of the environment did not remove the ability to use the spatial relationship between the symmetric landmarks and the goal to guide navigation (Biegler and Morris 1996b; Roberts and Pearce 1998). The results thus give support to the hypothesis that the navigation is guided by spatial relationships instead of by local views of the goal. Another supporting evidence for the cognitive map theory is that the ability of rats to find escape platforms is not degraded by partial removal of landmarks in the environment (Fenton et al. 1994), which also argues against the interpretation that orienting towards the escape platform relies upon the local view of the environment.

1.4 Allocentric and egocentric reference frames

As we have already discussed briefly above, using path integration for navigation requires a continuous updating of the animal's present location based on self motion cues with respect to a reference point, such as the location of home. This is sometimes interpreted as evidence that supports the existence of a cognitive map representing the surrounding environment. However,

navigating with path integration does not necessarily require a cognitive map. For example, dead reckoning based on path integration requires the animal to keep track of a homing vector. There are many more aspects of an environment that can be encoded to aid future navigation, such as specific landmarks, the location of home or the reward site. In the subsequent discussion of reference frames, these will all be referred to as landmarks of an environment. The relationship between the animal and the landmarks of the surrounding environment is referred to as an egocentric reference frame in the literature. In contrast, an allocentric reference frame encodes the relationships between landmarks of the environment and is independent of the present location of the animal (Klatzky et al. 1998). An allocentric reference frame is essentially a mental representation of the surrounding environment, i.e. a cognitive map. Path integration based on an allocentric reference frame does not require the animal to update the reference frame continuously. For example, a lab rat might learn that the reward site is located at the left of the white cue card, and this spatial knowledge does not change while the rat moves around the environment. What needs to be updated, is the relationship between the location of the animal with respect to the allocentric reference frame (Mou et al. 2004; O'Keefe 1991). Evidence supporting the use of allocentric references is generally treated as support for the existence of cognitive maps. However, an allocentric reference frame is not the only option that can be used to encode the surrounding environment. An animal can choose to use an egocentric reference instead. When an animal chooses to encode the surrounding environment using an egocentric reference frame, movement information needs to be used by a path integration mechanism to update the environment encoding. For example, if a rat learns that the reward site is located to its left, after it turns toward the reward site, this information needs to be updated to encode that the reward site is now directly in front of the rat. Egocentric reference frames do not explicitly encode the relationships between objects, nor a global representation of space. Thus evidence of animals using egocentric reference frames to guide navigation is treated as against the cognitive map theory.

So what are the main differences between navigation using allocentric or egocentric reference frames? Theoretically there is no difference in the spatial information coded by the two reference frames. Figure 1.1 provides an illustration for the encoding of the reference frames. For egocentric reference frames, despite the relationships between landmarks not being explicitly encoded, they can nonetheless be calculated by vector summation. Similarly vector summation can also be used to calculate the relationships between the landmarks and the animal in an allocentric frame. Adding a new landmark into an existing reference frame also requires similar computation. In the case of an allocentric reference frame, the minimum information required is the spatial relationship between the new landmark and one of the existing landmarks, and for an egocentric frame, the relationship between the location of the animal and the new landmark is added. On the other hand, updating an egocentric reference frame when

the animal moves around the environment requires considerably more effort than an allocentric one. As each of the self to landmark relationships needs to be updated, an egocentric encoding with n landmarks will require amount of computation that is proportional n to update. With allocentric encoding, the animal only needs to update its relationship with the allocentric map hence requiring a fixed cost of computation for updating, which is independent of the number of landmarks n in the environment, which is more efficient than egocentric updating when n is large. One additional problem for egocentric encoding is that since each of the self to landmark relationship needs to be updated while the animal is moving, the errors associated with the update accumulates independently for each self to landmark relationship. This implies that object to object relationships from an egocentric reference system are more susceptible to path integration errors. An allocentric reference system codes the inter-object relationship explicitly and thus would be more resistant to path integration errors. This differential susceptibility to path integration errors has been used to test whether human uses a cognitive map for navigation (Holmes and Sholl 2005; Wang and Spelke 2000). The authors allowed the subject to learn about the landmark configuration of a room first. The subject was then disoriented and asked to point at the two landmarks in the room. The authors argued that if an allocentric reference frame is used to guide navigation, the configural error of the two landmarks would be small. On the other hand, if an egocentric reference frame is used to encode the environment, a large configural error should also be observed. The results, however, were not consistent, with one group (Wang and Spelke 2000) reporting evidence supporting an egocentric system and another (Holmes and Sholl 2005) supporting an allocentric system. Another distinguishing feature between an allocentric and an egocentric reference frame is that it is generally assumed that an allocentric encoding of space is global as it encodes relationships between landmarks. Such a constraint does not apply to an egocentric reference frame as each landmark is encoded with respect to the animal. Single unit recording experiments, which will be discussed in greater detail in chapter 3, have found that both head direction cells (Yoganarasimha et al. 2006) and grid cells (Fyhn et al. 2007) generally maintain a global representation even when facing conflicting information from the environment. On the other hand, place cells from the hippocampus have been shown to follow different landmarks in an environment (Renaudineau et al. 2007; Shapiro et al. 1997; Yoganarasimha et al. 2006), which conforms with the characteristics of an egocentric reference frame. However, it was also reported recently that CA1 place cell ensembles tended to exhibit a split representation when encountering cue conflicts whereas CA3 ensembles exhibited a more coherent representation, suggesting an allocentric encoding scheme (Lee et al. 2004).

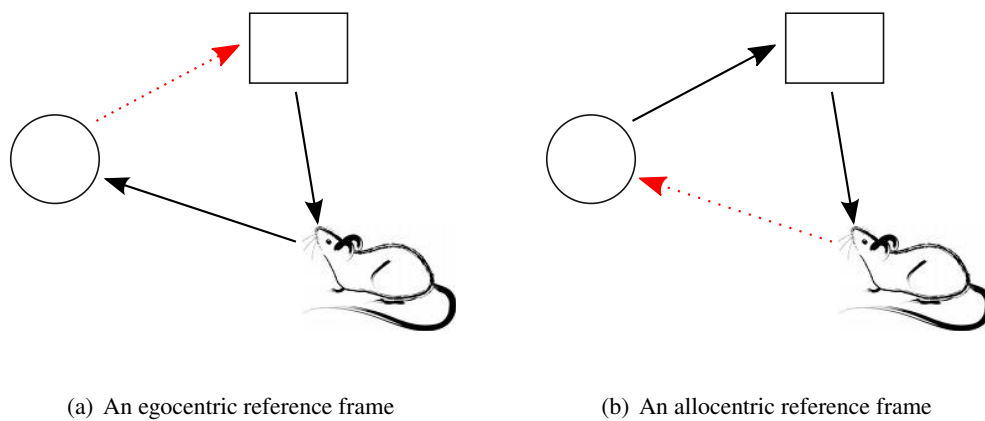


Figure 1.1: Allocentric vs. egocentric spatial encoding. The figure intends to illustrate that encoding based on allocentric and egocentric reference frames contain equivalent spatial information providing that all landmarks are encoded. Black solid arrows represent encoded relationships and red dotted arrows represent computed relationships. (a) illustrates an egocentric reference frame. Despite the relationships between the landmarks not being specifically encoded, it can be derived using vector summation. (b) illustrates an allocentric reference frame in which only the relationships between landmarks are encoded. As long as the animal can determine its relationship with one of the landmarks in the allocentric frame, all the rest of the egocentric relationships can be computed by vector summation.

Chapter 2

Neural basis of navigation

In the previous chapter, I have briefly outlined different aspects of navigation without discussing much regarding the brain structures involved. When a proposed navigation mechanism can be directly dissociated and mapped to a structure of the brain, it is more convincing that such a mechanism forms part of the navigation capacity of the animal. I will now briefly discuss the evidence supporting the involvement of different brain structures in navigation.

2.1 Anatomy and connectivity

Before going into the involvement of the different structures in the brain for navigation, I will first summarise the anatomy and connectivity of some of the areas in the brain as it is often helpful to understand the characteristics of physical medium supporting the flow of navigation information. The summary is not meant to be exhaustive and is concentrated on the regions and connectivities that are relevant to the subsequent discussions. An extensive information for the anatomy of rat nervous system can be found in Paxinos (2004), which is also the main source of information in the subsequent anatomical summary. A summary of the connectivity is presented in figure 2.1.

Entorhinal cortex

The entorhinal cortex (EC) provides the major cortical input into the hippocampus. The rat EC is conventionally subdivided into medial entorhinal area (MEA) and the lateral entorhinal area (LEA) and the laminar structure of the EC is traditionally classified into six layers, where layer I is mainly consisted of transversely oriented axons and layer II-VI contain different populations of cells. The traditional pathway originated from the EC is the perforant pathway, which is the major source of input into the dentate gyrus (Dolorfo and Amaral 1998). More recently, it has been demonstrated that this perforant path also projects to the CA1, the CA3 and the subiculum regions of the hippocampus. Among the targeted areas of the entorhinal

perforant path projection, only the CA1 and the subiculum contain reciprocal projections back to the EC. Typically the output projections of the EC originate from the superficial layers and the input projections terminate at the deep layers of the EC.

Hippocampal formation

The rat hippocampal formation is typically divided into three regions, the dentate gyrus, the hippocampus proper which consists of area CA1 and CA3, and the subiculum. The connectivity between the three regions are mostly unidirectional. The dentate gyrus projects to the CA3 via mossy fibres. The cells in the CA3 area has strong recurrent CA3-CA3 projections and also gives rise to CA3-CA1 projections called Schaffer collaterals. Unlike the CA3, the cells in the CA1 area do not possess strong recurrent CA1-CA1 projections. On top of the CA3 input, CA1 also receives strong projections from the amygdala and the thalamic midline nucleus reuniens. CA1 is one of the major sources of outputs (the other being the subiculum) of the hippocampal formation and projects to the subiculum, the retrosplenial cortex, the medial prefrontal cortex, the amygdala and several other cortical areas (see Paxinos 2004, p. 660 for more detail).

As a major output of the hippocampal formation, the subiculum projects to many areas of the brain, many of which are reciprocal projections. The subiculum contains a minor projection to CA1, and strong projections to the parahippocampal areas, including the entorhinal, perirhinal and postrhinal cortices. It has a significant projection to the dorsal portion of the presubiculum, which is also called postsubiculum in the literature. The subiculum also contains strong projection to the medial prefrontal cortex, the retrosplenial cortex, the medial portion of the mammillary bodies, the nucleus accumbens, which is part of the basal ganglia, the anteromedial thalamic nuclei (AMN) and the amygdala. Based on the summary, we can see that many of the efferent areas from CA1 is also targeted by the subiculum.

Basal Ganglia

The basal ganglia is consisted of four main areas, the striatum which is sub-divided into the caudate, putamen and nucleus accumbens, the globus pallidus, the substantia nigra which is sub-divided into pars reticulata and pars compacta, and the subthalamic nucleus. Among these areas, the striatum is the main input region to the basal ganglia system and receives extensive projections from most parts of the neocortex. The striatum projects to the medial and lateral globus pallidus and the substantia nigra. The lateral globus pallidus in turn projects to the medial globus pallidus and has a reciprocal projection with the subthalamic nucleus. The substantia pars compacta contains dopamine modulated projections that target the striatum. The substantia nigra pars reticulata and the medial globus pallidus are the output areas of the basal ganglia and projects to ventral medial thalamus, superior colliculus and pedunculopontine nucleus.

Mammillary body

The mammillary body is located at the medial zone of the hypothalamus and consists of the medial and lateral mammillary body. The most important input received by the mammillary body is from the subicular region of the hippocampal formation. In addition, the mammillary body receives and reciprocates projections from tegmental nucleus with the medial mammillary connecting with the ventral tegmental nucleus and the lateral mammillary body connecting with the dorsal tegmental nucleus. The mammillary body also sends unidirectional projections to the anterior thalamic nuclei.

Anterior thalamic nuclei

There are three distinct regions that form the anterior thalamic nuclei (ATN) complex, anterodorsal (AD), anteroventral (AV) and anteromedial (AM) thalamic nuclei. Due to the similarity in connectivity, the lateral dorsal (LD) thalamic nuclei is also included in this section. The major afferent inputs into the region include the limbic cortices in the medial wall of the cerebral hemisphere, the hippocampal formation and the mammillary body. The subiculum in the hippocampal formation sends projections to all areas of the ATN complex and also to the LD. The dorsal portion of the presubiculum (the area is also called postsubiculum in the literature) projects mainly to the AD and LD areas whereas the ventral portion of the presubiculum projects mainly to the AV and the LD areas. As for projections originated from the mammillary body, those that come from the medial mammillary body targets mainly the AM region and the ones originated from the lateral mammillary body preferentially target the AD and LD regions of the ATN. The LD area also receives projections from the presubiculum, entorhinal cortex, superior colliculus and visual area 17 and 18 whereas the frontal eye field has a substantial projection to the entire ATN complex.

The efferents from the ATN region target a wide range of brain regions. The retrosplenial cortex is a major target structure from the ATN complex and AD, AV, AM and LD all contain efferent projections to this area. In particular, the projections from the LD area is reciprocal. In addition, the AM region projects to the entorhinal cortex, the subiculum, the presubiculum and the visual area 18b. Both the AD and AV area also project to the dorsal portion of the presubiculum (postsubiculum) and the LD area projects to the subiculum and the entorhinal cortex in addition to the retrosplenial connectivity.

Postsubiculum

The postsubiculum (PoS) is the dorsal portion of the presubiculum. There has not been a consensus in the literature about whether the PoS is an anatomically distinct region or is a part of the presubiculum. The PoS has reciprocal connection with the ventral presubiculum and

also with the subiculum. The most prominent extrahippocampal input into the PoS originates from the retrosplenial cortex. Visual area 18b also projects to the PoS. The PoS receives inputs from the ATN, predominantly from the anterodorsal and anteroventral areas, and also from the mammillary body.

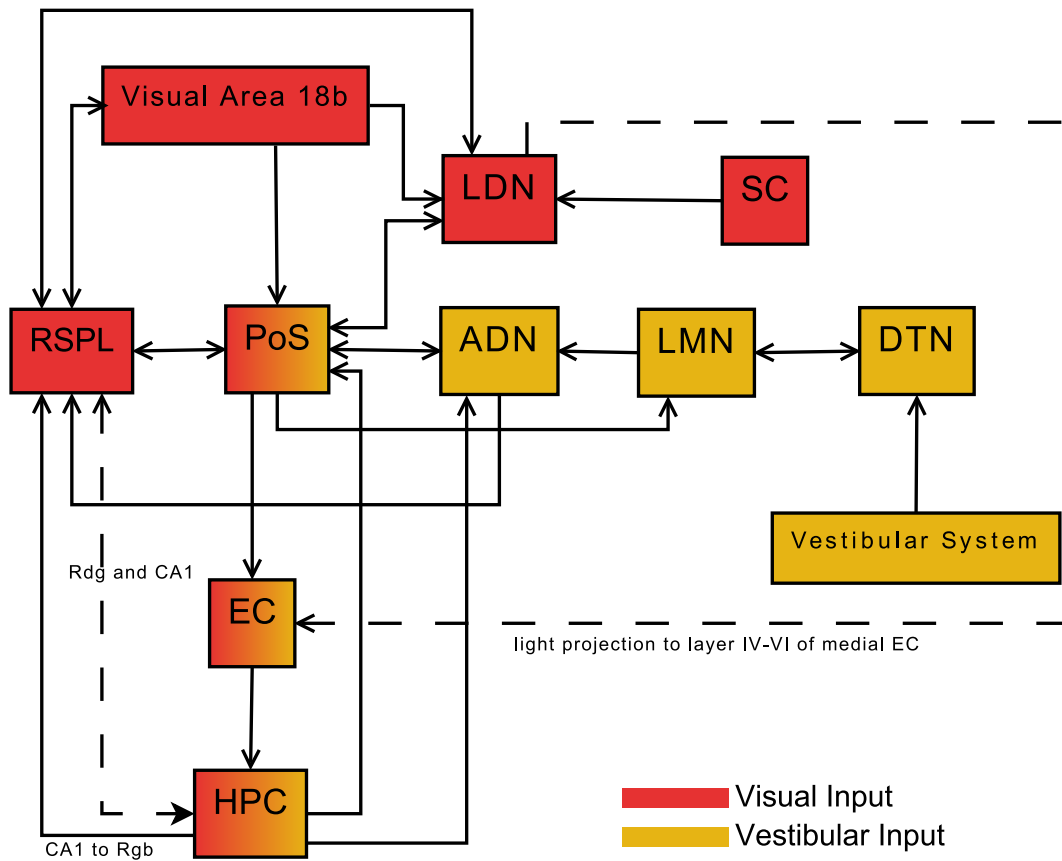
The PoS targets the medial portion of the entorhinal cortex, the anterodorsal, anteroventral and lateral dorsal area of the thalamus, and the retrosplenial cortex. There is also a weak projection to all fields of the hippocampus and to the dentate gyrus. The PoS also projects bilaterally to the medial and lateral nuclei of the mammillary body.

Retrosplenial cortex

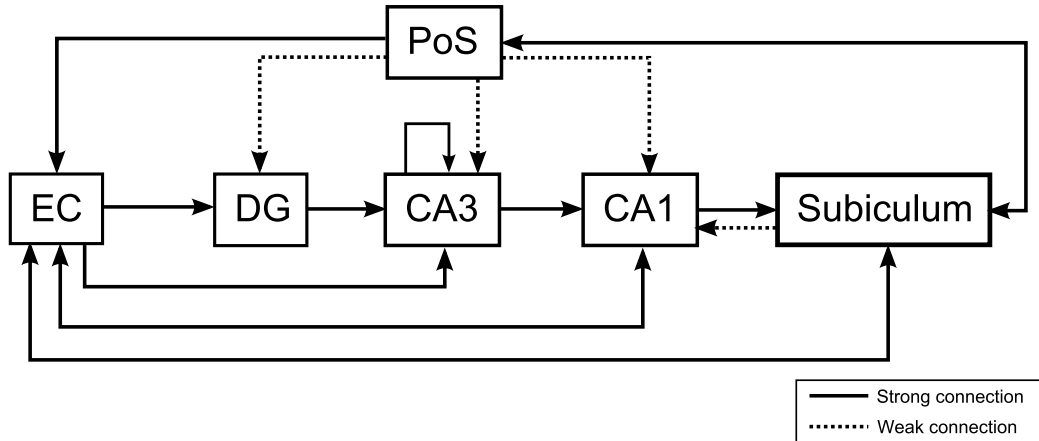
The retrosplenial cortex of rats is commonly classified into three areas, the retrosplenial granular cortex a (Rga, corresponding to area 29a and 29b), the retrosplenial granular cortex b (Rgb, corresponding to area 29c), and the retrosplenial dysgranular cortex (Rdg, corresponding to either area 29d or 30 due to inconsistent terminology in the literature). The retrosplenial cortex receives extensive inputs from visually related areas, including area 17, 18a and 18b. In addition, it also receives inputs from the subiculum, the postsubiculum (PoS), the entorhinal cortex (EC) and all of the areas in the anterior thalamic nuclei (ATN) (including lateral dorsal thalamic nuclei). The efferents of the retrosplenial cortex include the CA1 area of the hippocampus, dorsal portion of the subiculum, the PoS and the ATN.

2.2 Hippocampus

Ever since Scoville and Milner (1957) reported a profound deficit of forming recent memories after bilateral removal of the medial temporal lobes, the hippocampus has been extensively studied. Subsequent studies reported that bilateral damage of the hippocampus in human resulted in several impairments when learning to navigate through a stylus maze (Corkin 1965; Milner 1965). It was also reported that hypoxia induced hippocampal damage resulted in impairment in navigating around familiar environments even when the patients demonstrated normal or near normal test scores in school (Vargha-Khadem et al. 1997). The discovery of place cells in the hippocampus of rats (O'Keefe 1976; O'Keefe and Dostrovsky 1971, see chapter 3 for a review) also supports the structure's role in navigation. This led to the hypothesis that the hippocampus is the structure containing cognitive maps of the environment (O'Keefe and Nadel 1978). In order to determine the hippocampus's contribution to navigation, several research groups exposed rats with hippocampal lesions to a variety of spatial navigation tasks. One of the earliest report came from Morris et al. (1982) in which the authors showed that a bilateral lesion of the hippocampus impaired the rat's ability to find the hidden platform in the water maze when the location of the platform could only be identified with respect to the allo-



(a) Connectivity of the head direction system



(b) Connectivity of the hippocampal formation

Figure 2.1: Two connectivity diagrams. An arrow points from an upstream to a downstream structure. A double-sided arrow represents reciprocal connections. A dash line represents weak projections between the structures. The abbreviated names used in the diagram are, anterodorsal thalamic nuclei (ADN), dorsal tegmental nuclei (DTN), entorhinal cortex (EC), dentate gyrus (DG), hippocampus (HPC), lateral mammillary nuclei (LMN), postsubiculum (PoS), retrosplenial cortex (RSPL), and superior colliculus (SC). (a) shows an illustrated diagram of the connectivity between structures that are thought to be involved in the formation of head direction information. (b) is a connectivity diagram of the sub-structures in the hippocampal formation, the entorhinal cortex and the postsubiculum.

centric configuration of the landmarks in the environment. This impairment was not observed when the escape platform was clearly visible. The result suggests that the hippocampus is not required for taxon navigation but is needed when using multiple landmarks to identify a location in an environment, which suggests that the structure is important for navigation strategies requiring the formation of cognitive maps. Since then, other research groups also reported similar results where lesion of the hippocampus selectively impaired the place but not cued version of navigation tasks (Barnes 1988; Jarrard 1993). It has also been shown that hippocampal lesions cause impairments in delayed match-to-sample (DMS) and delayed nonmatch-to-sample (DNMS) tasks only when the tasks require spatial information (Cassaday and Rawlins 1995, 1997; Dudchenko et al. 2000). However, rats without hippocampus do not lose all ability to use spatial information of landmarks to guide navigation. This was demonstrated by Pearce et al. (1998), who showed that rats with bilateral hippocampal lesion only lost the ability to search at the correct platform location with respect to the landmarks used in the water maze experiment, whereas the ability to search at the right orientation at a fixed angle displacement from the landmark was retained. This suggests that directional information of place navigation is computed outside the hippocampus. Overall, the literature summarised above suggests that hippocampus is important for mapping location information to the allocentric configuration of the environment and likely to play a role in aligning external landmark information with respect to an internal coordinate system (Redish 2001). On the other hand, extensive training does rescue the navigation impairment of rats with hippocampal lesion in the water maze (Day et al. 1999; Morris et al. 1990). Only when the subiculum is also lesioned does the navigation impairment persist even after extensive training (Morris et al. 1990), suggesting other compensating navigation systems in the brain. However, when the location of the escape platform is changed everyday in a familiar environment, rats with hippocampal lesions are severely impaired in learning the new location (Whishaw and Jarrard 1996) whereas normal rats learn the location in one trial (Steele and Morris 1999). The result is also replicated on an open field maze (Whishaw and Maaswinkel 1998). This supports the hypothesis that the hippocampus does not hold the cognitive map of the environment, but instead is responsible for associating it with additional elements such as goals to guide navigation.

The above literature suggests the involvement of hippocampus in locale navigation. However, there is another group of experiments that explored the role of hippocampus in path integration. One of the first pieces of evidence that supports the role of hippocampus in path integration comes from Whishaw and Maaswinkel (1998). The authors showed that normal rats chose dead reckoning as a navigation strategy when blind folded whereas the rats with hippocampus lesions appeared to rely on uncontrolled landmarks in the environment for navigation. This, however, does not preclude the lesioned rat's ability to use path integration and may simply reflect an inability to flexibly switch between strategies. In the subsequent exper-

iment, the rat's ability to perform dead reckoning was assessed and the authors found that rats with hippocampal lesions were worse than normal rats in dead reckoning though the performance was still better than chance (Maaswinkel et al. 1999; Whishaw et al. 2001a). Similarly Alyan and McNaughton (1999) reported that rats with hippocampal lesions could still perform path integration though the lesioned rats had worse path integration performance than the normal rats. Finally, it was reported that human with lesion in the hippocampus or entorhinal cortex could still use path integration to keep track of a start location, suggesting that other structures can at least compensate for the loss of the two structures to maintain path integration capacity (Shrager et al. 2008). Overall, it appears that lesions of the hippocampus do produce a mild deficit in path integration but the animals still retain some ability to perform dead reckoning. It should also be noted that all of the path integration tests mentioned above can be solved by maintaining a directional vector alone without the need for the animals to keep track of its location in the environment.

2.3 Basal ganglia

The basal ganglia are made up of distinct anatomical areas including the striatum, substantia nigra, pallidum, and subthalamic nucleus. Among these structures, the striatum has most frequently been implicated to be involved in spatial navigation. The striatum is affected in several neurological diseases such as Parkinson's and Huntington's disease. It has also been implicated to be involved in navigation. The striatum can be anatomically sub-divided into the caudate nucleus and putamen. Studies that focus on exploring the functions of the two sub-structures in navigation will be discussed.

One of the earlier reports of the striatum's involvement in navigation came from Whishaw et al. (1987). The authors reported that lesions of the caudate nucleus produced deficits in both the place and the cued version of the water maze task, which was manifested by taking a longer time to reach the escape platform. On the other hand, in a subsequent study, which attempted to dissociate the place and the cued version of the water maze task by configuring the place and cue information to be in conflict with other, the authors found that rats with caudate nucleus lesion were just as accurate as the normal rats in navigating towards the correct platform location despite taking longer time to reach the escape platform in the place version of the task (Packard and McGaugh 1992). The accuracy performance was only impaired in the cued version of the task. This mirrors the result reported by Cunha et al. (2003) where lesion of substantia nigra pars compacta also selectively impaired the cue version of the water maze task. Coupled with the reports which showed that lesion of the caudate nucleus caused a performance impairment when the rat was required to use a light cue to find the rewarded arm on an eight arm radial maze (McDonald and White 1993; Packard et al. 1989), the literature supports the role

of striatum in taxon navigation. In a similar study, McDonald and White (1994) first trained the rat to find a visible escape platform in a water maze. The platform, which remained visible to the rat, was then moved to a new location. Rats with lesions of dorsal striatum would visit the previous location of the platform as if it was using a locale strategy. Once it failed to find the platform, it would swim to the visible platform. A subsequent report also found similar results when locale navigation was set up to be in conflict with taxon navigation (Devan and White 1999). This suggests that striatal lesions do not abolish the ability to use taxon navigation, but rather shifts the preference towards a locale navigation strategy. Devan et al. (1996) confirmed this observation by showing that rats with striatal lesion were only impaired during the learning phase of the cued water maze task. The authors also found similar results in the place version of the water maze task which showed that the rats with striatal lesion were impaired at learning the task though during the probe trials the rats were searching at the correct quadrant, albeit less accurately than the normal rats. It is likely that other brain structures also support taxon navigation, and thus serve as redundant backups when the striatum is lesioned. For example, both superior colliculus and parietal cortex have also been implicated in guiding the orientation towards visual stimuli (reviewed in Redish 1999). Finally, recent fMRI studies reported that the caudate nucleus was activated during route following in a virtual environment in human (Hartley et al. 2003; Laria et al. 2003) which lends support to the striatum's role in taxon navigation in human.

On top of taxon navigation, the striatum has also been shown to be responsible for praxic navigation. Kesner et al. (1993) tested spatial navigation in rats on a plus maze and found that caudate nucleus lesions impaired the performance of the procedural version of the task, which required the rat to always execute a fixed motor sequence (e.g. always turn right at the choice point) to locate the reward. This agrees with an earlier report that stimulation of the caudate nucleus interferes with complex movement tasks (Wilburn and Kesner 1974). In addition, several subsequent reports (Oliveira et al. 1997; Packard and McGaugh 1996) showed that lesion or pharmacological inactivation of the striatum encouraged rats to use a place instead of a procedural strategy on a plus maze, which also supports the role of the striatum in praxic navigation. Additional evidence came from the studies that looked at the ratio of acetylcholine release in the hippocampus and striatum and found that when the acetylcholine release level was comparatively higher in the striatum, the rat was more likely to engage in a response strategy (Chang and Gold 2003b; McIntyre et al. 2003).

2.4 Head direction cell system

One of the most amazing discoveries achieved by the development of single unit recording technique is the observation of head direction cells (Ranck 1984) in rats. The cells are strongly

modulated by the current head direction of the rat in the environment. Head direction cells will be discussed in more details at chapter 3, but properties that are relevant to the present discussion will be briefly outlined. Head direction cells were first discovered from the postsubiculum (PoS) of rats (Taube et al. 1990b). Each head direction (HD) cell has a preferred firing direction (PFD) and the cell exhibits maximum firing rate when the rat is facing the PFD of the cell and becomes almost silent when the rat turns away. One interesting property discovered from the HD cells is that simultaneously recorded HD cells always shifted their PFDs in register (Yoganarasimha et al. 2006), which suggests that HD cells in an ensemble encode a single orientation. This unique representation points to a possible role in the directional component of an allocentric cognitive map of the environment. On the other hand, HD cells are capable of maintaining their directionality in the dark (Goodridge et al. 1998) and the directionality of the cells are sensitive to the lesion of vestibular system (Muir et al. 2004; Stackman and Taube 1997), which provides linear and angular head velocity information that is useful for path integration. These attributes suggests that HD cells could serve as the system supporting the orientation aspect of path integration. Head direction cells have been discovered in several areas of the brain. The effect of lesioning these structures to spatial navigation will be discussed.

Lesion of anterior thalamic nuclei or Mammillary bodies

Sutherland and Rodriguez (1989) explored how lesions of the anterior thalamic nuclei (ATN) and mammillary bodies (MB) affected the rat's performance on a reference memory water maze task. It was shown that ATN lesions slowed the acquisition of the reference memory task where the location of the escape platform was fixed, but if rats were pretrained, ATN lesion did not impair the performance of the rats. On the other hand, MB lesion impaired the performance of rats both with and without pretraining, although the rats with pretraining eventually performed at a comparable level to the control rats. A similar result from ATN lesioned rats was also reported by Warburton and Aggleton (1999) and Wolff et al. (2008). However, Warburton et al. (1999) did find a small retention impairment of the water maze reference memory task after ATN lesion. Santín et al. (1999) on the other hand, found no significant effects of MB lesion on the acquisition of the water maze reference memory task but did find a deficit in the DMP version of the task, which consisted of an acquisition trial and a retention trial everyday. Rats needed to relearn the location of the escape platform during the acquisition trial as the platform location changed everyday. Performance impairment on the DMP water maze task from MB lesioned rats was also observed in Vann and Aggleton (2003) and from rats with complete ATN lesion (van Groen et al. 2002a).

Vann and Aggleton (2003) also tested rats with MB lesions on a radial arm maze working memory task, in which the optimal strategy to obtain rewards was to visit each of the eight arms of the maze exactly once, to test the effect of MB lesions and showed that rats with MB lesion

were slower in acquiring the task but eventually reached the same performance level as the control rats. Additional manipulations by rotating the maze by 45° after the rat retrieved four of the eight rewards with the location of the still baited arms determined by the distal landmarks in the room demonstrated that the MB lesioned rats were not using the distal landmarks in the room to guide navigation and such rotation disrupted the lesioned rat's performance. As the observed deficit could not be overcome with additional training, the result suggests that the MB lesioned rats lacked the ability to use landmarks in the room allocentrically rather than simply preferred to use intramaze cues to guide navigation. Neave et al. (1997) used a plus maze alternation task to test the effect of MB lesion on both allocentric and egocentric forms of navigation. Similar to a T-maze forced alternation task, a rat in the plus maze task was first given a sample phase during which it was forced to visit one of the arms on the maze. In the subsequent choice phase, the rat had to visit the opposite arm to the one it previously visited to obtain reward. The main difference from a T-maze forced alternation task was that there were two possible start arms opposite each other, which allowed both allocentric and egocentric navigation to be tested on the same maze. If the rat was always placed on the same start arm between the sample and the choice phase, it could solve the task using an egocentric strategy, i.e. by always turning to the opposite direction to the turn experienced during the sample phase. On the other hand, if the location of the start arm was chosen randomly, the rat would then need to determine the location of the reward arm with respect to the room cues, i.e. an allocentric strategy, to solve the task. The authors found that rats with MB lesion were more impaired on the allocentric version of the alternation task. However, it is unclear whether additional training would have allowed the MB lesioned rats to overcome the deficit or whether this deficit was due specifically to the lesioned rats' inability to solve the task using an allocentric strategy as even the control rats had lower performance on the allocentric alternation task than that observed during the egocentric alternation task.

Aggleton et al. (1996) and Warburton et al. (1997) also used the plus maze forced alternation and radial arm maze with rotated intramaze cues to test the effect of ATN lesion on rats. The authors found that the ATN lesioned rats were impaired on both the T-maze forced alternation task as well as both the allocentric and egocentric version of the plus maze forced alternation task. Although when tested on a different egocentric task where rats were placed on a randomly chosen arm on the plus maze and the reward arm could be reached if the rats executed a fixed motor sequence (e.g. turn left at the intersection), the ATN lesioned rats were not impaired. Finally, Sziklas and Petrides (1999) tested the rats on two types of conditional associative tasks. In the first task, two distinct objects were placed side by side on an open field maze and the identity of the reward object was dependent on the location of the objects. In the second task, the authors used a T-maze and the location of the reward arm was determined by the identity of the object at the choice point of the maze. It was shown that the performance

of the ATN lesioned rats were impaired on the first task where the identity of the rewarded object was associated with its location in the environment, but not the second task in which rats could solve it by recalling the correct egocentric strategy based on the object at the choice point. The result supports ATN's role in allocentric but not egocentric navigation. However, a subsequent experiment modified the T-maze task by using a plus maze and random start location and found that ATN lesioned rats were still not impaired (Sziklas and Petrides 2007) when comparing their performance to that of the control rats, which argues against ATN's role in allocentric navigation. When testing rats with MB lesion on the same task, the authors also did not find an impairment when comparing to the control rats (Sziklas and Petrides 2000).

Overall, ATN and MB lesion have been reported to impair the rats' performance from a wide range of tasks. However, the most severe deficits were observed from the tasks that required rapid acquisition of some knowledge such as the location of the previously visited arm on a radial arm maze or the location of the escape platform in the previous trial on a water maze, i.e. working memory tasks. Furthermore, the lesion induced impairment was exacerbated by forcing the rats to use extramaze allocentric cues to solve the tasks. For those tasks which the rule to reach the reward location remained fixed, e.g. a fixed escape platform location on a water maze or a fixed motor sequence on a T-maze, the lesioned rats appeared to be able to overcome the initial learning deficit with additional training. Finally, the lesion did not affect the tasks that could be solved by associating reward directly with specific identity of the objects.

Lesion of areas that specifically contain head direction cells

The literature that has been discussed so far does not selectively lesion areas that contain head direction cells. Components of ATN includes anterodorsal thalamic nuclei (ADN), anteromedial thalamic nuclei (AMN) and anteroventral thalamic nuclei (AVN). Among these structures, head direction cells have only been reported from the ADN (Blair and Sharp 1995; Taube 1995) of rats. MB includes two anatomically distinct components, the medial mammillary nuclei and lateral mammillary nuclei (LMN), and only LMN contains head direction cells (Blair et al. 1998). Several studies selectively lesioned areas containing head direction cells in order to explore the role of head direction cells in navigation. Aggleton et al. (1996) explored selective lesion of AMN, ADN+AVN, and also complete lesion of ATN and compared the performance on the allocentric and egocentric version of the T-maze forced alternation task as well as on the radial arm maze working memory task and found that rats with complete ATN lesion exhibited the strongest deficit whereas rats with AMN or ADN+AVN lesion were mildly impaired. This suggests that each of the three areas in ATN contributes to navigation. Subsequent experiments using an allocentric forced alternation on a plus maze, a DMP water maze or a radial arm maze working memory task to test for lesion impairments also found similar results (Byatt

and Dalrymple-Alford 1996; van Groen et al. 2002a). Several studies have also explored the effect of lesioning anterodorsal thalamic nuclei (ADN) and laterodorsal thalamic nuclei (LDN) currently, both structures containing head direction cells (Mizumori and Williams 1993; Taube 1995), to spatial navigation. Wilton et al. (2001) used a beacon water maze task in which the location of the escape platform changed everyday but always maintained a fixed relationship with the 'beacon' object, and demonstrated that rats with concurrent ADN and LDN lesion failed to use the extramaze cues to aid navigation, similar to the effect of hippocampal lesion reported in Pearce et al. (1998). However, it is unclear whether the rats with ADN+LDN lesion actually learned to use the beacon to guide navigation, which was the case for the hippocampal lesioned rats in Pearce et al. (1998). The ADN+LDN lesioned rats were also impaired on the forced T-maze alternation task and object place version of the spontaneous object recognition task, but was not impaired on novel object recognition. The authors did not specifically test whether the combined ADN+LDN lesion produced a more severe deficit and lesion of the either structure alone and thus we cannot draw a conclusion on whether it was the loss of head direction signals that contributed specifically to the deficits. Other studies combined LDN lesion with complete ATN lesion and the results suggest that lesioning LDN does not produce significantly greater deficit than ATN lesion alone (Warburton et al. 1997). On the other hand, lesion of the LDN alone produced a mild deficit on a DMP water maze task, and a greater deficit was reported when the lesion area extended to the ATN (van Groen et al. 2002b). This suggests that the ATN appears to be the main structure contributing to the observed deficit and the LDN did not contribute strongly to the performance of the working memory tasks. Selective lesions of lateral mammillary nuclei (LMN), which is the part of the mammillary bodies (MB) that contains head direction cells, resulted in a mild impairment on the DMP water maze task but not the T-maze forced alternation task (Vann 2005). The results suggest that the structures that contain head direction cells do not have a particular importance in working memory tasks. The result reported by Wilton et al. (2001) did provide some evidence of the involvement of the ADN and LDN in the learning of extramaze cues. However, the authors did not specifically test whether other surrounding structures are also involved nor was the effect of ADN+LDN lesion in the learning of the water maze 'beacon' task tested. Lesions of the postsubiculum, another structure that contains head direction cells, results in impairment in acquiring the reference memory version of the water maze task and the working memory eight arm radial maze task (Taube et al. 1992). In the case of the water maze reference memory task the lesioned rats eventually performed at a comparable level to the control rats. In addition, the lesioned rats were not impaired on the cued version of the water maze task. These studies found a similar pattern of deficits to those rats with ATN lesion where the most severely affected task was the radial maze working memory task. For the water maze reference memory task where allocentric place information was required, the lesioned rats had a initial performance deficit but could

eventually learn the task with additional training. The least affected task was the cued version of the water maze task, which only required a simple association between the escape platform and the cue object to solve the task. However, whether the observed similarity in impairment between the lesion of the structures that contained head direction cells was caused by the loss of head direction signals cannot be conclusively determined with these results.

None of the experiments discussed above looked at the effect of lesions on path integration selectively, which is one of the proposed functions for head direction cells. Frohardt et al. (2006) explored this topic by subjecting rats either with lesions of anterodorsal thalamic nuclei (ADN) or of dorsal tegmental nuclei (DTN) to a homing task. Unfortunately the rats with lesions were impaired both under light and dark conditions with the DTN lesion producing greater deficit. The role of these structures in path integration thus could not be conclusively determined.

Lesion of retrosplenial cortex

I considered retrosplenial cortex to be outside classical head direction cells pathway, which consisted of DTN, LMN, ADN, and PoS, because head direction cells in the retrosplenial cortex do not seem to encode a single, coherent directional signal (Chen et al. 1994a,b) and there has been no report of the effects of retrosplenial cortex lesion on the head direction cells in other structures. The ability for these cells to change their PFDs independently makes them more suitable to encode an egocentric orientation representation of the environment. Due to its connectivity with hippocampus and anterior thalamic nuclei (ATN), both of which are involved in spatial navigation, the role of retrosplenial cortex in spatial navigation has also been heavily investigated (reviewed in Harker and Whishaw 2004b and Aggleton and Vann 2004). Despite several inconsistencies, the literature supports its role in using allocentric information to guide navigation with deficits being shown from several place navigation tasks such as the reference memory water maze task, the place version of the radial arm maze task where the intramaze cues are rotated in the middle of the task to force rats to use extramaze cues, and the object-place version of the spontaneous objection recognition task (Harker and Whishaw 2004a; Vann and Aggleton 2002; Vann et al. 2003). On the other hand, lesions of the retrosplenial cortex in rats did not impair the performance of either the egocentric version of the plus-maze task (Vann and Aggleton 2002) or the egocentric version of the water maze task (Zheng et al. 2003). The study on the role of retrosplenial cortex in path integration is, again, quite limited. Cooper et al. (2001) aimed at addressing this issue by subjecting the rats with temporarily inactivated retrosplenial cortex to a homing task. Similar to the problem encountered by Frohardt et al. (2006), the drug manipulation resulted in deficit both under light and dark condition, thus precluding a direct conclusion on the role of the structure in path integration. Furthermore, the control rats appeared to be able to find the original training quadrant in the dark even when

the start box was shifted by 180°, suggesting that they were able to orient themselves by some kind of uncontrolled landmarks in the experiment. In contrast, Whishaw et al. (2001b) used a similar task but controlled the intramaze odour trails and found that rats with lesion of the retrosplenial cortex were impaired on homing, suggesting a path integration deficit. Lastly, Wesierska et al. (2009) used a place avoidance paradigm and found that retrosplenial cortex lesion selectively impaired the rat's ability to avoid foot shock by using only the relevant subset of distal landmarks. This suggests that one role of retrosplenial cortex is to resolve conflicts of spatial information by selecting the most informative landmarks to guide navigation. However, the experiment also suggests that rats with retrosplenial cortex lesion still retain the ability to use configuration of distal cues for navigation, suggesting a spared locale navigation capacity that is in conflict with the literature result discussed above. It is unclear how such a discrepancy arises though some of the earlier experiments did find similar sparing of locale navigation capacity after the lesion (which is thoroughly discussed in Harker and Whishaw 2004b and Aggleton and Vann 2004). It would be interesting to explore how retrosplenial cortex selectively encodes the informative landmarks as references. A single unit recording experiment monitoring the head direction cells from retrosplenial cortex perhaps would be informative in how these conflicting landmarks control the head direction codes in the structure.

2.5 Other structures

Many other structures have also been implicated in spatial navigation and several of these structures will be discussed briefly. One of the structures that has recently gained much attention is the entorhinal cortex. Ever since the discovery of grid cells from the entorhinal cortex of rats (Hafting et al. 2005), much effort has been spent on determining the role of these cells. The spatially regular firing pattern of grid cells has the appearance of a coordinate system and, combined with the property that they are always active even in different environments (Fyhn et al. 2007), these cells form an ideal system to compute path integration. Indeed Parron and Save (2004) showed that lesion of the entorhinal cortex impaired the rat's ability to perform accurate dead reckoning by path integration. Entorhinal cortex has also been implicated in the retention of place learning, which is evident by the loss of platform location memory in a water maze reference memory task after the entorhinal cortex lesion (Steffenach et al. 2005). However, the lesioned rats still retained their ability to learn a new platform location in the water maze reference memory task. It was also shown that this deficit in the water maze was specific to the use of distal cues to guide navigation but the lesioned rats still retained the ability to use proximal cues to locate the escape platform (Parron et al. 2004). In general, the effect of entorhinal cortex lesions on place navigation appears to be weaker than that obtained from hippocampal lesion (reviewed in Aggleton et al. 2000). As the structure provides the majority

of the input to the hippocampus, these observed deficits may be caused by the loss of inputs to the hippocampus. The posterior parietal cortex has also been implicated in path integration (see Whitlock et al. 2008 for a review), and its lesion disrupts the accuracy of dead reckoning by path integration, albeit to a lesser degree than entorhinal cortex lesions (Parron and Save 2004). Similarly, Save et al. (2001) showed that lesions of the posterior parietal cortex impaired a homing task, though the effect was not as severe as for rats with hippocampal lesions. Posterior parietal cortex has also been shown to be involved in acquiring the reference memory water maze task, in the use of a discontinuous landmark to guide navigation (Kolb and Walkey 1987), as well as in determining the displaced object on a spontaneous objection exploration task but not the novel object recognition (Save et al. 1992). These results support the role of posterior parietal cortex in general locale navigation though a role in path integration would also cause these deficits.

2.6 Multiple navigation strategies

In the previous discussion we briefly looked at the contributions of several brain areas to spatial navigation. The general pattern is that lesions in many of the areas affect the performance of spatial navigation tasks. However, many of these deficits are only transient and disappear after extensive training. This suggests that the spared structures in the brain can take over, either by performing a similar role to the lesioned structure, or by solving the task using alternative strategies (Aggleton and Vann 2004). For example, navigating to the adjacent arm for reward on a plus maze can be guided using either a praxic or a locale strategy, and the choice of strategy changes with training (Packard and McGaugh 1996). Furthermore, selective lesion or inactivation of different structures can change strategy choices (Chang and Gold 2003a; Packard and McGaugh 1996; Schroeder et al. 2002). Some of the perceived transient impairments may thus be due to a shift in the preference of strategy choices instead of a genuine loss of capacity in executing certain navigation strategy. Another consideration is that there may be a certain hierarchical dependence between navigation strategies (Franz and Mallot 2000) and the execution of one spatial navigation may depend on the integrity of another. One trivial example is that for rats to identify a displaced object in spontaneous object recognition, it has to first be able to distinguish the identity of different objects (Eacott and Norman 2004). However, other forms of interdependency might not be obvious or even known. This may be the reason that lesioning a wide array of brain structures all produce deficits in tasks that are thought to be dependent on locale navigation. We thus need to consider interaction and competition between navigation strategies when interpreting the lesion literature.

Chapter 3

Cognitive representation of space and integration with external cues

In this chapter, I review the different type of cells reported from the literature that employs the single unit recording technique whose firing rates are modulated by different attributes of the spatial environment.

3.1 Neural code for the place cells

The development of single unit recording techniques for freely moving animals (Hubel 1957) has made it possible for researchers to correlate an animal's behaviour to the firing pattern of single neurons. This technique is a natural complement to spatial navigation tasks, as it allows the animals to move freely without constraint, a major pre-requisite for spatial navigation behaviours. Combined application of single unit recording and spatial navigation tasks in rats has led to the discovery of neuron spike trains that are strongly correlated with spatial attributes of the environment. Similar spatially modulated cells have also been found in humans (Ekstrom et al. 2003), suggesting that these cells are not specific to rodents. Here I will briefly discuss the the related literature under three categories, cells whose firing is correlated with present location, present head direction or a combination of spatial attributes.

Place cells in the hippocampus

Several populations of neurons recorded from different brain structures have been shown to exhibit spatial modulation. The first, and perhaps the most famous population is the place cells from the hippocampus of rats. Place cells were first reported by O'Keefe and Dostrovsky (1971) and their firing rates correlated strongly with the rat's specific locations of the environment, which were referred to as the place fields of the place cells. An example of place cells recorded from CA1 of the hippocampus is presented in figure 3.1. We can see that the firing

rate of a place cell is almost silent until the rat's head enters the place field of the cell in the environment, where the firing rate of the cell increases dramatically. This clear encoding of spatial information led O'Keefe and Nadel (1978) to propose that hippocampus is the structure where cognitive maps of environments reside (Tolman 1948), which allows information of movements and cues to be integrated into a mental representation of the environment. Since then, the properties of place cells have been extensively explored and several basic properties will be briefly described. The earlier experiments tend to look at the behaviours of individual place cells due to the technical difficulties of recording a large population of place cells from a rat simultaneously. Some of the more recent experiments treated simultaneously recorded place cells as a group and explored properties of place cells at an ensemble level, which would tell us more about the characteristics of place cell populations instead of the responses of individual cells. The place fields of hippocampal place cells recorded from rats exploring an open field maze do not change with respect to the orientation the rat is facing, i.e. the place fields are not polarised (Muller et al. 1994). On the other hand, if rats are running on linear tracks such as a radial arm maze, the place cells tend to have different place fields depending on the direction the rat is facing (Muller et al. 1994). Place cells maintained the spatial specificity of their place fields even when the rat was running in the dark (Markus et al. 1994), which suggests that they encode spatial information that is independent from sensory inputs. On the other hand, it has also been shown that the location of place fields are influenced by prominent cues in the environment (this will be discussed in more details in section 3.4), which supports the role of place cells in integrating spatial information in the environment. The dependence of place cells' spatial specificity on vestibular inputs has also suggested a role of these cells in path integration (Russell et al. 2003; Stackman et al. 2002).

Place cells have been identified from all three structures, namely dentate gyrus, CA1, and CA3 of the hippocampal trisynaptic loop (Jung and McNaughton 1993; O'Keefe 1979). Place cells from the three structures have different properties and will be briefly discussed. Place cells from the dentate gyrus are thought to come from the granule cells population (Jung and McNaughton 1993). Granule cells typically have low average firing rate (<0.5 Hz), which are very different from the theta-modulated interneurons whose average firing rates easily exceeds 2 Hz. These granule cells have shorter spike durations when comparing to pyramidal cells in CA1 and CA3 of the hippocampus and their firing rates are strongly correlated with the locations of rats in the environment, making them a population of place cells. Each dentate gyrus place cell typically has multiple place fields both on linear tracks (Jung and McNaughton 1993) and on open field mazes (Leutgeb et al. 2007). Due to a tendency to fire at multiple locations in an environment, the firing rate of a dentate gyrus place cell does not unambiguously signal the rat's location in the environment. Leutgeb et al. (2007) recorded the activity of dentate gyrus place cells while the rat was exploring a series of open field mazes that gradually

morphed from a square to a circle and found that these place cells are very sensitive to small changes in the shape of the maze and unlike the responses of CA3 and CA1 place cells which changed their place fields in response to the gradually morphing environment mostly with the changes in the firing rates of their place fields (which will be described in the next section), the dentate gyrus place cells changed the location of their place fields in response to even the small changes of the environment. This suggests that the place cells in the dentate gyrus play a role in distinguishing between similar environments.

Place cells in both CA1 and CA3 of the hippocampus comprise the pyramidal cells (Harris et al. 2003; O'Keefe 1979). The pyramidal cells have longer spike duration than the granule cells and fire in complex spikes (Olton et al. 1978), a term which describes a firing pattern where a cell would fire a sequence of action potentials with diminishing amplitudes and inter-spike intervals of typically 2–10 ms (Suzuki and Smith 1985). Similar to the granule cells, pyramidal cells in CA1 and CA3 of the hippocampus also have low average firing rates when comparing to theta-modulated inter-neurons (Fox and Ranck 1981). The place fields of these cells are dependent on the direction of the rat in linear tracks (McNaughton et al. 1983; Muller et al. 1994) but lose their directionality when the rats are exploring open fields (Muller et al. 1987, 1994). Unlike place cells in the dentate gyrus, place cells in CA1 and CA3 tend to have only one place field in a typical open field environment (see Muller et al. 1996 for a review).

Despite being formed by the same type of cells with similar firing characteristics, there are also many different characteristics between CA3 and CA1 place cells. For example, CA3 place cells only have one place field even when the rat was running on a very long linear track (up to 10 meters) (Kjelstrup et al. 2008), which suggests that CA3 place cells maintain the uniqueness of their place fields. On the other hand, Fenton et al. (2008) reported that CA1 place cells started to have multiple place fields when the size of the environment was very large, which suggests that CA1 place cells have a more limiting encoding scale in which they can maintain the uniqueness of the location of their place fields. However, in this study the authors used an open field maze instead of a long linear track used in Kjelstrup et al. (2008), and so it is not possible to determine whether the observed difference between CA3 and CA1 place cells was due to the different nature of the two environments or different properties of place cells in the two areas.

CA3 and CA1 place cells also respond differently to changes of local environments when they are recorded from rats experience a conflict between environmental cues in the form of a double rotation of two distinct set of cues in an environment. CA3 place cells in an ensemble tend to respond more coherently by rotating their place fields by a similar amount whereas CA1 place cells rotate their place fields independently from other place cells in the ensemble (Lee et al. 2004). Leutgeb et al. (2004) showed that a lower proportion of CA3 place cells were active in an environment when comparing to CA1 place cells. In addition, the authors also

demonstrated that the firing rates of place cells in CA3 place cells were independent between two distinct environments whereas there was a significant correlation between the firing rates of CA1 place cells in the two environments.

Vazdarjanova and Guzowski (2004) used an immediate early gene approach to study the activation pattern of CA3 and CA1 cells in two environments. The technique capitalises the different onset and shut off timing of the synaptic activity driven gene transcription of the two immediate early genes, *arc* and *Homer 1a*. By measuring the transcription level of the two genes, the different transcription timing of the two genes, researchers are able to estimate the synaptic activities of the neurons at two different time points. It was shown that when the two environments were similar, the proportion of co-activated cells was higher in CA3 than in CA1. However, if the two environments were very different, the proportion was higher in CA1 than in CA3. The results suggest that CA3 place cells tend to encode similar environments with same place fields but different environments with distinct place cells. On the other hand, CA1 place cells respond to changes of the environment in a more gradual manner.

Before continuing the discussion of how CA1 and CA3 place cells respond differently to changes of local environments, I will first describe the term “remapping”, which is commonly used in the literature to classify the responses of place cells to environmental changes. The term was first used by Bostock et al. (1991) to describe changes of place cells between two environments on an ensemble level. If each place cell in an ensemble changed its place fields between two environments in an unpredictable manner, the authors defined the ensemble response as a “complex remapping”. On the other hand, if the place fields of the simultaneously recorded place cells all rotated by a similar degree between two environments, then the ensemble response was classified as a “rotational remapping”. If only a sub-population of the place cell ensemble undergoes complex remapping, then the response is called a “partial remapping”. To determine the type of response of a place cell ensemble undergoes between two environments, it is necessary to look at the responses of each individual place cell and classify it to either rotate its place field between sessions or change its place field in an unpredictable manner, i.e. a remapping. In addition the remapping categories described in Bostock et al. (1991), Leutgeb et al. (2005b) found that both CA3 and CA1 place cells sometimes responded to changes in a local environment by only changing their active firing rates significantly without shifting the location of their place fields. The authors called the response a “rate remapping”. On the other hand, if the two environments were sufficiently different (e.g. two different rooms), the place cells responded by changing both the active firing rate and the location of their place fields, which was called a “global remapping”.

In order to explore how CA1 and CA3 place cells respond to gradual changes of local environments, several experiments utilised the morphing box maze (Leutgeb et al. 2005a; Wills et al. 2005). A morphing box maze is basically an open field maze whose surrounding walls are

configurable. The experiment involves in exposing rats to a series of exploration sessions inside the morphing box during which the walls of the box are changed gradually from one shape to another. Typically a square and a circle is used as the two end-point shapes of the morphing sequence. It was shown that CA3 place cells were capable of responding to gradual changes of the environment by gradually changing their place fields (Leutgeb et al. 2005a). On the other hand, CA1 place cells were responded to the changes in a more discrete manner where the place cells changed their place fields suddenly at some point of the morphing sequence (Wills et al. 2005). This again demonstrated that the characteristics of the place encoding in CA3 and CA1 place cells can be very different in nature. We have now described a few experiments that explored how environmental changes affect the place cells. A more detailed summary of existing literature will be presented in section 3.4.

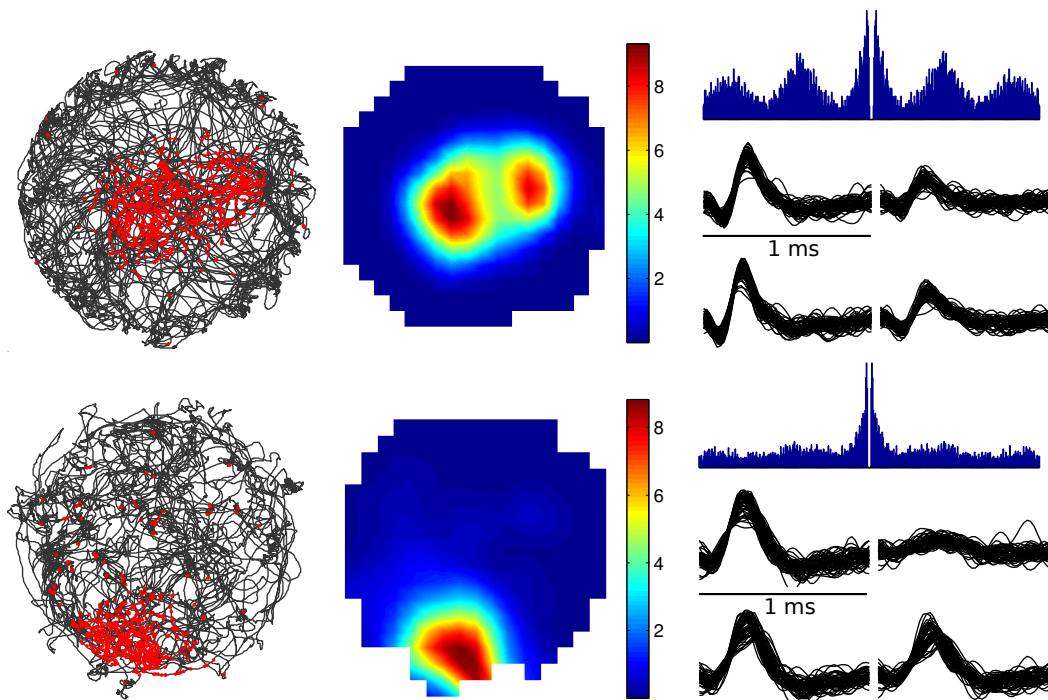


Figure 3.1: Two examples of the place cells I recorded from a rat doing random foraging on an open field circular maze. Each row of the figure is an example from one cell. The first panel of each example is the trajectory plot with the black line representing running trajectory of the rat during the recording session and each red dot indicated the positions of the rat when the place cell fired an action potential. The second panel is the colour coded spatial firing rate map of the place cell. The colour bar beside the rate map provides information about what the corresponding firing rates in Hz represented by each colour. The third panel contains both the waveforms and the time autocorrelogram (500 ms scale) of the place cell. The waveforms resemble action potentials of a pyramidal cell and theta modulation can be seen from the time autocorrelogram of the place cell.

Spatial code in the subiculum

The subiculum is a major output structure of hippocampus and it has also been shown to contain cells modulated by the present location of the animal (Sharp and Green 1994). Compared to place cells in the hippocampus whose firing rates when the rat is not in their place fields are almost zero, subicular cells tend to have high background firing rates. However, spatial modulation is still evident and is maintained during subsequent visits of the same environment. One of the main distinguishing properties of subicular place cells from those in the hippocampus is that they appear to maintain their place fields even in geometrically distinct environments (Sharp 1997, 2006), and the fields expand or contract with the size of the environment (Sharp 1999, 2006). Hippocampal place cells typically develop distinct place fields under similar environmental manipulations. This suggests that the spatial information encoded by subiculum is fundamentally different from that of hippocampus and may play a role in more mechanical aspects of spatial encoding such as maintaining the location update mechanisms or encoding the basic spatial properties of an environment such as the distance to the boundaries.

Spatial code in the striatum

Wiener (1993) first reported that some striatal cells showed location modulated firing. Cells that were strongly modulated by the head direction of the rats have also been found. However, as the behaviour used in the experiment encouraged movements along typical trajectories, it was unclear whether limited sampling of head directions contributed to the finding of head direction modulated cells. These striatal cells shifted either in register with intramaze or distal cues in the environment and the simultaneously recorded cells did not show coherent response to cue rotation (Shibata et al. 2001; Wiener 1993), which suggests an egocentric encoding scheme. It was later shown that striatal cells encode procedural aspects of the task instead of pure spatial codes and would fire at all the procedurally equivalent points such as reaching the reward box or turning right when exiting a side arm. This procedural encoding is particularly obvious on a plus maze (Berke et al. 2009). Schmitzer-Torbert and Redish (2008) attempted to reconstruct the encoded present location of the rat based on the simultaneously recorded striatal cells and found that the reconstruction was only successful when the rat was required to use spatial information to solve the behavioural task, further supporting the hypothesis that striatal cells do not specifically code for spatial information of the environment but rather encode the different behavioural aspects of the task at hand. This appears to fit the results from the lesion literature which supports the role of striatum in procedural encoding (discussed in section 2).

Grid cells in the entorhinal cortex

Entorhinal cortex provides the main source of input to the hippocampus (Hargreaves et al. 2005). Spatial modulation of entorhinal cells was first demonstrated on an eight arm radial maze (Mizumori et al. 1992) and an open field circular platform (Quirk et al. 1992). It was reported that cells recorded from the entorhinal cortex (EC) were spatially modulated by had lower signal to noise ratio than hippocampal place cells. The spatial modulation was directional on linear tracks (Mizumori et al. 1992). When the rat was exploring an open field maze, the place fields of thee EC cells rotated with prominent visual cues in the environment but the cells also maintained their spatial modulation when the cue was removed (Quirk et al. 1992). One of the major difference reported was that, unlike hippocampal place cells, the EC cells appeared to be active in different environments and did not change their place fields dramatically in between environments, which is similar to the behaviour of subicular place cells. Fyhn et al. (2004) investigated the spatial modulation of EC cells further and found that these cells exhibited strong, multi-peak location specific code with comparable spatial information to hippocampal place cells. The same research group then demonstrated using a larger maze that the location of these multi-peaked place fields followed a very regular hexagonal pattern. Due to the grid like pattern of their place fields, these cells are called grid cells (Hafting et al. 2005). Grid cells in the entorhinal cortex reference their fields to prominent cues in the environment but also maintain their grids without cues. The surprisingly regular firing pattern of grid cells has attracted much attention and many have proposed that they serve as an internal coordinate system for path integration (Fuhs and Touretzky 2006). The case is strengthened by the discovery of head direction cells and conjunctive cells, which exhibited both place and head direction modulation, in the same structure (Sargolini et al. 2006). The presence of head direction cells provides essential angular path integration information and the conjunctive cells can be seen as an intermediate step of integrating angular information into the spatial path integrator. Also, grid cells appear to maintain their grid fields in different environments (Hafting et al. 2005) and simultaneously recorded grid cells always shift or rotate in register with each other (Fyhn et al. 2007). The coherent representation further supports the role of these cells in providing an allocentric medium for path integration. However, it has also been shown that the grid spacing can be altered by deforming a familiar environment, though this effect disappears when exposing the rat to a novel environment with identical deformed shape (Barry et al. 2007). This suggests that grid cells use boundaries of the local environment to determine their spatial modulation in the environment, but the system can also detect the deformation when the rat has additional experience in the experience, which indicates that grid cell system can use other information (e.g. self motion cues) to maintain their grid spacing.

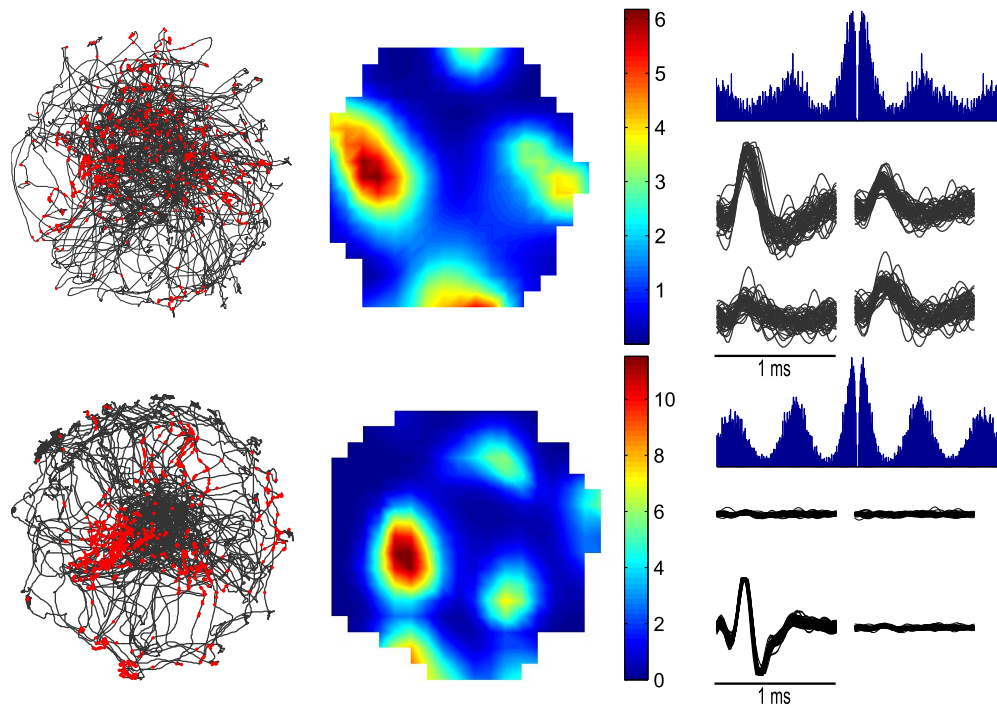


Figure 3.2: The figure presents two examples of grid cells I recorded while the rats were pellet chasing on an 80 cm diameter open field circular maze. The spatial histograms show multiple place fields organised in a grid like pattern. As evident from the temporal autocorrelograms, both cells were strongly modulated by a theta frequency rhythm.

Encoding of routes in the posterior parietal cortex

Single unit recording studies targeting posterior parietal cortex of rats did not find cells that show strong location modulation, but did find another type of navigation related encoding. McNaughton et al. (1994) found that many cells in the posterior parietal cortex were modulated by movement sequences when the rat was navigating on a radial arm maze. It was later demonstrated that parietal cells exhibited distinct firing patterns along a learned route and this pattern remained consistent even when the physical locations traversed by the route changed dramatically (Nitz 2006). This encoding can serve as the basis for praxic or route based navigation that allows the recall of learned routes from any location.

3.2 Neural code for the head direction cells

Besides the location modulated cells, there are some cell populations that are strongly modulated by present head direction of the animals, which are usually referred to as head direction (HD) cells. HD cells were found from many structures of limbic system and in some structures were co-localised with other cells that encode angular acceleration during turning. It is hypothesised that head direction cell networks participate in the computation of path integration and

update current head direction using angular head velocity signals from vestibular system.

Head direction cells were first discovered from the postsubiculum (PoS) (Ranck 1984; Taube et al. 1990a). The firing rates of these cells are strongly modulated by the rat's present head direction in the horizontal plane and the tuning curves of these cells resemble a Gaussian distribution (Taube et al. 1990a). The head direction that a HD cell has the highest firing rate is referred to as its preferred firing direction (PFD) and the firing rate falls off symmetrically when present head direction deviates from the PFD in both directions. Subsequently, HD cells have been discovered in many structures of the limbic system circuit (Bassett and Taube 2001; Chen et al. 1994b; Mizumori and Williams 1993; Stackman and Taube 1998; Taube 1995; Taube et al. 1990a), as well as in other structures such as the dorsal tegmental nuclei (DTN) (Bassett and Taube 2001; Sharp et al. 2001b), the striatum (Wiener 1993), the hippocampus (Leutgeb et al. 2000), and very recently the entorhinal cortex (EC) (Sargolini et al. 2006). These HD cells have many similar properties such as the shapes of their tuning curves, a tendency to reference their PFDs to external cues (which will be discussed in more details in section 3.5), and the ability to maintain their directionality without external inputs. This is achieved by integrating over self motion generated information. Vestibular inputs provide angular acceleration information of locomotion, which is used to update the encoded head direction (Muir et al. 2004; Stackman et al. 2002; Stackman and Taube 1997). It has been demonstrated that directional modulation of HD cells in the anterodorsal thalamic nuclei (ADN) and PoS depends crucially on vestibular inputs (Muir et al. 2004; Stackman et al. 2002; Stackman and Taube 1997). Another interesting property is that simultaneously recorded HD cells from the PoS and ADN always rotate in register with each other (Yoganarasimha et al. 2006), which is consistent with the hypothesis that head direction cells behave like an attractor network in the brain and forms an allocentric representation of orientation. I will briefly discuss properties of the head direction cells recorded from different brain structures. An illustrative diagram of the anatomical relationships between the structures can be found in figure 2.1. For a detailed summary of the anatomy, see Wiener and Taube 2005, chapter 2.

Dorsal tegmental nuclei

The dorsal tegmental nuclei (DTN) sit downstream from the vestibular nuclei and send efferent projections to lateral mammillary nuclei (LMN) (Liu et al. 1984). Its anatomical position points to a role in integrating vestibular information into downstream head direction information. Indeed lesion of the structure abolish downstream head direction signals in the anterodorsal thalamic nuclei (ADN) of rats (Bassett et al. 2007). Both Bassett and Taube (2001) and Sharp et al. (2001b) characterised cells recorded from the DTN and found that the majority of the cells (~75%) were angular head velocity (AHV) cells. Two types of AHV cells were found. The asymmetric AHV cells increase their firing rates only when the rat is turning in one of

the two (clockwise or anti-clockwise) direction and the firing rates of these asymmetric cells can either be un-affected or even negatively correlated with turns in the opposite direction. These cells encode both direction and angular head velocity of turns. The symmetric AHV cells on the other hand only encode the AHV of turns. A small population of head direction cells was also found (~12%). However, these HD cells only showed clear tuning curve when the rat was turning, and exhibited a high level of background noise when the AHV input was low. This suggests a more primitive form of HD cells whose directional specificity can only be maintained during turning motion.

Lateral mammillary nuclei

Stackman and Taube (1998) targeted the lateral mammillary nuclei (LMN) with unit recording electrodes and, of the 87 cells recorded, 23% were characterised as HD cells, 16% as head pitch cells, and 44% as angular head velocity (AHV) cells. Unlike the AHV cells in the DTN, all of the recorded AHV cells in the LMN were symmetric and their firing rates were either positively or negatively correlated with the AHV. Comparing to the dorsal tegmental nuclei (DTN), a higher proportion of the cells in the LMN were head direction (HD) cells. These HD cells had comparable but slightly wider Gaussian tuning curves to the HD cells recorded from ADN and PoS and, unlike those in the DTN, also exhibited near silent background firing rates. Downstream head direction signals in the ADN have been shown to be critically dependent on the integrity of the LMN (Bassett et al. 2007; Blair et al. 1998) though it is unclear whether the LMN HD signal is dependent on the DTN input. The different composition of AHV cells and a HD cell population that exhibits more classical tuning curves suggest that LMN contains a more processed head direction information than DTN.

Anteral dorsal thalamic nuclei

Anatomically, anterodorsal thalamic nuclei (ADN) is the downstream structure of the lateral mammillary nuclei (LMN) and projects to the postsubiculum (PoS) and retrosplenial cortex (RSPL). Lesions of the ADN abolish head direction signals in the PoS (Goodridge and Taube 1997), which suggests that head direction cells in the PoS receive their directional information from the ADN. Unit recording targeting the structure found a large population (56%) of head direction cells but no angular head velocity (AHV) cells (Taube 1995). The HD cells in the ADN exhibited near silent background firing rates and Gaussian shaped tuning curves which remained stable in the dark. Blair and Sharp (1995) showed that the ADN HD cells anticipated future head directions of the rats when turning (Blair et al. 1998). They also maintain their firing rates under passive rotation, but cease firing when the rat is heavily restrained (Taube 1995).

Postsubiculum

Head direction (HD) cells were first found from the postsubiculum (PoS), also known as dorsal presubiculum (Ranck 1984; Taube et al. 1990a). PoS HD cells have classical Gaussian shaped tuning curves with near silent background firing rates, which is maintained in the dark. Despite being reciprocally connected, lesion of the PoS does not abolish head direction signals in the anterodorsal thalamic nuclei (ADN), suggesting it is the receiver of head direction information (Goodridge and Taube 1997). These cells provide sufficient information to reconstruct the rat's present head directions (Johnson et al. 2005), which supports the role of head direction cells in encoding present head direction. Head direction cells only account for ~20% of the recorded cells in the PoS. Recently it was shown that PoS contained a population of conjunctive place by head direction cells (Cacucci et al. 2004). These cells encode both place and head direction information and potentially serve a role in integrating head direction information into the place representation. On the other hand, preliminary data showed that these place by direction cells were either severely suppressed or have drifting PFD when being recorded in the dark, supporting a role of these cells in encoding local views of cues. Finally, there are also reports of angular head velocity (AHV) modulated neurons in the PoS (Sharp 1996). However, the reported sample was small (n=7), and six of the seven AHV cells were recorded from the same rat. More data is needed to confirm the observation.

Entorhinal cortex

The Entorhinal cortex (EC) receives projections from many structures, which include those that contain head direction signals such as the postsubiculum (PoS) and the laterodorsal thalamic nuclei (LDN), and is the main source of input to the hippocampus. It was recently found that the structure also contains head direction cells as well as conjunctive grid by head direction cells (Sargolini et al. 2006) similar to place by head direction cells found in the PoS. The HD cells found in the EC showed Gaussian shaped tuning curves and near zero background firing rates which were also stable in the dark. The authors also demonstrated that different layers of the EC had cells with different degrees of gridness and directionality, and these cells rotated their PFDs coherently with each other, suggesting that the population encoded a unique head direction. The characteristics of these head direction cells appear to be similar to the classical head direction cells observed in the PoS, ADN and LMN.

Based on the anatomical and lesion data, the structures that have been discussed so far appear to have a serial dependency that pass on head direction signals from dorsal tegmental nuclei (DTN) to lateral mammillary nuclei (LMN) to anterodorsal thalamic nuclei (ADN) to postsubiculum (PoS) to entorhinal cortex (EC). The head direction signal becomes increasingly refined from DTN to ADN and then become associated with place signals in PoS and EC.

However, there are two other structures that do not seem to belong to this pathway where cells with head direction modulation has also been found. These structures will be briefly discussed next.

Retrosplenial cortex

The retrosplenial cortex (RSPL) receives both visual inputs from area 18b and head direction (HD) inputs from laterodorsal thalamic nuclei (LDN), anterodorsal thalamic nuclei (ADN) and postsubiculum (PoS), which makes it one of the probable place where visual information is integrated into head direction representation. HD cells in the RSPL of rats were first reported by Chen et al. (1994b) using an eight arm radial maze. The authors found that ~9% of the recorded cells were HD cells with Gaussian tuning curves and near silent background firing rates. This suggests that the proportion of HD cells in RSPL is quite low. In addition, Cho and Sharp (2001) also found another type of cells with complex place and head direction modulation. These cells appeared to have different place fields depending on the direction the rat was facing in the environment. The authors proposed that these cells could encode local views of the environment. As discussed in the previous chapter, lesion of the RSPL impairs the rat's ability to selectively use only a subset of cues to guide navigation. These 'local view' cells and head direction cells might be associated with the computation of dissociating relevant cues from irrelevant ones. Additional behavioural and recording experiments will be needed to establish a firmer understanding of the relationships between the two phenomena. On the other hand, lesion of the RSPL does not abolish the ability of the anterodorsal thalamic nuclei (ADN) HD cells to reference to an external cue (Bassett and Taube 1999), which also fits the observation that rats with RSPL lesion still retained the ability to use distal cues to guide navigation (Wesierska et al. 2009).

Lateral dorsal thalamic nucleus

Afferent of laterodorsal thalamic nuclei (LDN) include superior colliculus (SC) and post-subiculum (PoS), which also provide both visual and head direction signals. LDN also projects to area 18b, which is the main visual input into retrosplenial cortex (RSPL) and PoS, and thus supporting its role in processing visual information for head direction system. Mizumori and Williams (1993) found head direction cells from the LDN of rats though the shape of the tuning curves could not be easily determined due to limited directional sampling on an eight arm radial maze. It was also shown that the preferred firing direction (PFD) of these HD cells depends critically on the presence of visual input and recording in the dark causes the PFD to drift rapidly. On the other hand, lesion of the LDN does not affect how PoS HD cells reference to external cues (Golob et al. 1998), which argues against the role of LDN in integrating visual inputs.

3.3 Interactions between place and head direction codes

The literature summarised so far explored the flow of head direction signals between structures. Some conjunctive cells that appeared to support integration between location and head direction information have also been reported from structures containing head direction cells. To correctly represent the surrounding environment, an animal has to keep track of its orientation. This is particularly true when an allocentric cognitive map is used for guiding navigation. For example, if we do not know how to orient a map of the surrounding environment, the map is useless in guiding our navigation. It is thus likely that the head direction signals are integrated into the mental place representation of the environment. Here I will summarise the experiments that have explored interactions between the structures that possess location or head direction modulated cells.

Simultaneous recording of place and head direction cells

Knierim et al. (1995) observed that simultaneously recorded head direction (HD) and place cells remained strongly coupled to each other when rotating their receptive fields unless the place cells remapped between sessions. Yoganarasimha and Knierim (2005) recorded place and head direction cells (from ADN) simultaneously and showed that rotation of the distal cues always caused an equal shift of the place and HD cells. This suggests that place and HD cells share their head direction information but does not rule out that the two population of cells reach the same orientation decision independently. On the other hand, Yoganarasimha et al. (2006) recorded CA1 place cells and ADN HD cells simultaneously and found that when two groups of cues in the environment were rotated in conflict with each other, some place cells followed one and others followed the second group of cues, showing a split representation, whereas simultaneously recorded HD cells always made coherent decisions and mostly followed the distal cues of the environment. This suggests that while head direction cells showed characteristics of an allocentric encoding, place cells are capable of representing the cue conflict egocentrically.

How hippocampal lesions affect head direction cell encoding

Golob and Taube (1997) recorded HD cells from both the anterodorsal thalamic nuclei (ADN) and postsubiculum (PoS) of rats with bilateral hippocampal lesions. It was shown that the ADN and PoS HD cells remained stable after the lesion and with properties comparable to those recorded from the control rats. The HD cells in the lesioned rats could also be controlled by the rotation of the salient cues as well as establishing cue controls in novel environments. For simultaneously recorded HD cells, the shifted angles were always coherent. This suggests that hippocampal lesion has little effect on HD cells. Golob and Taube (1999) explored further

the properties of the ADN and PoS HD cells in the rats that received bilateral lesion to the hippocampus. A dual chamber maze where two chambers were connected by a passageway was used in the experiment. Similar to previous findings, rats with intact hippocampus could maintain the preferred firing direction (PFD) of the HD cells when running from the familiar chamber to the novel chamber via the passageway. However, the rats that received hippocampal lesion could not maintain the PFD of the HD cells when running through the passageway to the novel chamber ($96.5 \pm 17.5^\circ$ drift) though the ability to reference the PFD to the visual cues inside the two chambers was intact. The result indicates that hippocampus is important for integrating idiothetic cues to update HD cells activities on a linear track, but is not essential for establishing cue control for HD cells. The result is surprising as much of the information required for angular path integration exists in the head direction cell system. It is not clear what computation the hippocampus contributes to angular path integration on the linear track.

How lesion of head direction cell structure affects hippocampal place code

In this section I reviewed the literature that explored the effects of lesioning the structures containing head direction (HD) cells to the place cells of the hippocampus. It is important to keep in mind that all the structures contain more than just HD cells and thus the effect of lesion might not be the direct result of losing the head direction cell population.

Mizumori et al. (1994) used an eight-arm radial maze to test how LDN inactivation affects the place cells of the hippocampus. It was shown that many of the place fields became disrupted in different manners, resembling a remapping response. Cooper and Mizumori (2001) again used an eight arm radial maze to explore the effects of the inactivation of retrosplenial cortex (RSPL) to the place cells of the hippocampus. Inactivation of RSPL impaired the performance of spatial memory in the dark, which is consistent with previous reports (Cooper and Mizumori 1999). On the other hand, RSPL inactivation caused a remapping of the place fields both under light and dark conditions, which appeared to be inconsistent with the dark selective behavioural deficiency. It is likely that the rats could use the additionally available information under light condition to guide navigation despite a general deterioration of the place representation. Calton et al. (2003) lesioned either the anterodorsal thalamic nuclei (ADN) or the postsubiculum (PoS) bilaterally and recorded place cells from the CA1 area of the hippocampus. It was found that the place cells recorded from the rats receiving bilateral ADN lesions had lower information content but could still establish cue control with the cue card in the environment. PoS lesions however impaired but did not completely abolish cue control of the place cells by the rotation of the cue card. Place fields appeared to remain stable within a recording session. The result suggests that PoS is important for the cue control of hippocampal place cells. One may thus jump to the conclusion that PoS HD cells are essential for associating place representation with external cues. However, considering that ADN lesion should remove the HD signals in

the PoS (Goodridge and Taube 1997), the experiment actually suggests that it is other, non-head direction related cells in the PoS that is essential to the cue control of place cells.

Overall, the literature suggests that cue control information flows from the PoS to the hippocampus and most of the head direction cell characteristics do not depend on an intact hippocampus. However, it is still not possible to determine whether cue control is incorporated into the head direction cells in the PoS, which in turn get integrated into the place representation of place cells, or some other cell population is responsible for this integration of external information into the internal representation of space.

3.4 Environmental influence on place cells

Many animals use information garnered from sensory organs such as vision or olfaction to guide navigation (see chapter 1). The influence of these inputs on the cell representation of space is thus heavily examined. I will now summarise the literature that has explored the influence of environmental features to the firing of spatially modulated cells. Most of the studies concentrate on hippocampal place cells. The experiments can be broadly divided into two categories. One concerns the effect of changing the orientation or position of cues in an environment, which is often refers to cue control of place cells. The other explores how changing non-geometric or non-polarising features of the environment or even goal of the navigation affects the encoding, which is called contextual encoding. The first category explores how a given place representation is modulated by information of the surrounding environment and the second category aims at addressing how distinct place representations can be formed to disambiguate subtle differences in environments.

Cue control of place cells

Cue control of hippocampal place cells was first demonstrated by Muller and Kubie (Muller and Kubie 1987). In the experiment the rats were allowed to forage for food in a walled cylinder with a prominent white cue card mounted onto the wall. It was shown that rotation of the cue card caused an equal rotation of the place fields from recorded place cells. On the other hand, removal of the cue card has minimal effects on the place fields of the place cells (Jeffery et al. 1997; O'Keefe and Speakman 1987; Quirk et al. 1990). This demonstrates that place cells reference their place fields to polarising cues in the environment but do not depend on the presence of the cues for location specific activities. Similar behaviours can also be observed from other location modulated cells such as those in the subiculum (Sharp and Green 1994), and entorhinal cortex (Hafting et al. 2005; Sargolini et al. 2006). Subsequent experiments aimed at addressing which cues place cells use as references in the environment and how directional conflicts between cues are resolved.

Types of cues

The most common type of cue used in cue control experiments is prominent visual cue cards located at the wall or periphery of the maze (Knierim et al. 1995; Muller and Kubie 1987; O'Keefe and Conway 1978). Despite their efficacy, visual cues are not the only type of environmental information integrated into the spatial representations of place cells. For example, Save et al. (1998) recorded place cells from rats that were blinded one month after birth, and found that these cells still referenced their place fields to objects placed against the wall of the maze. Other reports have also shown that non-visual sensory inputs can influence the hippocampal place cells (Jeffery et al. 1997; Knierim 2002; Save et al. 1998, 2000). On the other hand, influence of internally generated self motion information such as those from the vestibular system is also evident. First, spatial information of the hippocampal place cells are degraded by lesions or inactivation of the vestibular system (Horie et al. 1994; Russell et al. 2003; Stackman et al. 2002). Also, place cells sometimes follow the rotation of the body when the speed of rotation is above the detection threshold of the vestibular system, but invariably reference to the distal cue if the rotation speed is below the detection threshold (Knierim et al. 1998; Sharp et al. 1995), which suggests that vestibular information sometimes does dominate over distal cue to control the place representation of place cells.

Distal cues vs. intramaze cues

Although it is clear that visual cues exert control over the hippocampal place cells, different types of visual cues have different levels of stability and directional information. For the purpose of a directional reference, place cells would need to determine which cues in the environment are most suitable for cue control. Cressant et al. (1997) explored the effect of cue configuration on their ability to exert control over the place cells and found that intramaze objects could only exert cue control when they were placed against the wall of the maze or formed a barrier in one of the quadrants of the maze. This result highlights the fact that merely possessing directional information does not guarantee its integration into the place representation of place cells and the more polarising information a cue provides, the stronger the control over the place cells. The pattern is further supported by the observation that distal cues, for which rat could only see them from a small range of heading directions due to their being positioned outside the maze, tend to dominate over intramaze cues in controlling the place cells when they are in conflict with each other (Cressant et al. 2002; Knierim and Rao 2003; Yoganarasimha and Knierim 2005). In contrast, Knierim (2002) showed that place fields could be controlled either by the intramaze tactile cues or distal visual cues. However, in this experiment the rats were running on a circular track instead of exploring an open field, so the directions associated with the experience of the tactile cues were also very polarising and thus could be the reason

that the intramaze tactile surfaces demonstrated a stronger cue control when compared to other intramaze cues used in the literature. Tanila et al. (1997) used a plus maze to explore how hippocampal place cells respond to conflicts between distal visual cues and intramaze odour cues. The authors classified the response of place cells into 'no change', 'rotated with distal cues', 'rotated with intramaze cues' and 'new representation'. It was found that although a large proportion of simultaneously recorded place cells in an ensemble responded in a similar manner after the rat experienced the cue conflict (79%), only a small proportion of place cell ensembles in which all the place cells in the ensemble responded in exactly the same manner. The result suggests that it is common for a small subset of place cells to respond differently to others in the same ensemble. The subset of place cells can be used to encode small changes in an environment without completely alter the overall spatial encoding of the place cell ensemble. Lee et al. (2004) used a circular track and a double rotation of the distal visual cues and intramaze tactile cues to introduce cue conflict and found a population difference between CA3 and CA1 place cells in that CA1 place cells attempted to follow both intramaze and distal cues (thus forming a split representation) whereas the CA3 counterparts mostly followed only the intramaze cues when resolving conflicts. The result suggests differential roles between the two structures. Save et al. (1998) also showed that non-visual intramaze cues could exert control over place cells when they were only experienced by the rats from a small range of heading directions. Renaudineau et al. (2007) rotated the intramaze object cues placed against the wall and distal visual cues in conflict with each other and found that the majority of the place cells shifted their place fields unpredictably, i.e. a remapping response. However, for the place cells that rotated their place fields after the cue conflict, most rotated with the intramaze cues. This suggests that even in the case that the majority of the place cells in an ensemble remap between environments, the subset of place cells that rotate their place fields between sessions can still do so in a coherent manner. The reviewed literature also suggests that intramaze cues can dominate the distal counterparts if they are experienced only in restricted directions, especially when more than just visual information such as tactile or olfactory senses can be gathered from these cues. On the other hand, Save et al. (2000) demonstrated that intramaze odours, which are more suitable for location information than orientation information, were more important than distal visual cues for the stability of place fields. This suggests that place cells integrate different types of information differently depending on the spatial information provided by the cues. Siegel et al. (2008) used a square platform that was located inside a room and trained rats to retrieve rewards from one corner of the platform during standard sessions. The location of the reward site could be determined either with respect to the platform (i.e., the proximal cue frame), or with respect to the room (i.e., the distal cue frame). The authors then conducted a probe session in which the location of the platform inside the room was shifted horizontally. After the shift, the reward site as defined by the distal cue frame and by the proximal cue

frame become different from each other, and the rat was rewarded by visiting either of the two possible reward sites. Hippocampal place cells from CA3 and CA1 of the hippocampus were recorded during the standard and probe sessions and the authors found that the majority of the place cells shifted their place fields with respect to the proximal cue frame during the probe session. The result showed that, when location information conveyed by the proximal and distal cues (instead of orientation information commonly used in cue rotation experiments) were in conflict with each other, place cells preferred to reference their place fields to the proximal cue frame. The result fits the previous observations that intramaze cues are more prominent in guiding the location information of place cells' place fields whereas distal cues are more frequently used as a reference to guide the rotation of the place fields in cue rotation experiments.

Prior experience and perceived cue stability

Knierim et al. (1995) explored how prior experience of visual cues affected their control over the place cells. The rats searched for food in a cylinder with a white cue card mounted on the wall either under disorientation or non-disorientation conditions in two 15 minute sessions per day for one to four weeks. In the disorientation condition the static laboratory cues were masked (as much as possible) from the rats and they were carried to the cylinder in an opaque box. A uniform black curtain surrounded the maze and a white noise generator was used to mask uncontrolled auditory cues. Before entering the maze the rats were moved in an erratic path and occasionally turned in circles to disrupt their path integration. In the non-disorientation condition, the rats were carried directly to the maze from the preparation room on the experimenter's palms and both the black curtain and the white noise generator were removed, allowing unobstructed view of the experiment room. All probe trial sessions were done under the disorientation condition for both groups of rats and the white cue card was rotated to determine its strength of cue control over the place cells. It was found that the cue card exerted control over the place cells from the rats in the non-disorientation condition but not those in the disorientation condition. For those rats that ignored the cue card, additional training under the non-disorientation condition could not re-establish cue control. This suggests that the loss of cue control due to the disorientation was permanent. It was hypothesised that the weak cue control of the cue card in the disoriented group was due to its repeated conflicts with the rats' internal idiothetic directions. Similarly, Jeffery and O'Keefe (Jeffery 1998; Jeffery and O'Keefe 1999) showed that cue control of the distal cue cards degraded significantly when the rats had prior experience of them moving, thus conflicting with their internal idiothetic encoding. However, Chakraborty et al. (2004) also explored the effect of repeated conflict between distal and idiothetic cues on the cue control of place cells and found that place cells preferred to rotate their place fields with the distal cues after the rat experienced the repeated cue conflict. The authors allowed rats to forage in a symmetric square box surrounded by featureless black

curtains. A white cue card was used to provide polarising information in the otherwise four fold symmetric environment. A conflict between the distal and idiothetic cues was then introduced by first turning the light of the room off and then slowly rotating the box holding the rat and the cue card in the opposite direction. It was shown that place cells learned to rotate their place fields with respect to the distal cue card after the rats experienced repeated conflicts between the distal and internal idiothetic cues. This domination is unlearned when the cue conflict was introduced without turning the light off and thus the rats could see the movement of the cue card, which fits the observations reported in Jeffery (1998) and Jeffery and O'Keefe (1999). The result thus is inconsistent with what was reported by Knierim et al. (1995). A potential explanation for the discrepancy is that the observed loss of cue control from the distal cues in Knierim et al. (1995) was not due to the repeated conflicts between the distal and the idiothetic cues but rather due to the extensive disorientation procedure underwent by the rats. Shapiro et al. (1997) also explored the effect of repeated conflicts between the distal visual cues and the idiothetic cues by introducing repeated 90° conflicts between the visual and idiothetic cues while the rat was running on a plus maze. The authors showed that initially, many of the place cells followed the distal cue (43%). However, as the rats were given more conflict experiences, the majority of the place cells (70%) adopted distinct representations between the standard and conflict sessions. One issue for interpreting the result is that, with a plus maze, it is more difficult to distinguish between remapping and rotation of place fields if the rotation angle is not a multiple of 90°. Overall, the literature suggests that strength of cue control is influenced by prior experience. One of the mechanisms that suppresses the integration of external cue is the perceived movement of the cues. On the other hand, the mechanism that determines experience-based perceived cue stability has not been thoroughly explored.

Cue conflict resolution

Some of the literature specifically explored how conflicts between different types of cues are resolved. Several papers (Jeffery et al. 1997; Knierim 2002; Yoganarasimha et al. 2006) showed that each of the idiothetic, proximal and distal cues could exert control over the place cells independently, causing a split representation within the ensemble. Knierim et al. (1998) found that when the conflicts between the idiothetic direction and distal visual cues were small, the visual cues dominated over the idiothetic directions. As the conflict became large, the place cells either followed the cue card or remapped. On the other hand, if the body rotation was below the vestibular threshold, the place cells treated the discrepancy as self motion generated errors and almost always followed the visual cue. The observation that remapping can occur when conflicts between idiothetic direction and visual cues arise suggests that place cells could change their environmental representations when discrepancies in the environment become too large. Lastly, Lee et al. (2004) showed that CA3 and CA1 place cells reacted differently

to conflicting cues. Place cells in CA3 of the hippocampus tended to maintain a coherent representation when facing conflicting proximal and distal cues whereas CA1 place cells prefer to form a split representation to encode the conflict.

Contextual encoding of place cells

The literature discussed in the previous section mainly explored the effects of rotating or removing cues in the environment on the place fields of place cells. In this section, I will look at how other changes, such as changing the features of the environment or internal state of the rat affect the firing of place cells. As discussed in the beginning of this chapter, place cells can respond to changes in the environment by either rotating their place fields (rotation), changing its firing rate inside the place field (rate remapping) or change both the firing rate and the location of the place field in an unpredictable manner (global remapping). If the majority of the place cells in an ensemble exhibited global remapping between the two environments, the place cell ensemble responded very differently in the two environments and the distinct encoding would serve best to distinguish between the two environments. There have been several experiments that were designed to explore under what conditions a place cell ensembles would respond predominately with global remapping as opposed to rotation or rate remapping.

Several experiments have shown that repeated exposure to two similar environments encourage place cells to gradually differentiate their representations of the two environments. For example, Bostock et al. (1991) found that substituting a white cue card with a black cue card did not initially affect the place fields of the place cells, and the rotation of the substituted cue card also induced an equal rotation of the place fields. However, the place cells started showing distinct place fields for the two cue cards in subsequent visits. Similarly, Lever et al. (2002) showed that repeated exposure to two mazes with different geometric shapes encouraged the development of distinct place fields from hippocampal place cells. These experiments suggest that hippocampal place cells actively orthogonalise representations of similar environments after extensive experience. Whether the distinct representations of similar environments would aid the dissociation of experiences from the different environments is not clear despite attempts to address the problem (Hayman et al. 2003). This raises the question of what is encoded by the remapping of place cells. Altering a wide array of environmental features, including visual (Anderson and Jeffery 2003; Wible et al. 1986), auditory (Sakurai 1994), or odour (Wiebe and Stäubli 1999; Wood et al. 1999) inputs, could cause place cells to remap. It has also been shown that place cells can dissociate and encode different features of the environment separately instead of treating each combination of features as a separate environment (Anderson and Jeffery 2003). The result demonstrates that place cells not only identify changes in an environment, but also generalise common features over different environments.

Encoding of internal state and goals

The literature discussed above shows how place cells change their place fields to accommodate changes in the environment or simply distinguishing between different environments. This remapping process, however is not limited to responding to changes in environmental features but can also respond to changes in behaviour or motivation. One of the first studies that demonstrated this is from Markus et al. (1995). As discussed previously, the place fields of hippocampal place cells tend to be directional when the rat is running on linear tracks whereas if the rat is exploring an open field maze, the place fields tend to be directionally invariant. The authors thus designed a task in which rats needed to run between waypoints on an open field maze. It was shown that the place cells not only changed their place fields when the required behaviour for the rats was changed from random foraging on the open field maze to running between waypoints on the same maze, the place fields also became directional, similar to those recorded from rats running on linear tracks. The result demonstrated that changing the nature of the task could induce place cells to alter both the location and the characteristics of their place fields. Furthermore, Moita et al. (2003) used a contextual fear conditioning experiment to demonstrate that place cells changed their place fields when the environment became associated with fear conditioning but at the same time still retained their location specificity. Breese et al. (1989) recorded place cells from rats exploring a square open field maze. Several cups were placed inside the maze and one of the cup at a time was used to delivery water rewards. It was shown that changing the reward location was sufficient to cause the place cells to shift their place fields despite the rat was exploring an otherwise identical local environment. These results all support the role of hippocampal place cells in integrating non spatial information into their spatial representations, which could serve a role in dissociating different mental states in the same environment. The modulation of reward sites or goals can also be seen from several linear track experiments where rats were either required to do a win-stay or a win-shift task. We use the term 'goal-sensitive cells' to describe the cells whose firing rates are significantly modulated by the intended goal of the rat. We first summarise the results from win-stay experiments. Ferbinteanu and Shapiro (2003) recorded place cells from rats pretrained on a win-stay task on a plus maze. Briefly, one of the two arms at the east and west side of the maze was chosen to be the rewarded arm and the start location was chosen randomly between the north and the south arm of the maze. The random start location encouraged rats to use a place-based strategy. It was found that some hippocampal place cells only fired at their place fields when the rat came from a specific start location (i.e. retrospective encoding) and some other place cells only fired when the rat was visiting a specific goal (i.e. prospective encoding or a goal-sensitive cell). The result demonstrated that place cells could encode more than just the location information and might play a role in resolving the win-stay task. Similarly, Ainge et al. (2007a) trained rats on a double Y-maze win-stay task and recorded place cells from CA1

of the hippocampus. The authors also identified some goal-sensitive cells that changed their place fields depending on the intended goal of the trajectory. Goal-sensitive cells have also been recorded from rats performing win-shift tasks. Frank et al. (2000) first trained rats to perform a win-shift task on a W-maze where the rats had to visit the three arms in the order of centre-left-centre-right-centre to obtain rewards. Unit recording construct was then surgically implanted to target one of the three areas, CA1 of the hippocampus, the superficial layers of the entorhinal cortex (EC) and the deep layers of the EC. The authors found that, among those cells who were active at the central arm of the W-maze, cells with significant prospective or retrospective encoding were identified from all three areas. Wood et al. (2000) trained rats on a continuous T-maze alternation task and recorded place cells from the hippocampus. The authors found that a large proportion of the cells that were active at the central stem of the T-maze exhibited significant goal-sensitive activity. Later, Ainge et al. (2007b) recorded place cells from rats performing a delayed version of the same continuous T-maze alternation task with the only difference being that rats were confined at the start box for either 2s or 10s each time before the next attempt to reach the rewarded arm. It was found that, after introducing the delay period, most of the goal-sensitive activities were observed during the period which the rat was confined at the start box. Interestingly, it was also shown that hippocampal lesion only impaired the rat's performance on the delayed version of the task. This suggests that the changes in the distribution of goal-sensitive activities on the maze may be related to the dependence of the delayed T-maze alternation task on the hippocampus. Ji and Wilson (2008) also trained rats on a continuous T-maze alternation task before implanting electrodes that recorded activities from CA1 of the hippocampus. Similar to what was reported in Wood et al. (2000), the activity of some of the hippocampal cells with place fields at the central stem of the maze was significantly modulated by the goal of the trajectories. The authors then changed the nature of the alternation task into a win-stay task by fixing the location of the rewarded goal arm. This created a new running trajectory as, instead of running in a figure of eight trajectory, the rat now had to visit the same goal arm repeatedly. The authors then compared the activity of the hippocampal cells which were active at the central stem of the maze while the rat was running the new trajectory to the activity of these cells when the rats were running the old figure of eight trajectories. It was found that when the rat initially learned to run the new trajectory (and thus exhibiting a win-stay behaviour), the activity of the cells at the central stem was more similar to the activities on the central stem of the old trajectories that shared a common future destination. With additional training, however, the activities among trajectories that shared a common past became more similar. This demonstrated that when the rat is learning a new task, hippocampal cells can also exhibit a dynamic change of their firing characteristics. It is unclear though whether this dynamic change was related to the rat's learning rate of the new win-stay task.

The activity of prospective cells can be interpreted as the rat's intended destination and the activity of retrospective cells can theoretically be exploited to solve win-stay and win-shift tasks as they contained information of the previously visited goal. It is thus tempting to interpret the existence of these cells while the rat was running a task as evidences that the hippocampus is involved in solving the task. However, lesion of the hippocampus does not affect the rat's performance on some of the tasks in which goal-sensitive cells from the structure have been reported. For example, continuous T-maze alternation task without delay is not sensitive to lesion of the hippocampus (Ainge et al. 2007b) despite numerous reports on the existence of goal-sensitive cells while the rats are performing the task. Furthermore, in some of the experiments where a similar win-stay or win-shift task was used, no goal-sensitive cells were found from the hippocampus. For example, Lenck-Santini et al. (2001) trained rats to perform a continuous alternation task on a Y-maze and recorded place cells from the hippocampus. The authors reported that most cells showed very similar firing patterns on the common area of the maze despite the rat was alternating between the intended goals. Bower et al. (2005) used an open field circular maze but trained the rats to run through a series of waypoints to perform an alternation task with running trajectories similar to those in a continuous T-maze alternation task and initially found no goal-sensitive cells from the hippocampus. The authors then altered the pretraining condition by inserting forced choice barrier similar to the pretraining condition used in Wood et al. (2000). To make it more similar to the T-maze task, the reward at the start and the choice point waypoints was also removed. It was then shown that either of the two alternation resulted in the development of goal-sensitive cells. The result suggests that the development of goal-sensitive cells is not necessarily related to the performance of tasks but can also be caused by other aspects of training.

Overall, the activity of hippocampal place cells can be modulated by both the intended goal or the previously visited goal in many of the win-stay and win-shift tasks. However, the contribution of these cells on the performance of the tasks remains unclear, especially when most of the recording experiments were conducted after the rats were well-trained for the tasks. An investigation on the development of these goal sensitive cells and its relationship with the learning of win-stay or win-shift tasks shall allow a better understanding on the role of goal-sensitive cells in task performance.

3.5 Cue control of head direction cells

The study of environmental influences on head direction (HD) cells mainly concentrates on the influence of external cues on the orientation of HD cells. As discussed in section 3.3, head direction (HD) cells appear to share the same HD information with place cells. The results of HD cell cue control experiments, which will be reviewed soon, are thus very similar

to those obtained from place cells. One major difference is that the HD cell system does not appear to allow split representations, even when external cues are rotated in conflict with each other (Yoganarasimha et al. 2006). Head direction cells have been recorded from many structures of the brain and are shown to reference their PFDs to external cues (Chen et al. 1994a; Sargolini et al. 2006; Stackman and Taube 1998; Taube 1995; Taube et al. 1990b). These cells also maintain their directional correlations after the removal of the visual cues previously controlling their preferred firing direction (PFD). The HD cells also fire directionally in the dark (Chen et al. 1994b; Goodridge et al. 1998), which suggests that self motion generated idiothetic information is sufficient to maintain directional modulation of HD cells.

Influence of visual cues on head direction cells

Zugaro et al. (2001) explored how perception of visual cues affected their control over the preferred firing direction (PFD) of head direction (HD) cells. In the experiment the rats were allowed to search for food pellets on an elevated circular open field platform surrounded by black curtains. Three objects were placed at the edge of the platform and the rats were given one of the two conditions. In the distal cue condition, a wall was placed at the edge of the platform, making the three objects the most distal cues of the environment. In the proximal cue condition, no wall surrounded the platform and the objects, when contrasted with the black curtains, appeared to be more proximal. It was shown that rotation of the objects could exert cue control over the HD cells in the anterodorsal thalamic nuclei (ADN) only in the distal cue condition. As the objects in both conditions contained similar directional information, the result demonstrated the importance of perceived cue proximity in their capability to control HD cells. Later Zugaro et al. (2004) explored the effect of perceived distance to the visual cues' ability to gain control over the PFD of HD cells. The authors placed the rat on a small circular maze to restrict its movement but not rotation. Two visual cue cards were used in the experiment, with one placed further away from the maze than the other. The size of the cue cards were controlled such that the only perceptual difference between the two cue cards was their perceived distance. It was shown that when the two cue cards were rotated in conflict with other, the one that was further away mostly controlled the rotation of the HD cells. On the other hand, when the experiment was conducted under stroboscopic light to remove the distance information of the visual cues, the HD cells did not appear to prefer any one of the cue cards for cue control. Goodridge et al. (1998) looked at the amount of experience needed for a cue card to establish cue control over HD cells. It was shown that about half of the HD cells could be controlled by a novel cue card if the rats were exposed to them for one or three minutes. By eight minutes, all of the HD cells could be controlled by the novel cue card. This demonstrated that salient cues could rapidly gain control over the HD cells. Finally Knierim et al. (1995) also explored the effect of disorientation on the HD cells (see section 3.4 for a

more detailed summary) and showed that the HD cells responded similarly to the place cells after disorientation treatment and became uncoupled to the polarising cue card.

Non-visual external cues and role of vestibular inputs

Since rats that were deprived of their vision could still maintain the directionally specific firing of the head direction (HD) cells, other types of sensory information, external or internal, should also be able to modulate the firing rates of HD cells (Goodridge et al. 1998). It was found that olfactory cues, but not the auditory cues, could exert a small effect on the HD cells.

We have so far discussed the role of external sensory information in modulating the firing of HD cells. HD cells have been thought to be involved in integrating vestibular information to calculate present HD. Several research groups thus investigated the role of vestibular inputs in HD cells. Stackman et al. (2002) showed that temporary inactivation of the vestibular system suppressed directionally specific firing of postsubiculum (PoS) HD cells. Muir et al. (2004) used chinchilla to show that plugging the semicircular canals also removed directional specificity of the anterodorsal thalamic nuclei (ADN) HD cells. However, some of the ADN cells fired in a rapid bursting manner, similar to that observed from the ADN HD cells in intact chinchilla. Additional analysis showed that these bursting cells always followed a fixed sequence of activation, suggesting that the ADN HD cell network was still intact after the plugging but that the activities became decorrelated with the environment. Yoder and Taube (2009) recorded HD cells from mice and showed that otolith input in the vestibular system was also important for the directional activity of HD cells. The results support a critical role of vestibular inputs in maintaining directionally specific firing of HD cells. Taube and Burton (1995) used a dual chamber maze and showed that the rats could maintain the PFD of their HD cells when running across the linear track both under light or dark condition. However, if the rats were passively transported without being restrained, the PFD could not be maintained when travelling between the chambers (Stackman et al. 2003). As the rats that were passively transported still retain intact optic flow and vestibular input, the result stresses the role of proprioceptive information in maintaining the PFDs of HD cells.

Conflict resolution of head direction cells

In this section I will look at how head direction (HD) cells resolve conflicting orientation information. Yoganarasimha et al. (2006) investigated the behaviours of the anterodorsal thalamic nuclei (ADN) HD cells under the condition that would induce place cells to show split representations due to conflicting environmental cues. It was shown that simultaneously recorded HD cells always rotated in register with each other, maintaining a coherent directional representation. This suggests that ADN HD cells enforce an allocentric representation of the environment. Goodridge and Taube (1995) showed that when uncontrolled intramaze cues could be

used to guide the preferred firing direction (PFD) of the HD cells, they attenuated the control of distal cues when the two were rotated in conflict with each other, suggesting an incomplete dominance of distal cues over intramaze ones. It should be noted that the rats in the experiment experienced a session without the distal cue prior to the conflict, which might weaken the effect of the distal cue due to perceived instability. Knierim et al. (1998) also investigated the behaviours of the ADN HD cells when external cue and internal idiothetic information were in conflict with each other. Similar to hippocampal place cells, the ADN HD cells were dominated by distal visual cues when the conflict between the idiothetic direction and the distal cues was small. However, when the conflicting angle was large, the ADN HD cells either followed the idiothetic direction or the distal cues. The result was consistent with the behavioural data (Etienne et al. 1990) but not those obtained from the place cells where large conflict resulted in either place cells following the distal cue or remapping. The literature thus suggests that a remapping of the place cells does not necessarily entail a random reset of the HD cell system. The authors also observed the PFD of the HD cells drifted over time when the recording session was conducted in the dark. However, unlike what was reported by Mizumori and Williams (1993), the ADN HD cells only reset their PFD to the cue card after the light was turned back on when the drifting angles were smaller than 45° . The result suggests that one role of the distal visual cue is to correct the errors accumulated from path integration.

In contrast, Zugaro et al. (2000) showed that distal cue card dominated over intramaze and idiothetic frames in controlling PFD of the HD cells when in conflict. One explanation for the conflicting results is the differences in the speed of the rotation and the size of the conflicting angle. In Knierim et al. (1998), the rats were rotated at a faster speed (90° - 180° per second) and at a greater conflicting angle (135° - 180°) than was done in Zugaro et al. (2000) (10° per second for 90°). The greater rotational speed (and thus stronger idiothetic information) and larger conflicting angles might give the idiothetic frame a stronger control over PFD of the HD cells and hence can sometimes dominate over the distal visual cues. Taube and Burton (1995) also explored the conflict between the idiothetic information and the distal visual cues by rotating the cue card in one of the dual chambers connected by a passageway after the rats had prior experience in both of the chambers. It was shown that the first conflict experience between the distal cue and the idiothetic direction was always resolved by distal cues controlling the PFD of the HD cells. However, in the subsequent conflicts the idiothetic direction sometimes guided the PFD, suggesting that repeated conflict between distal cues and internal sense of direction weakened the ability of distal cues to control PFD of HD cells.

Dudchenko and Zinyuk (2005) also explored how HD cells resolved conflict between distal and idiothetic cues by using a four box maze, which was a square enclosure with walls that separated it into four equal sized square compartments at the four corners of the enclosure. Each square compartment had a cue card and an object that were visually distinct from those

in the other compartments. Rats were initially trained in and passively transported between two of the four compartments. As the result, the HD cells established different preferred firing direction (PFD) in the two compartments that were referenced to the cues. A conflict between distal and idiothetic cues was introduced later by letting the rat walk from one compartment to the second one. As the PFD in the two compartments were different, the rat needed to resolve the conflict when entering the second compartment. It was found that initially the distal cues dominated over the idiothetic cues in most rats, and this was maintained even after repeated conflict experience in five of the eight rats. The result was more complicated in the three other rats after repeated conflict experience but in very few cases did the idiothetic cues dominated over the distal cues in controlling the PFD of the HD cells. This result was similar to what was reported by Taube and Burton (1995) and suggests that HD cells prefer to use distal cues over idiothetic cues as an orientation reference. However, a repeated experience of cue conflict weakens the effectiveness of distal cues to control the PFD of the HD cells. However, even in the cases where distal cues lost cue control over the HD cells, the idiothetic cues rarely gain complete control over the HD cells.

Overall it appears that HD cells have a natural preference to use distal cues to maintain their directional specificity, but this preference can be altered by experience that suggest the instability of these cues. Though HD cells use different types of cues under different conditions, whether these preferences are hardwired or are experience based remains to be determined.

3.6 Models of head direction system

Based on the experimental results, several computational models have been proposed to explore the mechanisms that guide animal orientation in an environment. These models are either demonstrated as software simulations or as part of the navigation system in bio-robotics studies. As head direction cells are ideal in providing orientation information, many of these models simulate the characteristics of head direction cells reported in the experiments.

Attractors

An attractor is a form of stable persistent activity in the neural network that can sustain itself without the need of external inputs and can be configured to be resistant to small noise perturbation. This persistent activity can be used to represent memories of previous events and thus is commonly used to model different types of memory. Attractor networks can be roughly categorised into those that exhibit discrete attractor states, usually used to represent discrete memory items, and those that support continuous attractor state, which can be used to represent continuous variables. One of the most common neural network structure supporting an attractor state is via local recurrent excitation connection. Hopfield network is a well-known type

of network structure that supports discrete attractor states using this structure (Hopfield 1982). The network has been used to model associative memory as it can be trained to reach different attractor steady states based on initial network conditions. Amari (1977) began the exploration of the properties of neural networks that support continuous attractor states. As mentioned earlier, continuous attractors are most fitting to represent continuous variables. Most models of the head direction cell network thus use neural networks that support continuous attractors to represent head directions. In the next sections, several models of the head direction cell network is briefly described.

Hebbian learning rule

The Hebbian learning rule is one of the most popular learning rule used to adjust the weight of projections in neural networks. It was first proposed by Donald Hebb in his book "The Organization of Behavior" (Hebb 2002) in 1949. The principal of the rule is that if cell A take part in driving the firing of cell B via a $A \rightarrow B$ projection, then the weight of this projection is strengthened. There are several deficiencies for the Hebbian learning rule. The most severe ones are, 1) there is no mechanism to weaken the connection and, 2) the learning rule is unstable and the weight of the dominant projection will keep getting stronger. Several strategies, such as homeostatic plasticity (Turrigiano et al. 1998) or the BCM theory (Bienenstock et al. 1982), have been used to overcome the deficiencies.

Computational models that use recurrent excitation

Skaggs et al. (1995) proposed one of the first models of head direction cells. A diagram that represents the head direction cell network is presented in figure 3.3. The authors used a continuous attractor neural network (CANN, see Trappenberg 2002, pp. 207–232 for an overview) organised into a ring to model head direction cells. The direction encoded by the network was represented by the position of the attractor state (also called an activity bubble) in the ring network. The head direction cell units of the model had strong excitatory projections to the neighbouring units in the ring network and strong inhibitory projections to the distant units. This projection profile allows the formation of an attractor state inside the ring network without external inputs. Two other groups of units were used to rotate the position of the attractor state, and thus updated the encoded head direction of the system. The activity level of the vestibular units were strongly correlated with either left or right turns and they provided excitatory inputs to the rotation cell units. The rotation cell units received excitatory projections from both the head direction cell units and the vestibular units and were only activated when receiving inputs from both sources. They in turn projected excitatory inputs to the corresponding (left or right) neighbours of the head direction cell units for which they received excitatory inputs from. Their activation would allow the shifts of the attractor state and thus provided a

rotation mechanism for the model. The influence of external cue was modelled by injecting a positive current to a specific head direction cell unit in the ring network, thereby resetting the attractor state centering around the unit. This also served as an error correction mechanism as the rotation mechanism of the model was prone to error accumulation. Some characteristics of the model such as the concurrent excitatory and inhibitory projections from the head direction cell units do not seem to be biologically realistic. On the other hand, the firing characteristics of the angular head velocity (AHV) cells (reviewed in section 3.2) recorded from the dorsal tegmental nuclei (DTN) and the lateral mammillary nuclei (LMN) of rats fits the rotation cell units used in this model.

Zhang (1996) presented a model of head direction cells by also using a ring CANN. One major difference between this model and the Skaggs et al. (1995) model is that there was no rotation cell units nor vestibular units in this model. The authors instead chose to update the attractor state of the ring network by altering the projection weights of the head direction cell units. The rotation mechanism does not seem to be biologically plausible but has the advantage of being simple and less prone to errors. The simple implementation for the rotation mechanism is useful when the updating mechanism is not the main focus of the experiment as the modellers can concentrate on exploring other aspects of the head direction cells without worrying about how the update mechanism would affect other aspects of the model. The Zhang (1996) model also used a fixed excitatory input to model the cue control of HD cells and thus did not permit the learning or unlearning of external cues.

Redish et al. (1996) attempted to construct a more biologically realistic model of head direction cells by using a boolean value with one representing a spike as the output of a unit instead of the rate based output used in previous models. The authors also used two separate populations of head direction cell units with one population outputting excitatory projections and the other providing inhibitory projections to create a ring CANN. The excitatory population of head direction cell units projected strongly to their neighbours whereas the units in the inhibitory population projected weakly to all of the units in the excitatory population. The update mechanism was implemented by using two ring attractor modules just described with excitatory connections between all units of the two ring attractors, which aligned the position of the attractor states between the two modules. A diagram that illustrates the mechanism is presented in figure 3.4. One attractor module was used to represent the head direction cells in the postsubiculum (PoS) and another to represent those in the anterodorsal thalamic nuclei (ADN). On top of the excitatory connections between the two attractor modules that aligned the attractor states between them, the excitatory HD cell units in the PoS module also contained offset excitatory projections whose strengths were modulated by angular head velocity. This offset projections allowed the head direction cell units in the PoS module to shift the position of the attractor state in the ADN module. The alignment projections between the two

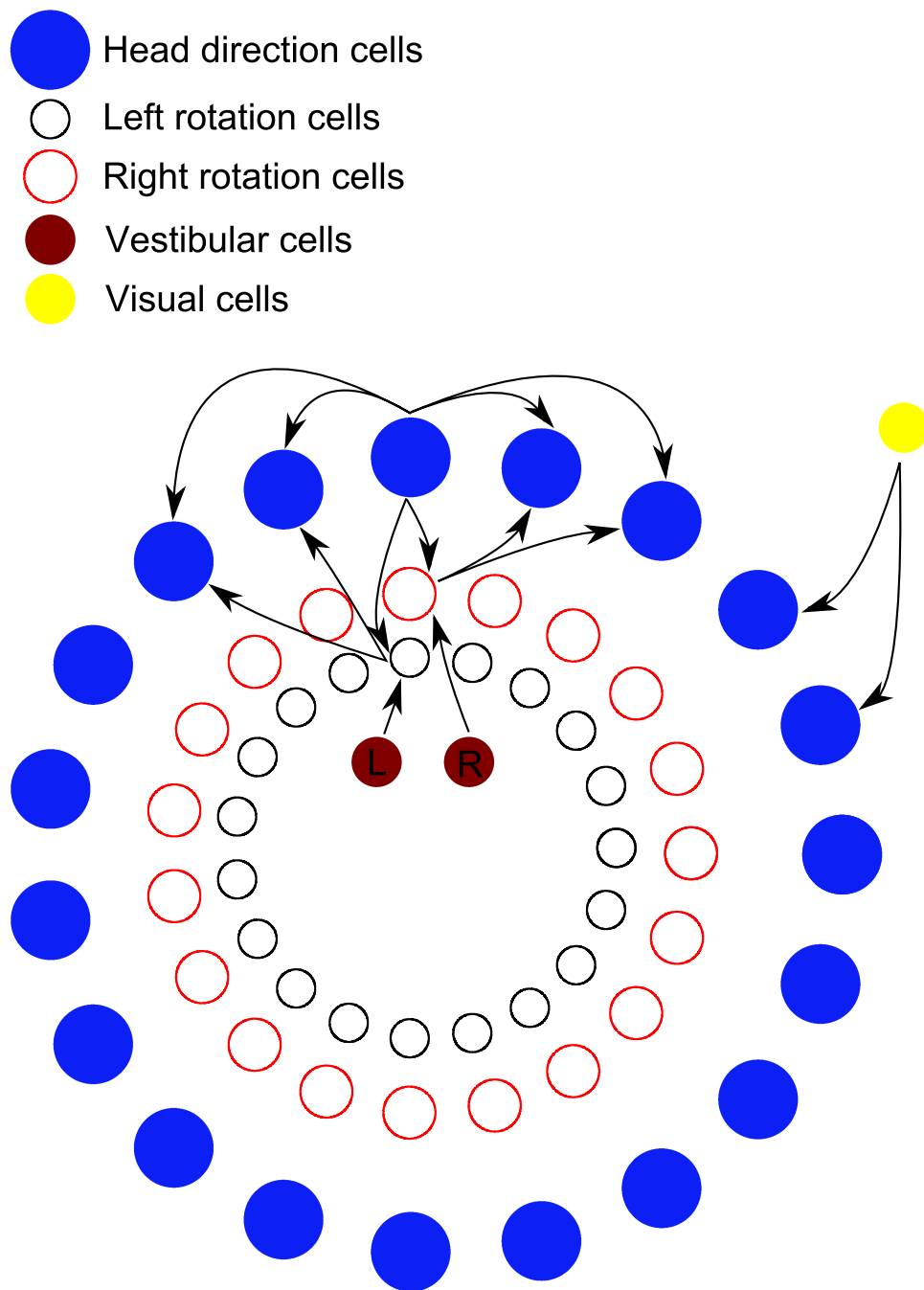


Figure 3.3: A diagram representing the head direction cell model in Skaggs et al. (1995) (The diagram was a replication of the network illustrative diagram from the article). The projections, which are represented by arrows in the diagram, are excitatory. The diagram illustrates local recurrent excitations between head direction cell units and asymmetric projections of rotational cells that facilitate the rotation of the continuous attractor state in the network. The left and right rotation cells receive excitatory inputs from the left rotation and right rotation vestibular cells respectively.

modules then shifted the attractor state in the PoS module to become aligned with that in the ADN module. This models the observation that the ADN HD cells anticipate the update of head directions (Blair and Sharp 1995). On the other hand, the adjustment of the strength of offset projections does not seem to be biologically realistic. An update mechanism that utilises the AHV cells in the DTN and the LMN, similar to the rotation cell units in Skaggs et al. (1995) would be a more realistic implementation. A follow-up model from the same research group indeed used the AHV cells as the update mechanism for the head direction cell model (Goodridge and Touretzky 2000).

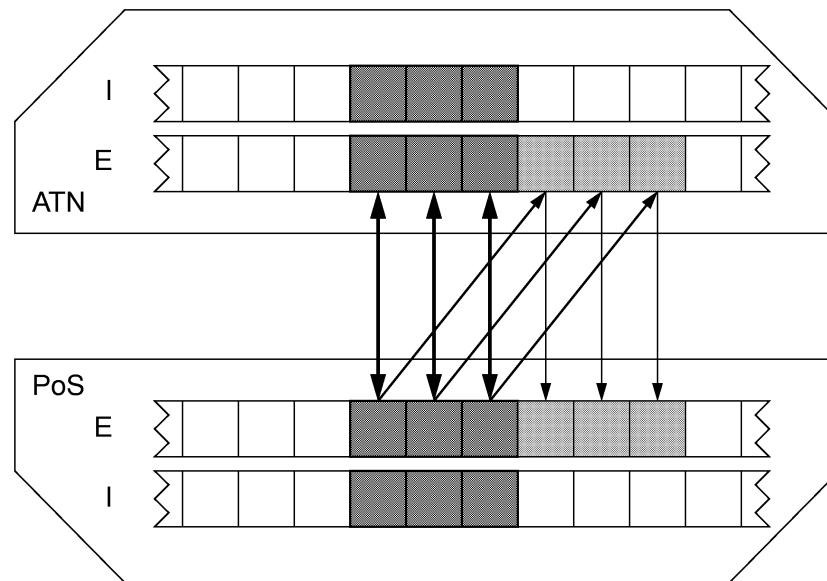


Figure 3.4: A diagram that illustrates the projections between the two ring attractors in Redish et al. (1996) (The diagram was extracted directly from the article). The diagram illustrates that the two ring attractors have reciprocal excitatory projections between the two rings that align the positions of the two attractors. In addition, the units in one of the ring attractors contain offset excitatory projections to the other ring, which is used to shift the attractor in the other ring attractor.

In the Degris et al. (2004) head direction cell model, the authors used leaky integrate and fire neurons (see Trappenberg 2002, pp. 38–55 for an overview) as units in the network and the structure of the attractor network was very similar to that in Redish et al. (1996). The authors used an update mechanism that was similar to what was implemented in Skaggs et al. (1995). One of the major differences was that the rotation cells used inhibitory outputs to drive the update of the attractor state instead of the excitatory outputs used in Skaggs et al. (1995). The main focus of the model was to explore the effect of external inputs on the update speed of the attractor state, which was interpreted as the reorientation of the encoded head direction of the system. The authors found that with appropriate parameters, the update speed was comparable to what was observed experimentally from the ADN HD cells (Zugaro et al. 2003). However, the authors did not explore the learning of cue association but simply used a fixed excitatory

input to represent the influence of external cues.

Computational models that do not use recurrent local excitatory projections

Both Song and Wang (2005) and Boucheny et al. (2005) removed the need of using recurrent excitatory connection when constructing a ring continuous attractor neural network (CANN) by using two populations of units with inhibitory outputs projecting to a population of units with excitatory outputs. The units from the excitatory population projected to all the units in the two inhibitory populations with the strongest excitatory projections going to the units in the inhibitory population with the same preferred firing direction (PFD). The units from one inhibitory population projected their strongest inhibitory output to the right of the excitatory units with the same PFD and the projections from the units in the other inhibitory population had a left offset. Unlike the models that used recurrent excitatory connections, these two models required continuously background excitatory inputs into all units to maintain the attractor state. In the Boucheny et al. (2005) model, the authors also used a strong excitatory input to model the reorientation of the head direction cell system. Overall, none of the head direction cell models explored how conflicts between external cues can be resolved by a head direction cell system. In order to resolve a cue conflict, a head direction cell model needs to possess some forms of learning mechanism. Without the adaptivity provided by learning mechanisms, any introduced conflict between external cues cannot be resolved.

Head direction system in robotics

In the field of robotics, the ability to correct errors from path integration is necessary for the navigation system as in real life navigation errors from path integrator invariably accumulates. Some of the robotics systems simply used built-in magnetic compass for orientation as it is easily implemented and the accuracy cannot be rivalled by an cue based orientation system (Gaussier et al. 2000). However, some of the research groups did attempt to build a more biologically realistic orientation model (for animals without magnetic orientation capacity) which used external cues to correct for errors accumulated in the path integration system (Giovannangeli and Gaussier 2007; Strösslín et al. 2005). The correction mechanism mostly used a one shot learning system where external cues were immediately associated with the internal encoded head direction when first seen and this record is then used to correct subsequent errors of the path integrator. Again the fault tolerant capacity of these systems when facing conflicting external cues have not been extensively tested.

3.7 Review of work carried out

This work addresses two themes.

1. Chapters 4 and 5 aim at testing whether a relative stability between cues, as predicted by the cognitive map theory, encourages rats to use them as orienting references. The advantage of using single unit recording techniques to test this hypothesis is that a reward-based paradigm, which complicates interpretation of cue control strength with reward-based associative learning, is not required to conduct the experiment. In chapter 4, we first use a computational model of head direction cell network to explore whether a simple Hebbian learning rule is sufficient to construct a head direction cell system that chooses the subset of cues with greater relative stability between each other as an orientation reference. In chapter 5, the hypothesis is then tested experimentally by recording place and head direction cells from rats foraging for food on an open field maze while the relative stability of distal visual cues are manipulated. By recording place and head direction cells over a period of time, we can determine both the short term and long term responses of place and head direction cells to distal cue conflict and how relative stability between cues affect the outcome of conflict resolution.
2. The second theme (chapter 6) aims at monitoring the development of goal-sensitive cells while the rat is learning a win-stay task on the double Y-maze. By recording the activity of place cells from before a rat learns the win-stay task until it is well-trained on the task allows us to determine the time course of the development of goal sensitive cells in the hippocampus and its relationship with the rat's task performance. The experiment will permit a better understanding of the role of these goal sensitive cells on the win-stay task and whether over-training has any effect on the firing characteristics of hippocampal cells.

Part II

Experiments

Chapter 4

Interactions between distal cues for landmark control - A model study

4.1 Introduction

Efficient navigation is essential for animal survival and many of the animal intelligences are expressed through their navigational strategies. As mechanisms to move around complex environments is highly desired in fields such as autonomous robotics (Pfeifer et al. 2007), many studies have been aiming at understanding the sophisticated navigational behaviours of animals.

In vivo recording experiments have identified several neuron groups that are strongly modulated by spatial attribute of an environment without a direct dependence on sensory inputs. In particular, the discoveries of place cells (O'Keefe 1979; O'Keefe and Dostrovsky 1971), head directions cells (Ranck 1984; Taube et al. 1990a; Taube 2007) and grid cells (Hafting et al. 2005; Moser et al. 2008) from various structures of rat's brain have led to the proposal that these cells have significant roles in navigation by serving as the cognitive representation of an environment. In particular, despite being able to maintain their spatial specificity without external inputs (Fyhn et al. 2007; Goodridge et al. 1998; Quirk et al. 1990; Taube et al. 1996), these cells also integrate sensory information into their spatial representations of environments when available (Hafting et al. 2005; Muller and Kubie 1987; Sargolini et al. 2006; Taube et al. 1990b). The most common experiment used to demonstrate sensory integration is by rotating a prominent visual cue in the environment of recording and demonstrating that spatially modulated receptive fields of the recorded cells rotated with the visual cue. Further investigations suggest that this integration originates from postsubiculum (PoS) (Calton et al. 2003; Golob and Taube 1999; Goodridge and Taube 1997), which is a structure with a prominent population of classical head direction cells (Ranck 1984; Taube et al. 1990a). As the most obvious spatial information conveyed by the rotating distal visual cue is orientation, the head direc-

tion cell network is well placed to integrate such information into the system. Several reports have also shown that place field orientation of hippocampal place cells is in register with the encoded head direction of HD cells (Knierim et al. 1995; Yoganarasimha and Knierim 2005), suggesting a common source of orientation information, likely provided by the HD system.

Orientation information provided by head direction systems is important for navigation. Without tracking present orientation accurately, any cognitive representation would quickly become mis-aligned with the actual environment, which would render the internal map useless. It has been shown that head direction cells recorded from the postsubiculum (PoS) are adequate to encode all directions in an environment (Johnson et al. 2005), and thus are well positioned to perform such computation. Despite being able to track orientation without sensory information, directional specificity of head direction cells becomes less reliable in the dark (Goodridge et al. 1998), likely due the reduced sensory information of the surrounding environment. This demonstrates one benefit of integrating visual information into the head direction system. However, HD cells are also modulated by other sources of information when constructing the encoded head directions. Examples of the information used by head direction cells include vestibular (Stackman et al. 2002; Stackman and Taube 1997) and odour information (Goodridge et al. 1998). Integrating multiple information sources implies that conflicts invariably arise, be it within or between information modalities. As head direction cells in a network always rotate in register with each other (Taube and Burton 1995; Yoganarasimha et al. 2006) and do not appear to construct split representations when encountering conflicts as observed in place cells (Knierim 2002; Save et al. 2000; Shapiro et al. 1997; Tanila et al. 1997), HD systems need to resolve conflicts and reach the most probable present head directions. This rigidity makes the HD system an ideal place to study the mechanisms of conflict resolution of spatial information. Conflict experiments between different types of external and internal cues demonstrated that HD cells in general prefer distant visual cues as reference points for their preferred firing directions (Dudchenko and Zinyuk 2005; Knierim et al. 1998; Taube and Burton 1995; Zugaro et al. 2004, 2001, 2000). On the other hand, the literature base that explores how relative coherence between different cues affects the choice of HD system in conflict resolution is comparatively small. As proposed in the cognitive map theory (O'Keefe and Nadel 1978), cognitive representation of space should follow the most coherent spatial frame in the environment. This implies that, when integrating multiple sources of directional information, head direction cells should choose the most coherent set of information as the reference frame to anchor their preferred firing directions. So far there has been no recording experiments designed to explore such hypothesis, though roles of information coherence to saliency have been explored in other fields (Biegler and Morris 1993; Stanford and Stein 2007).

One possible approach to explore how multiple cues in an environment affect encoded head direction of a HD system is via computer simulations. Many computational models of head di-

rection cells have been proposed (Boucheny et al. 2005; Degris et al. 2004; Goodridge and Touretzky 2000; Redish et al. 1996; Redish and Touretzky 1996; Rubin et al. 2001; Skaggs et al. 1995; Song and Wang 2005; Stringer and Rolls 2006; Stringer et al. 2002; Zhang 1996) (see Sharp et al. 2001a for a review), most of which were based on a continuous ring attractor network structure using a local attractor state to encode present head directions (Amari 1977). Four of these models included elements that simulate how prominent visual cues in an environment control the preferred firing directions of HD cells. In Skaggs et al. (1995), the visual cue is modelled by adding a unit that is only active at a specific direction in the simulation environment. The unit projects weak excitatory connections to all units in the HD network and projections are governed by a Hebbian learning rule. With experience, the connections between the visual cue unit and the subset of HD units with preferred firing directions similar to the orientation of the visual cue are strengthened due to co-activation of pre- and post-synaptic cells. This additional excitatory currents from the cue unit allows it to reset the position of the attractor state in the HD network, which simulates the effect of cue control from visual cues. Zhang (1996) also used a similar implementation for modelling of visual cues. Degris et al. (2004), on the other hand, used a Gaussian profile visual input to represent visual cues, which was thought to be a more appropriate representation as visual cues generally can be viewed by rats from a range of head directions. Due to the goal of the investigation, the projections from the cue units were static instead of being plastic in the simulation. Finally, Boucheny et al. (2005) briefly explored how fast a HD system can be reoriented by visual cues. Visual cue in the model was simply simulated by applying a large excitatory input to a subset of head direction cell units. None of the reports discussed above investigated interactions between visual cues in their models.

In the field of biologically inspired robotic model of navigation, the importance of maintaining correct present orientation is well appreciated (Strösslin et al. 2005), and many simply recruit the aid of magnetic compass to track orientation accurately (Gaussier et al. 2000). For those research groups attempting to build a more biologically realistic model of robotic navigation, the significance of error correction effects of integrating allocentric cues quickly become apparent as noise induced drifts in homing vector inevitably accumulate over time in the system (Arleo and Gerstner 2001; Giovannangeli and Gaussier 2007). Strösslin et al. (2005) described a head direction system with path integration capacity that used a one-shot Hebbian learning rule to integrate allothetic visual cues into the HD system. The authors reported that the system was able to keep accumulated orientation errors under control but did not explicitly test how such a system resolves conflicts between in visual information. Giovannangeli and Gaussier (2007) reported a visual compass that determined present head directions based on integrating visual information in an environment with a idiothetic path integrator. Each newly sighted visual cue is rapidly associated with the encoded head direction at the time. This stored in-

formation can then be used to compute a present head direction based on the orientations of different visual cues with respect to the system. The authors showed that such visual compass complements the navigation system in determining the present orientation of the navigation system but again did not explicitly test how such a system resolves a conflict between visual cues in an environment. These robotic systems demonstrate the benefits of using one or multiple visual landmarks in navigation but did not explore how such robots cope with changing visual information in a learned environment.

The aim of this experiment is to explore whether relative stability between visual cues in an environment can strengthen their ability to exert landmark control over the HD system. We use a continuous ring attractor model of head direction cells based on the model in Zhang (1996). We add multiple visual cue units with excitatory Hebbian projections to the HD system. We test how the HD system resolves the introduced orientation conflicts between the visual cue units using both artificial and realistic head direction profiles. We find that, under such a setting, the visual cue units with the most coherent relative orientation dominate the control of the HD system after introduction of conflicts. The result demonstrates that the simple mechanism used to simulate landmark control in the model is adequate to support the HD system to select the most coherent spatial reference frame to reference its encoded head directions.

4.2 Methods

4.2.1 The head direction cell network model

The head direction cell network used in the simulation is a rate based ring attractor network similar to the model used in Zhang (1996), which is designed to integrate angular head velocity (AHV) input to update the encoded head direction. The network consists of head direction cell units with recurrent projections between them. Briefly, the mechanism of the model can be visualised easily by arranging the units into a ring, though the physical arrangement of the units is not important. This ring network can then be used to encode present head directions by configuring the weights of recurrent projections to support a local Gaussian shaped activity bubble, or attractor state (Amari 1977). The angular position of the activity bubble in the ring can be thought of as the encoded head direction of the network. To keep this encoded head direction aligned to the actual head direction, the network needs to move the angular position of the activity bubble according to the AHV inputs. The preferred firing direction of each head direction cell unit is than the angular position of the unit in the ring structure.

Model implementation and simulation is written in Matlab (MathWorks, Massachusetts, USA). To implement a network with the above mentioned properties, we follow Zhang (1996) to model the activity level of unit i in the HD network $u_i(t)$ by

$$\tau \frac{du_i(t)}{dt} = -u_i(t) + \sum_j w_{ij}(t) F(u_j(t)) \quad (4.1)$$

where τ is the time constant of the unit and $F(u)$ is a non-linear sigmoid activation function

$$F(u) = a \ln^\beta \left(1 + e^{b(u+c)} \right) \quad (4.2)$$

with a , b and c being scaling parameters of the sigmoid curve and β determines the steepness of the sigmoid transition. To maintain a local attractor state, recurrent projections from each unit implements a standard local excitatory and global inhibitory connectivity w^e . The exact implementation follows what was described in Zhang (1996). Briefly, a desired shape of Gaussian activity bubble f_n is first defined. The weight matrix in the Fourier domain that would support such activity bubble is then calculated by

$$\hat{w}_n^e = \frac{\hat{u}_n \hat{f}_n}{\lambda + |\hat{f}_n|^2} \quad (4.3)$$

where λ controls the quantity of weight regularisation approximation and should be set optimally to find the best approximation to the desired activity bubble and \hat{f}_n is f_n in the Fourier domain. The actual weight matrix is readily calculated by applying inverse Fourier transform to \hat{w}^e . To integrate angular head velocity input $\omega(t)$, we add an asymmetric weight component to the weight matrix to induce a shift in the position of the Gaussian shaped activity bubble. We calculate the asymmetric weight component $w^a = 1^{\text{st}}$ derivative of w^e . The final weight matrix is calculated by

$$w(t) = w^e + \gamma(t)w^a \quad (4.4)$$

where

$$\gamma(t) = -\omega(t)\tau \quad (4.5)$$

Integration of AHV input is thus achieved by modifying the weight matrix of the recurrent projections. Despite the mechanism being biologically unrealistic, this allows us to concentrate on the main objective of the experiment, which is to explore how interactions between visual information in an environment affects the encoded head directions of the HD network.

Encoded head direction of a HD network is calculated by taking the circular mean of the firing rate of each unit in the network,

$$\varphi = \arctan \left(\sum_i \frac{\sin(r_i)}{\cos(r_i)} \right) \quad (4.6)$$

where $r_i = F(u)$ is the firing rate of the i^{th} head direction cell unit in the network (see equation 4.1 for $F(u)$).

4.2.2 The visual cue units

Addition to the Zhang's model are units representing the views of visual cues in the environment, which are termed visual cue units. Figure 4.1(a) shows an illustrative diagram of the network. Each of the visual cue units is assigned an orientation, which reflects the orientation of the corresponding distal visual cue in the environment and the cue unit has a Gaussian activation profile centering at its orientation. The orientation of the visual cues can also be interpreted as the orientation of the HD system when the cue is viewed. A Gaussian profile firing rate reflects that a given visual cue in the environment can be seen from a range of angles. Firing rates of the visual cue units are calculated by,

$$F_{rate} = A + B \exp(K \cos(d)) \quad (4.7)$$

where A = the background firing rate, $B = (f_{max} - A) / \exp(K)$, and f_{max} = the maximum firing rate. K determines the width of the Gaussian profile, and d = the preferred orientation. An example of such receptive field can be found at figure 4.1(b). Rotation of a visual cue unit is performed by changing its orientation in the environment (see figure 4.1(c) for an example). Each cue unit projects to all head direction cell units in the network, and the strength of the projections are determined by a Hebbian learning rule,

$$\Delta W = \alpha F_{pre} (W_{max} - W) (F_{post} - \langle F_{post} \rangle) \quad (4.8)$$

where F_{pre} and F_{post} are pre- and post- synaptic firing rates, which in turn corresponds to the firing rates of visual cue units (pre-synaptic) and units in the HD system (post-synaptic) in the model. $\langle F_{post} \rangle$ represents the mean post-synaptic firing rate downstream of the visual cue unit, which are all the units in the head direction system. W_{max} = determines the value of maximum synaptic weight and α is the learning rate, which controls how fast the synaptic weights evolves. ΔW is the change of weight value of the projection, which is determined by this formula. The Hebbian learning rule ensures that the weights are only modified when the visual cue unit is active. This implies that the association between the visual cue unit and the HD system does not get modified in the absence of the cue unit. To promote competition between the projections originated from one visual cue unit, a constraint on the $\sum W$ is also imposed that restricts its maximum value to $20W_{max}$. If $\sum W$ exceeds $20W_{max}$ after updating the weight values with ΔW , all weights will be re-normalised by divisive enforcement to comply with this constraint (Miller and MacKay 1994). The heightened competition speeds up the evolution of the weight of projections as potentiation of some of the projections rapidly translates to depression of other projections from the same cue unit. If the orientation of a visual cue unit is stable, it would be consistently activated together with the same group of units in the HD system. The Hebbian learning rule causes the projections from the visual cue unit to

the HD units to be strengthened. When the weights of the projections become strong enough for the visual cue units to reset the encoded head direction of the HD system, the HD units of the whole HD system become referenced to the visual cue unit. The rotation of the visual cue unit would then cause the tuning curves of the head direction cell units to rotate in register. Figure 4.1(d) provides an example of how a projection profile from a visual cue unit evolves over time.

4.3 Results

4.3.1 Encoded head directions of the model without visual cue units

After implementing the model as described in section 4.2, we first explore how well the model tracks head directions based on angular head velocity inputs. In order to determine how well the head direction cell model tracks realistic head directions, we recorded head directions while the rats were searching for food pellets on an open field circular maze. The head direction time-series is then converted into comparable angular head velocities. The encoded head directions of the head direction cell network model based on the angular head velocities were then compared with the actual head directions to determine how well the model kept track of the head direction. We found that, in a five minutes period, the deviation between the encoded head directions and the actual head directions is $1.7^{\circ} \pm 0.3^{\circ}$ (mean \pm 95% C.I., $n=10$). An example of the difference between the encoded head directions and the actual head directions is presented in figure 4.2.

4.3.2 Properties of visual cue units

After verifying the model's ability to track head directions accurately, we then explored the properties of newly added visual cue units and their effectiveness in exerting control over the HD system. To simplify interpretation of subsequent analyses, we used constant angular head velocity (AHV) input for simulation. The AHV is chosen to be 85.1° per second, which is the average AHV from several recording sessions of rats searching for food pellets on an open field circular platform.

Stability of the projections from visual cue units

Stability of the projection weights from visual cue units affects the ability of the units to exert control over the head direction system. When holding everything else constant, a more stable projection should exert stronger control over the head direction system, but would also be more difficult both to establishing control of the HD system in the first place and to resolve conflicts between visual cue units as it take longer for the projections to adopt a new weight profile.

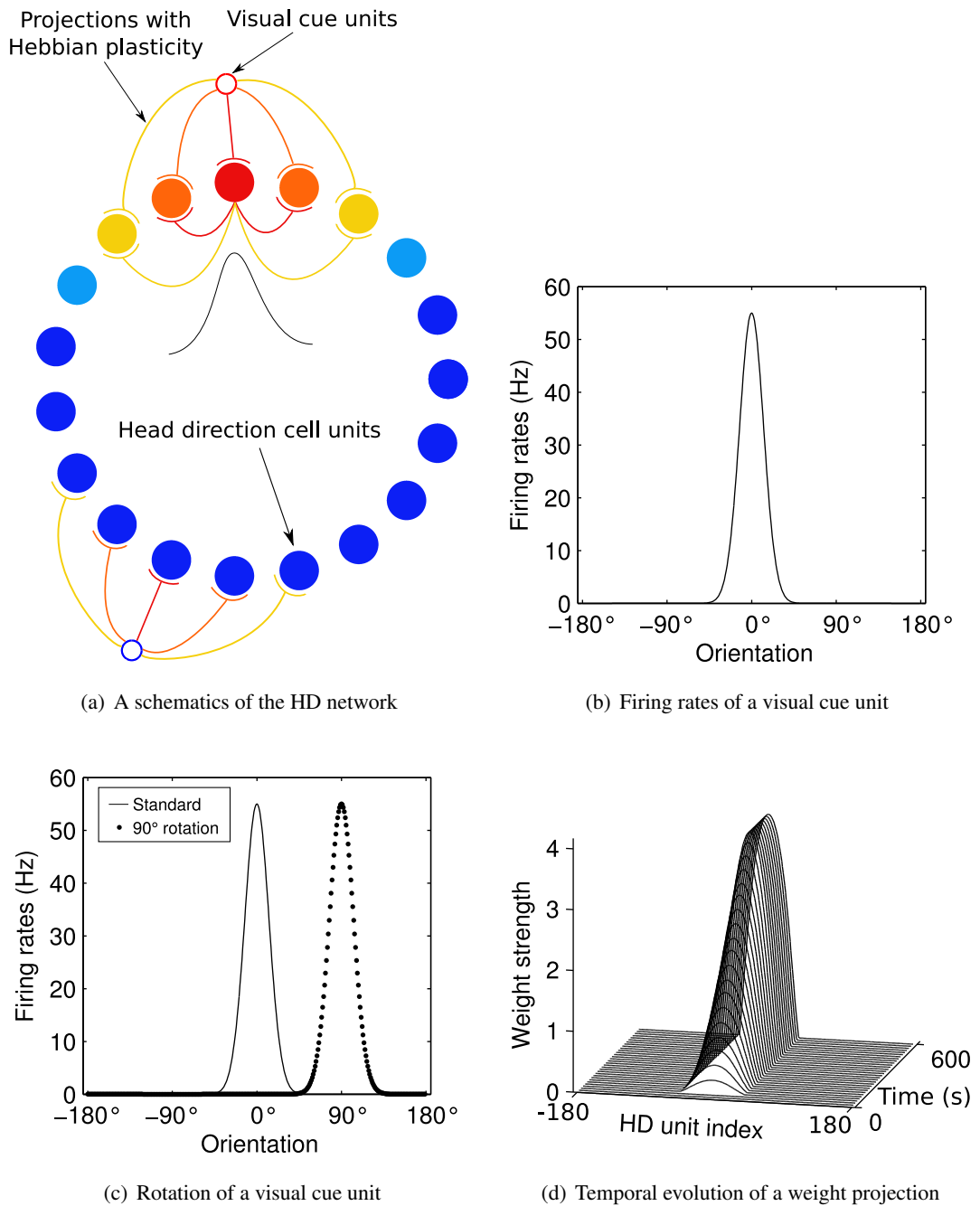


Figure 4.1: (a) is an illustration of the head direction network with two visual cue units. Hot colours indicate either high firing rates or strong projections and cold colour represents low firing rates or weak projections. (b) shows an example of the firing rates of one visual cue unit with respect to the orientation of the system in an environment. (c) shows how to represent the rotation of the visual cue in the simulation. In the example the visual cue is rotated by 90° which is represented by shifting the orientation of the visual cue unit also by 90° . (d) is an example of how the Hebbian projections from a visual cue unit develop over time. Initially the weights of all the projections are zero, representing that the novel visual cue exert no control over the HD network. Over time, the Hebbian learning rule strengthens the projection between the visual cue unit and the subset of head direction units that are most frequently co-activated. Given that the updating mechanism based on angular head velocity works correctly, this subset of head direction units should be the one that with preferred firing directions similar to the orientation of the visual cue.

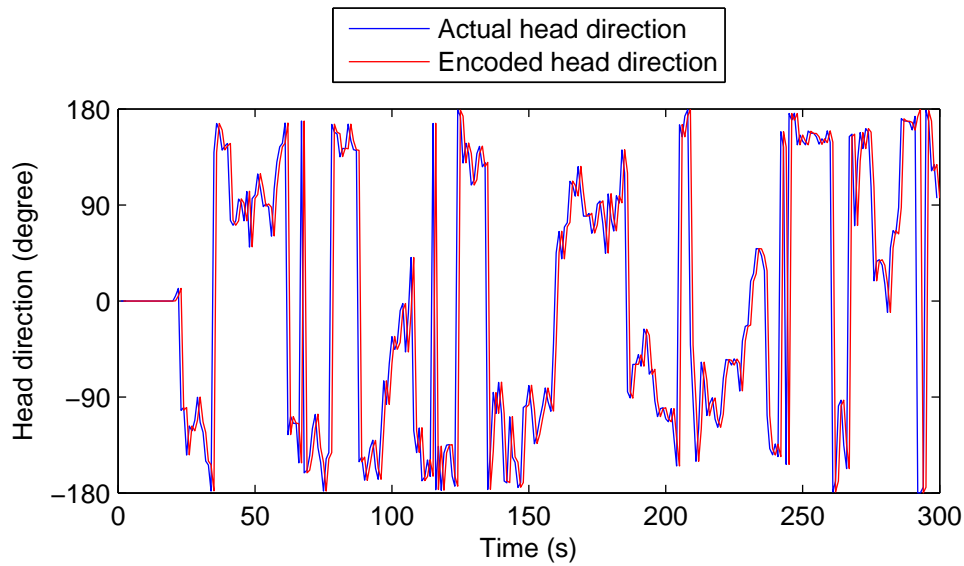
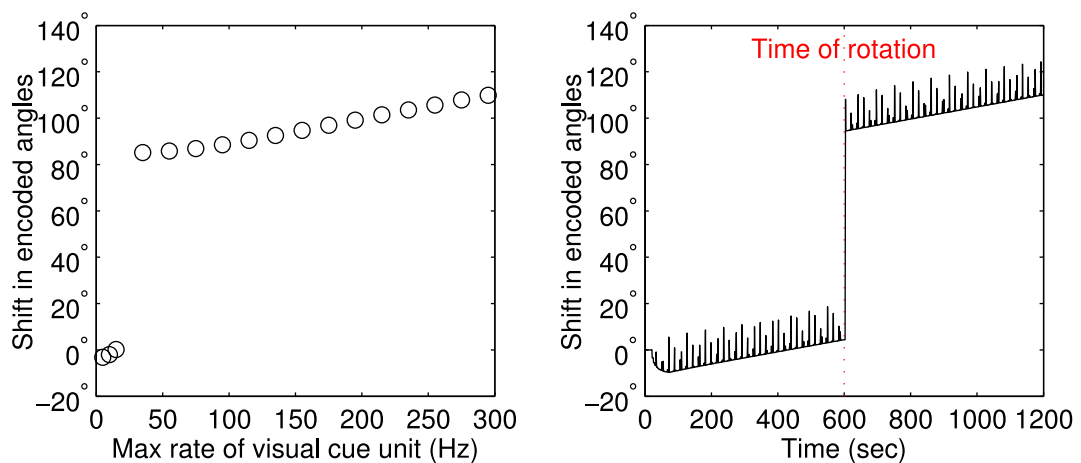


Figure 4.2: An example of the deviation of the encoded head directions from actual head directions. The time of the encoded head direction time-series is intentionally shifted right by one second to allow easier comparison between the two head direction time-series.

On the other hand, a learning rule with fast weight evolution, in extreme cases, could void the influence of visual cue units to the HD system as the projections evolve too fast to reset the encoded head direction. The parameters in the Hebbian learning rule that affect the learning rate could have strong influence on how visual cue units exert control over the HD system. We thus start the investigation of the model by first exploring the effect of Hebbian projection stability on the ability of the visual cue units to control the HD system. From the Hebbian learning rule used in the model, we identified two of the components that might influence the stability of projections from visual cue units. The first parameter in the Hebbian learning rule that affects the learning rate is the firing rates of visual cue units. The higher the firing rate, the stronger a visual cue unit could exert influence over the HD system. On the other hand, stronger pre-synaptic firing rates also imply faster weight evolution when a mismatch between pre- and post-synaptic firing occurs. We thus explored how the firing rates of visual cue units affect their ability to exert control over the HD system. A simulation was set up to include one visual cue unit with constant AHV input. After the projections from the unit reaches an asymptotic state, the orientation of the cue unit is rotated by 90° . If the unit exerts control over the head direction (HD) system, the encoded head direction would also shift by 90° . We hold the learning rate α constant and systematically vary the maximum firing rates of the cue unit while recording whether the encoded head direction of the HD system shifts with the visual cue unit. The result of the simulation is presented in figure 4.3(a). The figure suggests that increasing the firing rate of a visual cue unit does not abolish its ability to control the HD system. There is a upward

drifts in shifted angle with increasing firing rate which does not relate to the ability of the visual cue unit to control the encoded head direction after rotation, but rather is due to the strong input from the visual cue unit causing a continuous drift in encoded head direction of the HD system. This is likely caused by the constant AHV inputs and the fact that the activity of the visual cue unit is governed by a Gaussian activation profile. As the system rotates through the activation profile of the visual cue unit, a strong input from the visual cue unit would create a temporal deviation. At the same time, the faster weight evolution due to higher pre-synaptic firing rate encourages the weight profile to adjust to this temporal deviation and hence create a constant drift of the encoded head direction. The second parameter that directly affects the stability is the learning rate α in the learning rule. A simulation is set up to explore the effect of α on a visual cue unit's ability to control the encoded head direction of the HD system. Three different maximum firing rates for the visual cue unit (35, 45 and 55 Hz) is also used to determine how the pre-synaptic firing rate and the α parameters together contribute to the strength of cue control from the visual cue unit. The result of the simulation is presented in figure 4.4 and shows that when α is too high, visual cue units lose their ability to control the encoded head directions. Higher firing rate offsets this effect and allows the cue units to use higher learning rates without losing the cue control ability though it also encourages a continuous drift in the encoded head direction.



(a) Effects of firing rates on cue control of the HD system

(b) An example of drift in encoded head direction

Figure 4.3: Firing rates and control of encoded head direction. The figure presents results from the simulation that explores how increasing the firing rates of a visual cue unit affects its ability to control the encoded head direction of the HD system. (a) presents the shifted angles of the HD system after a 90° rotation of the visual cue unit. The shifted angles were calculated by averaging the encoded head directions in the last minute of the simulation. (b) shows the encoded head directions of the HD system over time when the maximum firing rate of the visual cue unit is set to 295 Hz. Rotation of the visual cue unit occurs at 300 seconds. There is a continuous drift of encoded head direction along with small burst of deviations. The bursts occur when the visual cue unit is active and the continuous drift is particularly prominent when the visual cue unit has high firing rates.

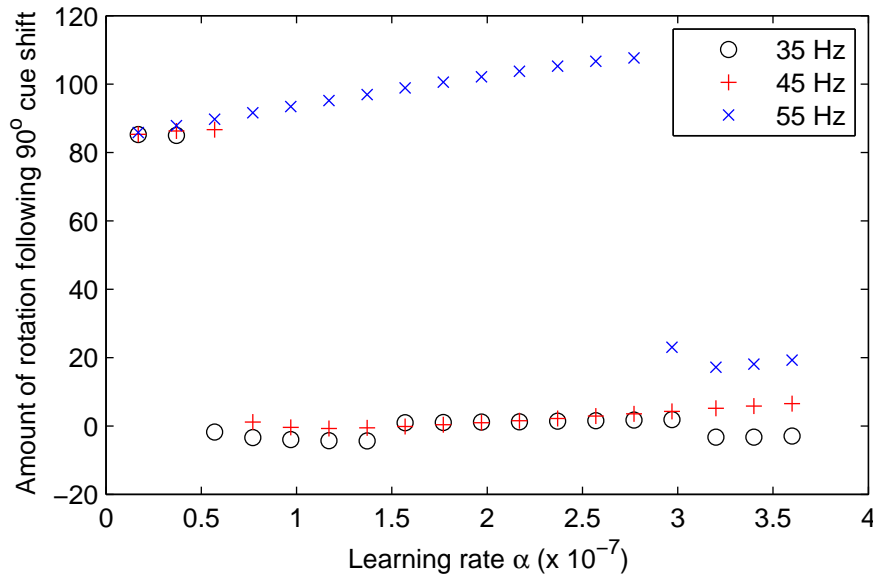
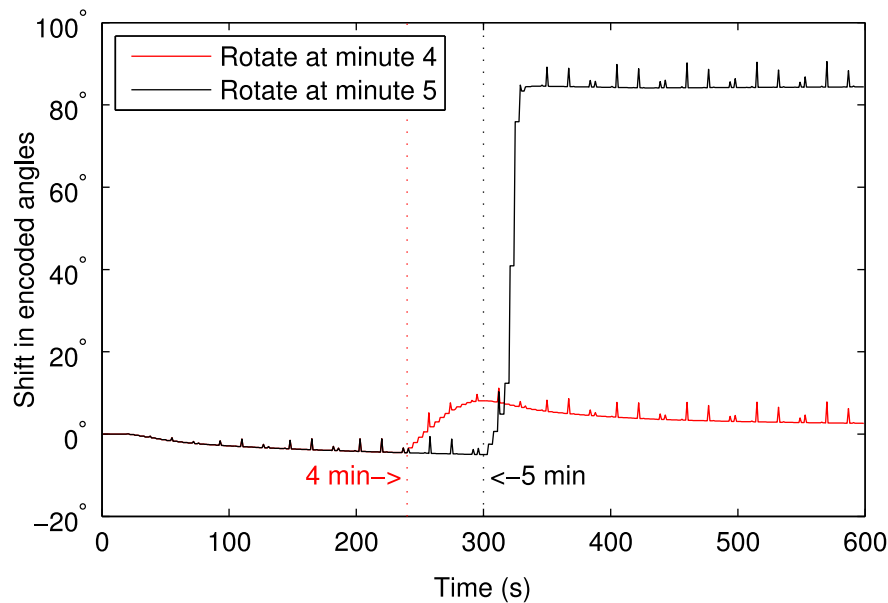


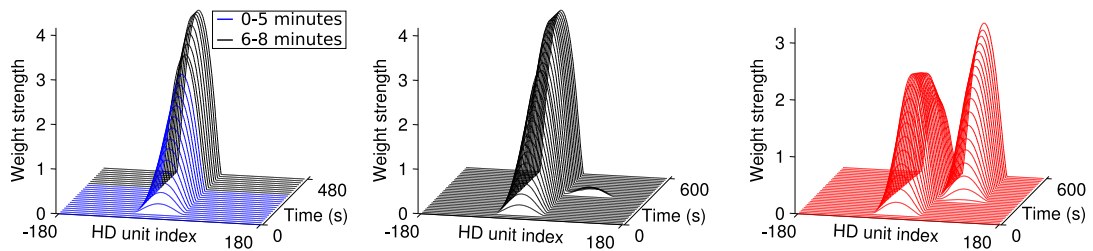
Figure 4.4: Learning rate and cue control. The figure shows the result of the simulation that explores the effect of learning rate α on a visual cue unit's ability to control the encoded head direction of the HD system. When α is too high, the visual cue unit loses its ability to control the head direction system. The loss is partially offset by giving the cue unit a higher firing rate as stronger input from the visual cue unit could reset the encoded head direction of the HD system before the projections adopt a new weight profile.

The result shows that a lower learning rate allows the visual cue unit to exert greater control over the encoded head directions. On the other hand, a cue unit with low learning rate also takes longer time to establish control in the first place. This can be overcome by giving the visual cue unit a higher firing rate, which offsets the loss of control from higher learning rates and allows the projections of the visual cue unit to have reasonable flexibility but still retain control over the HD system. The above exploration demonstrates that the dynamics of cue control from visual cue units can be influenced by multiple factors and thus need to be carefully calibrated. As the stability of the projections from visual cue units can affect how they control the HD system and how conflicts between cue units are resolved, we calibrate the parameters of the Hebbian projections against experimental observations. In Goodridge et al. (1998), the authors reported that, in a 76 cm cylindrical environment with a prominent white cue card on the wall, five minutes of exposure to the novel environment allows the cue card to establish landmark control over the place cells in only half of the tested rats and an eight minute experience is enough for reliable cue control to be established in all of the rats. We choose the parameters of the model so that the projection weight profile from a visual cue unit is fully developed after eight minutes of simulation time and the cue unit becomes capable of controlling the HD network by the fifth minute of simulation time. With the above requirement, we choose $\alpha = 1.7 \times 10^{-7}$, and $f_{max} = 55$ Hz. Figure 4.5 shows the output of a simulation containing a visual

cue unit using the calibrated parameters. The orientation of the visual cue unit is rotated by 90° either at the fourth or the fifth minute of the simulation. The figure shows that the visual cue unit only starts controlling the encoded head direction after five minutes of simulation and that the weights of the projections stabilise by the eighth minutes.



(a) Rotation of the visual cue unit at minute four and five



(b) Development of weight profile

(c) Weights: minute 5 rotation

(d) Weights: minute 4 rotation

Figure 4.5: The figure shows a model with one visual cue unit using the calibrated parameters for its Hebbian projections. (a) shows how the encoded head direction deviates from the actual one when the visual cue unit is rotated either at the fourth or the fifth minute of the simulation. The deviation shows that the visual cue unit only successfully controls the encoded head direction on the fifth minute, which is evident by a 90° shift of deviation. (b) illustrates the temporal profile of projection weights from the visual cue unit. The weights are still increasing after five minutes of simulation but stabilise after eight minutes. (c) shows the weight profiles from the visual cue unit that is rotated at the fifth minute of simulation. The cue unit successfully shifts the encoded head directions of the HD system, and the weight profile of the projections also remains at the same place despite a slight disturbance right after the rotation. (d) is the weight profile from the cue unit that is rotated at the fourth minute of the simulation and the failure to control the encoded head direction is evident from the temporal weight profile where a new peak is developed after the rotation. This indicates that the HD system assigns a new orientation to this visual cue unit, reflecting the angular shift of the cue rotation.

Tracking errors caused by the visual cue units

From the graphs of deviations between encoded and actual head directions presented in figure 4.3 and figure 4.5, it is obvious that there are periodic bursts of deviations. This burst of deviation is only seen after the introduction of visual cue units and is likely to be the result of the excitatory inputs from the cue units. In this section, I explore how additional inputs from the visual cue unit affects the head direction system's ability to keep track of the present head direction. Simulations with and without the visual cue units were executed and two measures, the drift, and the variance of the deviation were calculated. In the simulations with visual cue units, the measures were calculated after the weights of the cue units were fully developed. The drift was calculated first by averaging the discrepancy between the actual head directions and the encoded head directions (sampled every 100ms) for two minutes. The differences between the average discrepancy of the two one-minute-intervals were the drift of the simulation. The drift represents the accumulation of tracking errors over an one minute period. The variance of deviations is the variance of the discrepancy between the encoded and the actual head directions in a one minute interval and is used as a measure of tracking consistency.

For the simulation without the visual cue unit, the drift was 0.20° per minute, and the variance of deviations = 0.003° . This suggests that the HD system does not keep track of the actual head direction perfectly and a very small drift can be observed over time. For the simulations with one visual cue unit, the drift and the variance of the deviation varied slightly depending on the orientation of the visual cue unit. Ten simulations were performed with which the orientations of the visual cue unit were randomly assigned. Mean drift from the simulations was $0.08 \pm 0.002^\circ$, and the average variance of deviations was $1.06 \pm 0.05^\circ$. The results suggest that the addition of the visual cue unit reduced the tracking error of the system (one tailed t-test, $t=-30.8$; d.f.=9; $p<0.001$). However, it also increased the fluctuation on the encoded head direction of the HD system, which is evident from the significantly larger variance of deviations measure (one tailed t-test, $t=140$; d.f.=9; $p<0.001$). Figure 4.6 shows the tracking error of the head direction system with and without a visual cue unit over a 30 seconds interval, and the source of the large variance of deviations could be clearly spotted as the peaks of large tracking errors occur when the visual cue unit became activated. The reason that the activation of the visual cue unit caused large spikes in tracking errors is because the cue unit fired with a Gaussian profile with respect to the actual head directions (to be tracked by the HD system) of the simulation implied by the accumulated angular head velocity inputs. If the firing rate of the visual cue unit is high enough, inputs from the cue unit can still be strong enough to affect the encoded head direction even when it is not maximally activated (i.e. when the system is not directly at the orientation of the cue unit). However, due to the Gaussian shaped projection weight profile, the strongest inputs to the head direction cell units in the HD system were the units that represented the orientation of the visual cue unit. This caused a shift in encoded head

direction away from the actual head direction when the system rotated through the orientation of the visual cue unit.

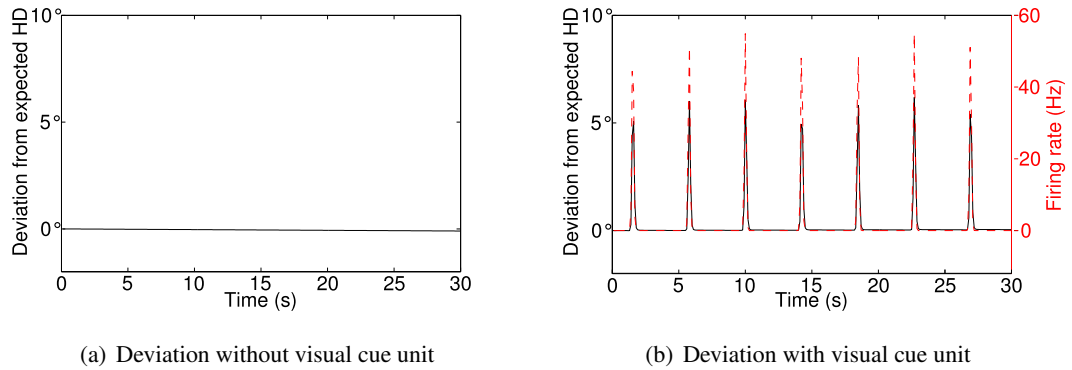


Figure 4.6: Tracking errors of the system over a 30 seconds interval. (a) is the tracking errors of a head direction system over a 30 seconds interval without a visual cue unit. With constant AHV inputs, small tracking errors accumulate over time. (b) contains the same tracking error measures from a HD system with the addition of a visual cue unit. Firing rates of the visual cue unit is also presented as dotted red line. From the graph, it is obvious that the periodic spikes of tracking errors happens concurrently with the activities of the visual cue unit. The source of these spikes is the inputs from the visual cue unit, which causes a temporal shift in encoded head directions.

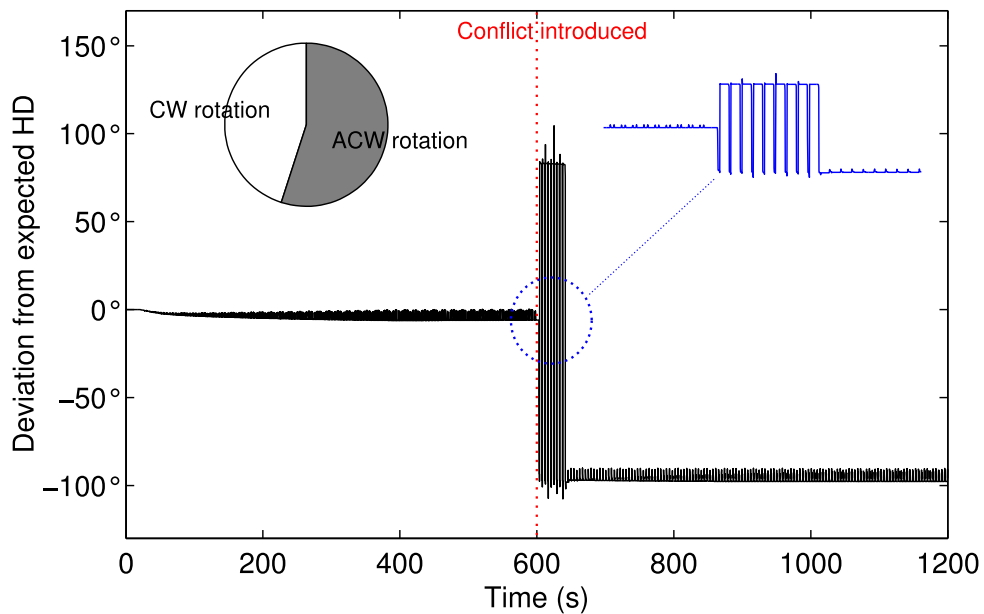
4.3.3 Landmark control and conflict resolution of visual cue units

Rotation of visual cue units

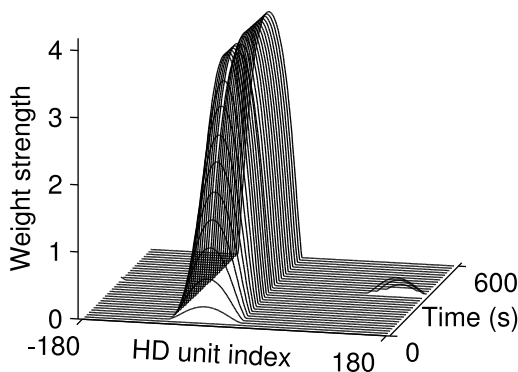
The goal of the model is to explore the interactions between visual cue units after a conflict between the cue units is introduced, which can be done by changing the orientation of the visual cue units in conflict with each other. Using the calibrated parameters as described in the previous section, we initially check whether one visual cue unit could reliably control the encoded head directions of the HD system. Twenty simulations were run with initial orientation of the visual cue unit assigned randomly. Each simulation lasted for twenty minutes of simulation time. At ten minutes, the orientation of the visual cue unit was rotated by either 90° clockwise or anti-clockwise. The system's response to the rotation was quantified by calculating the shift of encoded head direction after the rotation. As the encoded head direction was updated continuously according to the angular head velocity (AHV) inputs, the shift was calculated based on the tracking errors of the HD system. If the rotation of the visual cue unit induces an equal shift of the encoded head directions, the tracking errors would also change by the angle of rotation. A visual cue unit is considered to control the encoded head directions of the HD system if its rotation induces a shift that falls within a 45° range of the cue unit's rotated angle. In all twenty simulations the visual cue unit successfully controlled the encoded head direction of the HD system after rotation (see figure 4.5 for an example of the response of the head direction cell network after a cue rotation).

Conflicts between two cues

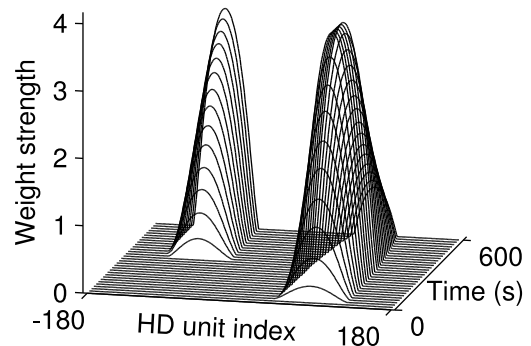
Next we explored the situations where there are two visual cue units and the rotation creates an orientation conflict between the cue units. We introduced a conflict by rotating one of the cue units by 90° clockwise and another by 90° anti-clockwise. The HD system can react to the conflict by one of the three possible ways, either follows one of the cue units, settles on a new orientation implied by neither of the cue units, or fails to resolve the conflict. In the case that the HD system fails to resolve conflicts, the encoded head directions would fluctuate between following one of the two cue units. Twenty simulations were performed and the beginning orientations of the two visual cue units were assigned randomly for each simulation. Again whether one cue unit controls the encoded head direction of the HD system is determined by measuring the shifted angle of the encoded head direction after cue rotation. A visual cue unit is said to control the HD system if the shifted angle falls within the 45° range centering at the expected shift based on the rotation of the cue unit. An additional check is also run to determine whether the introduced conflict has been resolved, which consists of sampling the one minute period at the end of the simulation for tracking errors of the HD system. A conflict is considered to be resolved if the biggest difference between the sampling errors in this period does not exceed 45°. The introduced conflicts were considered to be resolved in all of the simulations and each of the two visual cue units has roughly 50% chance of gaining control over the HD system after conflict resolution. Figure 4.7(a) shows that, after the introduction of a conflict, there was a period of about one minute where the encoded head directions fluctuated between following either of the cues before eventually settling down to following one of the visual cue unit. The pie chart inset in figure 4.7(a) summaries the HD system's response after conflict resolution from twenty simulations. In roughly half of the simulations the system followed the visual cue unit that was rotated by 90° clockwise and in the other half it was dominated by the cue unit that was rotated by 90° anti-clockwise. Chi-square test suggests that the observed result is as expected not significantly different from a 50:50 chance distribution ($\chi^2=0.2$; $p>0.5$). In all of the simulations the HD system successfully resolved the conflict by ten minutes after it was introduced. Figure 4.7(b) and 4.7(c) show the evolution of the projections of two visual cue units after a conflict was introduced. During the conflict, the strength of peak weight projections from both cue units were reduced. This was due to the discrepancies between the visual cue units and the encoded head directions of the HD system caused by the conflict. However, the winning cue unit eventually dominated the control and re-stabilised the weight profile. The cue unit that lost the conflict re-established a new weight profile so that it became consistent with the winning cue unit again.



(a) Tracking errors of the simulation



(b) Weight profile of the controlling cue unit



(c) Weight profile of the non-controlling cue unit

Figure 4.7: (a) shows an example of tracking errors of the HD system throughout the simulation. The time that the conflict was introduced is marked by a red dash line. The pie chart inset indicates the proportion of twenty simulations in which the introduced conflict is resolved by the HD system following the visual cue unit that was rotated by 90° clockwise or anti-clockwise. In all twenty cases the conflict was resolved by the HD system choosing to follow one of the two visual cue units. (b) and (c) show examples of temporal weight profile from a visual cue unit that gained control over the HD system after the conflict and another one lost the control after the conflict.

Conflicts between two coherent and one independent cues

After exploring conflict resolution between two visual cue units, we look at whether a coherent relationship between the cue units would encourage the HD network to follow the larger set of coherent cues. We setup a twenty minute simulation with three visual cue units. The initial orientations of the cue units were randomly assigned. At ten minutes of simulation time, a conflict was introduced by rotating two of the cue units by the same amount and in conflict with the third unit. 40 simulations in total were conducted with the two cues rotated by 90° clockwise and the third rotated by 90° anti-clockwise for twenty of the simulations and for the remaining the rotating directions of the cues were inverted. Responses of the HD system to the introduced conflict were assessed similar to what was described in previous sections. We found that the HD system always resolved the conflict and in all forty cases the two coherently rotated visual cue units always dominate over the third cue unit in controlling the encoded head direction of the HD system ($\chi^2=280$; $p<0.001$).

Conflicts between two coherent and two independent cues

In this section, we explore whether the dominance of the coherent set of cues observed in the previous section is the consequence of the coherent set of cues facing fewer cue conflict events than the independent cue instead of due to the relative stability between the coherent cues. Four visual cue units were used in the simulations with two being the coherent cues and two independent cues. The rotation angle of the independent cues were different from all other visual cue units in the simulation whereas the rotation angle of the coherent cues were identical to each other. 20 simulations were run. In ten of which, the coherent cues were rotated by 90° anti-clockwise and the two independent cues were rotated by 90° clockwise and 180° respectively. In the rest of the simulations the coherent cues were rotated by 90° clockwise and the independent cues were rotated by 90° anti-clockwise and 180° respectively. We found that in 19 of the 20 simulations the head direction cell network followed the coherent cues and in the remaining simulation the head direction cell network followed one of the independent cues. By using the circular V-test, we found that the coherent cues exerted significant control over the head direction cell network in both conditions ($\chi^2=4.46$; $p<0.001$ for 90° anti-clockwise coherent cue rotation and $\chi^2=3.99$; $p<0.001$ for 90° clockwise coherent cue rotation). The result demonstrates that the stronger cue control of the coherent cues is not only due the cue group having fewer conflict experience than the independent cues. The relative stability between the stable cues facilitates the cue group to dominant over the independent cues for cue control of the head direction cell network.

How Hebbian projection learning rate affects conflict resolution

We test how the learning rate α in the Hebbian learning rule affects the conflict resolution of the model. A simulation with two visual cue units was setup, and a conflict was introduced by rotating the orientation of the cue units in opposite directions. We define the time taken to resolve the introduced conflict as the period during which the head direction (HD) system showed fluctuations in encoded directions of $> 45^\circ$. Eleven simulations with varying levels of α were run and the result is presented in figure 4.8. The figure demonstrates that a slow learning rate, despite giving the visual cue unit a stronger influence over the HD system, makes it more difficult for the cue unit not only to establish control in the first place, but also to adapt to a new reference frame, which increased the amount of time for the HD system to resolve conflicts between the visual cue units.

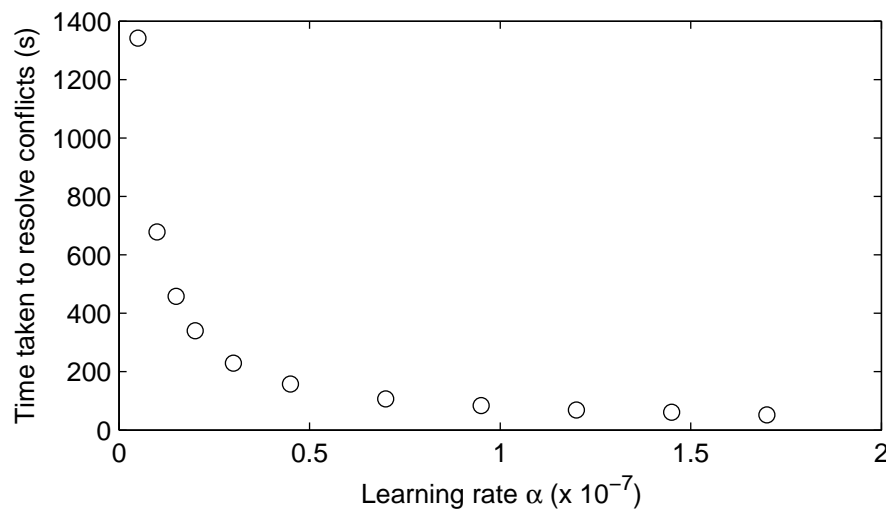


Figure 4.8: The figure shows how changing the learning rate α of the Hebbian learning rule affects the time required for a conflict introduced between two visual cue units to be resolved. The time required to resolve conflict appears to increase exponentially with decreasing learning rate.

4.3.4 Effect of angular head velocity inputs on conflict resolution

So far the simulations used constant angular head velocity (AHV) inputs. Here we test the model using the head direction profiles recorded from rats searching for food pellets on an open platform circular arena. We tested three different head direction profiles using simulations containing one, two or three visual cue units. The conflicts were introduced similarly to that described earlier. We found that, in simulations containing one visual cue unit, the rotation of the cue unit induced a similar shift in the encoded head directions of the HD system in all fifteen simulations. In simulations containing two visual cue units, the HD system shifted in register with the clockwise rotation in nine out of fifteen simulations and in the rest of the

simulations the HD system followed the visual cue that was rotated by 90° anticlockwise. There appears to be a slight preference over the visual cue unit that was rotated by 90° clockwise, but this preference is not significantly different from what would be expected by chance ($\chi^2=0.6$; $p>0.05$). In simulations with three visual cue units, the HD system resolved the introduced conflict by favouring the coherent cue set (i.e. the rotation of the two cue units that rotated in register with each other) in 27 out of 30 simulations. This domination, despite not being perfect, is significantly different from what would be expected by chance ($\chi^2=9.6$; $p<0.005$). Overall, the simulations that used real AHV data returned similar results to those collected from simulations using constant AHV inputs.

4.4 Discussion

We have implemented a model of head direction cells with additional units that represent the views of visual cues in an environment. These visual cue units have Gaussian shaped activation profiles with respect to the actual head directions of the system and connect to all the units in the HD system with excitatory Hebbian projections. We have shown that, under realistic angular head velocity (AHV) inputs, these cue units reliably control the encoded head directions of the HD system when their orientations are shifted and the Hebbian learning rule allows the conflicts between the angular shifts of multiple visual cue units to be resolved. In addition, the coherence of angular shifts between visual cue units strengthens the units ability to exert a similar shift in the encoded head direction of the head direction (HD) system. The facilitatory fact of the relative stability between the visual cue units on cue control of the head direction cell network is evident from the near complete dominance of the two coherent visual cue units over two independent visual cue units. This shows that the simple implementation of visual cue units is adequate to support the mechanism of selecting the most salient spatial reference frame in an environment as proposed in the cognitive map theory by O'Keefe and Conway (1978).

One of the functions of external visual inputs is to correct errors and drifts of the HD system (Goodridge et al. 1998; Mizumori and Williams 1993). As discussed in the introduction, such accumulated error in the HD system is inevitable and, if unchecked, can be detrimental to a navigation system. In the model that we implemented, activation of visual cue units creates a temporarily deviation of the encoded head direction from actual head direction. This is caused by the more realistic Gaussian shaped activation profile used for the visual cue unit, but appear to be detrimental to the drift stabilising property of visual cues observed in experiments. Additional analyses did show that, despite this temporarily deviation, simulations with visual cue units had significantly smaller accumulated errors over time, confirming the error correcting property of visual cue units.

It has been shown that it takes up to eight minutes for a novel visual cue to gain control

over head direction cells (Goodridge et al. 1998). On the other hand, some biologically inspired robotic models of navigation used one-shot Hebbian learning rule when associating newly observed visual information with internal representation of head direction (Strösslin et al. 2005), suggesting some benefits in rapid learning. As an internal representation of head direction should always be available even in a novel environment, the only limitation of the rate of learning is the rate of associative learning between the visual cues and the HD network. We explored how the learning rate of the Hebbian projections from visual cue units to the HD system affect properties of cue control in our model. We found that both high and low learning rates could have detrimental effects on a visual cue unit's ability to control the encoded head direction of the HD system. When learning rate becomes higher, the projections from visual cue units to the HD system become more volatile. This makes it more difficult for the cue units to establish control over the encoded head directions and also make the system more susceptible to drifts as temporal deviations easily trigger modification of the projections from the visual cue units. On the other hand, a slow learning rate, despite being more stable and having stronger influence over the encoded head directions, also takes a longer time to establish in the first place. In addition, systems with slow learning visual cue units take longer time to resolve an introduced conflict between the cue units and this increased amount of time needed to resolve cue conflicts expand exponentially with linear change in learning rate. The above computational exploration suggests that the rate a head direction cell network learns to associate with an external cue may be calibrated as a compromise between both stability and flexibility in the head direction system.

There are a few discrepancies between the experimental results and the observed results from our model which will be discussed in the subsequent section. The conflicts introduced to the head direction (HD) system in the simulations were always resolved by the HD system choosing one of the cue units as the new reference point. However, cue conflicts introduced to the head direction cells recorded during experiments were not always resolved this way. Zugaro et al. (2004) showed that, when facing conflicts between distal and intramaze cues, head direction cells can sometimes choose the combination of the cues as the new reference point. This phenomenon is very difficult to reproduce in the implementation of head direction cell model used in the experiment. Similar to what was observed in the experiment, the encoded head direction in the HD system is reset by the visual cue units very rapidly (Zugaro et al. 2003). This excludes the scenario that the encoded head direction appear to be controlled by two visual cue units due to an incomplete shifts induced by each visual cue unit. In order for the encoded head direction to be controlled by two cues, the visual cue units need to be activated at the same time and also that the summed excitatory inputs from the cue units need to be sufficiently strong to reset the location of activity bubble in the HD system. In order to fulfil the requirement, the Gaussian activation profile of the visual cue units need to be very

wide. This exacerbates the temporal deviations reported earlier and the whole HD system can become too unstable to be useful. This suggests that the structure of the model is not ideal to support such phenomenon and other mechanisms may be responsible for guiding the HD cells to follow a multi-cue complex. Another cue control property reported in the experiment is that some of the visual cues in the experiment can permanently lose their ability to exert control over the head direction network (Chakraborty et al. 2004; Jeffery 1998; Jeffery and O'Keefe 1999; Knierim et al. 1995). However, in the model, visual cue units always re-establish their weight profiles and would eventually regain control over the HD system even after repeated conflicts. Additional mechanisms, perhaps by adding new constraints in the Hebbian learning rule, are required to reproduce the phenomenon of visual cues being permanently suppressed from controlling the network.

Chapter 5

Cue control of place cells and head direction cells by conflicting distal cues

5.1 Introduction

The ability to navigate successfully in familiar and novel environments is essential for animal survival. With the ease of observation and similarity to natural behaviours, paradigms based on spatial navigation are popular for exploring animal cognition. Animals employ many different spatial navigation strategies to solve myriads of spatial navigation tasks (Redish 1999). Strategies of egocentric nature, such as praxic navigation where animals execute a fixed sequence of motor commands for navigation (Eichenbaum et al. 1990) or path integration (Barlow 1964; Dashiell 1930; Mittelstaedt and Mittelstaedt 1980) where animals use information generated by self motion (e.g. linear and angular head velocity information from the vestibular system), do not require sensory information of external environments. On the other hand, both taxon navigation, where animals follow a specific environmental cue (Gallistel 1990), and locale navigation, where animals encode relationships between cues in an environment to guide navigation (O'Keefe and Nadel 1978; Tolman 1948), require integration of environmental information. Even egocentric navigation can benefit from the availability of environmental information. For example, association of a particular praxic strategy with certain environmental cues would allow the learned strategy to be corrected applied the next time animals revisit the environment. While path integration only requires animals to keep track of the angular and linear displacement (Etienne 1992; Redish 1999) during navigation, presence of environmental cues allows animals to correct for the accumulated errors of an internal path integrator (for reviews see Etienne 1992; Etienne et al. 1996). Experimental evidence also supports the idea that animals can utilise multiple navigation strategies flexibly (Maaswinkel and Whishaw 1999), suggesting

that the availability of external sensory information would always contribute towards solving navigation tasks.

The development of the single unit recording technique on freely moving animals (Hubel 1957) has made it possible for researchers to correlate the behaviour of animals to the firing pattern of single neurons. The application of the single unit recording technique to the study of navigation led to the discovery of place and head direction (HD) cells in rats (O'Keefe and Dostrovsky 1971; Ranck 1984; Taube et al. 1990a). Place cells were first discovered in the hippocampus of rats. These cells fire only when a rat runs through specific locations in an environment. The preferred firing locations were called the place cells' place fields. Head direction cells were first discovered in postsubiculum (PoS) and their firing patterns were strongly modulated by the orientations of the rat's head, regardless of their locations. The orientation that activated the firing of a HD cell was its preferred firing direction (PFD). The similar modulation of these two population of neurons by the spatial attributes of an environment led to many subsequent experiments that explored their relationship in solving spatial navigation tasks. It has been shown that both place cells (Markus et al. 1994; Quirk et al. 1990; Wiener et al. 1995, for a review see McNaughton et al. 1996) and HD cells (Knierim et al. 1998; Stackman et al. 2003; Taube and Burton 1995) maintain their receptive fields using inertial cues, suggesting a path integration capacity (McNaughton et al. 2006). On the other hand, they also maintain their receptive fields between exposure to familiar environments (Muller et al. 1987; Stackman et al. 2003) and prominent visual cues exert strong influence on their firing (for reviews, see Muller 1996 for place cells and Wiener and Taube 2005 for head direction cells). It has also been reported that the HD cells recorded from rats that were deprived of external sensory information showed accumulation of path integration errors over time (Goodridge et al. 1998; Mizumori and Williams 1993; Stackman et al. 2003).

After the observation of environmental influence on the firing of place and head direction (HD) cells, the attention naturally shifted to investigating interactions between external and internal cues. One commonly used paradigm was to observe how the orientation of place cells' environmental representation and head direction cells' PFD are influenced by the different types of cues. Using HD orientation to investigate interactions simplifies experimental design and data interpretations as only one environmental attribute (i.e. angle of orientation) needs to be considered. It has been observed that HD cells as an ensemble respond coherently to changing environmental cues (Sargolini et al. 2006; Yoganasimha et al. 2006), which suggests that an ensemble of HD cells always make a coherent 'decision' even when facing conflicting information. The coherent behaviour raises the interesting question of how different sources of information are processed and integrated. As we live in a dynamic world with path integrators that accumulate error over time (Etienne et al. 1996), conflicts between spatial information either arise from a discrepancy between external cues and the internal path integrator or due

to changes in the position of some external cues. An animal would then need to resolve the conflicts before using the available information to guide navigation decisions. Observing how place and head direction cells respond to different types of conflicts could shed light on how the navigation system deals with changing and conflicting information in an environment.

Many observations have been made on how place and head direction (HD) cells resolve conflicting orientation information in an environment. Many factors affect which information (or combination of information) is used to modulate the firing of place and HD cells. Environmental information is typically favoured over inertial information when they are in conflict (Dudchenko and Zinyuk 2005; Goodridge and Taube 1995; Knierim et al. 1998; Paz-Villagrán et al. 2004; Sharp et al. 1995; Taube and Burton 1995; Zugaro et al. 2000), which agrees with the hypothesis that rats use external sensory information to correct for errors of internal path integrator. However, when a rat could feel the rotation of its local environment, external sensory information no longer dominated over inertial information during conflict resolution and the observed responses became more variable. Place cells tended to respond by changing the location of their place fields in an unpredictable manner or changing their firing rates dramatically, i.e. a global remapping. Although the preferred orientation of HD cells for each rat remained coherent, the response differed in different rats as if there was competition between external sensory and inertial cues to control the orientation of the place and HD cells' spatial representation. The results also highlight the differential effects of vestibular signals generated via active versus passive motion. Among the different types of sensory information, distal visual information is the most salient (Goodridge et al. 1998; Jeffery et al. 1997; Save et al. 2000) and the manipulation distal cues is widely used in the literature to investigate how sensory information influence the orientation of place and HD cells' receptive fields. The strength of cue control is also influenced by the perceived distance of visual cues (Zugaro et al. 2004), with the cues further away from rats exerting stronger influence over place and HD cells than closer cues. It was also reported that rotation of intramaze objects had little effect on the firing of place cells (Lenck-Santini et al. 2005; Tanila et al. 1997). However, since other reports provided evidence that intramaze cues could rival or dominate over distal visual cues in cue control (Knierim 2002; Knierim and Rao 2003; Lee et al. 2004; Renaudineau et al. 2007) of place and HD cells. This seems to be in direct conflict with the reports of visual cues exerting stronger cue control when further away. However, intramaze cues contain visual as well as tactile information, the discrepancies can then be reconciled by arguing that the combined tactile and visual information strengthen the cue control of intramaze cues, which, in some cases, rival or even overwhelm the cue control of distal visual cues. The lack of cue control results reported by Lenck-Santini et al. (2005) could be due to the configuration of intramaze cues used in the experiment as it has been reported previously that intramaze objects lose their cue control if they can be easily explored from all directions inside the maze (Cressant et al. 1997,

1999; Save et al. 1998).

The literature summarised thus far suggests that some types of cues exert stronger cue control over place and head direction (HD) cells but also demonstrates possible interaction and competition between cues for cue control. Cue control of cues can be seen as how prior experiences influence the present expression of the environment, as association of place representations to a landmark is a learned process (Goodridge et al. 1998). Influences of prior experience on cue control thus became the focus of many publications. Shapiro et al. (1997) used a four-arm radial maze to show that repeated rotation conflicts between distal visual cues and intramaze tactile cues initially resulted in place cells following the distal cues, but eventually place cells developed different representations to the two distinct cue configurations (i.e. standard and double rotation cue configurations). It has also been reported that prior experience of visual cue instability weakens their cue control (Jeffery 1998; Jeffery and O'Keefe 1999; Lenck-Santini et al. 2002), and this effect was transferred to a novel environment even under the situation in which place cell ensembles showed global remapping between the novel environment and the environment where the cue instability was learned (Chakraborty et al. 2004). Knierim et al. (1995) also reported that some disorientation procedures during training led to the loss of cue control over the recorded place cells, and the lost control was irreversible even after additional experiences that enforced the stability of the distal cue. Knierim et al. (1995) proposed that rats use idiothetic senses as the primary reference frame to determine cue stability. Repeated conflicts between idiothetic and distal cues caused distal cues to lose cue control ability as it was determined to be inconsistent with the primary reference frame. However, this hypothesis was inconsistent with what was reported in Chakraborty et al. (2004), where repeated conflicts between visual and idiothetic cues strengthened cue control of visual cues. Furthermore, given the evidence that distal cues reset idiothetic orientation in most cases, rats should not have experienced extensive conflicts between visual and idiothetic cues¹. It should also be noted that passive transportation of rats interfered with idiothetic orientation (Stackman et al. 2003). As rats are typically transported passively between their home cage and the experiment environment, the result questions rats' ability to maintain their idiothetic reference frames between repeated visit to the experiment environment without the aid of external cues. This raises issues on interpreting the idiothetic cues as the primary reference in determining cue stability.

An alternative to the primary reference frame view was that the cues' strength of cue control were determined by their relative stability with each other in the environment (O'Keefe and Nadel 1978, page 95). This hypothesis is based on the view that the spatial information provided by the location of a given cue is determined by how well it predicts the locations of

¹We would expect that conflicts between visual and idiothetic cues were quickly eliminated by visual cues resetting the idiothetic orientation. The two types of cues would then be consistent with each other during the rest of the recording session

other cues in an environment. This suggests that the more stable the relative relationship between cues, the more spatial information each of them provides and hence the stronger the cue control. Indeed it has been shown that rats were able to search for food more accurately when environmental cues were consistent with each other (Biegler and Morris 1993). However, in the subsequent experiments (Biegler and Morris 1996a,b), the authors had difficulties deciphering the relative contribution of distal cues and intramaze objects to the spatial learning task. As shown from the single unit recording literature, different types of cues can have different cue control properties, thus complicating the interpretation of these cue control results.

The aim of the study is to test the cognitive map hypothesis (O'Keefe and Nadel 1978) by exploring how the relative relationship between landmarks in an environment affects the strength of cue control on place and head direction cells. We hypothesise that relative landmark stability would affect the cue control strength of environmental cues. In order to remove the variation due to different types of landmarks, we concentrate our exploration on distal cues as we could assume the cues had similar cue control properties at the onset of experiments. The main attractions of distal visual cues are their single modality nature (i.e. visual information), effectiveness in establishing cue control over place and head direction (HD) cells, and the ability to generate a wide selection of distinctive cues. To explore the hypothesis, we set up a cue controlled environment in which the only sources of directional information available to rats were the distal visual cues provided (see figure 5.1). We predicted that distal visual cues that maintain relative stable relationship with each other would exert stronger cue control over place and HD cells than cues that were independent from other cues of the environment. We also explored how repeated exposure to cue conflicts affect the cue control of coherent and independent cues. In experiment 1 we used two coherent cues and one independent cue and recorded place cells from CA1 area of the hippocampus in rats. As the place cells responded to the cue conflicts predominantly by global remapping, we could not determine the relative strength of cue control from different cues. In experiment 2 we added a longer habituation period and also used three coherent cues and one independent cue to introduce cue conflicts. We recorded place cells from CA1 area of the hippocampus and head direction cells from the entorhinal cortex to test whether relative stability between cues affect their strength of cue control after repeated cue conflict experience.

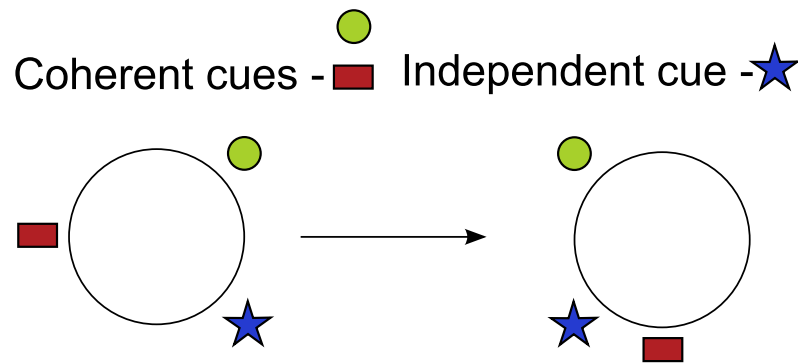


Figure 5.1: Illustration of relative landmark stability. The circle represents a circular environment where rats are free to roam and search for food pellets. Symbols surrounding the circle represent visually distinct objects provided in the experimental environment that serve as distal visual cues. As the environment is cue controlled, the only directional information available to rats is from these cues (if this condition holds, rats can not tell whether the physical position of any individual cue relative to outside environment has been changed). Between two exposures to the environment, the configuration of the cues are changed such that relative relationship between the coherent cues remains fixed. Based on our hypothesis, the coherent cues would dominate over the independent cue in cue control over place and HD cells when rats experience cue conflict between sessions.

Experiment one

5.2 Methods

5.2.1 Subjects

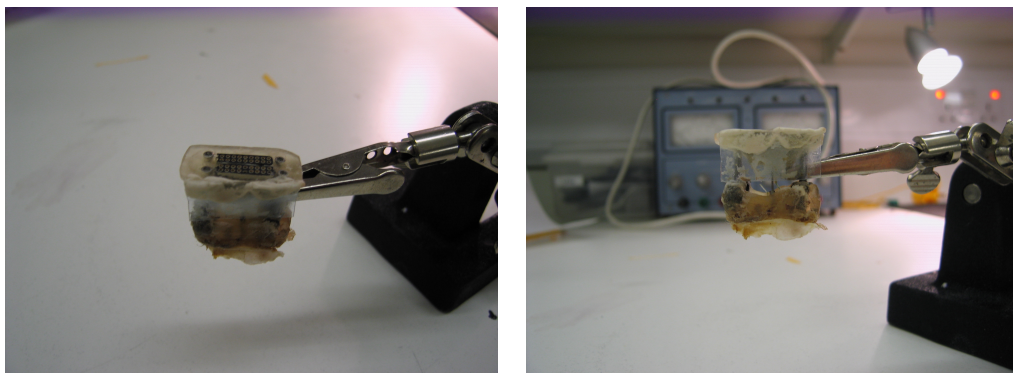
Three male adult Lister Hooded rats weighing 250–350g at the time of surgery were used. Rats were kept under a 12 hour light/dark cycle and were housed in individual cages after surgery. All experiments were carried out during the light phase of cycle. Rats were given *ab libitum* access to water and were food restricted to 85–90% free feeding weights during the experiment after surgery. All procedures were performed in compliance 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.

5.2.2 Recording device

A modified tripod design (Kubie 1984) was used for reconstructing single unit recording implants. Each implant contained either 16 or 32 HML coated 17 μm 90% platinum 10% iridium wires (California Fine Wire, Grover Beach, CA) grouped into tetrodes. Every four wires was bundled into one tetrode by twisting and heat annealing, which was achieved by exposing tetrodes to 250° hot air for five seconds. The hot air was generated using a variable temperature heat gun (GHG660LCD, Bosch). For protection purposes, tetrodes were threaded through

a thin-wall stainless steel cannula (27 Ga Hypo Tube, Small Parts Inc, Miramar, FL) with tips of the tetrodes protruding 7–8 mm from the end of the cannula. This protrusion ensured that only the tetrodes were inserted into the brain during implant surgeries. An outer metal cannula, which was fixed to the surface of the rat's brain during implant surgery (18Ga Hypo Tube, Small Parts Inc, Miramar, FL) was used to protect the the exposed tetrodes from being accidentally damaged by the rats.

A MillMax plug (MillMax, Oyster Bay, NY) was used as the interface between the recording system and recording implant. Each wire from the tetrodes of the implant was secured onto a separate pin on the millmax plug using silver conductive paint (Electrolube, Derbyshire UK). The HML insulation at the end of the wires were removed using a gas lighter to allow electric contacts between the wires and pins of the MillMax plug. Each recording implant also contained 3–4 feet which served as the main anchors for the implant and also provided a moving mechanism that allowed us to gradually lower the location of the tetrode tip after surgery. Each foot was assembled by threading an 80 thread per inch metal screw (Small Parts Inc, Miramar, FL) through a matching hexagonal metal nut (Small Parts Inc, Miramar, FL) into a tapped plastic Amphenol socket (Amphenol, Wallingford, CT). The metal nut was super-glued (Superglue, Hankel Loctite Ltd.) to the top of the Amphenol socket and provided strong support to the advance mechanism. The top of the screws were fixated to the MillMax plug using dental acrylic (Simplex Rapid Acrylic Denture Polymer, Kemdent). Prior to the surgery, the tip of the tetrodes were gold plated to reduce impedance of each wire against a saline solution to within 200–300 k Ω range. This reduction in impedance improved the signal sensitivity of the platinum wires. Figure 5.2 presents pictures of a 32 channel unit recording implant used in the experiment.



(a) The cable interface of a unit recording implant

(b) The side of a unit recording implant

Figure 5.2: (a) is a picture taken from the top of a unit recording implant. The MillMax plug interface can be seen as well as the sockets of the screw feet. The implant is lowered by using a screw driver to turn the screw feet. (b) is a picture taken from the side of a unit recording implant. The cemented feet as well as the metal cannula used to protect the tetrodes can be seen clearly.

5.2.3 Surgery

Anaesthesia was induced and maintained using Isoflurane inhalation anaesthetic (Abbott Laboratories Ltd.). Rats were secured to a stereotaxic frame after the induction of anaesthesia. A small hole was drilled above the implant site to expose the dura. After piercing the dura, the tip of the tetrodes was lowered to the target site (AP -3.5 mm from bregma, ML \pm 2.4–3.0 mm from midline, DV -1.8 mm from Dura) just above CA1 pyramidal cell layer. 5–7 skull screws (Fine Science Tools) were tapped into the skull and the recording implant was anchored to the skull screws using dental acrylics. The recording assembly was grounded to one of the skull screws using silver conductive paint. Rats were administered oral analgesic (1 ml per 500 ml of water, Large Animal Rimadyl, Pfizer, UK) via their water supply from 24 hours pre-surgery to up to four days post-surgery or until rats regained their pre-surgery weights, whenever is earlier. Rats were given at least one week of recovery time before screening and experiments.

5.2.4 Unit recording

Screening and recording of unit activity was achieved using an Axona 32-channel system (St. Albans, UK). During screening and recording, recording assemblies were attached to a headstage containing a unity gain buffer amplifier chip. The signals were relayed via a flexible tethered cable to a ceiling mounted commutator. Signals were then redirected to a pre-amplifier with 1000 fold amplification. The amplified signals were relayed to the main recording system, band-pass filtered between 600 and 6000 Hz, digitised at 50kHz and further amplified by 10–40 times, configurable via the DACQ software environment accompanying the Axona system. The final signals were visualised using the Oscilloscope module in the DACQ program which allowed visual inspection as well as recording of signals. During recording, only 1 ms snapshots of signals that exceeded a preset amplitude threshold (0.2 ms before and 0.8 ms after the threshold was reached) were recorded and timestamped to reduce data size.

Positions and head directions of rats were monitored by tracking the two clusters of infrared light-emitting diodes (LEDs) mounted on the headstage. The two LEDs clusters, with one big cluster consisting of 4 LEDs and one small cluster consisting of 1 LED, were 8 cm apart from each other. A ceiling mounted monochrome CCD camera fed the captured frames into a two-spot tracking system. The positions of the two LED clusters were recorded and timestamped at 50Hz.

5.2.5 Screening single unit activity

Rats were screened twice each day for single unit activity on a small, 30 cm diameter elevated circular dish outside the curtained environment. Tetrodes were advanced by 10–20 μ m if no desired unit activities were discovered. We waited for at least six hours between screening to

allow advanced tetrodes to settle to their new position. If significant activity was identified from visual inspection, a short session was recorded while rats were on the circular dish. Characteristics such as waveform and frequency modulation of the recorded data were used to determine whether additional investigation was warranted. If the recorded activity was suspected to originate from CA1 pyramidal neurons, an additional recording session was performed while the rat searched for food pellets on a 60 cm diameter elevated circular platform outside the curtained environment. Rats progressed to the actual experimental protocol as soon as definitive place or head direction cell activity was isolated on the elevated dish.

5.2.6 Experimental protocol

Apparatus

An 60 cm diameter wooden circular platform elevated 70 cm from the floor was used as the foraging environment. The platform was padded with a brown leather texture polyester surface which absorbed impacts of dropped pellets and was placed inside a cue control compartment surrounded by heavy black-out curtains. A ceiling mounted pellet dispenser was used to drop pellets onto the platform. The light source of the cue controlled compartment was located at the centre of the ceiling to preserve the symmetry of the cue controlled environment. Eight identical bulldog clips were attached to black threads that were in turn secured to the ceiling of the curtained environment. The bulldog clips were positioned against the black-out curtains and were 45° apart from each other, serving as place holders for distal cues. Three visually distinct objects clipped onto three of the bulldog clips were used as distal cues. A ceiling mounted speaker located at the centre of the curtained environment was used to emit white noise continuously during recording to mask all uncontrolled auditory cues (see figure 5.3 for a photo of the curtained environment and the three distal cues used in the experiment).

Pre-training

Rats were given five minutes of pellet chasing on the circular platform outside the curtained environment daily during screening. The experimenter walked around the platform in an erratic manner and scattered food pellets onto the platform. This encouraged rats to search for food on open platforms, which improved platform coverage during the experiment.

Cue conflict

After place cells were identified, the rats were allowed to forage for food pellets on the circular platform while the single unit activity was recorded. Before the recording session started, the rat's recording implant was connected to the tether cable of the recording system outside the curtained environment. The rat was then placed inside an opaque, high-walled bucket before

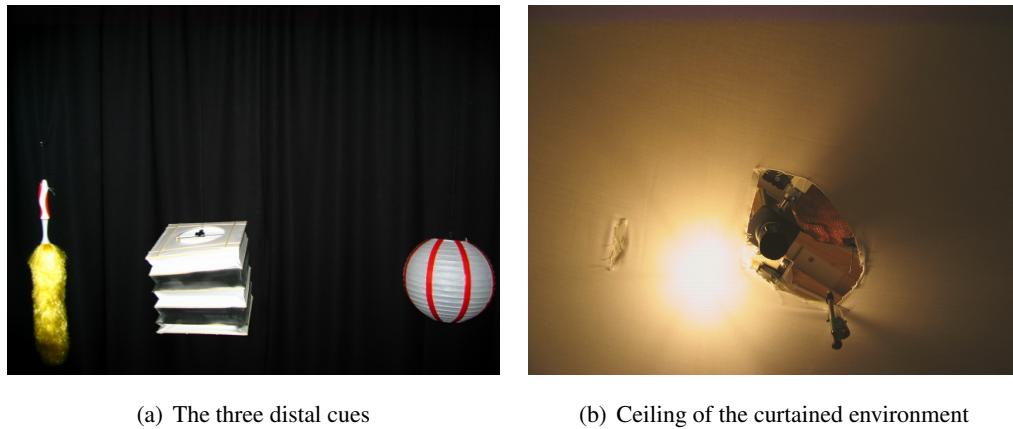


Figure 5.3: (a) is a photo of the three distal cues used in the experiment, which are similar in size but have distinct shapes and colour patterns. (b) is a photo of the ceiling of the curtained environment. The light source emitted light from the centre of the ceiling. The ceiling mounted camera, tube for dispensing food pellets and the speaker for generating the white noise are visible in the photo. In order to provide a better view of the ceiling, the tether cable of the recording system was removed. However, the position of the tether cable is clearly marked by the slit on the ceiling.

being transported into the curtained environment. In order to disrupt the rat's internal sense of direction, a disorientation procedure was performed before the start of each session. The disorientation procedure consisted of the experimenter carrying the bucket and walking around the maze in an erratic manner for 90 seconds. The bucket was then placed at the centre of the platform for at least five minutes before the start of a recording session. Rats were given two ten minute recording sessions each day on the 60 cm diameter circular platform, separated by a ten minute interval. The surface of the circular platform was cleaned with soapy water between recording sessions. The two recording sessions were flanked by five minute recording sessions both at the beginning and end of the day's experiment during which rats resided inside the bucket. These bucket sessions were used to assess intraday recording stability.

The first few days of recording were used to habituate rats to the experiment environment such as the distal cues, the circular platform, the automatically dropped pellets and the white noise. The ability of the distal cues to orient the place fields were then tested by rotating the distal cues by 90° between sessions. Once place cells were clearly controlled by the rotation of the distal cues, the rats were given three days of cue conflict manipulations. The sequence was constructed in a pseudo-random manner and followed the two rules:

1. Two of the cues, the coherent cues, always maintain fixed positions relative to each other despite the changes of their absolute positions in the environment. The third cue, which was the independent cue, changed its position with respect both to the environment and the coherent cues.
2. The absolute positions of the cues did not repeat during the cue manipulation sequence.

Figure 5.1 presented in the introduction of this chapter is an example of the cue configuration sequence used in cue conflict sessions. After the three days of cue conflict sessions, the rats were given a probe sequence which consisted of four recording sessions and three cue manipulations between sessions. An illustrative diagram of the probe sequence is shown in figure 5.4. The first cue manipulation was a 90° cue rotation, which was used to determine whether the distal cues could still control the orientation of the place fields reliably. The second one was a cue conflict manipulation, similar to the cue conflict sessions the rat experienced in the previous three days. The last cue manipulation was a 1v1 conflict where one of the coherent cues was removed from the environment and the remaining one was rotated in conflict with the independent cue. This was designed to test whether the rat would preferentially choose the coherent cue over the independent cue after experiencing the cue conflicts. On the day after rats had experienced the probe sequence, 90° cue rotation sessions were recorded to determine the strength of cue control of the distal cues over place cells after the rat experienced all the different cue manipulations. This would allow us to determine whether the rats still pay attention to the distal cues after experiencing all the cue manipulations.

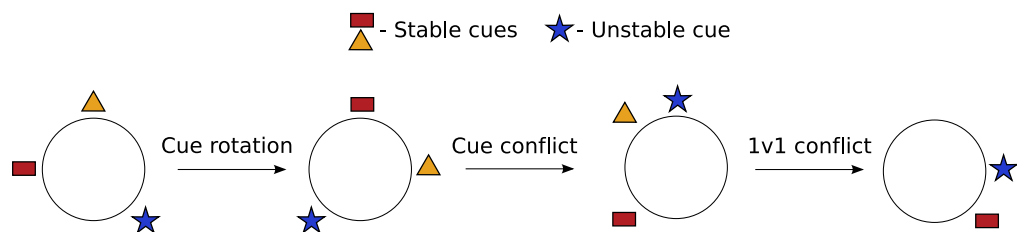


Figure 5.4: An illustration of a probe sequence used in the three distal cues experiment. The sequence contains, in order, one cue rotation, one cue conflict and one 1v1 conflict manipulations. During cue rotation the distal cues are rotated together by 90°. Cue conflict manipulation is similar to what is shown in figure 5.4 and the two coherent cues are rotated in conflict with the independent cue. During the 1v1 conflict manipulation, one of the coherent cue is removed and the remaining coherent cue is rotated in conflict with the independent cue. The big circle represents the circular platform. The square and triangle represents the orientation of the coherent distal cues and the star represents the orientation of the independent distal cue.

Introduction of new cues

After the completion of the three distal cues experiment, the cues were replaced by a set of four new cues. The four distal cues used were the same as those used in experiment 2 and are shown in figure 5.3(a). The main purpose of the experiment was to determine how place cells responded to the novel cue set in a familiar environment with prior cue conflict experience from a different set of cues. Other than the new set of cues, the experimental protocol was identical to that described in the previous section. Each day the rats were given two recording sessions with no cue manipulation between sessions.

5.2.7 Data analysis

Unit isolation

Time- and position- stamped putative neural spikes were analysed offline using custom written matlab scripts and freely available open source software. Recorded data on the same day were merged together using custom matlab scripts, which allowed uniform unit separation criteria to be applied to all recording sessions. To reduce data dimensions, two main features, energy² and first principal component³, were calculated to represent the sample waveforms and as basis for further unit separation analyses. The unit separation procedure followed a semi-automatic approach and recorded data was first clustered automatically (Harris et al. 2000) using KlustaKwik 1.5 (K. Harris, klustakwik.sourceforge.net). The output was then refined manually in Klusters (L. Hazan, Buzsaki lab, Rutgers, Newark NJ, klusters.sourceforge.net). Information from auto- and cross- correlograms of separated clusters were also used to aid unit isolation during manual cutting.

Spatial firing rate map of place cells

The firing rate map of each isolated unit was constructed based on the algorithm described in (Leutgeb et al. 2007). Briefly, the environment was divided into a series of 5 cm by 5 cm bins. The average firing rate of the unit in each bin was calculated by dividing the total occurrences of the spikes in the bin with the total amount of time the rat explored the bin. The result was then smoothed by a Gaussian kernel $g(x) = \exp\left(-\frac{x^2}{2}\right)$. The firing rate f of each bin was estimated using the following formula,

$$f = \frac{\sum_{i=1}^n g\left(\frac{S_i - b}{h}\right)}{\int_0^T g\left(\frac{p(t) - b}{h}\right) dt} \quad (5.1)$$

where S_i represented the positions of recorded spikes, b was the centre of the bin, the period $[0 \quad T)$ was the trial period, $p(t)$ represented the position of the rat at time t , and h was the smooth factor, which was set to 5 cm. A bin was regarded as not having been visited if the rat never explored the area within 5 cm radius from the centre of the bin.

Inclusion criteria for place cells

As the majority of subsequent analyses involved the comparison between two recording sessions, inclusion criteria for a cluster were based on its characteristics in the two sessions for

²Energy is calculated as the squared sum of the sampled waveform

³Which is the first coordinate of principal component analysis. First component projection of a multivariate dataset captures the greatest amount of variance from the data of any projection

comparison. A given isolated unit was only included as a putative place cell if it fulfilled the following criteria,

- An unit was said to be silent and was not included in subsequent analyses if its average firing rate was <0.1 Hz in both sessions. It was classified as an interneuron if its average spike width was smaller than $250 \mu\text{s}$, otherwise it was classified as a pyramidal cell. A pyramidal cell was only classified as a place cell when it fulfilled both of the criteria listed above. Two examples of place cells can be found in figure 3.1.
- The average peak amplitude of the waveform was $>80 \mu\text{V}$ and the average width of the largest waveform in both sessions, defined as the time between the peak to the subsequent trough of waveforms, was greater than $250 \mu\text{s}$.
- The average firing rate for the whole session was between $0.1\text{--}5$ Hz and the Skaggs⁴ spatial information content (Markus et al. 1994) was >0.5 in at least one of the sessions.

Rotation and remapping of place fields

For units that were classified as place cells, additional analyses were run to further classify their changes between the two recording sessions into three categories, rotation in which the rotated angles⁵ can be clearly determined, remapping, and rotation to which rotated angle cannot be determined because the field is too close to the centre of the maze.

For place cells whose spatial histograms only showed a clear place field⁶ in one of two sessions, the change was classified as remapping. However, the above classification rule was susceptible to borderline cases in which one of the sessions just missed the requirement and another just made the requirement. As we also incorporate a correlation based classification in the subsequent analysis, it was sensible to let the correlation based classification handle these borderline cases. We thus implemented rules that aimed at filtering out borderline cases. To qualify for a remapping classification at this stage, the cell needed to fulfil two additional rules,

- The difference between the Skaggs spatial information content of the two sessions was >0.1 . This filtered out the borderline cases where the spatial histogram of one session had a Skaggs value slightly >0.5 and another slightly <0.5
- The recording session with the higher average session firing rate was at least 2x the average session firing rate of the other session. This filtered the borderline cases where

⁴Skaggs spatial information = $\sum_i P_i \left(\frac{R_i}{R} \right) \ln \left(\frac{R_i}{R} \right)$, where i is the bin number in the spatial histogram, P_i is the probability that bin i is occupied, R_i is the mean firing rate of bin i and R is the overall mean firing rate.

⁵For place cells whose place fields remained stable between sessions, it would be classified as rotation with a rotated angle of 0°

⁶This is defined as having Skaggs >0.5 and session average firing rate between $0.1\text{--}5$ Hz.

a remapping classification was given when one of the session's average firing rate was slightly >0.1 Hz and another was slightly <0.1 Hz.

For place cells that failed to meet the above two rules, they were treated as having clearly defined place fields in both sessions.

For place cells whose place fields were clearly defined in both of the recording sessions, we first calculated a vector of Pearson's product-moment correlation coefficients r between the two spatial histograms, with the second spatial histogram rotating in 5° increments. r is calculated by

$$r = \frac{1}{n-1} \sum_{i=1}^n \left(\frac{X_i - \bar{X}}{s_X} \right) \left(\frac{Y_i - \bar{Y}}{s_Y} \right) \quad (5.2)$$

where X and Y are the two random variables with i samples, \bar{X} and \bar{Y} are means of the samples, s_X and s_Y are standard deviation of the samples respectively. Classification was based on the correlation coefficient vector calculated. The rules were,

- The response of a place cell between sessions was classified as *rotation with a well defined rotated angle* when the maximum correlation coefficient was > 0.5 , and minimum correlation coefficient <0 . The angle of rotation was the amount of angular shift applied to the spatial histogram that generated the maximum correlation coefficient between the two sessions. The angle of an anticlockwise rotation was assigned a positive value and negative for clockwise rotations. This kept the value of the rotation angle to between -180 – 180 degrees.
- A *remapping* classification was assigned when maximum correlation coefficient was <0.5 , which indicated that the place cell remapped its place field between sessions.
- The response was classified as *rotation to which rotated angle cannot be determined* when maximum correlation coefficient was >0.5 and minimum correlation coefficient was >0 . This suggested that the place fields were located at the centre of the maze or are otherwise too large when comparing to the maze to clearly identify the rotated angle between sessions.

Figure 5.5 presents examples of how Pearson's correlation coefficients were used to classify the change of place fields between sessions.

Circular variance was used to measure the angular coherence of rotated place cells. Given a vector z of all the rotated angles of simultaneously recorded place cells, circular variance $\text{var}(z) = 1 - r$. r is calculated by equations 5.3. Examples of the outputs of the quantitative classification can be found in figure 5.6, figure 5.7 and figure 5.8.

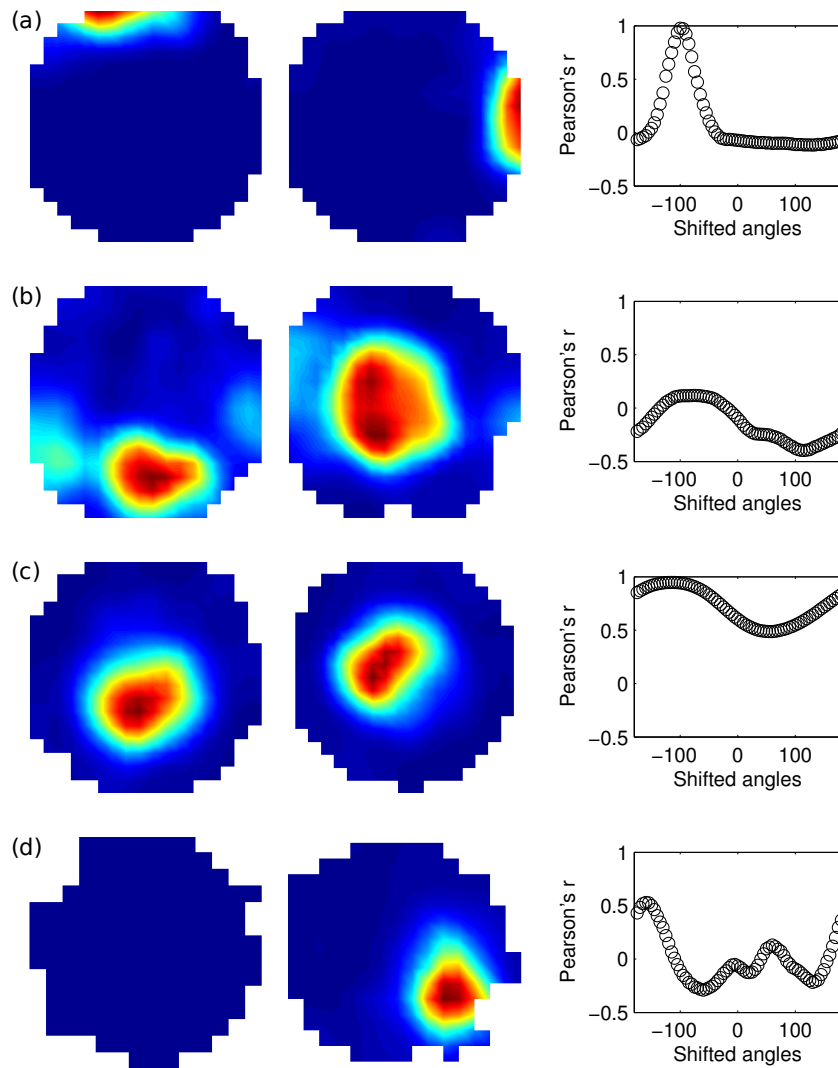


Figure 5.5: Pearson's correlation coefficients and classification of place field changes. (a) Rotation with a well defined rotated angle. The place field of the place cell clearly rotated by 90° clockwise between the two sessions. The plot of correlation coefficients against the increment angular shift applied to the second spatial histogram showed a clear peak. (b) Remapping. Place fields of the place cell shifted from the bottom of the maze to the centre. Correlation coefficients were low for all angular shifts. (c) Rotation to which rotated angle cannot be determined. The place field of the place cell was located close to the centre of the maze. Correlation coefficients were high for all angular shift applied. (d) Remapping due to place cell being silent in one of the recording sessions. The place cell firing was almost silent in session one despite having a clear and strong place field in session two. This was also classified as remapping, not by the pattern of Pearson's correlation, but by the definition of clearly defined place fields.

$$r = \sqrt{\left(\sum_{i=1}^n \frac{\sin z(i)}{n}\right)^2 + \left(\sum_{i=1}^n \frac{\cos z(i)}{n}\right)^2} \quad (5.3)$$

where n is the length of vector z . If the rotated angles are uniformly distributed, the circular variance equals to 1, and if all of the rotated angles have the same value, the circular variance equals to 0.

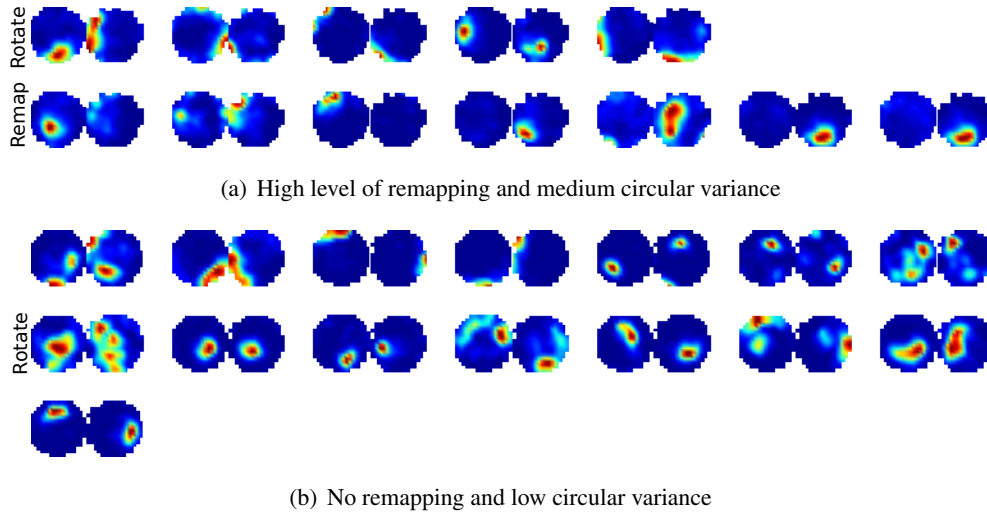


Figure 5.6: Quantitative classification of place cell response. (a) presents an example of a recorded place cell ensemble which the quantitative classification algorithm classified 58% of the recorded place cells as remapped between sessions. The circular variance of the angles of rotated place cells = 0.30. (b) is an example of a recorded place cell ensemble with no place cells classified as remapping and low level of circular variance (= 0.01).

5.2.8 Perfusion and Histology

After completing the experiments, rats were terminally anaesthetised with sodium pentobarbitol (Euthatal, Merial Animal Health, UK) and then perfused intracardially with 0.9% saline followed by 4% formalin. Smaller electrolytic lesions marking the tips of the tetrodes were applied using a 9V battery. The brains were then removed and stored in glass jars filled with 4% formalin. Histology was performed by Kate Shires for rats with CA1 implants, and by Jane Tulloch for rats with implants targeting the Entorhinal cortex. Briefly, brains were sectioned on a cryostat, with 30 μm coronal sections taken from the areas of implants targeting CA1 area of Hippocampus. For implants targeting layer III of Entorhinal cortex, Sagittal sections were taken instead. The sections were mounted on gelatine coated slides and were stained with 0.1% cresyl violet acetate to visualise the lesion track caused by the insertion of the tetrodes.

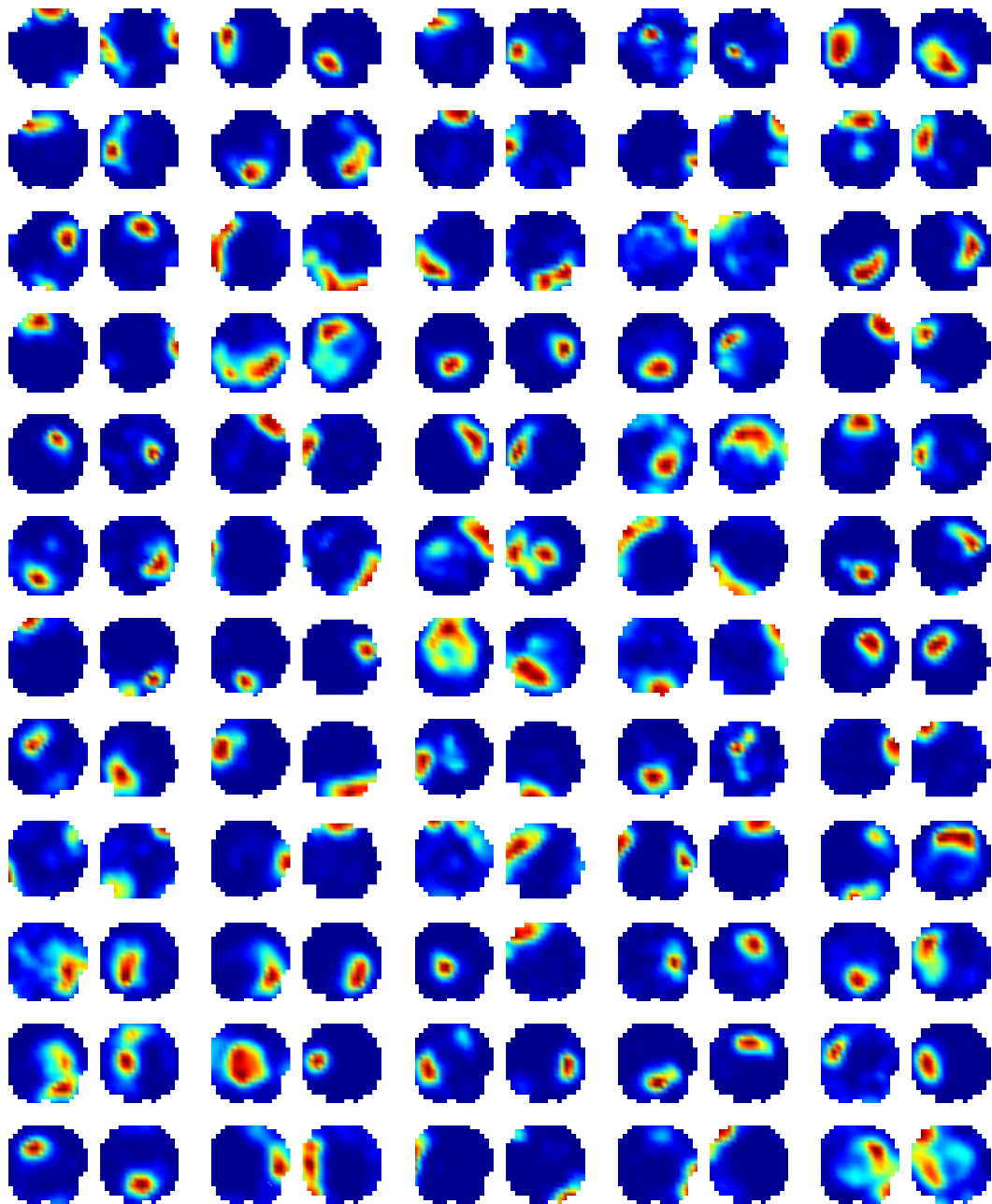


Figure 5.7: A sample of place cells that are classified as rotated between sessions. This figure contains a sample of place cells that were recorded during the experiment and were classified as rotated between sessions based on the criteria outlined in the previous sections.

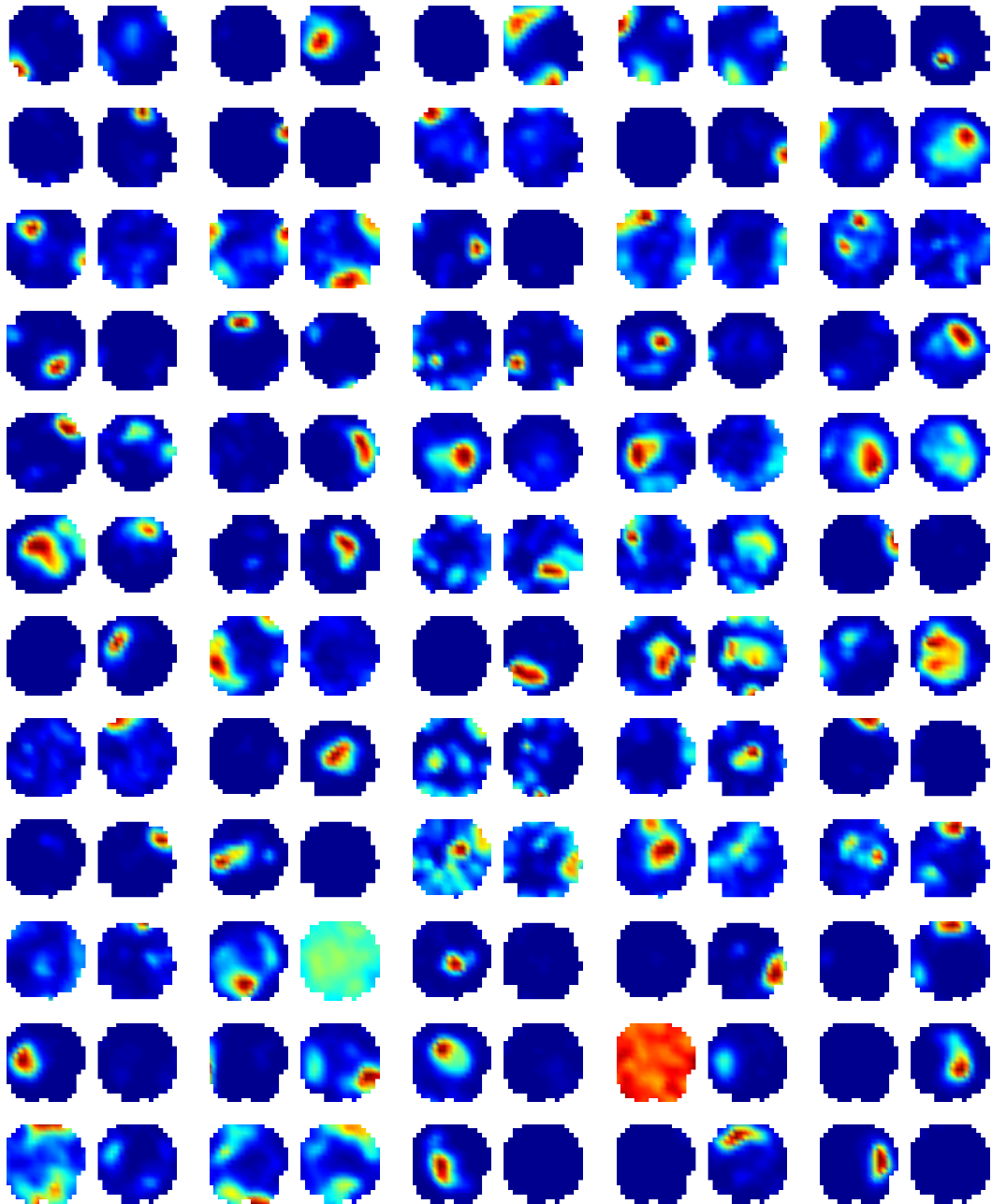


Figure 5.8: A sample of place cells that are classified as remapped between sessions. This figure contains a sample of place cells that were recorded during the experiment and were classified as remapped between sessions based on the criteria outlined in the previous sections. The colour scale of the spatial firing rate histogram between the two sessions for comparison is calibrated to permit a direct comparison of the firing rates of the cells in the two sessions.

5.3 Results

5.3.1 Histology

The position of the electrode tracks from two of the three rats with place cells were identified from the histology to either target or have gone through the CA1 cell layers. None of the electrode tracks ended anywhere near the CA3 cell layer, suggesting that the recorded place cells were originated from the CA1 cell layer. We failed to obtain histology from one of the rats as insufficient formalin was used for preservation which resulted in irreversible damage of the brain tissue. An example of the histology is given at figure 5.9.

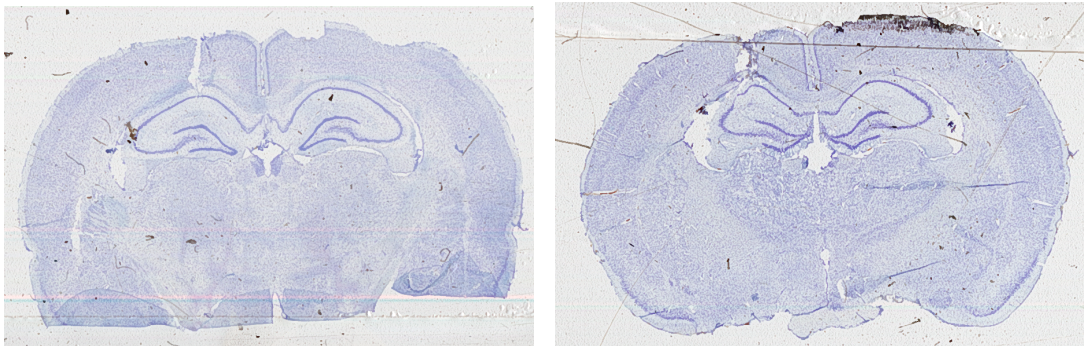


Figure 5.9: Cresyl-violet staining of the histology from two of the rats. The electrode track from both rats targets CA1 cell layer of the hippocampus though the exact location of the tip is difficult to determine. The end of the electrode track is far away from CA3, suggesting that the recorded pyramidal cell activities were originated from CA1 of the hippocampus.

5.3.2 Cue manipulation

Three rats with recording electrodes targeting CA1 area of hippocampus were used in this experiment. As analyses focused on how recorded place cells reacted to different cue manipulation conditions, each day of the experiment represented a different experimental condition, and hence there was no need to determine whether the same cells were recorded over multiple days. To give an idea of how many cells were recorded, a daily average number of cells recorded was calculated. On average, total of 33 cells were recorded across the three rats each day, 17 (52%) of which were classified as place cells (see section 5.2.7 for the classification rules). A table that summarises the number of cells recorded from each rat is presented in figure 5.10.

Remapping of place cells

Based on our analysis procedure (see section 5.2.7), a place cell is classified as either rotate or remap between two recording sessions. If a place cell maintained the location of its place field

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
E2201	No. cells	5	5	4	7	4	10	6	6	7	5	7
	No. pyramidal cells	1	1	1	2	0	5	2	4	5	2	2
E2206	No. cells	8	7	11	8	9	7	10	11	15	13	2
	No. pyramidal cells	6	5	5	6	8	3	4	6	8	7	1
E2208	No. cells	24	17	21	16	24	22	22	22	13	22	18
	No. pyramidal cells	9	7	15	5	13	14	10	9	7	12	10

Figure 5.10: Number of cells recorded in the 3 cue experiment. The table summarises the number of cells and the number of pyramidal cells recorded each day from the three rats.

between sessions, it would be classified as rotated between sessions with a rotation angle of 0° . We first looked at the proportion of place cell ensembles that remapped between sessions. A high proportion of place cells remapping between sessions would suggest that the place cell ensemble responded to the cue manipulation with global remapping and would make it difficult to determine the relative strength of landmark control from the distal cues. In order to get a good estimate of the percentage measurement, only recording ensembles with at least five place cells were used to calculate the remapping percentage.

Overall, 49% ($49 \pm 10\%$, $n=21$ ensembles) of the place cells remapped between sessions. Next we looked at recording sessions collected from different types of cue manipulation separately to determine whether place cell ensembles exhibited higher levels of remapping when being exposed to certain type of cue manipulation (e.g. one might predict that place cell ensembles would show a higher level of remapping when being exposed to cue conflict when comparing to cue rotation). For 90° cue rotations, which included sessions recorded both before and after rats experienced cue conflict manipulation, 42% ($42 \pm 16\%$, $n=10$) of the place cells remapped between sessions. The results collected during cue conflict sessions, 45% ($45 \pm 19\%$, $n=4$) of the place cells remapped between sessions. For recording sessions of rats experiencing the new set of four distal cues without cue manipulation, 66% ($66 \pm 10\%$, $n=7$) of the place cells remapped between sessions. Though the mean level of place cell remapping during the new distal cue sessions is higher than those from cue rotation and cue conflict sessions, one-way unbalanced Anova failed to detect a significant difference between percentage of place cells that remapped under three types of conditions ($F_{(2,18)}=2.66$; $p=0.097$). The analysis shows that in average about half of the place cells in an ensemble remapped between sessions, which suggests a high level of place cell remapping between between sessions.

Rotation of place cells

Another way to assess how coherency a place cell ensemble responds to cue manipulations is to look at the rotated angles of the place cells that are classified as rotated between sessions. If a place cell ensemble rotates its place fields, the rotated angles from the place cells should have a low level of circular variance. On the other hand, a high level of circular variance between the

rotated angles would suggest that the ensemble either remapped between sessions or failed to respond to the cue manipulation coherently. For a place cell ensemble to be used for estimating the circular variance, at least five place cells that were classified as rotated between sessions were recorded from the ensemble. As some of the recorded place cells were classified as remapped between sessions, the number of rotated place cells was smaller, especially when the level of place cell remapping was quite high. Hence there were fewer recording sessions that contained at least five place cells that rotated between sessions. Average circular variance of the rotated angle was 0.42 (0.42 ± 0.18 , $n=7$ ensembles). Due to the small number of ensembles that fulfilled the inclusion criteria, we did not analyse the data separately for each type of cue manipulation. We also would like to look at the relationship between the level of place cell remapping and the circular variance of the rotated angles. Specifically, we are interested in determining whether a coherent rotation among rotated place fields can occur even under a high level of place cell remapping. We plotted the circular variance of the place cell ensembles against the proportion of place cell remapping between sessions, which is shown in figure 5.11. We then used linear regression analysis to analyse the relationship between the two variables. We did not find any significant linear relationship between the two variables ($p=0.11$), though this could be due to the low number of samples included in the analysis ($n=7$). A R^2 of 0.43 and a positive slope suggested that high circular variance observed from a place cell ensemble is often accompanied by a high percentage of remapping. The figure also showed that the prominent remapping observed from the place cell ensembles reduced the number of rotated place cells and excluded many data points from the regression analysis.

Landmark control of the rotated place cells

We now turn our attention to the rotated angles of the place cells that were classified as rotated between sessions. We would like to determine whether the rotation of the place fields followed the rotation of any of the distal cues, i.e. the landmark control of the distal cues over the place cells. As the number of simultaneously recorded place cells varied between rats and days, the best way to assess the landmark control strength of different types of distal cues was to calculate the percentage of place cell ensembles that used the cues as a reference point. However, the recording sessions with an adequate number of rotated place cells were too limited for most analyses techniques. Instead, the proportion of place cells following each type of cues was calculated by pooling together multiple recording sessions together and an overall percentage was calculated. It should be noted that, under such an approach, recording sessions with more place cells would have more influence on the overall proportion than recording sessions with a small number of place cells recorded.

Place cells were classified as following one type of cues if the rotated angle fell within a 45° range of the rotated angles of the cues between sessions. For example, if the distal cues are

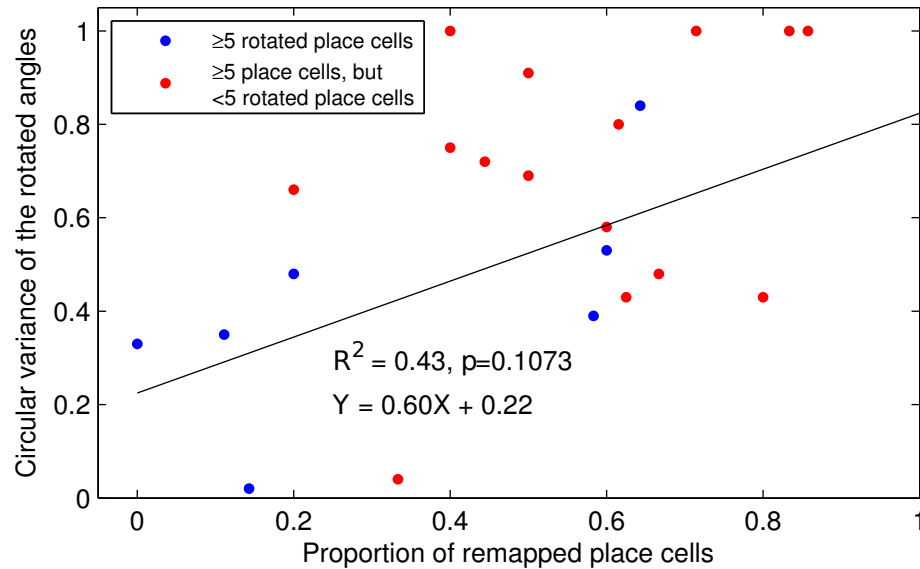


Figure 5.11: Rotation vs. remapping under 3 distal cue setting. The scatter plot illustrates the relationship between percentage remapping and coherence of rotation among simultaneously recorded place cells. The line was fitted by linear regression. A positive slope suggests that high percentage of remapped place cells is often accompanied by high circular variance of the rotated angles. However, the p -value of the estimated regression coefficient is >0.05 , suggesting that they are not significantly different from 0. Only recording sessions with at least five rotated place cells were included in the regression analysis (blue dots), recording sessions with at least five place cells, but less than five rotated place cells (due to some being classified as remapping) are plotted in red. The circular variance of the recording sessions with no rotated place cells was set to 1. The distribution of red dots suggests that high level of remapping between sessions resulted in many sessions not being included due to low number of place cells being classified as rotated between sessions.

rotated by 90° between recording sessions, than a recorded place cell is classified as following the distal cues if the rotated angle of its place field falls within the 67.5–112.5° range between sessions. On top of the two types of distal cues (i.e. the coherent and the independent cues) used in the cue manipulations to introduce cue conflict, we also added 'room cues' into the analysis, which represented the uncontrolled background information in the environment that could be used by place cells to reference their orientation. Hence if the place fields of the place cells remained in the same place between sessions while the distal cues were rotated, we classified that the rotation of the place fields was controlled by the 'room cues'.

The summary of the landmark control results is presented in figure 5.12. The chance level in the figure was calculated by determining what would be the proportion of the rotated angles falls under each category if the rotation angle was uniformly distributed between 0–360°. For example, the chance level proportion of a 45° range is $\frac{45}{360} = 0.125$. The chi-square goodness of fit test with Monte Carlo *p*-value was used to test whether the observed proportion of place cells controlled by each type of cues was significantly different than what was expected by chance. The test failed to find a significant difference for the no rotation group ($\chi^2=2.19$; $p>0.05$) nor the cue conflict group ($\chi^2=7.19$; $p>0.05$), though the test did find that the observed proportion of landmark control from the distal cues was significantly different from chance in the cue rotation group ($\chi^2=10.03$; $p<0.01$), suggesting that the observed rotation angle of the rotated place cells was different from random. However, the proportion of place cells following the distal cues in the cue rotation group was still very low (~25% of the rotated place cells followed the distal cues). Combining the analysis results from this section and the observation that a high proportion of place cells remapped between sessions suggests that remapping was the dominant response of place cells after cue manipulations. As place cell remapping appears to be the dominating response even between cue rotation sessions or the subsequent no rotation sessions with a new set of distal cues, it is difficult to determine how place cells respond to cue conflicts in this experiment. We thus modified our experiment protocol to address this issue. The methods and the results of the modified protocol will be presented in experiment two in the next two sections.

Experiment two

As reported in experiment one, after the rats experienced conflicts of distal cues in the environment, the place fields of the place cells became very unstable and the distal cues lost all ability to cue control the place cells. This experiment aims at addressing this short-coming by trying to encourage place cell ensembles to form stable environmental representations before letting the rat experienced conflicts between distal cues.

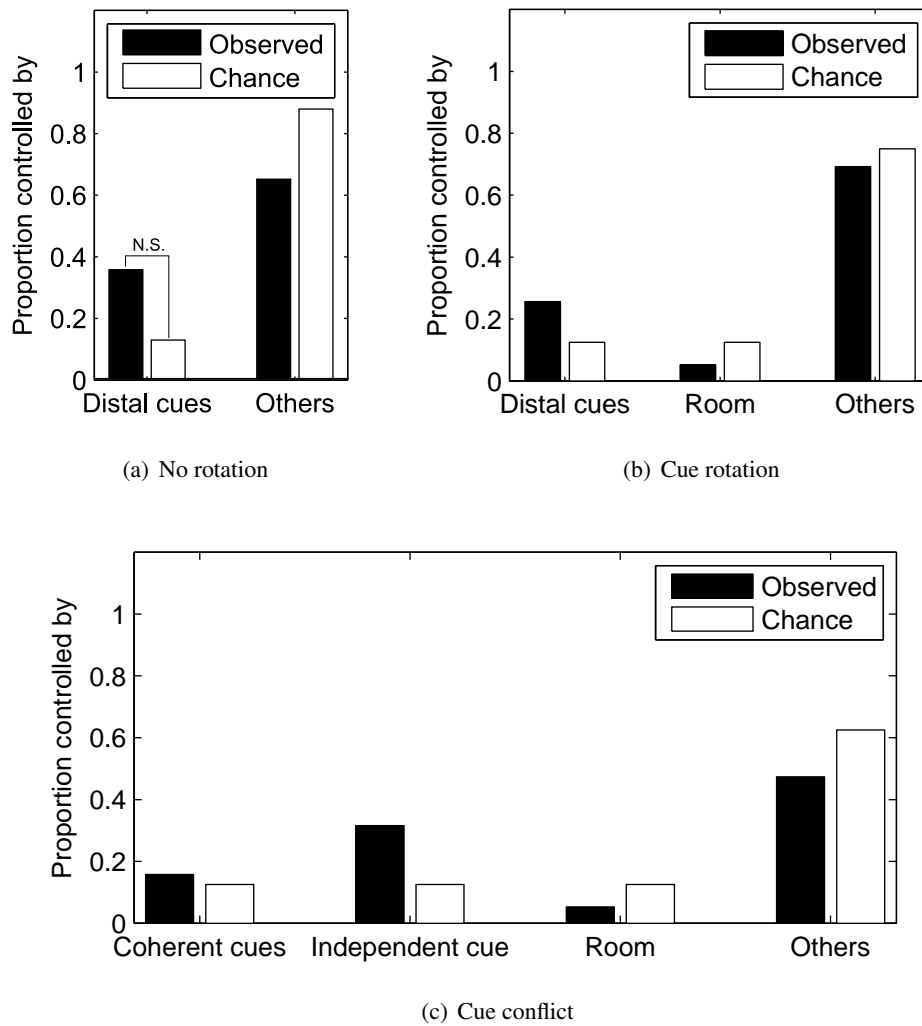


Figure 5.12: Landmark control of rotated place cells. The black bar illustrates the proportion of recorded place cells that rotated their place fields with each type of cues, and the white bar represents the proportion expected when the rotated angle is uniformly distributed. (a) shows results from recording sessions with no cue manipulations. If place cells maintained their place fields between sessions, they would be classified as following the distal cues. Chi-square test showed the observed frequency did not differ from chance. (b) summarises the recording sessions with cue rotation manipulations. Distal cues did not appear to exert strong landmark control over the rotation of place cells though the observed frequency distribution was different from chance. The room cue group encompasses those place cells that maintained their place fields relative to the external world. (c) summarises the results from cue conflict sessions. Coherent and independent cues represented portions of place cells following each type cues after cue conflict manipulations. Chi-square test suggests that the observed frequency distribution was not significantly different from a uniform distribution.

5.4 Methods

5.4.1 Subjects

Eight male adult Lister Hooded rats weighing 250–350g at the time of surgery were used. Six of the rats were used to record cells from CA1 area of the hippocampus, and two rats were used for recording cells from the entorhinal cortex. Housing and care conditions were identical to what was outlined in experiment one (section 5.2.1).

5.4.2 Recording device

The procedure was identical to what was outlined in experiment one.

5.4.3 Surgery

Surgery procedure was identical to what was outlined in experiment one for rats with unit recording device targeting CA1 of the hippocampus. For surgeries that targeted the entorhinal cortex, the assemblies were implanted at a 12° angle from the vertical plane tilting toward the posterior direction of the rat's head. Figure 5.13 provides an illustration of the implant angle. The implant coordinate was, AP -0.5 mm from the anterior border of the lambda sinus, ML +4.3 mm from midline, DV -1.4 mm from Dura.

5.4.4 Unit recording and screening

The procedures were identical to what were outlined in experiment one.

5.4.5 Experimental protocol

Apparatus

Most of the experimental setup was identical to the one used in the three cue experiment. The main differences were firstly, an 80 cm diameter circular platform with fabricated wall and no detectable asymmetric features was used as the pellet chasing environment in the experiment instead of the wooden platform used in the three cue experiment. Secondly, a new set of four distal cues were used instead of the three distal cues used in the previous experiment. A picture of the four distal cues along with the circular platform is presented in figure 5.14.

Pre-training

The procedure was identical to what was outlined in experiment one. See figure 5.3 for the distal cues used and the circular platform used in the experiment.

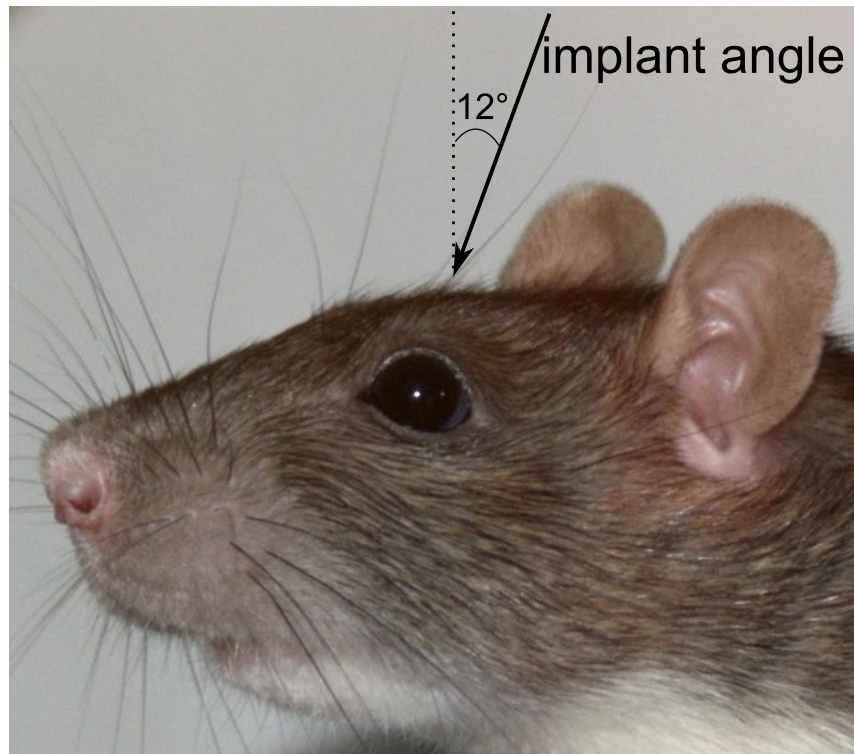


Figure 5.13: An illustration of the implant angle of the entorhinal cortex recording assemblies. The arrow on top of the rat's head illustrates the angle in which the tetrodes are inserted into the brain.

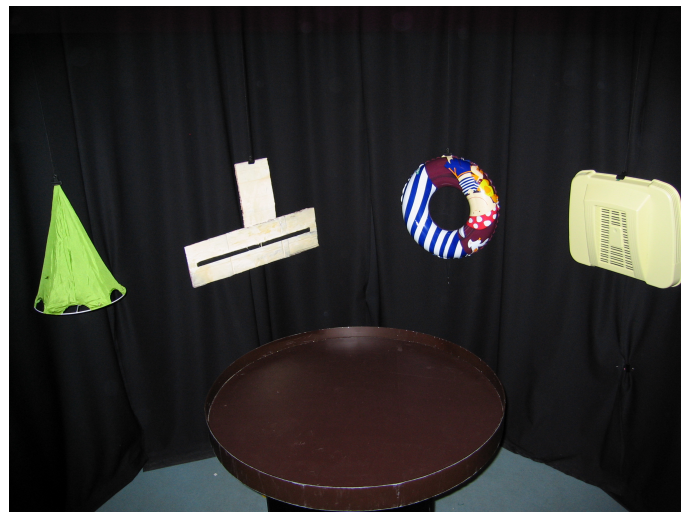


Figure 5.14: This is a photo of the curtained environment with the circular platform and four distal cues used in the experiment. Each place holder is 45° part from the neighbouring holders. The distal cues are similar in size but have distinct shapes and colour patterns.

Cue conflict

In order to address the issue of place cells exhibiting global remapping after the rats experienced cue conflict encountered in experiment one, we modified the protocol to include three coherent cues instead of two and added a habituation period during which rats could get familiarised with the distal cues before experiencing cue conflicts. After place or head direction cells were identified from screening sessions, rats were allowed to search for food pellets dropped from a ceiling mounted pellet dispenser onto the 80 cm circular platform surrounded by black out curtains while the single unit activity was recorded. There were four types of cue manipulations used in the protocol and a diagrammatic illustration of these manipulations is shown in figure 5.15. The four manipulations are,

- No rotation: The distal cues were left in their original locations between recording sessions. This was used to test whether place cells could maintain their place fields between recording sessions.
- Cue rotation: The distal cues were rotated by the same amounts, at either 90° or 135°, between recording sessions. This was used to test whether the rotation of the distal cues could exert an equal rotation from the place field of place cells or the preferred firing direction of head direction cells.
- Cue conflict: The three coherent cues were rotated together and the independent cue was rotated in conflict with the coherent cues between recording sessions. The purpose of the cue manipulation was to test whether relative stability between distal cues affects their influence on place and head direction cells.
- 1v1 conflict: Two of the coherent cues were removed and the remaining coherent and the independent cue were rotated in conflict with each other between recording sessions. Removing two of the coherent cues allow us to assess whether repeated cue conflict experience encouraged place and head direction cells to bound to the distal cues in the coherent cue group.

The experimental protocol is summarised in figure 5.16. Briefly, each rat initially had three days of habituation, which consisted of two 15 minutes recording sessions while rats searched for food pellets on the platform. No cue manipulation was given between sessions. This allowed rats to become familiarised with the experiment procedure and the distal cues, and also provided opportunities to fine tune the position of recording electrodes to maximise the number of simultaneously recorded cells. On day four, rats were given one day of cue rotation sessions, followed by two days of cue conflict sessions. On day seven, rats were given the probe sequence, which consisted of a cue rotation, a cue conflict and a 1v1 conflict manipulation

between four recording sessions. Rats were then given one day of cue rotation sessions on day eight to test the landmark control strengths of the distal cues after rats experienced the conflict and probe cue manipulations. The experiment protocol from day 9–12 was identical to day 5–8 in order to determine the effect of repeated cue manipulation experience to the distal cues' ability to exert landmark control. One rat from the CA1 place cells group, E2214, experienced a slightly different protocol where it had only one day of cue conflict sessions per repetition instead of two for the other rats.

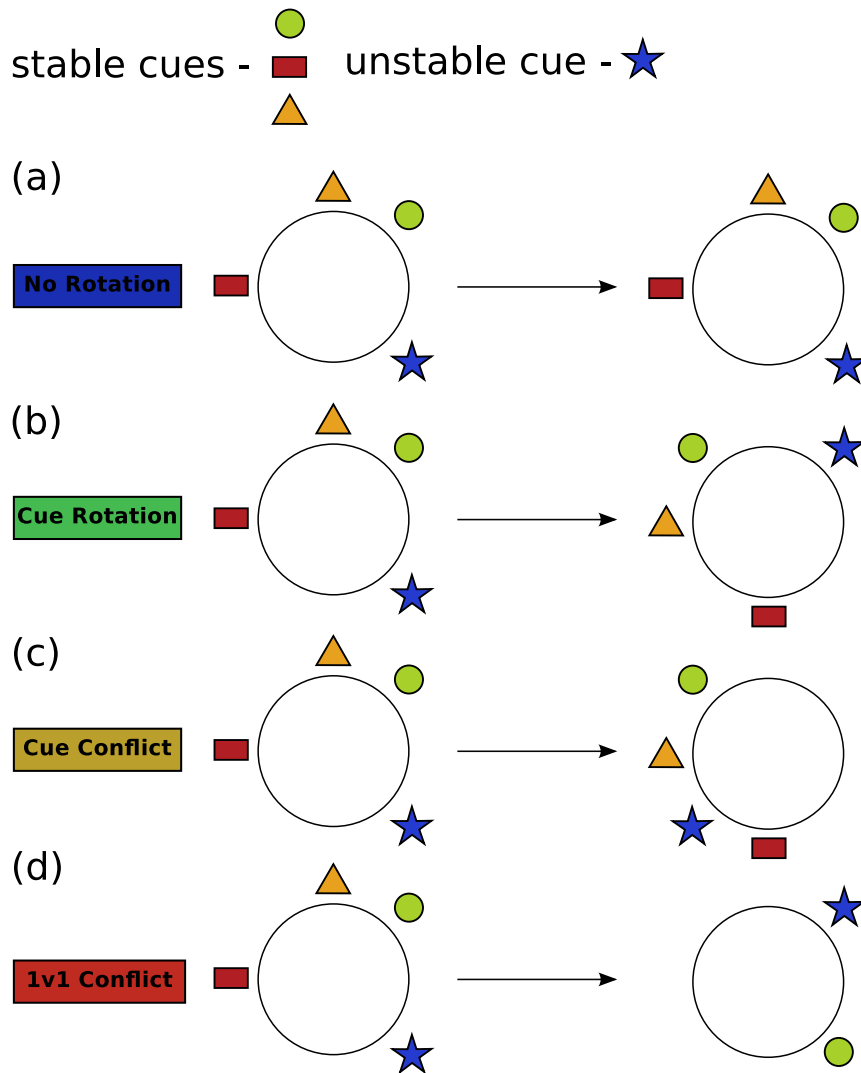


Figure 5.15: Different types of cue manipulations. Three coherent cues and one independent cue were used in the experiment. The symbols representing the coherent cues and the independent cue in the diagram are shown at the top of the figure. (a) Positions of the distal cues remain constant between sessions. (b) Distal cues are rotated coherently between sessions. (c) The coherent cues and the independent cue are rotated by different angles between sessions, creating a conflict between the two cue groups. (d) Two of the coherent cues are removed between sessions and the remaining coherent and independent cues are rotated in conflict with each other.

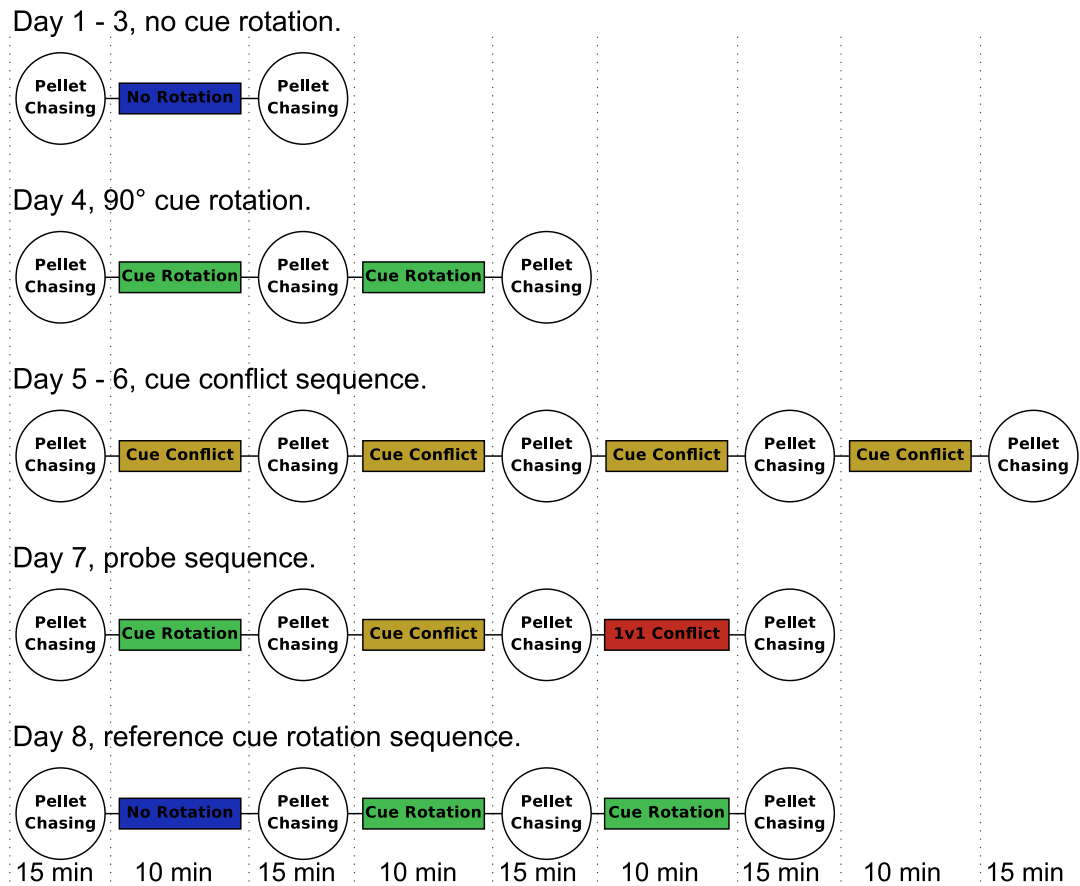


Figure 5.16: flowchart illustration of the cue manipulation protocol. The cue configurations of different types of cue manipulations are depicted in figure 5.15. The two cue rotations each day in day four and eight were 90° and in opposite directions, i.e. a clockwise cue rotation was followed by an anti-clockwise rotation and vice versa. During the cue conflict sequence in day 5–6, the cue configuration in the same day did not repeat. As there were eight possible locations for distal cues in the curtained environment, with three coherent cues (whose relative configuration cannot change) and one independent cue used, there were only five different cue configurations for cue conflicts. All five cue configurations were given in the cue conflicts days, resulting in five 15 minutes recording sessions per day. Also the absolute location of each distal cue (i.e. the locations of distal cues relative to the environment) did not repeat in the same day. This was to control for the contributions of uncontrolled room cues to the landmark control of the distal cues.

Cue control of individual distal cues

Two of the six rats from the CA1 place cells group underwent additional cue manipulation sequences. The sequence is illustrated in figure 5.17. One concern for interpreting the results from the 1v1 conflict cue manipulation is that two of the coherent cues were removed and it was unclear how this would affect the influence of the remaining cues on place and head direction cells. Here we tested, after removing three distal cues from the environment, how well the remaining cue could control the orientation of place fields after it was rotated between recording sessions.

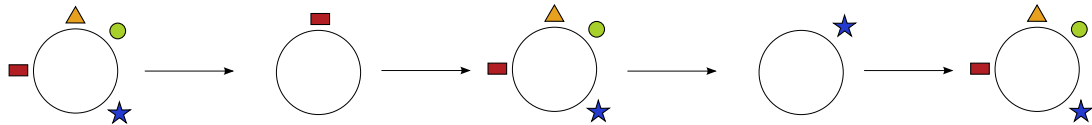


Figure 5.17: An illustration of the cue manipulation sequence used to test landmark control of individual cues. The sequence was designed to test whether each distal cue alone was capable of exerting landmark control over place cells. Landmark control of each cue was tested by removing three other cues from the curtained environment and rotating the remaining cue by 90° . The cue was then rotated back to the original position and the removed cues were again restored to the original position in the subsequent session. The sequence was repeated to test the cue control of all four cues used in the experiment. Due to the constraints on the number of session rats could perform each day, two cues were tested everyday, taking two days to test all the distal cues used in the prior experiment.

5.4.6 Data analysis

Hippocampal CA1 place cells

The data analysis procedure for the CA1 place cell group was identical to what was outlined in experiment one.

Entorhinal head direction cells

The unit isolation procedure was identical to that used for analysing recording data obtained from the CA1 area of hippocampus and any unit whose average waveform had peak amplitude $>80\mu\text{V}$ was included for further analysis. The circular histogram of these units was then constructed by calculating angular firing rates over a 22° wide sliding window with 1° increment, giving rise to 360 angular firing rate values for every unit. The length $|r|$ of the directional vector, which measured the strength of directional firing was then calculated by,

$$|r| = \sqrt{\left(\frac{\sum_i f_i \sin(a_i)}{\sum_i f_i}\right)^2 + \left(\frac{\sum_i f_i \cos(a_i)}{\sum_i f_i}\right)^2} \quad (5.4)$$

and the preferred firing direction (PFD) A of the unit was calculated by,

$$A = \arctan \left(\frac{\sum_i \frac{f_i \sin(a_i)}{\sum_i f_i}}{\sum_i \frac{f_i \cos(a_i)}{\sum_i f_i}} \right) \quad (5.5)$$

where f_i is the i^{th} angular firing rate and a_i is the angle of the i^{th} bin from the polar histogram. An unit isolated from the entorhinal cortex recording data was only classified as a head direction (HD) cell if $|r|$ of the unit was >0.3 and the maximum firing rate in the circular histogram was >3 Hz. The shift angle of a HD cell's PFD between two sessions was simply the difference between the PFD calculated from each session. We did not make any attempt to separate pure head direction cells from grid by head direction cells. A cell would be included in subsequent analyses if it exhibited strong head direction modulation in both recording sessions. Two examples of the recorded head direction cells with their circular histograms constructed from two consecutive recording sessions are shown in figure 5.18.

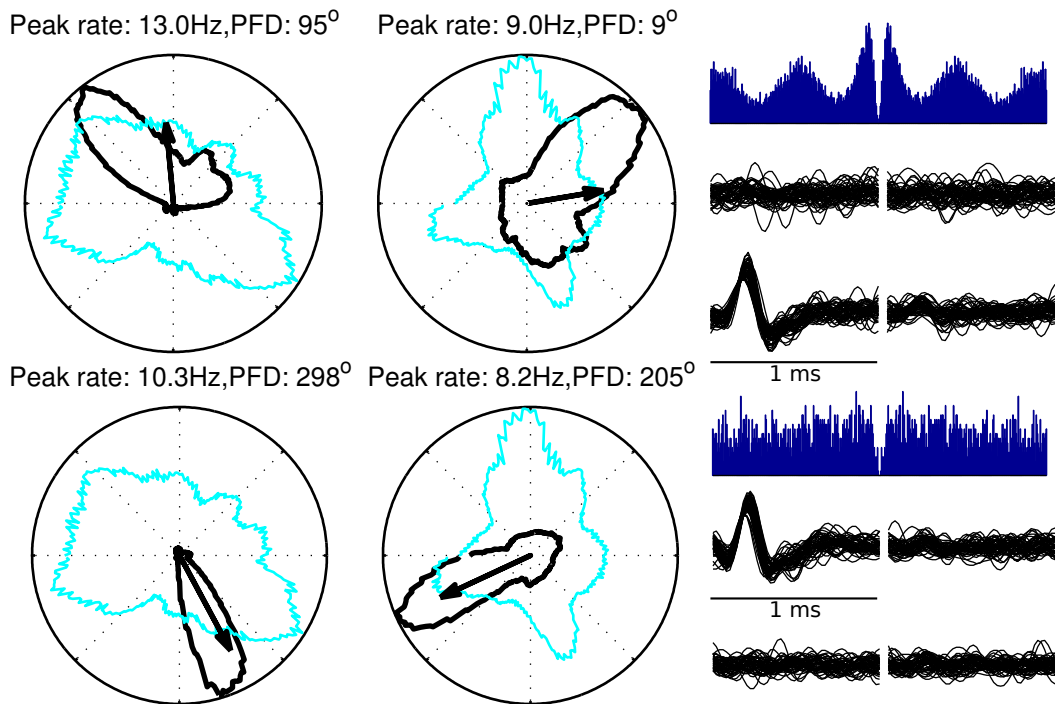


Figure 5.18: Two examples of head direction cells. Each row of the figure is one example. The first and second panels of each example are circular histograms of the head direction cell constructed from two consecutive recording sessions. The distal cues in the environment were rotated between sessions. The black line in a circular histogram represents average firing rates of the head direction cell when the rat faced the corresponding direction whereas the cyan coloured line represents the normalised amount of time the rat spent facing each direction during the recording session. The black arrow is the circular mean of the firing rate histogram. The third panel shows the waveforms and the time autocorrelogram of the head direction cell. The time autocorrelogram of one example showed strong theta modulation, but the firing of another cell was not modulated by theta frequency.

5.5 Results

5.5.1 Histology

The position of the electrode tracks from five of the six rats with place cells were identified from the histology to either target or have gone through the CA1 cell layers. None of the electrode tracks ended anywhere near the CA3 cell layer, suggesting that the recorded place cells were originated from the CA1 cell layer. We failed to obtain histology from one of the rats as insufficient formalin was used for preservation which resulted in irreversible damage of the brain tissue. An example of the histology is given at figure 5.9 in experiment 1.

We failed to clearly identify the electrode tracks targeting layer III of entorhinal cortex from the two rats used in the experiment. Thus the locations of the recording electrodes can only be inferred via the implant coordinates and unit properties. We found that some of the units recorded concurrently with the head direction cells showed a grid like spatial firing pattern similar to what was described in (Fyhn et al. 2004) (see figure 3.2 for an example). Some of these grid cells are also conjunctive cells similar to the ones reported by Sargolini et al. (2006) (see figure 5.19). Based on these observations, we conclude that the recorded head direction cells most likely originated from the entorhinal cortex.

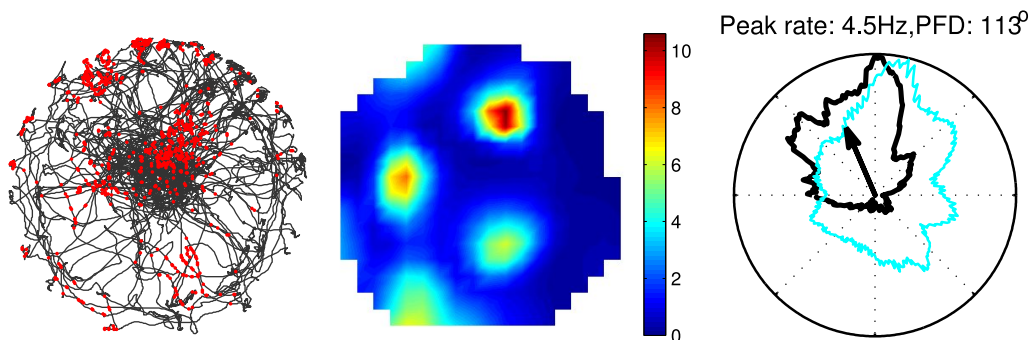


Figure 5.19: The figure presents an example of a conjunctive cell that was recorded simultaneously with the head direction cells from the rats with electrodes targeting layer III of entorhinal cortex. The spatial histogram shows multiple place fields organised in a grid like pattern and the polar histogram showed that the cell was also strongly modulated by the orientation of the rat's head.

5.5.2 Cue manipulation

Six rats with recording electrodes targeting CA1 area of hippocampus were used in this experiment. On average, 142 cells (~ 24 cells per rat per day) were recorded from the six rats each day and on average 81 cells were identified as place cells every day. A summary table of the number of cells and pyramidal cells recorded from the six rats is presented in figure 5.20.

		Day 1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12
E2204	Total cells	10	11	12	14	7	10	11	9	8	9		
	Pyramidal cells	2	3	5	7	1	4	5	4	5	2		
E2209	Total cells	11	7	9	9	9	10	13	15	11	15	15	15
	Pyramidal cells	4	1	2	5	6	7	10	10	9	14	13	13
E2210	Total cells	lost	8	8	6	7	10	12	12	13	20	15	15
	Pyramidal cells		3	3	5	6	6	7	8	8	12	9	10
E2211	Total cells	21	23	28	32	42	38	34	36	33	35	34	39
	Pyramidal cells	13	16	23	16	22	27	20	24	20	28	14	24
E2218	Total cells	lost	lost	33	23	24	26	25	35	38	37	31	34
	Pyramidal cells			23	14	20	19	21	21	31	29	29	29
E2221	Total cells	lost	lost	38	43	60	41	50	39	50	42	41	47
	Pyramidal cells			16	19	30	17	27	18	26	28	14	25

Figure 5.20: The number of cells recorded from CA1 of the hippocampus in the four cue experiment. The number of cells and the number of those classified as pyramidal cells is presented in the table.

Place field rotation of the place cells

The main goal of the experiment is to explore how different types of cues compete with each other to exert landmark control over the rotation of place cells in a cue conflict situation. Similar to what was done in experiment one, we first looked at whether the proportion of place cells following each type of cues was different from what would be expected if the rotation angle of the ensemble was uniformly distributed from 0–360°. The ensemble angle was calculated by equation 5.5 and only sessions with at least five rotated place cells were included in the analysis. Figure 5.21 illustrates the average proportion of place cell ensembles controlled by each type of cues and the expected proportion if the rotation angle was random. Chi-square goodness of fit test with Monte Carlo p -value was used to test whether the observed cue control distribution was significantly different from what would be expected by random. We found that the observed cue control distribution was significantly different from random in no-rotation manipulations ($\chi^2=30.23$; $p<0.001$), cue rotation manipulations ($\chi^2=131.68$; $p<0.001$), and cue conflict manipulations ($\chi^2=50.38$; $p<0.001$), but not in probe manipulations ($\chi^2=6.82$; $p>0.05$). The analysis suggests that the rotation angle of place cell ensembles was not random in all but the probe manipulations. Figure 5.21 also shows that the majority of the place cell ensembles followed the distal cues in no-rotation and cue rotation sessions. However, additional analyses will be needed in order to identify whether any distal cue exerted significant control over the rotation of the place cell ensembles.

Next we analysed the place cell ensembles recorded from the four days of cue conflict sessions (e.g. day 6–7 and day 9–10, see figure 5.16) to determine whether the coherent cues exerted greater control over the rotation of place cell ensembles over the independent cue. To assess relative landmark control between the different cues, we calculated the proportion of place cell ensembles that were controlled by each type of cues each day. As shown in figure 5.16, each day of cue conflict sequence contained five separate recording sessions with

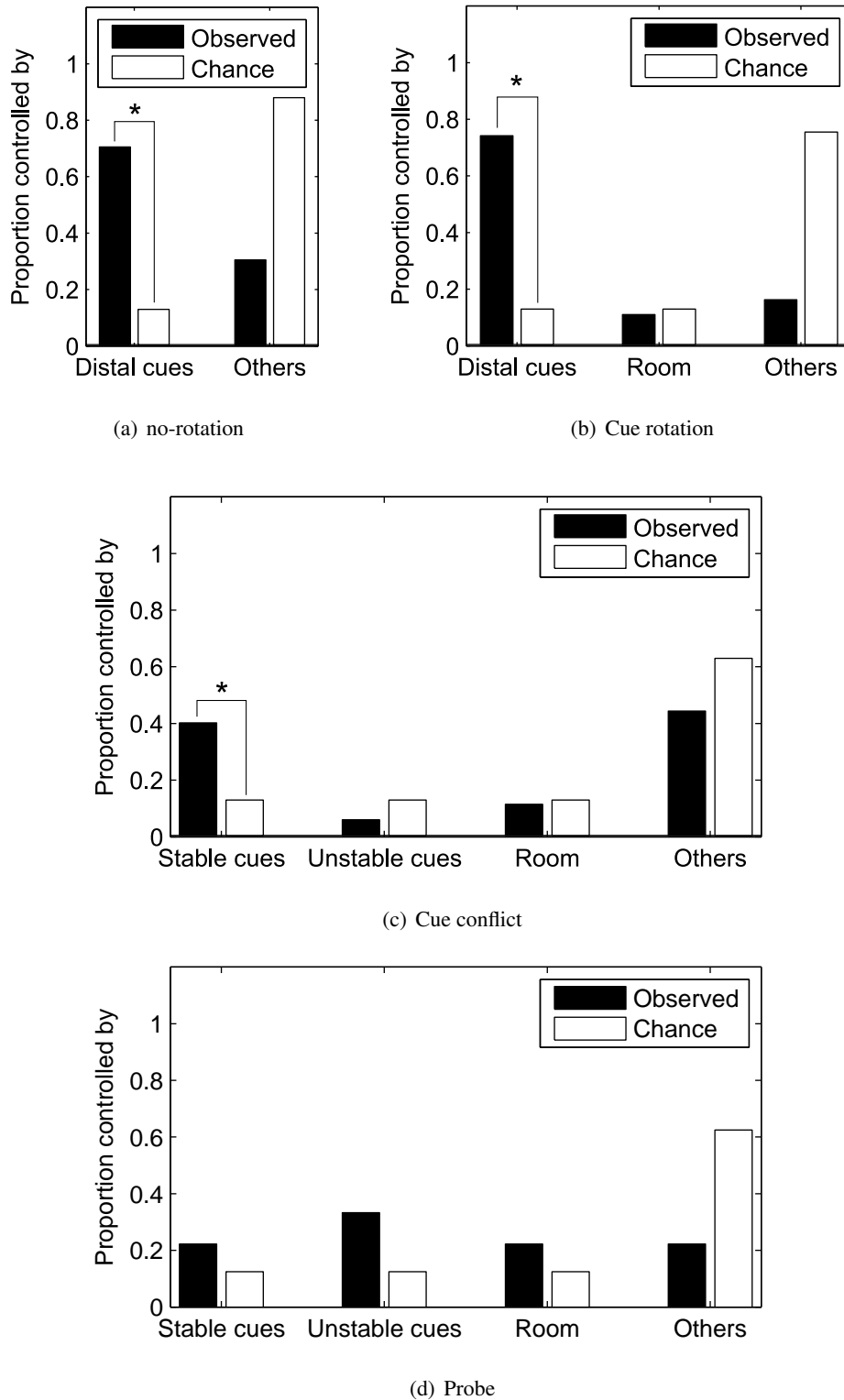


Figure 5.21: Landmark control of place cell ensembles with different cue manipulation conditions. Black bars show the proportion of place cell ensembles rotated with each type of cues, and white bars represent the proportion expected when the rotations are random. (a) shows results collected from recording sessions with no cue manipulations between them, (b) summarises the results collected under the cue rotations condition, (c) are the results from the cue conflict sessions and (d) are the results from the probe sessions. Chi-square test shows that the observed frequency distribution is significantly different from the uniform distribution in the no-rotation, cue rotation and cue conflict sessions, but not from the probe sessions.

different distal cue configurations. Each consecutive pair of recording sessions can be used to determine how place cell ensembles resolve the introduced cue conflict, giving rise to four measurements of ensemble cue conflict resolution every day (i.e. session 1–2, 2–3, 3–4, 4–5). We thus used the four measures to calculate the proportion of place cell ensembles following each type of cues. We then used two way Anova to analyse, 1) whether the proportion of place cell ensembles following each type of cues was different, i.e. the type of cues factor and 2) whether the proportion changed with additional cue conflict experience, i.e. the repetition factor. The analysis found a significant difference from the type of cues factor ($F_{(2,48)}=21.2$; $p<0.001$) but found no significant difference across the repetition factor ($F_{(3,48)}=0.57$; $p>0.05$). *Post hoc* analysis using Sidák correction for multiple comparison found that the proportion of place cell ensembles following the coherent cues was significantly higher than those following the independent and the room cues. The analysis shows that, during cue conflict resolution, the coherent cues exerted greater control over the rotation of the place cell ensembles. However, additional exposure to cue conflicts did not encourage nor discourage the place cell ensembles to follow the coherent cues in the environment. Figure 5.22 summarises the results.

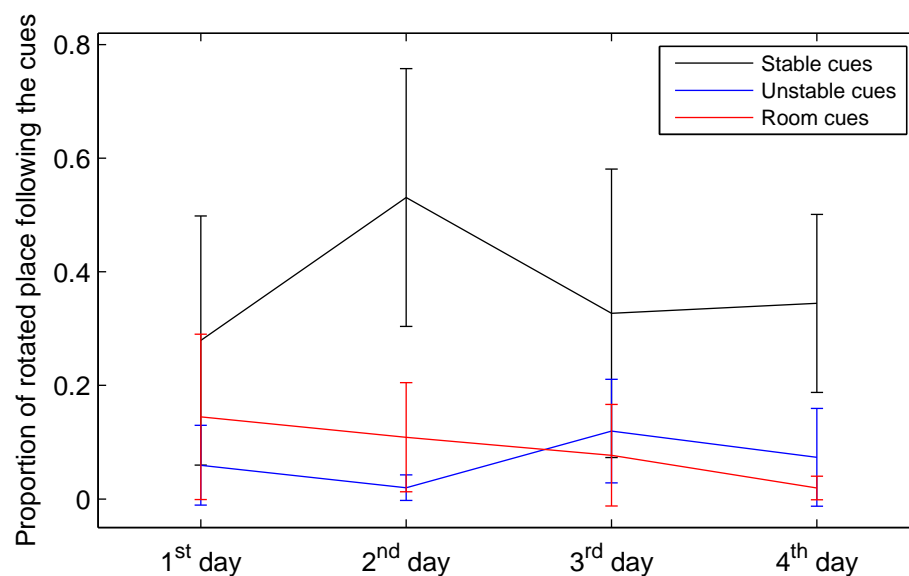


Figure 5.22: Proportion of place cells ensembles controlled by each type of cues during cue conflict sequences. Mean \pm 95% C.I. of the proportion was plotted. More rotated place cells followed the coherent cues when comparing to the independent and room cues. However, repeated cue conflict exposure did not encourage more place cell to follow the coherent cues set, as evident from the lack of significant effect from the replication factor when two-way Anova was used for the analysis.

The analysis above made the assumption that the mean rotation angle of a place cell ensemble is representative of the response of the place cells. However, if the majority of the place cells in an ensemble either remap or rotate independently from each other, the mean rotation angle of the ensemble is not representative of the ensemble's response. In the subsequent sec-

tions, we explore whether the mean rotation angle is representative of an ensemble's response in this experiment.

Remapping of the place cells

Similarly to experiment one, we only used recording sessions with at least five place cells to calculate the proportion of place cells that remapped between sessions. Overall, 20% ($20.29 \pm 2.31\%$, $n=160$ ensembles) of the place cells remapped between sessions. The level of remapping was much lower than that observed in the experiment one, which is presented in section 5.3.2. We thus tested whether the observed proportion of remapped place cells differed significantly from that observed in experiment one using Wilcoxon rank sum test. The mean percentage of multiple recording sessions from the same rat was used. The test found the level of place cell remapping observed in experiment two is significantly lower than that observed in experiment one ($p < 0.05$, ranksum = 24), which suggests that the modified protocol discouraged place cell remapping and more place cells in the ensemble rotated their place fields between sessions. Whether the rotated place cells in an ensemble rotated coherently will be determined in the next section where we will be looking at the circular variance of the rotated angles.

Next we examined whether the level of place cell remapping was different under different cue manipulation conditions. The average remapping percentage under the four cue manipulation conditions, i.e. no-rotation, cue rotation, cue conflict, and probes, were calculated. One-way repeated measure Anova returned a small but significant difference between the means ($F_{(3,15)}=3.43$; $p < 0.05$). Sidák correction for multiple comparison was used as the *post hoc* analysis and found that the level of place cell remapping in the no-rotation manipulation was significantly higher than that in the probe manipulation, which was a surprising result as the configuration of the distal cues changed dramatically in probe manipulations but stayed the same in no-rotation manipulations. A bar chart summarising the result is presented in figure 5.23.

As described in section 5.4.5, the cue manipulation protocol used in day 9–12 was the same as that in day 5–8 for five of the six rats used in the experiment. We thus explored whether repeated exposure to cue manipulations affected the level of place cell remapping. Recording sessions were separated into those obtained during the first cue manipulation sequence and those collected from the repetition. A two-way Anova was used to test the effect of time and cue manipulation conditions on the level of place cell remapping. When multiple recording sessions existed for the same combination of factors (e.g. rats were exposed to the cue conflict manipulations for multiple times in each cue manipulation sequence), the mean value was used in the analysis. Anova detected significant main effects for both cue manipulation condition factor ($F_{(3,32)}=3.03$; $p < 0.05$), and the time factor ($F_{(1,32)}=5.58$; $p < 0.05$). The interaction effect

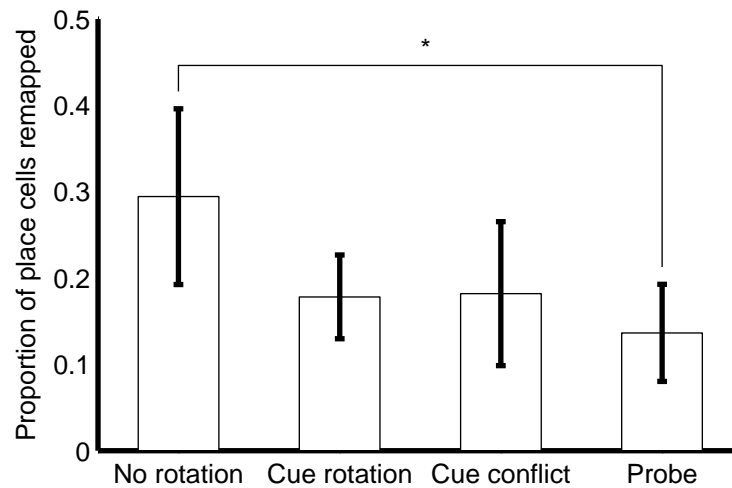


Figure 5.23: Percentage of place cells remapped after the four types of cue manipulation. Error bars were constructed using 95% confidence interval (C.I.) of the samples. A diagram of the different types of cue manipulations can be found in figure 5.15. One-way repeated measure Anova and *post hoc* analysis identified the mean place cell remapping percentage under no-rotation condition was significantly higher than those observed under probe cue manipulations.

between the two factors was not significant ($F_{(3,32)}=0.54$; $p=0.66$). *Post hoc* analysis using Sidák correction for multiple comparison found that the level of place cell remapping was significantly higher in day 9–12 than in day 5–8, which suggests that repeated exposure to cue manipulation increases the level of place cell remapping and thus reduces the stability of place fields between sessions. Though as we don't have a control group of rats with a comparable amount of experimental procedure experience but without cue manipulation, we cannot rule out the possibility that the increased level of place field instability is due to repeated exposure to the experiment procedure instead. The result is summarised in figure 5.24.

Circular variance of the rotated place cells

In the previous section we looked at the remapping population of place cells and concluded that the interdependence of the remapping and the rotation of place cells was weak. In the subsequent analysis, we explore the consistency of the rotation angle of the rotated place cells in an ensemble (as represented by the circular variance), which would give us additional information on the stability of the place representation from the place cell ensembles. The average circular variance observed from place cell ensembles with least five rotating place cells was 0.13 (0.13 ± 0.012 , $n=135$). This accounts for 84% of the recorded place cell ensembles that contained at least five place cells. Because of the low level of place cell remapping, most of the place cells in an ensemble were classified as rotated between sessions and only a few of the place cell ensembles were excluded due to not having enough place cells that rotated

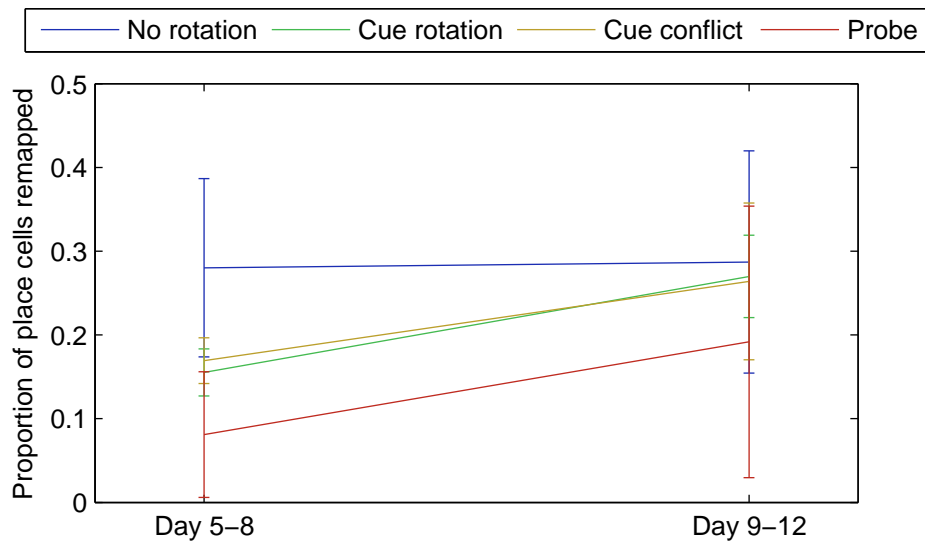


Figure 5.24: Effects of repeated cue manipulation experiences on the remapping of place cells. The figure plots mean \pm confidence interval (C.I.) of the proportion of recorded place cells that remapped between sessions during the first and second replication of the cue manipulation sequence. The results for different cue manipulation conditions are plotted separately. Two-way Anova found significant effect from both replication (i.e. the time factor) and cue manipulation conditions.

between sessions. Based on the observation of the low place cell remapping level shown in the previous section and low circular variance from the rotation angles of the rotated place cells, we conclude that place cell ensembles in experiment two maintained stable place representation between sessions and thus the dominant response of a place cell ensemble after cue manipulations was the rotation of its place fields.

To investigate whether the circular variance of the rotated place cells in an ensemble varied systematically under different cue manipulation conditions, we grouped the recording sessions accordingly. The mean circular variance was used when multiple recording sessions were collected from one rat experiencing a cue manipulation condition multiple times. A bar graph summarising the result is presented in figure 5.25. One way repeated measure Anova finds that there is a significant difference between circular variances under different cue manipulation conditions ($F_{(3,12)}=3.99$; $p<0.05$). Due to the heterogeneous variance observed between groups, (as represented by the error bars in figure 5.25), we used Mauchly's Test to determine whether the sphericity assumption of repeated-measure Anova was still tenable and found that the sphericity assumption was not rejected ($p > 0.05$) by the test. *Post hoc* analysis using Sidák correction for multiple comparison identified the mean circular variance observed in the no-rotation cue manipulations was significantly higher than that in the probe manipulations. The result mirrors what was observed from the place cell remapping level measurement (see figure 5.23) and surprisingly found that the level of variation was higher in the no-rotation cue

manipulation when compared to the probe manipulation, which changed distal cue configuration dramatically.

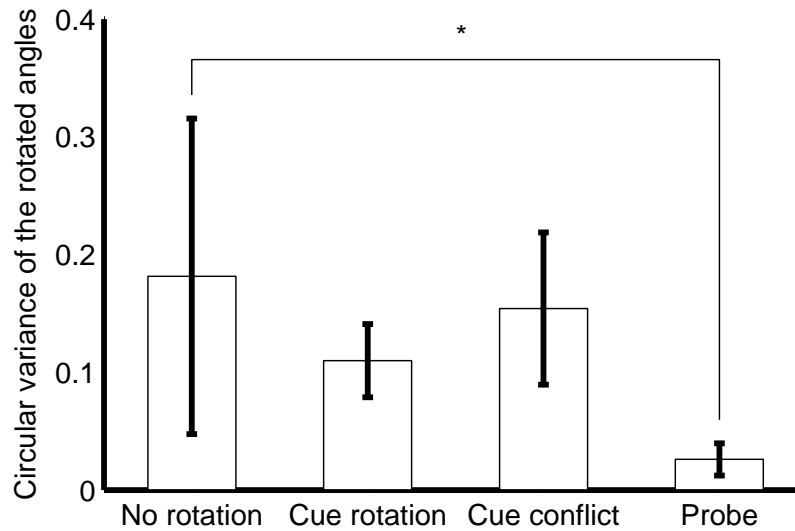


Figure 5.25: Circular variance of the rotated place cells. The bar graph shows the mean \pm 95% confidence interval (C.I.) circular variance of rotated place cells under different cue manipulation conditions. The means between the no cue rotation and probe conditions are significantly different from each other ($p < 0.05$).

We also investigated whether repeated exposure to cue manipulations affects the rotation coherence of place cell ensembles. We first separated the recording sessions into those obtained from the first and second replication of the cue manipulation sequence. Similarly the mean values from multiple sampling within the same subject were used in the analysis. The circular variance of rotated place cells under different cue manipulation conditions during the first and the second replication is shown in figure 5.26. The analysis again identified the cue manipulation condition factor as being significantly different ($F_{(3,32)}=3.39$; $p < 0.05$). Sidák correction for multiple comparison found that the circular variance of the rotated place cells was significantly lower than those observed in cue conflict sessions. However, neither the replication factor ($F_{(1,32)}=3.03$; $p=0.09$) nor the interaction ($F_{(3,32)}=0.47$; $p=0.71$) was significant. This suggests that, unlike what was observed in the remapping level of place cell ensembles (see figure 5.24), the circular variance of the rotation angles in a place cell ensemble did not increase after repeated exposure to cue manipulations.

Relationship between rotation coherence and remapping

As in the subsequent analyses we will be looking at how place cell ensembles rotated with the distal cues in the environment and hence will only concentrate on place cell ensembles with at least five place cells that rotated between sessions. There is a risk that, by only selecting

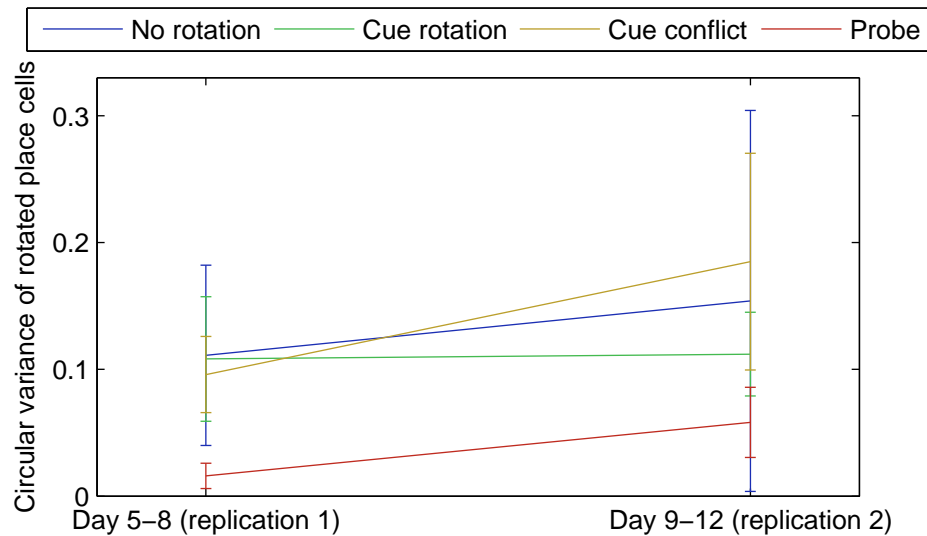


Figure 5.26: Circular variance of the rotated place cells in the first the second replication. The figure plots the mean \pm 95% C.I. circular variance of rotated place cells in the first and second replication of the cue manipulation sequence. Results from different cue manipulation conditions are plotted separately. Two-way Anova shows significant difference between cue manipulation conditions, but neither the replication nor the interaction factor was significant.

the place cell ensembles with at least five place cells that rotated between sessions, we might bias our sampling to those ensembles with a low level of place cell remapping. Here we thus explore the relationship between remapping level and circular variance to determine whether the selection criterion will introduce a strong sampling bias. A linear regression analysis was used to explore the relationship between place cell remapping and rotating circular variance. Only recording sessions with at least five rotating place cells were included in the analysis. Figure 5.27 shows the scatter plot of the recording sessions that fulfil the criteria. The x-axis of the scatter plot is the proportion of place cells that remapped between sessions and the y-axis is the circular variance of the rotated angles of the cells that rotated in an ensemble. The result of the regression analysis is represented by the black line. The small R^2 value suggests that the percentages of remapped place cells provide little explanatory power to the observed circular variances from the recording sessions. This suggests that a percentage of place cell remapping does not directly translate to the loss of rotation coherence. Analysis using Spearman's rank correlation however suggests that there is a weak but significant positive correlation between the two variables ($\rho=0.30$, $p<0.001$, $df=133$).

One concern for excluding the recording sessions with fewer than five rotated places would be that this elimination selectively ignored recording sessions with high proportion of place cells being classified as remapped between sessions. To explore whether such concern could have major effect on the analyses, we plotted quantile-quantile plot of remapping percentage

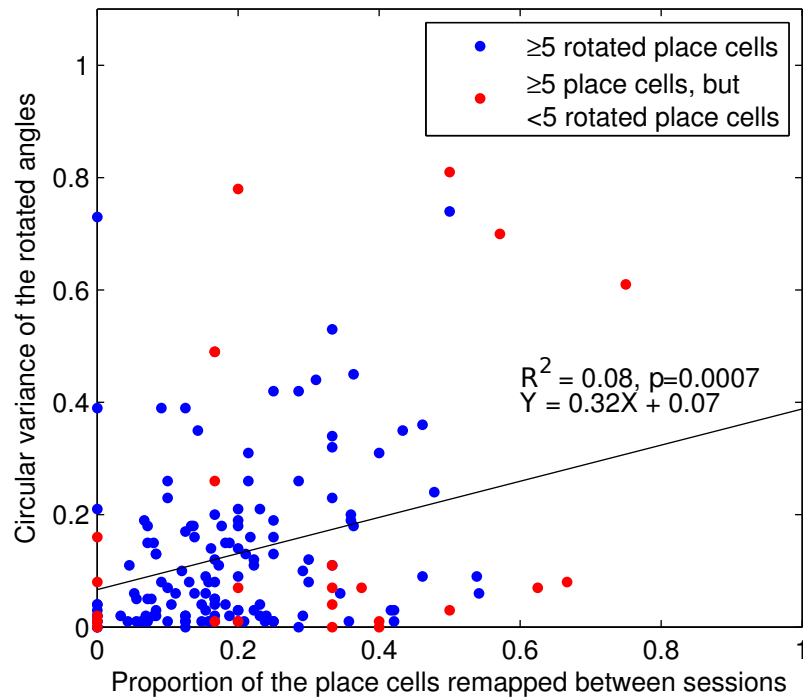


Figure 5.27: Relationship between rotation coherence and remapping in the four distal cues experiment. The line is fitted by linear regression. Despite a significant p -value, the small R^2 suggests that linear regression does not adequately explain the relationship between the remapping and circular variance of place cell ensembles. Recording sessions with at least five place cells but fewer than five rotating place cells due to some being classified as remapped between sessions were also plotted in the scatter plot as red dots. These data points were not included in the analysis. The red dots do not appear to concentrate on recording sessions with a high level of place cell remapping, which addresses the concern that excluding recording sessions with less than five rotating place cells might selectively remove recording sessions with high place cell remapping percentage.

between recording sessions with fewer than five rotated place cells and those with at least five place cells rotated between sessions. The plot is shown in figure 5.28. Despite a tendency of recording sessions with less than five rotated place cells to have higher remapping ratio, which would be expected as higher level of place cell remapping suggests a smaller number of rotated place cells, the effect is small and most of the excluded data points also have low remapping ratios. Combined with the earlier observation that only 16% of the recording sessions were excluded due to the number of rotated place cells restriction, we conclude that the effect of this exclusion criteria would be limited.

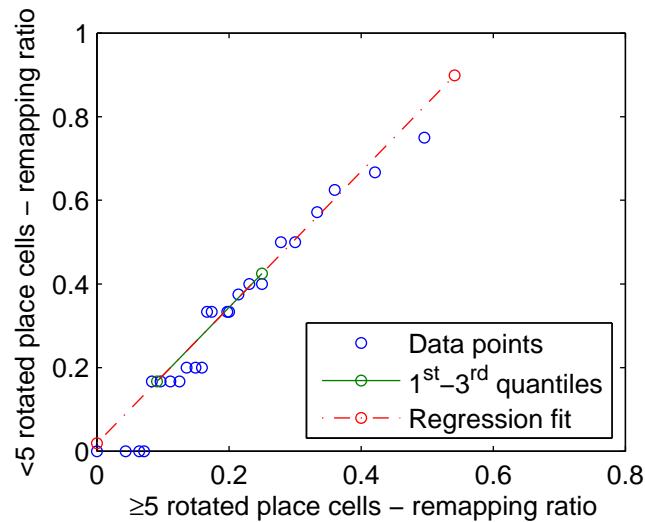


Figure 5.28: Quantile plots to compare remapping ratio between sessions having ≥ 5 rotated place cells and sessions with < 5 rotated place cells. It is a concern that, by ignoring sessions with less than five rotated place cells for some of the analyses, we would be biased against recording sessions with high remapping percentage. The quantile-quantile plot showed that sessions with less than five rotated place cells did have a tendency of having higher remapping ratio, evident from the line of the regression fit tilting towards the Y-axis, which represents the remapping ratios of recording sessions having less than five rotated place cells. However, the range of remapping ratio observed between the first and third quantiles was 0.2–0.4, suggesting low remapping ratios in general for both groups of data points.

Cue control of environmental cues

In the subsequent sections, we analysed the ensemble rotation data in a slightly different way. Instead of looking at the proportion of place cell ensembles following each type of cues, we looked at whether each type of cues exerted significant control over the rotation of place cell ensembles using circular statistics. Again, we only included place cell ensembles with at least five place cells that rotated between sessions. We then used V-test to determine whether the rotation clustered significantly around the cues. The results from the no-rotation and cue rotation sessions are plotted as circular histograms in figure 5.29. The rotation angles in the circular histograms were referenced to the cues that had been tested for significant landmark control.

For example, if we are testing the landmark control of the distal cues, a 0° in the circular histogram means the ensemble rotated with the distal cues. In the no-rotation session (figure 5.29(a)), rotation of the place ensembles were significantly clustered around 0° ($|r|=0.51$; $p=0.017$), which suggests that the place cell ensembles could maintain the orientation of their place fields between sessions either using the distal cues or some other uncontrolled room cues in the environment. In the cue rotation sessions, rotation of the place cell ensembles were significantly controlled by the rotation of the distal cues ($|r|=0.55$; $p<0.001$), but not not the uncontrolled room cues in the environment ($|r|=0.10$; $p=0.221$). See figure 5.29(b) for the circular histograms. The analysis verified that the rotation of the distal cues exerted significant control over the rotation of the place cell ensembles.

Rotation of the place cell ensembles after cue conflict manipulations was now analysed. The results are summarised in figure 5.30, and, among the three types of cues analysed (coherent cues, independent cue and room cues), only the coherent cues exerted significant control over the rotation of the place cell ensembles ($|r|=0.32$; $p<0.001$). For the ensemble rotation data collected after probe cue manipulations, none of the cues analysed showed significant control over rotation of the place cell ensembles. The analysis result showed that after cue conflict manipulations, the coherent cues were the only type of cues that exerted significant rotation control over place cell ensembles whereas after probe manipulations, the place cell ensembles appeared to rotate irrespective of any of the cues in the environment.

It has been shown that repeated cue conflict experience can cause the distal cues to lose their ability to control the rotation of place cells (Knierim et al. 1995). To determine whether the landmark control strength of distal cues was adversely affected by rats' repeated experiences to cue manipulations, results from cue rotation sessions recorded before any cue conflict sessions (day 4), after the first replication of the cue manipulation sequence (day 8), and after the second replication of the cue manipulation sequence were analysed separately (day 12). The results are summarised in figure 5.32. The distal cues exerted significant landmark control over ensemble rotations at all these time points ($|r|=0.99$; $p<0.001$ before cue conflict, $|r|=0.43$; $p<0.05$ after first replication of cue manipulation sequence and $|r|=0.67$; $p<0.001$ after the second replication). The result suggests that the rats continued to pay attention to the distal cues in the environment throughout the experiment, which excludes the scenario that rats ceased to consider the orientation of the distal cues in the environment some time during the experiment and allows us to interpret the observed ensemble rotations as responses to the cue manipulations throughout the experiment.

In order to examine the effect of repeated exposure to cue conflict manipulation on the landmark control of place cells, recording sessions collected on different days of cue conflict experience were analysed separately. As shown in figure 5.33, the rotation of place cell ensembles clustered significantly around the coherent cues on three of the four days. Circular V-test

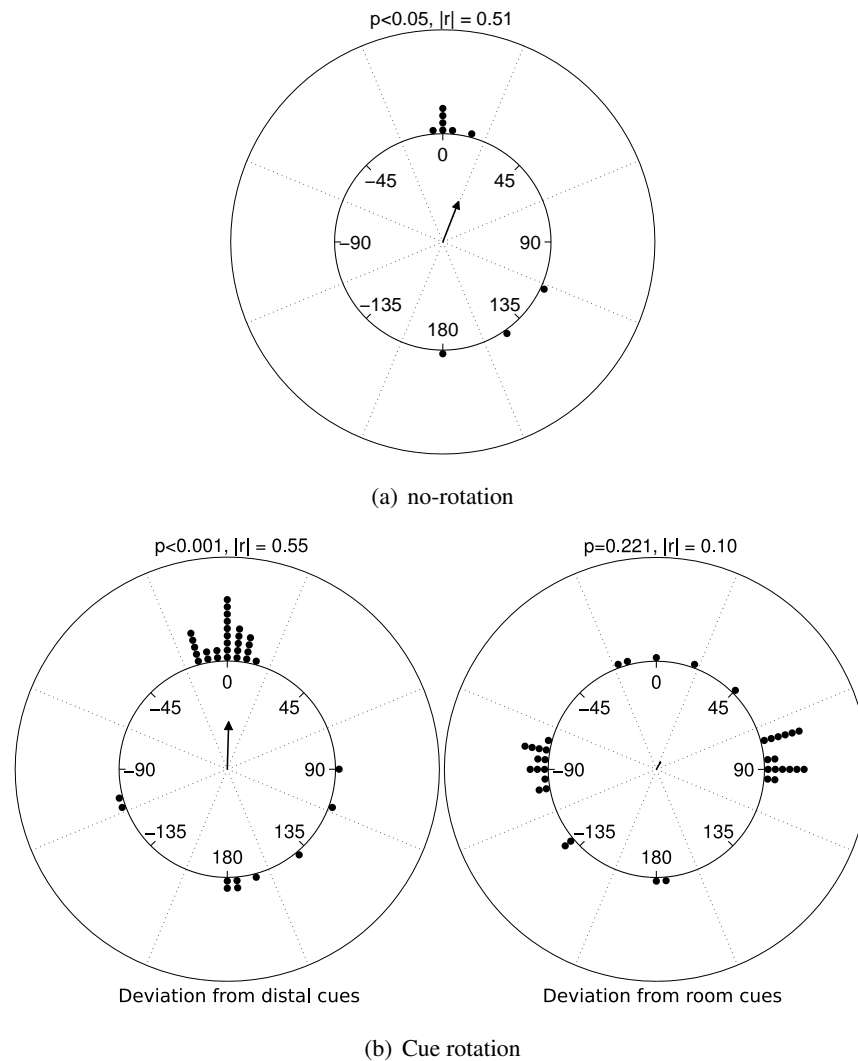
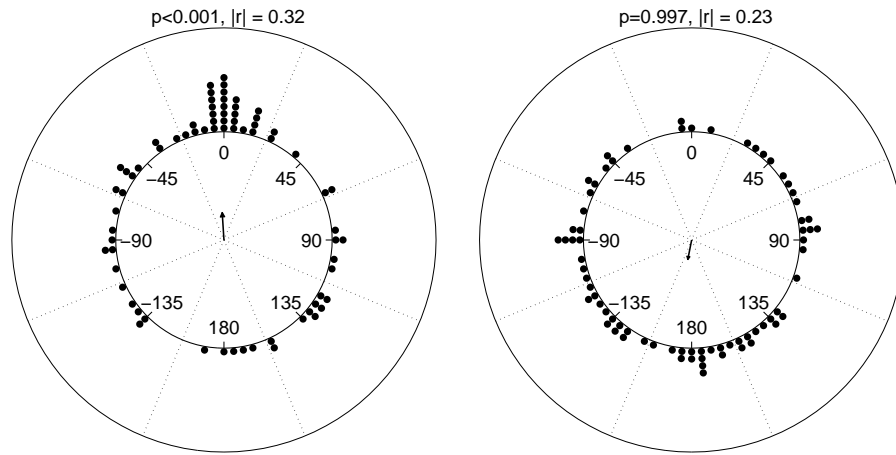
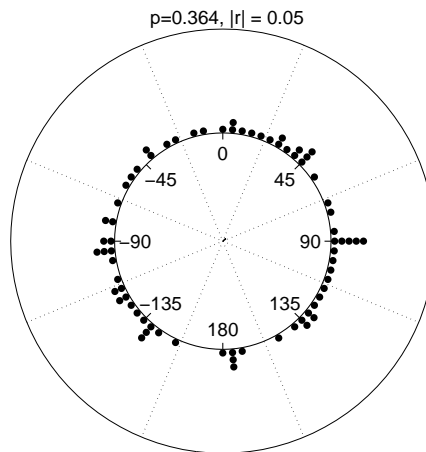


Figure 5.29: Landmark control in no-rotation and cue rotation sessions. The mean direction of the circular mean calculated from the rotation angles of rotated place cells was used as the ensemble rotation angle. Ensemble rotations between sessions are summarised based on their deviation from expected rotation angle based on each type of cues. $|r|$ is the vector length of the circular mean of the deviations and the p -value is determined by testing whether the deviations cluster significantly around 0° using circular V-test. The dotted lines divided the circular histograms into 45° segments centring at each of the eight tick marks at 45° interval. The closest tick mark to a data point would be the tick mark of the segment that included the data point. (a) Rotation of place cell ensembles during recording sessions with no cue rotations. (b) Deviation of place cell ensembles from the rotation of the distal cues during cue rotation sessions and the rotation of ensembles during cue rotation sessions, i.e. deviation from room cues. If the rotation angles clustered around 0° with respect to the room cues despite the rotation of the distal cues, there were uncontrolled room cues that exerted significant landmark control over the rotation of place cell ensembles.



(a) Cue conflict - deviation from coherent cues (b) Cue conflict - deviation from independent cues



(c) Cue conflict - deviation from room cues

Figure 5.30: Landmark control in cue conflict sessions. The circular histograms were constructed similarly to what was described in figure 5.29. (a) presents deviation of ensemble rotation from the coherent cues, (b) presents deviation from the independent cues and (c) are the deviations from the uncontrolled room cues, which is essentially the rotation of place cell ensembles. The p -values were calculated using circular V-test with 0° as the expected rotation. $|r|$ is the length of the circular mean vector. The analysis identifies only the coherent cues exerted significant landmark control over the rotation of place cell ensembles.

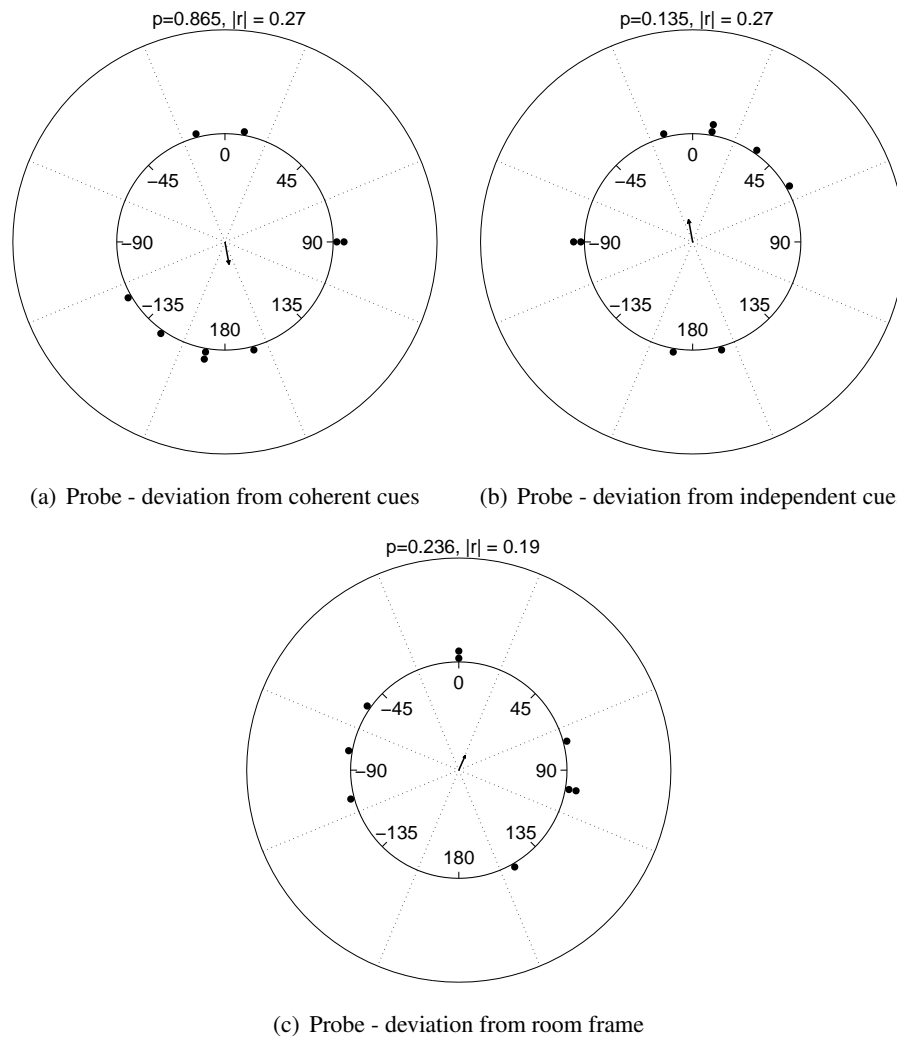


Figure 5.31: Landmark control in the probe sessions. The circular histograms were constructed similarly to what was described in figure 5.29. (a) presents the deviations of ensemble rotations from the coherent cues, (b) presents the deviations from the independent cues and (c) are the rotation angles of the place cell ensembles, which represent the deviations from the uncontrolled room cues. The p -values were calculated using circular V-test with 0° as the expected rotation. $|r|$ is the length of the circular mean vector. None of the cues exhibited significant landmark controls over the rotation of place cell ensembles.

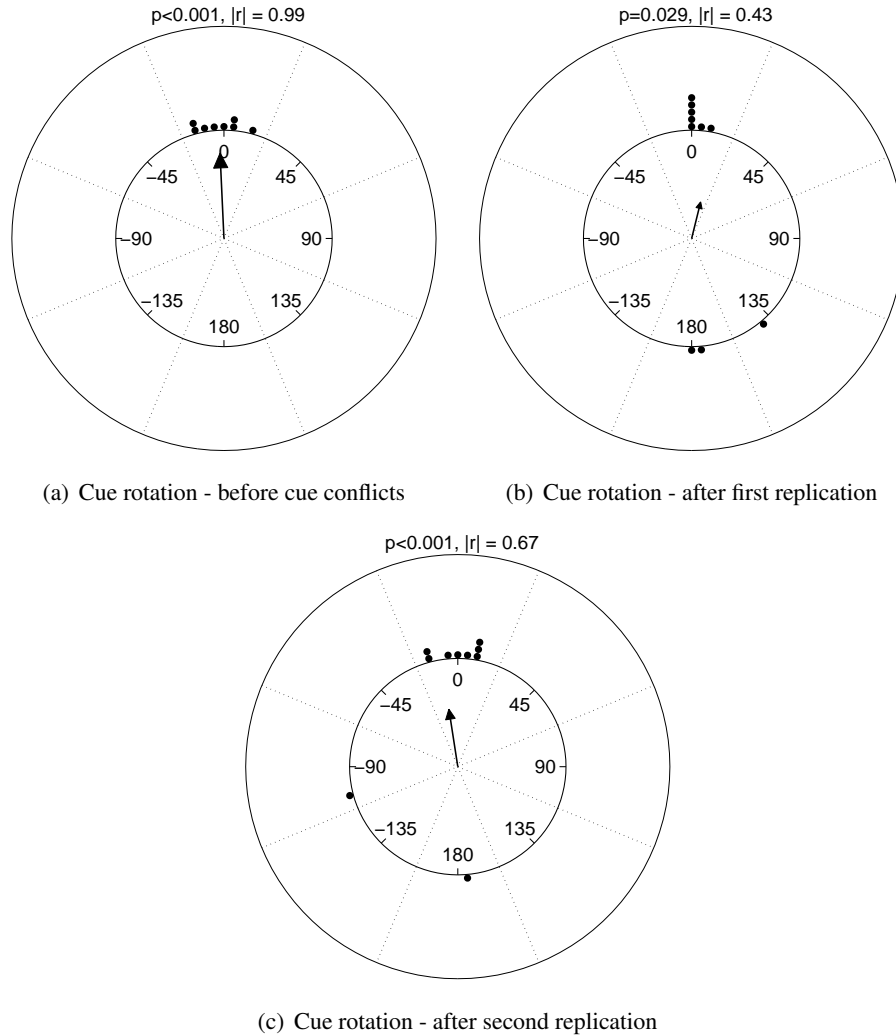


Figure 5.32: Landmark control of distal cues before and after cue conflicts. The circular histograms were constructed similar to what was described in figure 5.29. The ensemble rotation data were separated into those obtained from cue rotation sessions before cue conflict experiences, after first replication of cue manipulation sequence, and after second replication of cue manipulation sequence. V-test showed the rotated distal cues maintained significant landmark control over the rotation of place cell ensembles even after experiences of cue conflicts.

returned significant p -values for the first ($|r|=0.39$; $p<0.05$) and second ($|r|=0.65$; $p<0.001$) cue conflict days during the first replication of the cue manipulation sequence as well as for the second ($|r|=0.42$; $p<0.01$) cue conflict day during the second replication of the cue manipulation sequence. Circular V-test failed to detect a significant landmark control from the coherent cues over the rotation of place cell ensembles on the first cue conflict day during the second cue manipulation sequence ($|r|=0.30$; $p=0.06$).

It appears that the coherent cues exerted stronger landmark control over the rotation of place cell on the second days of each replication (a trend of lower p -values and lower circular variance). We thus used the equal-kappa test to check the homogeneity of the concentration factor of the rotation angles between the first and second days of the cue conflict sequences. The test failed to detect any significant deviation from homogeneity both in the first ($\chi^2=1.27$; $p>0.05$) and second ($\chi^2=0.25$; $p>0.05$) replications, suggesting this observed improvement in landmark control from the coherent cues were not statistically significant.

One explanation for the higher proportion of recording sessions that rotated with the coherent cues is that there were more coherent cues ($n=3$) than independent cue ($n=1$). If we assume that each cue is equally likely to establish landmark control over the rotation of place cells, we would expect the numbers of sessions following the coherent cues and the independent cue to have 3:1 ratio. We asked whether the observed frequency deviated significantly from this ratio and although the coherent cues were seven times more likely than the independent cue to control rotation of the place cell ensembles ($n_{coherent}=29$, $n_{independent}=4$), chi-square test did not find the observed frequency to be significantly different from the 3:1 ratio ($\chi^2=2.92$; $p>0.05$). We therefore cannot rule out the hypothesis that the coherent cues exerted greater control over the rotation of the place cell ensembles due to it having three times as many cues as the independent cue.

Cue control by individual cues

Two of the six rats from the CA1 place cells group were used in this experiment, which was designed to explore whether each individual distal cue by itself could establish landmark control over the rotation of place cells. As described in figure 5.17, the experiment involved removing three of the cues and rotating the remaining cue by 90° . One of the main concerns when interpreting the results was that the dramatic changes in distal cue configuration would cause place cells to remap strongly between sessions, rendering the interpretation of the rotation results impossible. The first step of the analysis aimed at addressing the issue of place cell ensembles' degrees of remapping and rotation coherencies. On average 25% ($25.44\pm 7.3\%$) of the place cells within a recorded ensemble were classified as remapped between sessions, which was comparable to what was observed in the recording sessions collected during the cue manipulation experiment (Wilcoxon ranksum test, $p>0.05$, ranksum = 57). The average

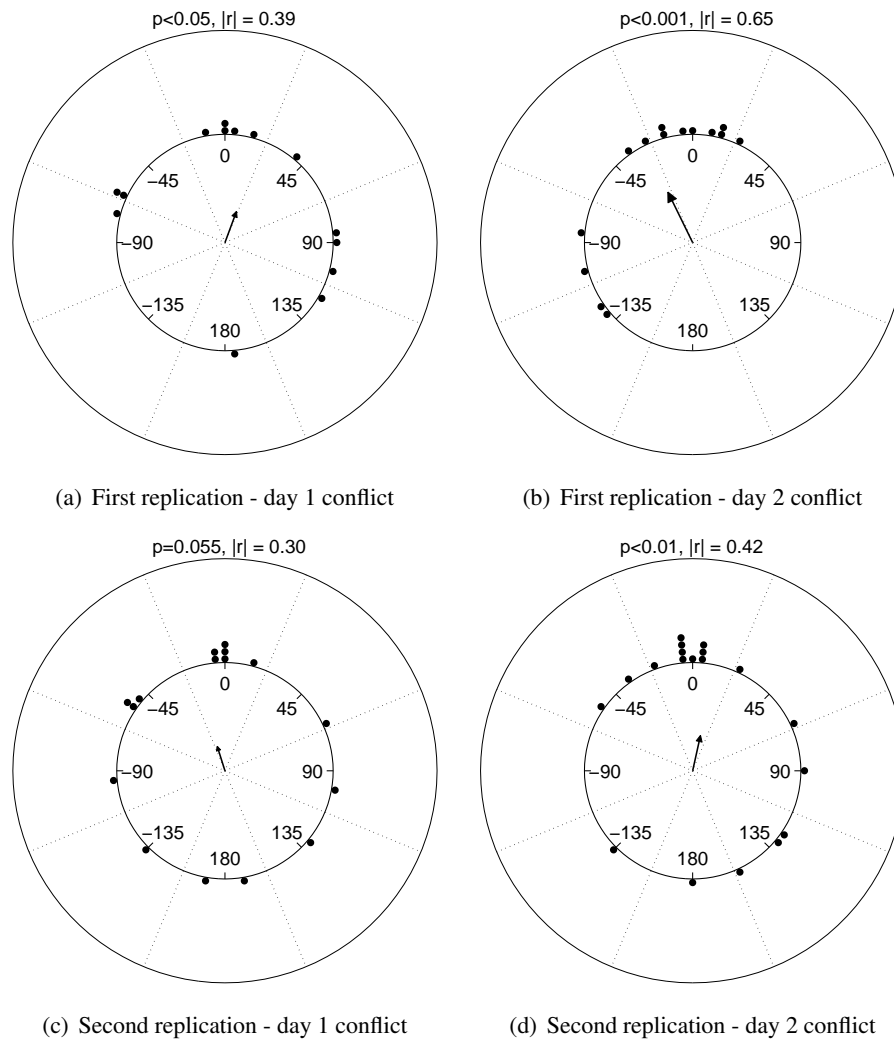


Figure 5.33: Landmark control of the coherent cues in cue conflict sessions. The circular histograms were constructed similar to what was described in figure 5.29. Each rat was exposed to four cue conflict sequence days, two during the first replication and two in the second replication of the cue manipulation sequence. The rotation angles of place cell ensembles from the four days were analysed separately. The V-test showed rotation angle of the ensembles clustered around the coherent cues significantly in three of the four days. Despite a trend of having a smaller p -value and lower circular variance from the second day of each replication, the differences between the dispersion of rotation angles were not statistically significant.

circular variance of the rotated ensemble was 0.19 (0.19 ± 0.08) which also suggested a comparable rotation coherency to those observed in the previous experiment. To assess the strength of landmark control from each distal cue, the deviations of the rotated place cell ensembles from the rotation of the distal cue were calculated. Circular V-test was then used to calculate whether the deviations clustered significantly around 0° . Figure 5.34 uses circular histograms to summarise the angles of deviation with respect to the distal cues and uncontrolled room cues. The V-test failed to detect significant non-uniformity around 0° either with respect to the distal cues ($|r|=0.26$; $p=0.075$), or to the room cues ($|r|=0.06$; $p=0.532$). One potential explanation to their result is that rats did not distinguish between the individual cues and instead chose one of the four distal cues to reference the orientation of place cell ensembles. If this was the case, we would expect to see the rotation of place cell ensembles to fall within one of the four shifted angles, based on the orientation of the four distal cues and subsequent rotated location of the lone cue. Among the sixteen such cue manipulations, the rotated angles of ten place cell ensembles fell within the 45° range of the four shifted angles. As all possible rotations could be grouped into each of the eight 45° areas, we tested the 10:6 observations against a 50:50 distribution expected from an uniform distribution using a chi-square goodness of fit test. The test returned an insignificant p -value ($\chi^2=1$; $p>0.05$). We thus failed to find statistical support for the hypothesis that rats chose one of the four distal cues randomly to reference the spatial representations of their place cell ensembles.

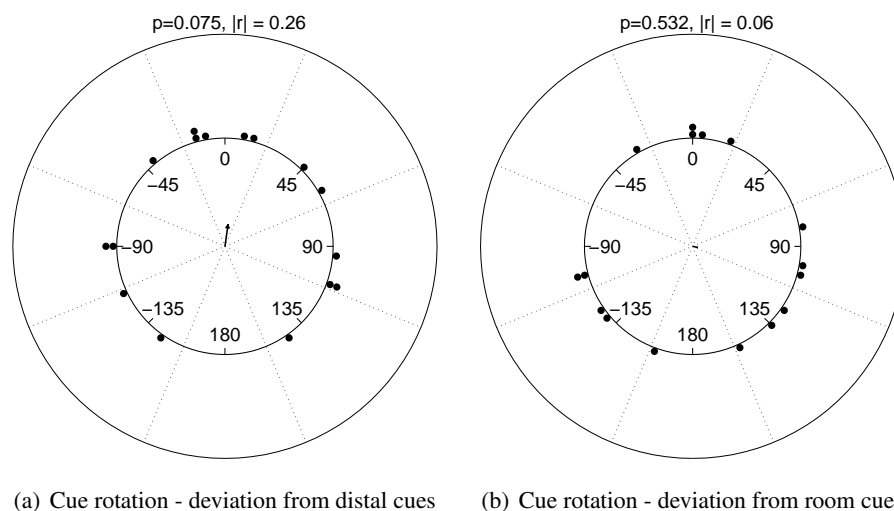


Figure 5.34: Landmark control by individual distal cues. The figure summarises the rotation of place cell ensembles in response to cue rotation of individual distal cues. The cue manipulation configurations experienced by the rats are illustrated in figure 5.17. (a) summarises the deviation of the rotated place cell ensembles from the rotation of distal cues. (b) summarises the rotation of the place cell ensembles, which could also be seen as the deviation from the uncontrolled room cues in the environment. Neither of the types of cues showed significant landmark controls over the rotation of place cell ensembles.

The cue manipulation sequence that was used to explore the landmark control of individual distal cues consisted of two distinct types of manipulations. One was the removal of three

distal cues and the rotation of the remaining cue. The second was the rotation of the lone distal cue and replacement of the three removed distal cues back to the standard configuration. Figure 5.35 summarises ensemble rotations with respect to the distal cues from the two distinct types of cue manipulations. Distal cues failed to demonstrate significant landmark control in either type of the cue manipulations. Therefore, the removal of a subset of distal cues from the environment or the addition of distal cues into the environment appears to attenuate the distal cues' ability to exert equal rotation from place cell ensembles.

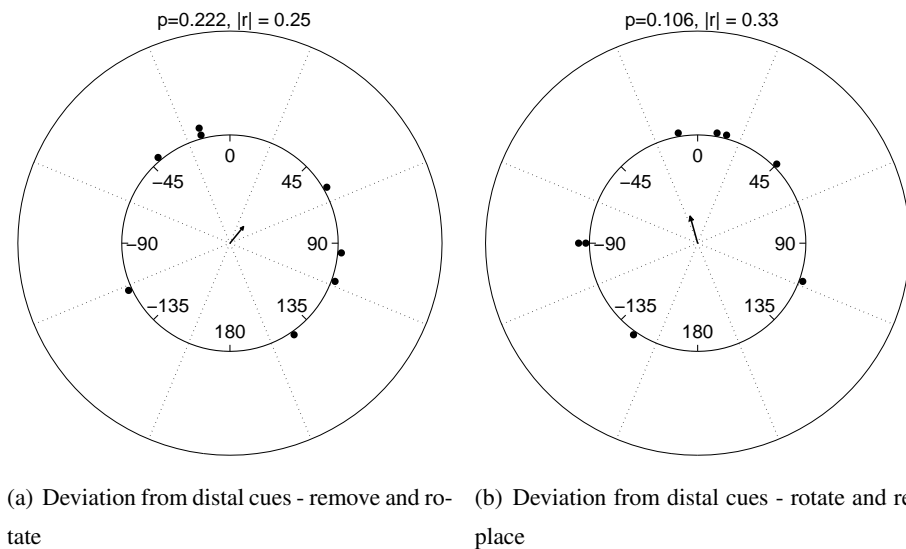


Figure 5.35: Landmark control in cue removal and cue replacement sessions. The results presented in figure 5.34 were subdivided into (a) those obtained from sessions pairs during which three distal cues were removed and the remaining cue was rotated by 90° between sessions and (b) were recording sessions during which the lone distal cue was rotated back to the standard location (a 90° rotation) and the three removed distal cues were again replaced in the original position between sessions.

5.5.3 Entorhinal head direction cells

Head direction cells have been recorded from entorhinal cortex (Sargolini et al. 2006) of rats and the literature suggests that place cells integrate orientation information provided by the head direction cell network (Calton et al. 2003, but more recently see Cauter et al. 2008). This experiment aimed at exploring the landmark control of entorhinal head direction cells when rats were given cue manipulation sequences similar to those used in section 5.5.2. Mean rotated angles of simultaneously recorded head direction cells were used to represent ensemble rotation. A summary of the number of cells recorded from the two rats used in this experiment is presented at figure 5.36. As experimental evidence suggested that head direction cells always rotated coherently as an ensemble (Yoganarasimha et al. 2006), we decided that there was no need for having an inclusion criteria based on the number of simultaneously recorded head direction cells. The results are summarised in figure 5.37. The circular V-test was used to verify

whether different types of cues controlled the rotation of head direction cells significantly after cue manipulations. In the cue rotation sessions, the rotation of the distal visual cues controlled the rotation of head direction cells significantly ($|r|=0.53$; $p<0.001$). The coherent cues in the cue conflict sessions also exerted significant landmark control over the rotation of head direction cells in entorhinal cortex ($|r|=0.65$; $p<0.001$). Neither the independent cues ($|r|=0.08$; $p=0.33$) nor the uncontrolled room cues ($|r|=0.12$; $p=0.776$) achieved significant landmark control over the rotation of head direction cells. Unfortunately there were not enough probe sessions with head direction cells recorded to perform statistical tests on the rotation of head direction cells after the probe manipulations ($n=4$). We also tested whether the ratio of head direction cell ensembles following the coherent cues against those following the independent cues was significantly different from the 3:1 ratio⁷ using chi-square goodness of fit test and found that the observed proportion of head direction cells following the coherent cues did not differ significantly from the 3:1 ratio ($n_{coherent}=16$, $n_{independent}=3$; $\chi^2=0.86$; $p>0.05$). The results are similar to what was seen from the CA1 place cells group, which suggests that how place and head direction cells rotate their receptive fields after cue manipulations follows a similar mechanism and potentially shares a common structure supporting the decisions.

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
E5301	No. cells	9	8	8	4	2	4	4	6
	No. head direction ce	2	4	2	3	1	2	1	1
E5305	No. cells	13	16	17	16	20	20	25	25
	No. head direction ce	1	3	4	3	3	2	4	5

Figure 5.36: The number of cells recorded from the two rats in the entorhinal cortex experiment. The number of cells and the number of head direction cells recorded each day is summarised here.

5.6 Discussion

5.6.1 Remapping ratio and circular variance of place cell ensembles

We tested whether the relative stability between distal visual cues facilitated their strength of landmark control over the rotation of hippocampal place cells and entorhinal head direction cells. We classified the behaviours of place cells quantitatively (see section 5.2.7 for the criteria) into those that remapped or rotated their place fields between recording sessions. In the three distal cues experiment (two coherent cues and one independent cue), we observed that a high proportion of place cells remapped between sessions, especially when compared to the re-

⁷If we hypothesise a scenario where the HD cells choose one of the four cues randomly to reference their rotation, the number of recording sessions following the coherent cues against those following the independent cues would follow this 3 to 1 ratio as there were three coherent cues and one independent cue in the distal cue set.

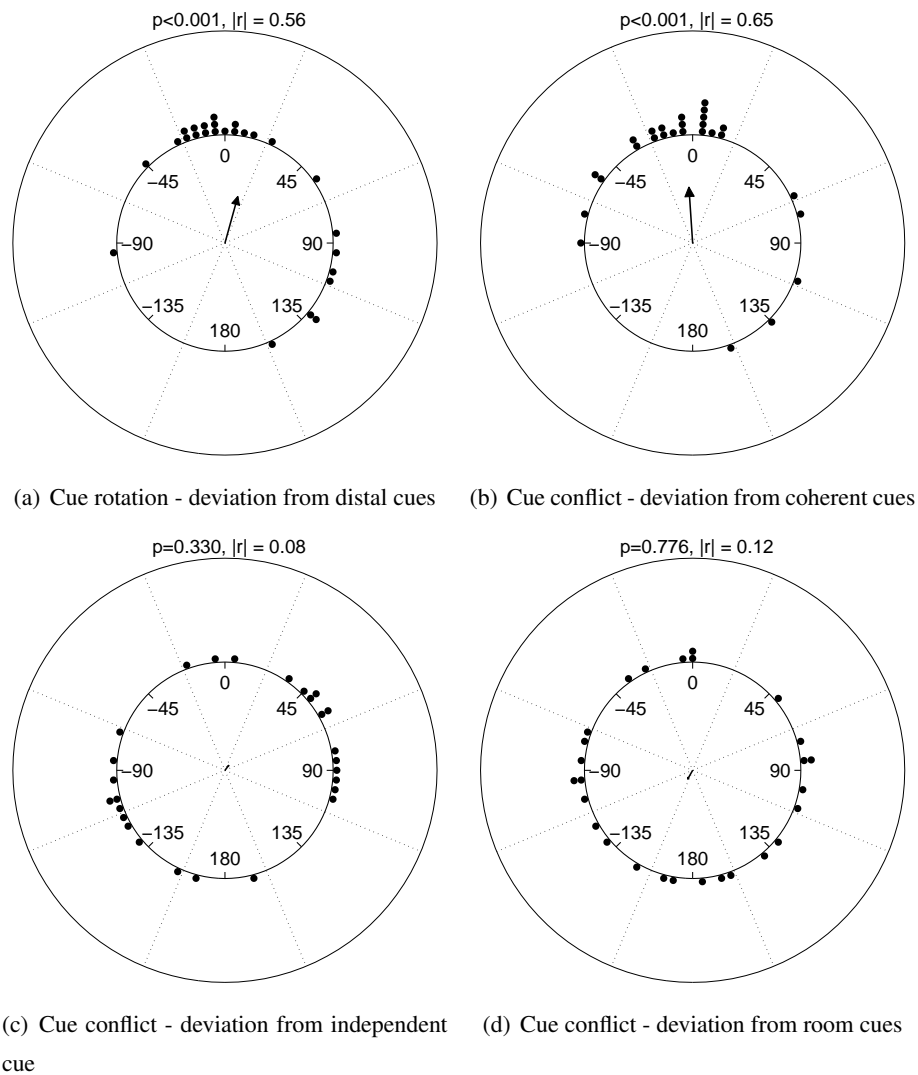


Figure 5.37: Landmark control of Entorhinal head direction cells. Mean rotation angles were used to represent the rotations of head direction cell ensembles between recording sessions. (a) summarises the deviation of the rotations from the rotation of distal cues in the cue rotation sessions. (b)–(d) present results from cue conflicts sessions. (b) summarises the deviations from the coherent cues, (c) presents the deviations from the independent cues and (d) are the rotated angles of the head direction cells, which can also be interpreted as deviations from the uncontrolled room cues. Using circular V-test, both the distal cues in the cue rotation sessions and the coherent cues in the cue conflicts are shown to exert significant landmark control over the rotations of head direction cells.

sults obtained in the four distal cues experiment. The exact cause of high remapping proportion cannot be determined, though we propose two potential causes for the differences observed:

1. Rats in the three distal cues experiment were exposed to cue rotations on the first day in the experimental environment, whereas rats in the four distal cues experiments were given three days of no rotation sessions at the beginning of the experiment. The lack of stable environment experience in the beginning of the three distal cues experiment might have encouraged the place cells to remap between sessions.
2. The coherent cue set in the three distal experiment was too small (two coherent cues) such that rats treated the different cue conflict sessions as different environments and the repeated conflict experience caused the tendency of place cells to remap between sessions.

One way to explore which of the above is a more likely cause for the high level of place cell remapping observed is to look at the remapping ratio before rats experienced cue conflicts in the three cues experiment. The second scenario implies that a high level of place cell remapping would only be observed after rats have experienced repeated cue conflicts. Unfortunately, insufficient recording sessions with at least five simultaneously recorded place cells were collected before rats experienced cue conflicts to determine the level of place cell remapping before rats experienced cue conflicts in the three cue experiment. One result to be noted is that this high level of place cell remapping persisted in subsequent recording sessions with a set of four new distal cues even when no cue manipulation was done to this new set of cues. The observation suggests that high remapping ratio is not a direct response to either the prior conflict experience of the cues or the perception of the altered cue configuration. Though this perceived instability of place fields can be a reflection of rats' prior cue manipulation experiences in the recording environment. The observation resembles the results reported by Knierim et al. (1995) where prior conflicting experiences in the environment have a long lasting effect on place cells' spatial representation despite more recent enforcing experiences of a stable environment. On the other hand, Fenton et al. (2000) reported no effects of repeated exposure to cue manipulations on place cell representation in coherent cue environments. There were several discrepancies between the two experiments that could potentially explain the results. Firstly, the rats used in the Fenton et al. (2000) experiment experienced a few days of coherent cue environment similar to what was given to rats in the four distal cue experiments, which could encourage place cells to form coherent representations of the environment. Secondly, the nature of cue conflicts between the two experiments was very different, which could also contribute to the differential effects of cue manipulations to the stability of place cells' spatial representation.

The level of place cell remapping observed in the four distal cue experiment were significantly lower than those observed in the three cues experiment, suggesting a more coherent ensemble response, which was similar to what was reported in previous cue conflict experiments (see Fenton et al. 2000; Knierim 2002; Tanila et al. 1997, though Shapiro et al. 1997 reported place cell remapping between cue conflicts after repeated exposure to the conflicts). This permits us to look at both remapping and rotation of place cells under different cue manipulation conditions. Surprisingly, the remapping ratios of place cells recorded during the probe sessions, which, with two distal cues from the coherent cue group removed and the remaining coherent cue rotated in conflict with the independent cue, arguably was the most dramatic type of cue manipulation, were lower than those recorded in the no rotation sessions. The result mirrored the observation that place cells recorded during the probe sessions also had significantly lower circular variance among the rotated place cells when compared to the recording sessions from the no rotation sessions, suggesting an overall higher level of spatial coherence exhibited by place cell ensembles.

One explanation for this was that as rats always experienced the probe sessions after the no rotation sessions, the reduced place cell remapping and rotation circular variance could be due to the habituation to the experiment protocol. To explore this possibility, we separated the recording sessions into those obtained from the first and second replication of the cue manipulation sequence and found a significant replication effect on the remapping ratios of place cell ensembles. However, further analysis showed that the remapping ratios in the second replication were significantly higher than those observed during the first replication, suggesting that repeated exposure to the experimental protocol actually increased the tendency for place cells to remap between sessions. Similar analysis performed on the circular variance of rotated place cells found no replication effects. The analyses argue against the hypothesis that repeated exposure to the experimental protocol could improve coherence of place cells' spatial representation between recording sessions. The observed differences of the coherence of place cells' spatial representation between the no rotation and probe sessions are then likely to be rooted in the different types of cue manipulations rats experienced. This conclusion raises the question of why place cells respond to the probe cue manipulations more coherently than sessions with no changes of distal cue configurations. It has been reported that adding additional visual cues in a familiar environment degrades rats' performance in a watermaze task slightly (Fenton et al. 1994), which can be interpreted as increasing difficulty caused by encoding additional cues in the environment. However, a cue enriched environment can also aid spatial navigation (Lopez et al. 2008).

From the unit recording literature, it has been reported that cue removal reduces spatial information content in CA3 place cells (Hetherington and Shapiro 1997) though Fenton et al. (2000) observed minimal effects on place cell properties after removal of one of the two cue

cards used in the experiment. The same paper also reported that a configural conflict of the two cue cards affected several field properties of the recorded place cells. However, the paper did not make a distinction of whether the place cells were recorded simultaneously and hence presented no result regarding the coherence of place cell ensembles. In Tanila et al. (1997), the authors reported that place cells in a given ensemble tended to respond to cue conflict in a similar way though the responses also included place cell remapping between sessions. This thus does not explain why place cell representations after probe cue manipulations became more coherent, especially when Shapiro et al. (1997) also reported that repeated exposures to cue conflicts encouraged the place cells to remap instead of rotate with distal cues after cue conflict. More recently Lee et al. (2004) also reported that CA1 place cells exhibited ambiguous or split representations when facing cue conflicts between intramaze and distal cues. The unit recording literature suggests that place cells should respond with less coherence after rats experience probe cue manipulations when comparing to recording sessions with no cue manipulations, which is contrary to what the analyses of the recording sessions from the present four-cues experiment shows. This suggests that, instead of the cue configurations, it is the prior cue manipulation experience that causes place cells to exhibit stronger coherence during the probe sessions. As the experiment was not designed to test this phenomenon directly, it is difficult to isolate a plausible cause for the phenomenon.

5.6.2 Cue control of place and head direction cells

Recording sessions collected during the cue rotation sessions⁸ in the three cue experiment show that the distal cues did not exert strong landmark control over the rotation of place cells. Combined with the high level of place cell remapping and circular variance exhibited by the recorded place cell ensembles, we conclude that the dominating response of place cell ensembles to cue manipulations is global remapping in the three cue experiment, which makes interpretation of the rotation of landmark control irrelevant.

Place cell ensembles recorded from the four cue experiment showed high degrees of internal coherence between sessions. This allows the analysis of how different types of cues control the rotation of place cell ensembles after cue manipulation. Rotation angles of the place cell ensembles recorded during cue rotation sessions, both before and after rats experienced cue conflicts, confirmed that the distal cues remained capable of exerting strong landmark control of the place cells even after experience of cue conflicts. The analysis of place cell rotation during cue conflict sessions showed that the coherent cues were the only type of cues that exerted significant landmark control over the place cell ensembles. The result of the landmark control experiment observed from the head direction cells recorded from entorhinal cortex was similar to those collected from place cells with only the coherent cues exerting significant land-

⁸This includes cue rotation sessions both before and after the cue conflict sessions

mark control over the head direction cell ensembles. The proportion of place cells following the coherent cues was also significantly higher than that following the independent cue or the uncontrolled room cues. There was also a trend that there were more place cell ensembles following the coherent cues in the second consecutive day of cue conflict experience, suggesting that repeated cue conflict experience encouraged the place cell ensembles to follow the coherent cues. However, when we tested whether the circular variance of the rotated angles of the place cell ensembles with respect to the coherent cues was smaller on the second cue conflict day than the that on the first cue conflict day (a small circular variance would indicate greater cue control), we failed to find statistical evidence suggesting an experience dependent strengthening of landmark control from the coherent cues. Combined with the observations that the frequencies of place cell ensembles controlled by the coherent and the independent cues did not differ significantly from a 3:1 ratio, we concluded that there was no significant evidence suggesting the benefits of cue stability to the landmark control of place and head direction cells. It is unclear though whether even more consecutive cue conflict experience would encourage the coherent cues to finally gain significantly greater control than the independent cue for the rotation of place cell ensembles.

We also explored the effectiveness of each individual cue to control the rotation of place cell ensembles by removing three of the four distal cues and rotating the remaining cue between sessions. Low remapping ratio and circular variance exhibited by the place cell ensembles suggest strong ensemble coherence after rats experienced the removal and rotation of the cues. The analysis of the rotation angle of place cell ensembles between sessions found that a lone distal cue could not reliably control the rotation of the place cell ensembles if the other distal cues were removed from the environment from one of the two consecutive recording sessions. We have also tested two alternative scenarios, one was that the place cell ensembles instead referenced their orientation to the uncontrolled room cues in the environment, and in the second scenario the place cell ensembles did not distinguish the identities between distal cues. However, we did not find the result to support either of the scenarios. As the place cells recorded during the cue rotation sessions rotated with the distal cues between sessions, we rejected the scenario that rats no longer pay attention to the distal cues due to repeated cue conflicts. One possible explanation is that place cells referenced their place fields to a combination of cues. This causes unexpected rotation angles from the place cell ensembles if some cues in the combined set are removed. It has been reported that place cells can follow the centre of two cue cards when rats experienced cue manipulations (Fenton et al. 2000). Though it was also reported in the same paper that the removal of one cue card did not induce a rotation of the recorded place cells, suggesting, unlike the results reported here, place cells could flexibly use the remaining cue card to maintain orientation after cue removal. It was possible that rats only used a subset of the four distal cues as a reference for orientation and thus cue removal

could result in all distal cues being used as a reference in the previous session being removed. Under such conditions, the rotation angles of place cell ensembles could arguably be arbitrary as a random cue needed to be chosen as the reference for rotation. The observation also makes it difficult to interpret the rotation result collected after probe cue manipulations. As probe cue manipulations were also involved in the removal of a subset of the coherent cues, the observed randomness in the rotation angle of place cell ensembles could be due to the effects from the removal of some coherent cues. It is thus unclear whether a lone coherent cue could exert greater rotational control over the place cell ensembles than the independent cue.

5.6.3 Implications

We developed a cue conflict task in which the recorded place cells remained referenced to the rotation of distal cues even after rats experienced repeat cue conflicts. This suggests continuous contribution of the distal cues to the orientation of place cell ensembles. With low levels of place cell remapping and circular variances observed, the ensemble rotation angles deduced from the recorded place cells should also reflect the rotation of the head direction cell system (Calton et al. 2003; Yoganasimha et al. 2006). The main results of the experiments can thus be used to address the question of how the head direction cell system resolves conflicting orientation information in an environment. To establish a consistent mental representation of an environment, it is necessary to choose an orientation for the representation. We showed that in a cue conflict situation where some of the distal cues maintained relative stability, this set of cues exerted significantly stronger landmark control over the orientation of place cell and head direction cell ensembles when compared to other cues in the environment. However, the observed proportion of place and head direction cell ensembles following the coherent cue sets when compared to those following the independent cue did not differ significantly from 3:1 ratio expected by chance (there were three distal cues in the coherent cues set and only one independent cue). Furthermore, the proportion of place cell ensembles following any distal cue reference frame (including coherent and independent cues) was also lower in the cue conflict sessions when compared to the cue rotation sessions. These observations argue against the idea that relative stability between cues strengthen the landmark control of the distal cues (Biegler and Morris 1996a, 1993, 1996b; O'Keefe and Nadel 1978). On the other hand, an associative account of landmark control (see Chamizo 2003 for a review) treats each individual cue as an associable landmark and states that the best predictor of a reinforcement reward signal wins out. This view of landmark learning presents a particular challenge when interpreting a task that is purely exploratory in an environment with no explicit goals. The associative learning theorem under such a scenario still requires an unconditional stimulus, which can be roughly translated to a need for a primary reference frame. A match with this hypothetical reference frame then returns a positive reinforcing signal. This train of thought brings us back to the problem of

what is the primary reference frame in spatial navigation, which has been discussed in the introduction (section 5.1). The predicted outcome based on associative learning paradigm thus is critically dependent on what is assumed to be the *unconditional stimulus* in spatial navigation tasks without a specific goal. In any case, results collected from both cue conflict and cue removal sessions did not provide evidence of any individual distal cue gaining a dominating role over landmark control of place cell ensembles. The results obtained from the recording sessions in which only one distal cue was presented in the first session and in the subsequent session the cue was rotated by 90° with the other three distal cues added to the environment also suggested that the presence of the lone distal cues in a single fifteen minutes session, which was previously shown to be adequate for a novel distal cue to establish landmark control in an environment (Goodridge et al. 1998), could not establish landmark control to the place cell ensembles after cue rotation.

The results obtained from this experiment do not exclude the scenario where place cell ensembles use multi-cue configurations as reference frames. With rats' wide field of vision, it should not be a problem for them to see more than one distal cue from a single view of the environment, especially as the distal cues could be as close as 45° from each other. This opens to the possibility that more than one cue is treated as a single cue complex and this complex is susceptible to be altered in cue conflict or removal sessions, which could be the root cause of place cells seemingly referenced to none of the distal cues nor to the room reference frame in cue conflict and cue removal sessions. To explore such a scenario, a combination of cue removal and rotation sessions that also includes multiple configurations of cue complexes needs to be included. Unfortunately such cue manipulations were not performed in this experiment as the number of recording sessions required to explore all possible combinations was too large to be practical.

In summary, we conducted an experiment that explored the effect of relative stability between distal landmarks on their influence over place and head direction cell ensembles in rats. The use of the pellet chasing task allowed us to explore the learning of landmarks in a pure spatial exploration sense without the complication of goals and rewards. We found that the coherent cues set did exert stronger landmark control than the independent cue though the stable relationship of the coherent cue set did not provide significantly stronger landmark control over place and head direction cell ensembles when taking the larger number of cues in the coherent cues set into consideration. Combined with the observation that a high proportion of place cell ensembles appeared to be controlled neither by the coherent cues nor by the independent cue, we conclude that, at least with the amount of cue conflict experience given to rats in this experiment, the relative stability between distal cues did not provide additional landmark control strength to the coherent cues set. The reliable landmark control from the distal cues during cue rotation sessions recorded after rats experienced the cue conflict and the probe sessions pro-

vide supporting evidence that experience of cue manipulations did not encourage rats to ignore landmark information from the distal cues. The pattern of landmark control tentatively suggests that, in addition to a single distal cue, rats may use a multiple cue complex as a reference frame. A trend of improving landmark control by the coherent cue set after repeated exposure was observed though additional experiments need to be done to explore this phenomenon conclusively.

Chapter 6

Development of prospective goal cells on a double Y-maze task

6.1 Introduction

The development of single unit recording techniques led to the discovery of place cells from the hippocampus of rats (O'Keefe and Dostrovsky 1971). These cells are strongly modulated by location of a rats in its environment, and their place preferences, which are commonly referred to as their place fields, remain stable across days (Agnihotri et al. 2004; Thompson and Best 1989). This neural representation of space can be used to incorporate spatial information in the environment for navigation (see Muller 1996 for a review) and has been proposed to form the neural basis of cognitive map theory (O'Keefe 1999; O'Keefe and Nadel 1978).

Evidence suggesting that hippocampal place cells are not purely modulated by the locations of rats quickly emerged in the literature. One of the first such experiments came from the observation that place cells established different place fields depending on which direction the rat was running on a linear track (Gothard et al. 1996; Markus et al. 1994; McNaughton et al. 1983; Muller et al. 1994), whereas place fields observed from open field environments typically showed directional symmetry (O'Keefe 1976, 1979). In particular, Markus et al. (1995) reported that changing the characteristics of the behavioural tasks given to the rats altered directionality and location of the place fields. This provides strong evidences that place cells encode more than just the current locations of rats. Many other experiments were designed to explore whether place cells also encode non-spatial information (Eichenbaum 2004; Eichenbaum et al. 1999; Muller 1996; Smith and Mizumori 2006a) in an environment. Some failed to find such evidence (Speakman and O'Keefe 1990), but others demonstrated that different non-geometric attributes, such as visual (Anderson and Jeffery 2003; Bostock et al. 1991; Hayman et al. 2003; Jeffery and Anderson 2003; Wible et al. 1986; Young et al. 1994), odour (Anderson and Jeffery 2003; Wiebe and Stäubli 1999; Wiener et al. 1989; Wood et al. 1999),

or auditory (Sakurai 1994) features, as well as the reward locations (Breese et al. 1989; Hok et al. 2007; Kobayashi et al. 1997), can induce the place cells to develop alternative spatial representations of the environment. Some interpreted the results as evidence supporting the role of hippocampus in contextual encoding, though critics suggested that such changes simply reflect distinctive spatial representation of different environments with different attributes. To address the argument, Anderson and Jeffery (2003) showed that some place cells specifically encoded for the identity of odour or colour contexts in an environment instead of forming a unique representation for each combination of features. Wood et al. (1999) also showed that hippocampal cells could encode for non-geometric contexts independently from their locations. Other studies showed that some place cells encode different phases of both a spatial delayed-nonmatch-to-sample (DNMS) task (Deadwyler et al. 1996; Eichenbaum et al. 1987; Hampson et al. 1999b) and a delayed-match-to-sample (DMS) task (Hampson et al. 1993; Wible et al. 1986), or comparisons between temporally discontinuous stimuli (Fyhn et al. 2002; Otto and Eichenbaum 1992; Wiebe and Stäubli 1999) despite a stationary local environment. These reports provide supporting evidence for non-spatial roles of hippocampal cells. Several studies then began to explore the link between a rat's behaviour and activities of the hippocampal cells to further support the role of hippocampus in tasks requiring contextual information. In Moita et al. (2003), the authors showed that some hippocampal cells only started responding to the conditional stimulus after it was paired with the unconditional stimulus in contextual fear conditioning. Hampson and Deadwyler (1996) demonstrated how temporal mnemonic events interfere with each other and degrade a rat's performance on a DNMS task. Interestingly, this interference is also evident from the activities of hippocampal cells, which suggests a potential link between the hippocampal code and the rat's memory performance. In Hampson et al. (1999b), the authors showed that ensemble activities of the recorded hippocampal cells could be used to predict the subsequent choices of a DNMS task, which also supports the role of hippocampal cells in solving the task.

The experiments discussed so far examined the firing properties of hippocampal cells in open field environments. Many investigators also used linear tracks to explore whether hippocampus is involved in contextual encoding (see Shapiro et al. 2006 for a review). An advantage of using linear tracks is that it limits the number of possible paths, which ensures that rats run through the place fields of hippocampal cells multiple times in an experiment. This ensures multiple measurements of the modulation of each context and simplifies statistical assessments of the contextual effects on neural activities. Many of the linear track tasks require rats to choose between several possible destinations to obtain rewards. Location of the reward destination is typically governed by either a win-stay rule, meaning that the reward location does not change after each visit, or a win-shift rule whereby the reward location changes after each visit. Experiments are typically set up so that running paths leading to different locations

overlap with each other to create a shared common segment. Hippocampal cell activity on the common segment are then used to determine whether the intended future destinations (i.e. the contexts) influence the firing of these cells. This kind of modulation is termed prospective encoding and may represent either goal directed activity (Hok et al. 2007) or simulation of the choice consequences (Johnson and Redish 2007). Some investigators also explored whether the rat's previously visited locations modulate the firing of hippocampal cells at the common segment. This is usually called retrospective encoding and may represent a memory component of previous experiences which can be used to solve win-stay or win-shift tasks. In order to distinguish between prospective and retrospective encoding, an experiment has to be designed to ensure adequate sampling between all combinations of past and future locations¹. This is not the case for a win-stay task (past and future location are usually the same) and an alternation task (a past locations is usually followed by the alternative future locations). In Frank et al. (2000), the authors used a W-maze alternation task to show that cells recorded from the hippocampus and entorhinal cortex showed both prospective and retrospective encoding. Ferbinteanu and Shapiro (2003) reported similar finding using a plus-maze and a win-stay rule, and also found more cells that showed retrospective encoding than prospective encoding. It is unclear whether such distribution is due to the design of the task or a common preference of hippocampal cells though it was reported that prospective codes deteriorated more than retrospective codes during error trials, suggesting a role in decision making. Ji and Wilson (2008) reported a similar preference toward retrospective encoding with the additional observation that prospective encoding developed initially in a new environment but hippocampal cells gradually shifted to retrospective encoding over time. Goal dependent hippocampal codes have also been reported from rats performing a win-stay task on a double Y-maze (Ainge et al. 2007a), and from experiments that used an alternation protocol on a continuous T-maze both with and without delay between trials (Ainge et al. 2007b; Ji and Wilson 2008; Wood et al. 2000). The incorporation of a delay period shifted the goal dependent firing from the central stem of the T-maze to the area where the rat spent during the delay. On the other hand, several investigators reported little (Hölscher et al. 2004) or no (Berke et al. 2009; Lenck-Santini et al. 2001) prospectively/retrospectively modulated hippocampal cells despite successful task acquisition by the rats. The result reported by Bower et al. (2005) suggests that this discrepancy may be due to how rats are trained and also the reward locations. In general, prospective and retrospective codes are frequently observed in win-stay and win-shift tasks. By calculating the ensemble represented locations of hippocampal cells, Johnson and Redish (2007) demonstrated another form of prospective encoding on a multiple-T maze where, at the choice point, the hippocampal ensemble briefly moved forward to sweep down the alternative choice arms without

¹One can only dissociate the effects of two different factors if the values of each factor is changed independently from another during sampling

the rat traversing down the paths physically. This can be interpreted as a form of prospective encoding that perhaps facilitates decision making at the choice point by simulating different consequences of the available choices.

The functional relevance of hippocampal cells' firing properties could be interpreted to provide support of the structure's involvement in solving tasks which require contextual information. However, an observed firing pattern that appears to be supportive (Ainge et al. 2007b) or detrimental (Jeffery et al. 2003) to a task does not necessarily translate to an observable behavioural effect. A more convincing case is usually established if an impairment is also observed after lesion or inactivation of the hippocampus. Here I will summarise the literature that explores the effect of hippocampal lesion to the performance of spatial win-stay and win-shift tasks. Several reports have shown that lesion or inactivation of the hippocampus impairs spatial win-shift (Ainge et al. 2007a; Becker et al. 1980; Douglas 1967; Higgs et al. 2001; Kim and Frank 2009; Olton and Feustle 1981; Packard et al. 1989), and win-stay (Ferbinteanu and Shapiro 2003; Kesner et al. 1993; Smith and Mizumori 2006a) tasks, which suggests a dependence of the task performance on hippocampus. However, reports which found no impairments from hippocampal lesion have also been published for both win-stay (Ainge et al. 2007a) and win-shift (Ainge et al. 2007b) tasks, with one report even suggesting that the lesion improved the rat's performance on a win-stay task (Packard et al. 1989). It should be noted that though the win-stay task used in Packard et al. (1989) involved in signalling the rewarded goal arms with light cues, which was more like a cue guided taxon navigation and required no knowledge of place to solve the task. Several of the experimental settings are noticeably different between these reports and may underly the discrepancies in the lesion literature. One of the factors that appears to determine whether an impairment is observed after the lesion of the hippocampus is the delay period between trials. Specifically, Ainge et al. (2007b) reported that a lesion deficit was only observed in a win-shift task when a delay period was explicitly imposed between trials. Indeed all of the previously discussed literature that reported a deficit after hippocampal lesion used delay periods between trials. This is similar to what was reported by Hampson et al. (1999a) where the lesion impaired both the delayed-match (DMS) and delayed-nonmatch-to-sample (DNMS) when the delay period was long enough. One explanation for the effect of delay periods is that the delay makes it more difficult for rats to execute a procedural strategy. Both Packard and McGaugh (1996) and Smith and Mizumori (2006a) reported that the rats with hippocampal lesion or inactivation preferred a procedural strategy and thus should be more susceptible to the disruption of delay period between trials. Similarly, the win-stay tasks used in both reports that showed a lesion deficit (Ferbinteanu and Shapiro 2003; Smith and Mizumori 2006a) could not be resolved using a procedural strategy whereas the win-stay task used in (Ainge et al. 2007a) (which reported no win-stay deficit following hippocampal lesion) could be resolved using a procedural strategy. Another factor that may contribute to

the inconsistency of whether a lesion deficit is observed is whether the test is done while a rat was learning or has acquired the task. Kim and Frank (2009) reported a hippocampal lesion induced deficit only during the learning phase of the task. The win-shift deficit reported in Ainge et al. (2007a) was also only observable during the first few days of the win-shift alternation task after the rats had been trained on the win-stay task on a double Y-maze and the performance of the lesioned rats eventually become comparable to the controls. This suggests that some of the negative results reported in the lesion literature may be due to testing the rats' performance after task acquisition. For example, Ainge et al. (2007a) reported no impairments from the lesioned rats while performing the win-stay tasks, but it is not clear whether the lack of deficit was due to an over-training induced shifts in structure dependence or a genuine lack of involvement from the hippocampus. There are also minor differences in the difficulty of the win-stay task. Some of the tasks used different start locations within a session (Ferbinteanu and Shapiro 2003), which would require the rat to navigate toward a fixed location via different routes. This is similar to the water maze working memory task which has also been shown to be sensitive to hippocampal lesion (Whishaw and Jarrard 1996). While others used a fixed start box location throughout the experiment, which might enable the task to be solved via a route based praxic strategy (Ainge et al. 2007a).

A deficit observed from lesion studies would suggest the requirement of the lesioned structure for the execution of the behavioural task. However, a negative result does not eliminate the possibility of the structure's contribution. For example, lesion of the hippocampus only affects the expression of contextual fear conditioning memory when it is done after training. On the other hand, if the lesion is performed before training, no deficit is observable (Maren et al. 1997). This suggests that a rat can acquire contextual fear memory even without a hippocampus, but the involvement of the structure is also apparent from the deficit observed after post-training lesions. A temporal observation of the firing characteristics of hippocampal cells during and after the learning phase may shade additional light upon the involvement of hippocampus in the learning of win-stay and win-shift tasks. It has been shown that some of the contextually distinctive hippocampal codes only develop after repeated experiences of different contexts (Hayman et al. 2003; Lever et al. 2002), suggesting a gradual differentiation of similar environments. Bower et al. (2005) reported that, when the reward was given after the choice points, strong goal sensitive activity only developed after the rat had been well trained for the task. In addition, repeated exposure to the task did not increase the percentage of hippocampal cells that showed goal sensitive activities. The temporal sequence of the development of goal sensitive cells provides some support of their involvements in the win-shift task. Similarly, Smith and Mizumori (2006b) reported that context dependent firing modulation of hippocampal cells is only apparent when the context is required to solve the behavioural tasks. However, it is not clear whether the reported context dependent firing was due to the directionality of

hippocampal place fields. Karlsson and Frank (2008) compared the activity of hippocampal cells in a novel environment to those recorded from a familiar environment and found that the firing rates of CA1 but not CA3 cells were significantly higher in the novel environment. Several investigators also reported within day changes in hippocampal codes, most notably backward shifts (Lee et al. 2006; Mehta et al. 1997, 2000) and forward shifts (Lee et al. 2006) of the place fields. The backward shift phenomenon was interpreted as evidence of synaptic plasticity whereas Lee et al. (2006) suggested that the forward shift observed was related to the intended future destinations. However, a forward-shift of future intentions suggests that the rat makes its decision later and later at the common path within the same day, which may not fit well with the interpretation that this signifies the rat's increasing proficiency of solving the task. Lee et al. (2006) also reported that the number of goal sensitive cells did not differ on the first four days. However, as the rats learned the task on the first day, it was difficult to infer the correlation between the rats' performance and the percentage of goal sensitive cells observed.

Despite many reports exploring the phenomenon of goal sensitive cells, it is still unclear how this particular characteristic of hippocampal code develops and its correlation with behavioural performance of the rats. Bower et al. (2005) analysed the development of goal sensitive cells over days but did not associate the results with the performance of the rats. Here, we have designed an experiment to specifically explore the development of goal sensitive cells on a double Y-maze identical to the one used in Ainge et al. (2007a). Single unit activity from the CA1 area of hippocampus are recorded while a rat is learning the spatial win-stay task. There are three possible outcomes from the experiment,

1. Goal sensitive cells develop before the rat learns the win-stay task.
2. Goal sensitive cells develop after the rat learns the task.
3. Goal sensitive cells develop as the rat is learning the task.

The first two outcomes would argue against the hypothesis that these goal sensitive cells are involved in the win-stay task, whereas the third outcome supports the idea that goal sensitive cells in the hippocampus play a role in learning and execution of the task. We show that the percentage of goal sensitive cells increase with the rat's performance during the learning phase of the win-stay and there is a significant linear relationship between task performance and the observed percentage of goal sensitive cells.

6.2 Methods

6.2.1 Subjects

Seven male adult Lister Hooded rats weighing 250–350g at the time of surgery were used. Five of the rats received the cue conflict experiments as described in chapter 5. Rats were

kept under a 12 hour light/dark cycle and were housed in individual cages after surgery. All experiments were carried out during the light phase of the cycle. Rats were given *ad libitum* access to water and food during the one week post surgery recovery period. Food access was then restricted to maintain the weights of the rats at 85–90% of their free feeding weights. All procedures were performed in compliance 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 Surgery, screening, recording and perfusion

The surgery, screening, recording and perfusion procedures were identical to the CA1 single unit recording experiment procedure described in section 5.2.

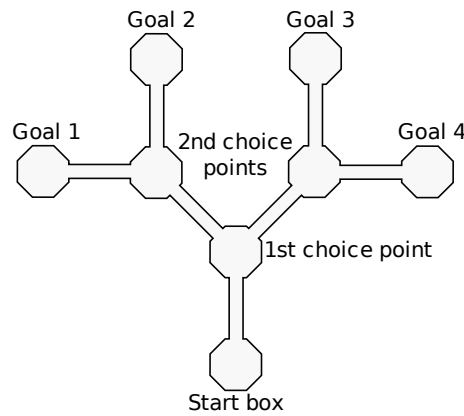
6.2.3 Experiment protocol

Apparatus

The maze used in the experiment was identical to the one used in Ainge et al. (2007a). An illustration and a picture of the maze is shown in figure 6.1. Briefly, the maze was constructed from wood with its surface painted black to minimise reflection from lights and consisted of eight octagonal boxes with seven connecting bridges. Each octagonal box was surrounded by 30-cm high walls, and the bridges were 25 cm long, 8 cm wide with 10-cm-high walls. One of the octagonal boxes was the start box, four served as the goal boxes and the last three were used as the choice points where paths to goal boxes branched out. There were two levels of choice points (one choice point on the first level and two choice points on the second level) with each choice point having one entrance and two exits. The two levels of choice points gave rise to four goal boxes from a single exit at the start box. To facilitate differentiation among the four goal boxes, each goal box contained a distinct perspex cue mounted on the wall and an object cue placed on the floor against the wall. The perspex cues were different in shapes and colours and the four objects used in the experiment were a rectangular metal plate, an unopened plastic shampoo bottle, a metal rod mounted on a circular disk, and a metal wine glass. The maze was mounted on circular stools such that it was 64cm above the ground and rats' views of the room were obstructed only by the walls of the maze. A ceramic bowl was placed at the centre of each goal box and was used to hold food rewards.

Behavioural training and recording

Rats only started the double Y-maze experiment after spatially modulated single unit activity (i.e. place cells) were recorded. The rats were then trained for up to fourteen days on the double



(a) An illustration of the double Y-maze



(b) A picture of the double Y-maze

Figure 6.1: The double Y-maze used in the experiment. (a) shows an illustration of the double Y-maze and (b) is the picture of the maze used in the experiment. Rats were placed in the start box at the beginning of each trial and one of the four goal boxes would be rewarded with chocolate weetos.

Y-maze win-stay task. In each session one of the four goal boxes was baited with multiple food rewards (weetos chocolate cereal loops, Weetabix, Kettering UK). The rats ran for four sessions each day, with at least ten trials per session. One of the four goal boxes was chosen in turn as the rewarded goal box in one session and the order of the rewarded goal box was determined at random. Each trial started with the rat being placed in the start box. It was then allowed to choose one of the four goal boxes. After the rat fully entered the bridge connecting to one of the goal boxes a barrier was placed behind it for ten seconds. If the goal box was rewarded, the rat was allowed to consume as many weetos as possible during the ten second period. At the end of the trial, the rat was placed back into the start box and stayed there for twenty seconds before the start of next trial. During this time the surface of the maze was wiped by a tablecloth soaked with soapy water. At the beginning of each session, the rat was allowed to run unlimited number of trials until it located the rewarded goal box. After the rat visited the rewarded goal box for the first time, it was then given nine additional trials during which the rewarded goal box remained in the same location and this completed the session. After this the reward was moved to a different goal box while the rat was in the start box and this marked the start of the next session.

6.2.4 Data analysis

Unit isolation

The unit isolation procedure was identical to that described in section 5.2.7.

Performance of the double Y-maze task

The performance of the on the double Y-maze task was measured by calculating the percentage of trials that ended at the rewarded goal box after finding the reward goal box for the first time within a session.

Differential firing of pyramidal cells

Classification of putative pyramidal neurons was primarily based on the average width of the waveforms. Unit clusters were classified as likely pyramidal cells when the average width of the waveform exceeded $250 \mu\text{s}$ and the average amplitude $>80 \mu\text{V}$ from at least one of the recording channels. Four areas of interest were defined on the double Y-maze: the start box (area 1), the central stem (area 2), the left central stem (area 3) and the right central stem (area 4). These areas were sections on the double Y-maze where running paths leading to different goal boxes overlap (see figure 6.2 for a schematics of the locations of the four areas). The number of spikes that a unit fired in a given area and the time the rat spent in that area was used to calculate the average firing rate of the unit in the area. A cluster was considered to be active and was included in the analysis of one area if the average firing rate in that area was $>1 \text{ Hz}$. Trial-by-trial average firing rate in each area was calculated and was used to determine whether the unit exhibited goal sensitive firing. A univariate unbalanced Anova was then used to determine whether the observed average firing rates differed significantly with respect to goal boxes. A $0.05 p$ -value was used as the significance threshold. If an isolated cell was deemed to be active in more than one areas and was tested for goal sensitive firing more than one time, the p -value threshold was adjusted accordingly to maintain the same level of false positive rate².

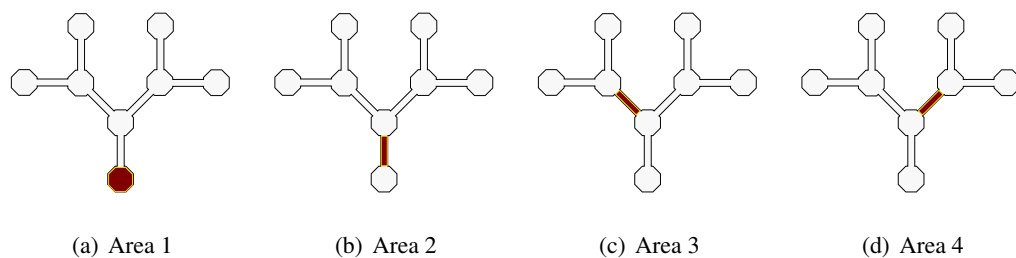


Figure 6.2: Four defined areas on the double Y-maze. Average firing rates in the four areas were used to determine whether the recorded pyramidal cells exhibited goal sensitive firing pattern. Area 1 is the start box of the double Y-maze, area 2 encompasses the passage way from the start box to the first choice point. Area 3 and 4 are the passage ways connecting the first choice point to the left (3) and the right (4) second choice points.

²If a cluster was deemed to be active in two areas, than a p -value threshold of 0.025 was used to determine where the cluster exhibited goal sensitive firing behaviour, this maintained consistent false positive rates between cells that were active in different number of areas.

6.2.5 Perfusion and Histology

The procedure is identical to that described in section 5.2.8.

6.3 Results

6.3.1 Histology

The histology is identical to section 5.3.1. The lesion track caused by the inserted electrodes was identified from six of the seven rats and were verified to have either targeted or passed through the CA1 cell layer of the hippocampus.

6.3.2 Performance of the rats on the win-stay task

Win-stay performance of the rats on the double Y-maze is presented in figure 6.3. The rats performed better than chance (25% correct) from day one ($t=3.93$; d.f.=6; $p<0.01$) and quickly acquired the win-stay task to reached 80% correct by day three. A repeated measures Anova confirmed that performance across days were significantly different ($F_{((13,78))}=12.96$; $p<0.001$). *Post hoc* analysis using Sidák correction for multiple comparison shows that performance reached plateau on day three, which was significantly better than the performance observed on day one and two. As different rats learned the win-stay task at different rates, we defined a quantitative approach to determine the learning phase of the task for each rat. The first step was to define the rat's asymptotic performance. Based on the performance result presented in figure 6.3, we concluded that the performance reached asymptote well before the second half (days 8–14) of the experiment. We thus used the daily performance from day 8–14 to construct a 95% confidence interval (C.I.) of the asymptotic performance for each rat. The learning phase was defined to be from the start of the training to the first day that the rat's performance exceeded the lower bound of its 95% C.I. asymptotic performance. Figure 6.4 showed the win-stay performance of each rat across days and the 95% C.I. of its asymptotic performance.

6.3.3 Identification and firing distribution of pyramidal cells

As the focus of the experiment is to explore the development of goal sensitive cells across days, no attempt was made to determine whether same cells were recorded over multiple days. Overall, 722 units fulfilled the waveform width criteria and were deemed to be active in at least one of the four areas, 195 (27%) of these units were determined to exhibit goal sensitive activity (see figure 6.5 and figure 6.6 for examples). Similarly to what was reported in Ainge et al. (2007a), we saw more complex spikes cells that were active before the first choice point (63%. 400 cells in area 1, the start box and 373 cells in area 2, the central stem.) than between the first and the second choice points (37%. 218 cells in area 3, the left passageway after

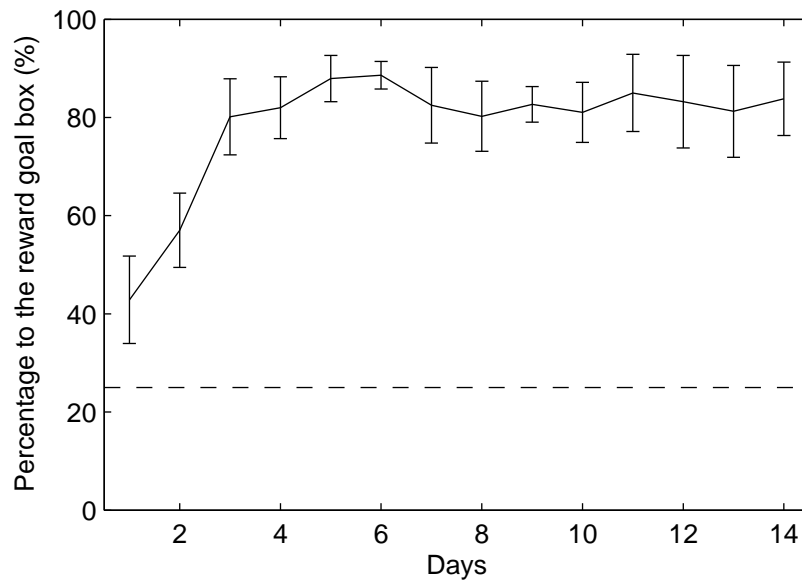


Figure 6.3: Performance of the rats on the double Y-maze task across days. The mean \pm 95% C.I. was plotted. The dashed line marks the level of performance expected by chance. The figure shows that the rats performed better than chance on day one and reached the plateau performance of \sim 80% correctness by day three.

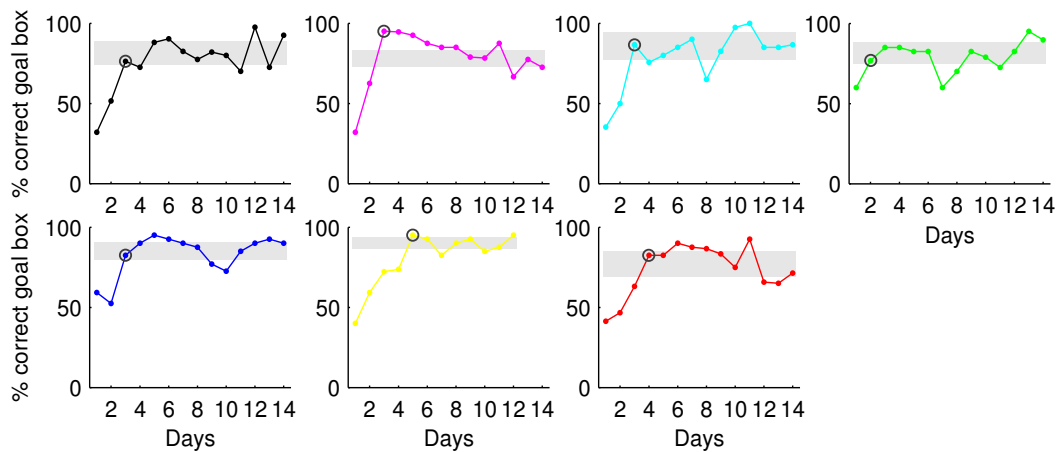


Figure 6.4: Determination of the learning phase of the win-stay task. The performance of the win-stay task of each individual rat was plotted. The grey shaded areas represent 95% C.I. of each rat's performance from day 8–14. The first day the rat's performance exceeded the lower bound of the C.I. was treated as the last day of the learning phase for the rat. The data point of the day that the rat reached this performance criterion was circled in the figure. One rat reached the criterion on day 2, four on day 3, one on day 4 and one on day 5. This showed that different rats learned the win-stay task at different rates.

the first choice point. 236 cells in area 4, the right passageway after the first choice point.). Figure 6.7 summaries the number of active cells in each area. We also plotted the data from day 1–4 and day 8–14 separately to explore whether the spatial distribution of active pyramidal cells differs between the learning and the plateau phase of the win-stay task. The distribution of cells that were active in each area appears to be similar between the two datasets. A chi-square test comparing the distribution of the cells in the two time periods also failed to reject the hypothesis that the two distributions are identical ($\chi^2=12$; $p>0.05$). As some of the cells were active in more than one areas, the sum of active cells from each area (1227) was greater than the total number of active cells recorded. The activation patterns of the active cells and the goal sensitive cells recorded is summarised in figure 6.8. One concern of the analysis is that cells that are active in more than one area are tested multiple times for goal sensitive activity and hence are more likely to be classified as goal sensitive cells by chance. We adjusted the probability cutoff according to how many times a cell is tested for goal sensitive activities, which should address the issue by maintaining the false positive rates constant. Figure 6.8 shows that cells that were active in only one area were just as likely to be classified as goal sensitive cells as those that were active in more than one area.

6.3.4 Development of goal sensitive place cell activity

One of the main goals of the experiment is to look at the development of goal sensitive cells during the learning phase of the task. Only recording sessions with at least five pyramidal cells active in one of the four areas were included in the analysis. Percentage of pyramidal cells that demonstrated goal sensitive activities (based on the procedure described in section 6.2.4) were plotted in figure 6.9. As the number of recorded neurons fluctuated between days, not all recording sessions obtained sufficient data to contain five active pyramidal cells. In order to associate the percentage of goal sensitive cells to performance, we re-aligned the recording data using the last day of the learning phase as the reference point. Figure 6.9 summaries the results with day 0 = the last day of the learning phase. Only days with at least four rats with adequate recording data were included in the analysis, which encompasses results from day -2–3³. Analysis using univariate unbalanced Anova shows that the percentage of goal sensitive hippocampal cells differs significantly across days ($F_{((5,21))}=6.27$; $p<0.001$). *Post hoc* analysis using Sidák correction for multiple comparison confirms that the percentage observed in day -2 was significantly lower from those observed in day 0 and 1 but did not differ significantly from other days. Those observed in day -1 was also significantly lower than in day 0 but not other days. A summary of the *post hoc* analysis is also presented in figure 6.9.

To further investigate the relationship between learning of the win-stay task and the de-

³As the placement of unit recording electrodes are usually optimised at the start of the experiment. The number of recorded cells tends to decrease over time.

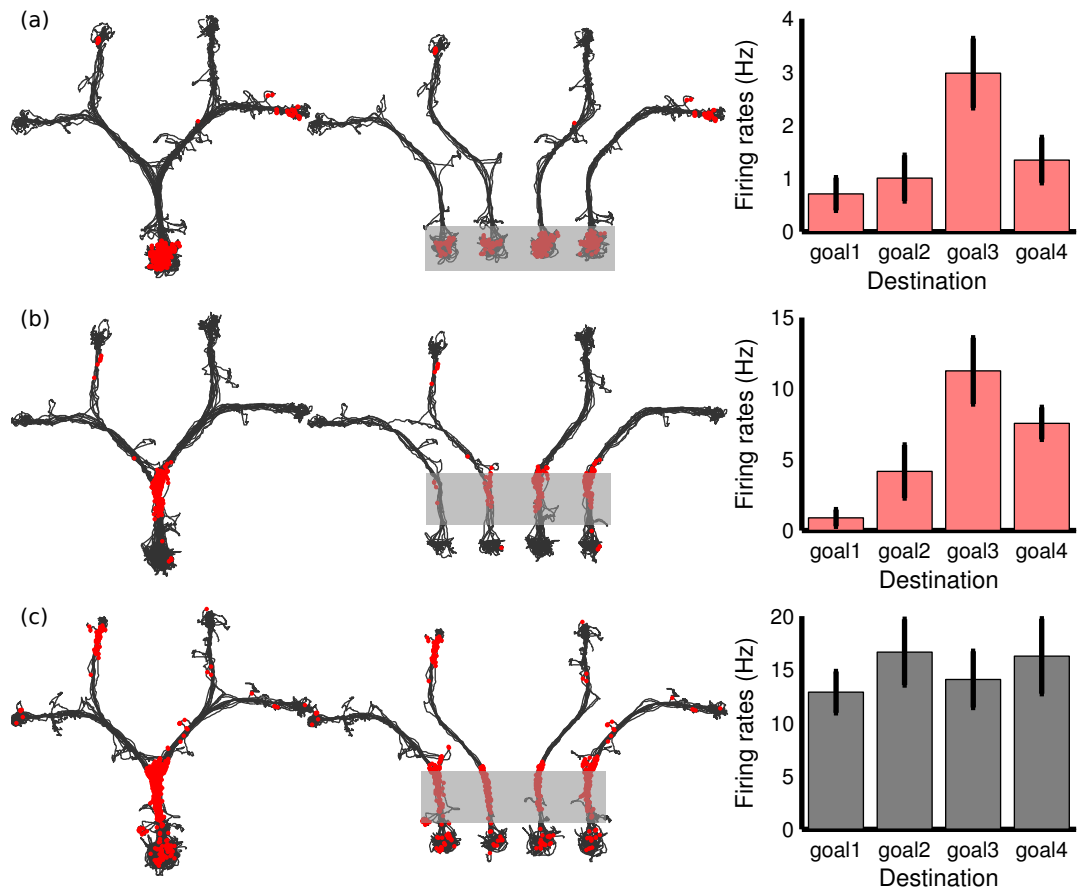


Figure 6.5: Examples of goal sensitive pyramidal cells before the 1st choice point. Pink shading on the firing rate histogram indicates that the cell exhibited significant goal sensitive activities. (a) presents an example of a goal sensitive cell firing at the start box (area 1) of the double Y-maze. The rats were confined at the start box (area 1) for ~20 seconds at the beginning of each trial. This example demonstrates that goal sensitive firing activities were also found in areas that did not belong to a running trajectory. (b) is an example of a goal sensitive cell that was active at the central passageway (area 2) of the double Y-maze. (c) is an example of a cell who was also active at the central passageway of the maze but did not exhibit any significant goal sensitive firing.

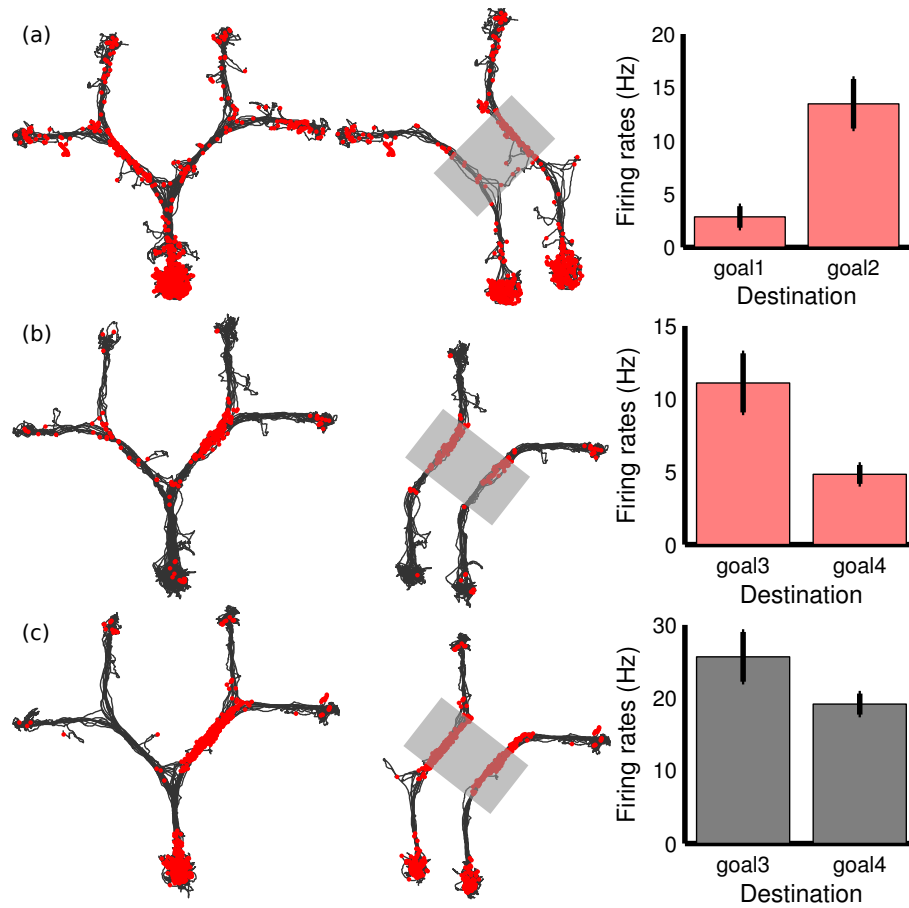
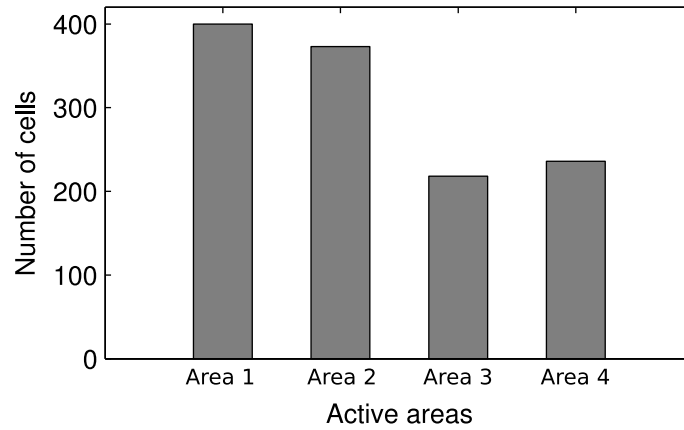
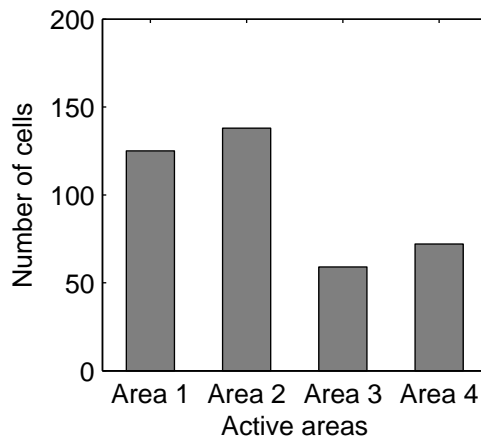


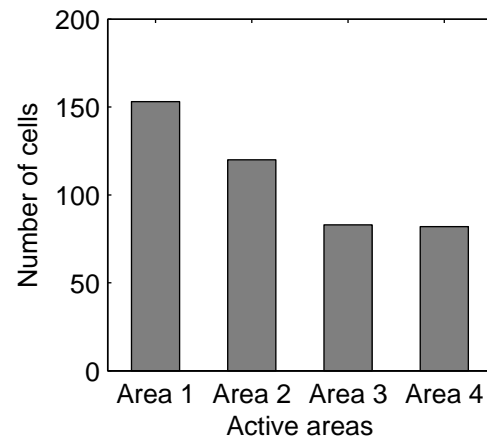
Figure 6.6: Examples of goal sensitive pyramidal cells between the 1st and the 2nd choice points. (a) is an example of a goal sensitive cell that was active at the left passageway (area 3) after the 1st choice point, and (b) is an example demonstrating goal sensitive activities at the right passageway (area 4). Finally, (c) is an example of a non goal sensitive cell which was active after the 1st choice point.



(a) Number of active cells from all recording sessions



(b) Number of active cells from day 1–4



(c) Number of active cells from day 8–14

Figure 6.7: Number of cells that was active in each of the four areas. If a cell was active in more than one area, it was counted once in each of the active areas. Figure 6.8 presents how many cells are active in multiple areas. (a) includes data from all recording sessions, and (b) contains only the data collected during day 1–4 of training. This represents the learning phase of the win-stay task. (c) contains only the data during day 8–14 of training and represents the plateau (over-training) phase of the win-stay task.

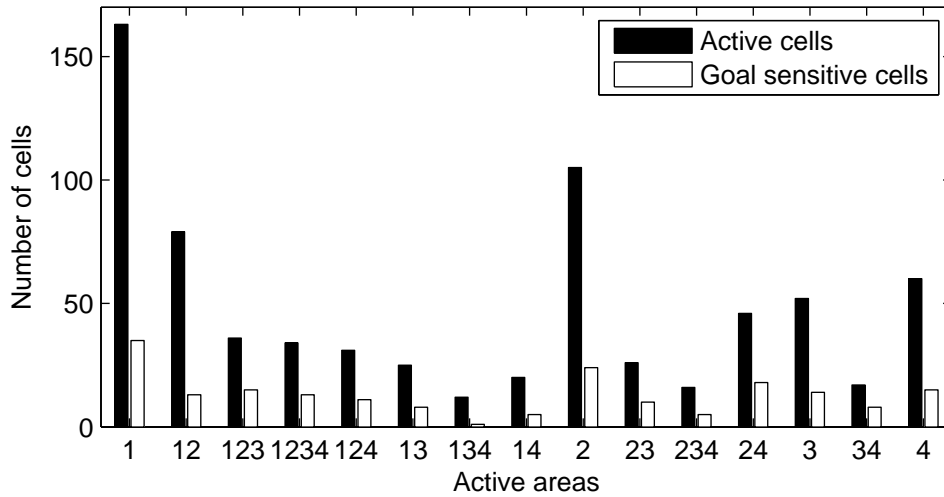
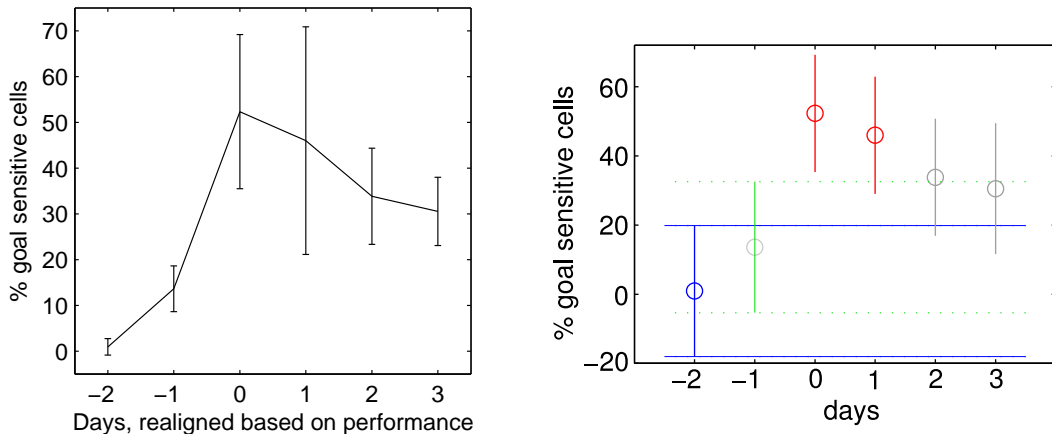


Figure 6.8: Distribution of active and goal sensitive pyramidal cells. The histogram summarizes the distribution of active and goals sensitive pyramidal cells in different areas. Cells that are active in different combination of areas were separated into different groups. E.g. an x-axis label of 12 means the cell was active in both area 1 and 2 of the double Y-maze but was silent in area 3 and 4.



(a) Percentage of goal sensitive pyramidal cells across days

(b) Sidák correction for multiple comparison

Figure 6.9: Percentage of goal sensitive pyramidal cells across days. As the rats learned the win-stay task at different rates (see figure 6.4), we realigned the percentage of goal sensitive cell based on the day each rat reached asymptotic performance. Day 0 = the day each rat reached asymptotic performance, which was the last day of the learning phase of the win-stay task. (a) illustrates mean \pm 95% C.I. of the percentage of goal sensitive cells. As percentage was only calculated from recording sessions containing at least five pyramidal cells, not all recording sessions contain sufficient data to calculate the percentage. Only days with at least four recording sessions representing data collected from at least four rats were included. This includes the data from two days before to three days after the rats reached asymptotic performance. (b) summarizes the results of the *post hoc* analysis using Sidák correction for multiple comparison. The means are significantly different from each other if the bars in the figure do not overlap. The figure shows that the percentage of goal sensitive cells from day -2 is significantly different from those observed in day 0 and day 1. The observed percentage in day -1 is also significantly lower than those observed in day 0.

velopment of goal sensitive cells, a regression analysis was performed using the performance of the rats on the win-stay task as the independent variable and the percentage of goal sensitive cells as the dependent variable. We separated the collected data into three groups. The first group comprised those collected from the first day of training to the day the rat reached asymptotic performance, which represents data collected during the learning phase of the task. The three day period after task acquisition was classified as the transition phase. Finally, the third group included all data collected after the transition phase, which is classified as the plateau/over-training phase. The main motivation for including a transition period stems from the observation that the percentage of goal sensitive cells appears to decline in the days after the rat reached asymptotic performance. This raises the question of whether the relationship between the behaviour and the percentage of goal sensitive cells changes after a rat acquires the win-stay task. The results from the linear regression analysis are summarised in figure 6.10. Briefly, the analysis found a strong linear relationship from the data collected during the learning phase ($R^2=0.80$; $p<0.001$), but did not find any significant linear relationship from data collected during the transition phase ($R^2=0.08$; $p=0.3$). A linear relationship was also found during the plateau phase ($R^2=0.34$; $p<0.005$) though it was not as strong as in the learning phase. The regression relationship also suggests that, given the same level of win-stay performance, the percentage of goal sensitive cells observed in the plateau phase of the experiment was lower than that observed during the learning phase. The analysis suggests that the linear relationship between the performance of the rats and the percentage of goal sensitive cells disappeared temporarily in the days immediately after task acquisition and reappeared afterwards. However, one can criticise the interpretation by pointing out that there are less data recorded during the transition phase than those recorded during the plateau phase. The absence of a linear relationship during the transition phase may thus be attributed to the different statistical power. To address this criticism, we ran regression analysis on a new set of data from the plateau phase which only included the recording sessions with which the win-stay performance was comparable to that observed during the transition phase. The size of this new data set is comparable to the data set of the transition phase and the regression analysis still found a significant linear relationship between behaviour and the percentage of goal sensitive cells ($R^2=0.35$; $p<0.05$). This suggests a significant linear correlation between the performance of the rats and the proportion of the goal sensitive cells specifically during the learning phase of the task, and argues against the interpretation that the development of goal sensitive cells is dependent on the amount of win-stay task experience.

6.3.5 Firing rate variance of pyramidal cells

For a cell to demonstrate goal sensitive firing behaviour, it has to fire differentially when the rat is running towards different goals, but it also has to fire consistently when the rat is running

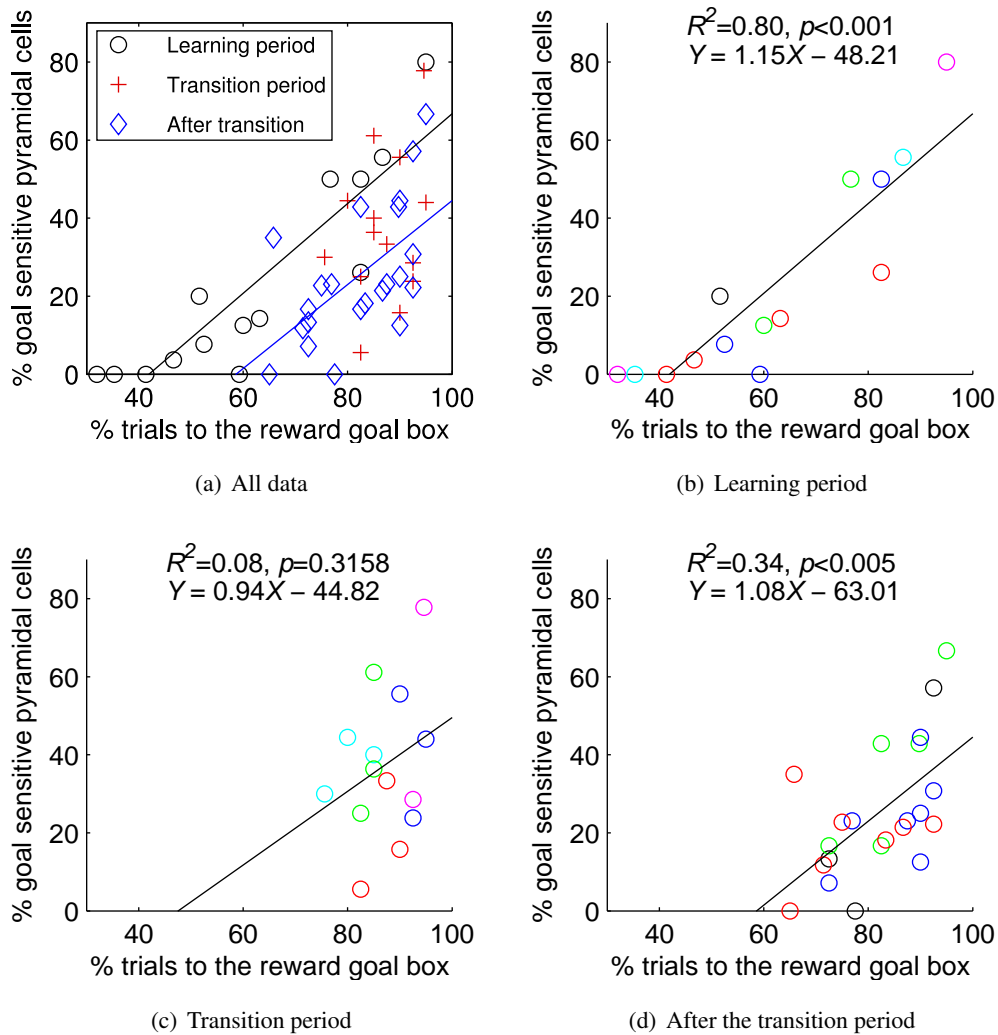


Figure 6.10: Regression analysis of the rat's performance and the development of goal sensitive cells. The recording sessions were separated into three groups. The first group contained sessions recorded during the learning phase of the task, defined as from the first day of the training to the day the rat reached asymptotic performance. The criterion for asymptotic performance is shown in figure 6.4. The second group represents data collected from the transition phase, defined as the three day period right after the rats reached asymptotic performance. The last group includes all the data from the plateau phase, which is defined as the training sessions after the transition phase. (a) presents the data from all three groups. Best fit lines constructed by linear regression were also plotted for the data sets from the learning phase and plateau phase as regression analyses suggested significant linear relationship from these two groups of data. The results of linear regression from all three groups of data can be found in (b)–(d). The data points from (b)–(d) are colour coded by identities of the rats and used the same colour codes as the ones used in figure 6.4 and figure 6.9. (b) presents data collected from the learning phase of the win-stay task. Linear regression suggests a strong relationship between the win-stay performance of the rats and the percentage of goal-sensitive cells ($R^2=0.80$; $p<0.001$). (c) presents data from the transition phase. Linear regression failed to detect a significant linear relationship from the dataset. The low R^2 value also suggests that the fitted line does not adequately explain the relationship between the percentage of goal sensitive cells and the performance of rats from this data set ($R^2=0.08$; $p=0.3$). (c) contains all data collected after the transition phase. Linear regression found a significant linear relationship from the dataset though the relationship is weaker when comparing to the relationship observed during the learning phase of the task ($R^2=0.34$; $p<0.005$).

to the same goal. High trial-to-trial variation in firing rates would make it harder for Anova analysis to identify goal sensitive firing activity and can thus affect the level of goal sensitive cells observed. We analysed the within day trial by trial variation of pyramidal cells' average firing rates in the four areas on the double Y-maze when the rats were running to the same goals during the first six days of the win-stay task. Only recording sessions containing at least five pyramidal cells were included for analysis. Figure 6.11 presents mean \pm 95% confidence interval (C.I.) of the average coefficient of variation of the pyramidal cells' trial by trial average firing rates at the four areas of the double Y-maze. The coefficient of variation of an area was only included in the analysis if the cell is considered to be active in that area⁴. The figure did show a decline in average coefficient of variation from day two onwards, though an univariate unbalanced Anova failed to detect a significant change across days ($F_{(5,23)}=2.61$; $p=0.052$). The small difference between the maximum and the minimum value also suggests that even when the declining trend of coefficient of variations across days is real, the effect is small. Increasing stability of same trajectory firing rates may also reflect the process of goal sensitive cell development. The analysis suggests that the increase in the proportion of goal sensitive cells observed across days is not due to increasing firing rate stability (manifested as reduced coefficient of variation) across days (Cacucci et al. 2007) which also argues against the interpretation that increasing number of goal sensitive cues across days is dependent on the amount of experience the rats had on the win-stay task.

In Ainge et al. (2007a), it was reported that the same trajectory firing rates of pyramidal cells sometimes changed significantly within the same day. Examples shown included pyramidal cells that became active or silent for trials ending at the same goal box. This could be interpreted as the development of goal sensitive activity. We thus explored whether there were more such incidences during the learning phase of the win-stay task. Some cells recorded from the experiment also showed intraday changes in firing rates similar to those reported by Ainge et al.. Some of the examples are shown in figure 6.12. In order to analyse such phenomenon quantitatively, we defined a significant change in firing as a significant difference in average firing rates from three consecutive trials to the three subsequent trials to the same goal destination when tested using unpaired t-test. The significance level was defined as 0.05 divided by the number of times the t-test was performed for the cell. This dynamic adjustment of the significance threshold ensures identical false positive rates for all evaluations. We then calculated the percentage of pyramidal cells that exhibited within-day significant changes in firing over days. Again, only recording sessions with at least five pyramidal cells were included in the analysis. Figure 6.13 presents the output of the analysis and we fail to find a significant effect across days using univariate unbalanced Anova ($F_{(5,23)}=1.09$; $p=0.39$).

⁴The requirements are, the average firing rate on the area when the rat was running towards the same goal box exceeded 1 Hz and there were at least six trials with the goal box being the final destination

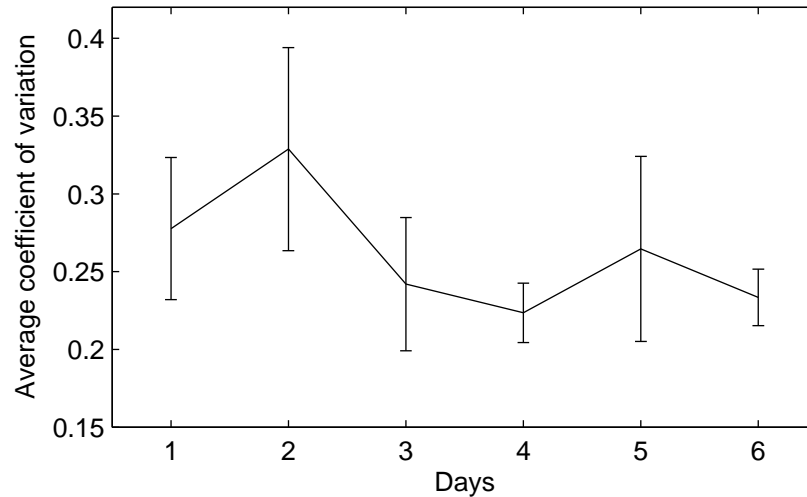


Figure 6.11: Firing rate variance of pyramidal cells. Journey by journey average firing rates of each pyramidal cell in the four defined areas on the double Y-maze were calculated. If the overall mean firing rate from trajectories leading to the same goal box exceeded 1 Hz and there were at least six journeys to the goal box during the recording session, the coefficient of variation of the firing rates was calculated. The mean coefficient of variations from each day was then calculated for each rat if there were at least five active pyramidal cells on the day of recording. Mean \pm 95% C.I. from the first six days of training are presented. Each day contained data from at least four rats. Univariate unbalanced Anova failed to obtain a significant p -value, though the result was borderline to being significant ($F_{(5,23)}=2.61$; $p=0.052$).

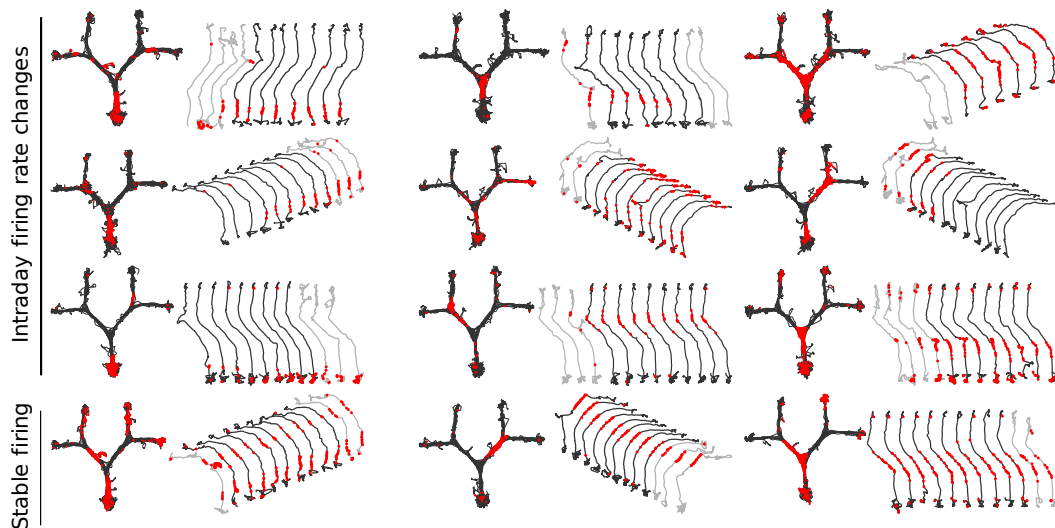


Figure 6.12: Nine examples of pyramidal cells that showed significant same trajectory intraday changes in firing rates are shown along with examples from three pyramidal cells which showed consistent intraday firing rates. Black lines are trajectories of the rats and the red dots are the positions of the rats when the cells fired an action potential. The trajectories are ordered by trial time from left to right. For individual trajectories, the light grey lines indicate error trials (i.e. the goal box was not the rewarded goal box) and the black lines indicate correct trials.

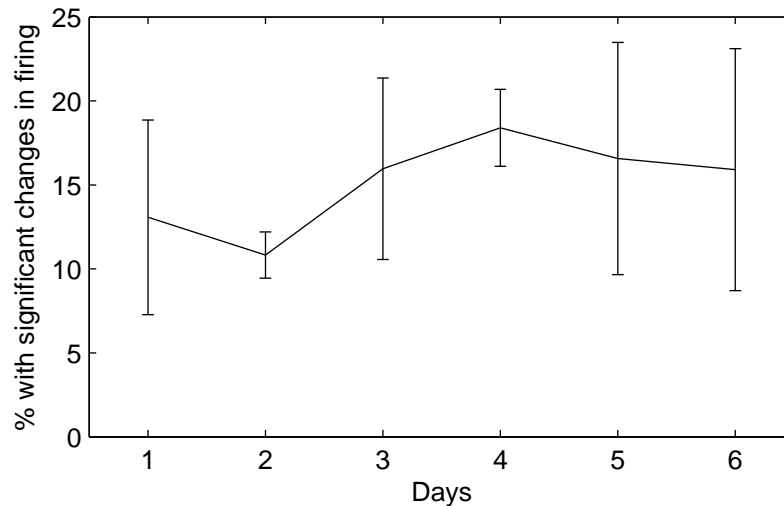


Figure 6.13: Percentage of within day significant changes in firing rates. We looked at the time-series average firing rates in one of the four areas defined on the double Y-maze when the rat was travelling to one of the goal boxes. A significant change in firing rates was defined as when the average firing rates of three adjacent time-series data points differed significantly from the subsequent three data points when tested using unpaired t-test. The time series was essentially tested by a sliding window that encompasses six data points at one time. The significance level was defined as 0.05 divided by the number of times the t-test was employed in testing the time series. Univariate unbalanced Anova analysis failed to detect a significant difference of the proportion of cells that showed significant changes in firing rates across days ($F_{(5,23)}=1.09$; $p=0.39$).

6.4 Discussion

In a double Y-maze win-stay task in which a rat, after finding the location of the rewarded goal box, needs to return to the same location for additional rewards, the proportion of CA1 pyramidal cells that shows goal sensitive firing increases with the rat's performance during the learning phase of the task. There is a significant linear relationship between the rat's performance and the proportion of the goal sensitive cells both before and after learning. The result supports the idea that the goal sensitive cells reflect the rat's ability to perform the win-stay task and may represent the neural codes involved in the computation employed by the rat to solve the win-stay task.

6.4.1 Learning of the double Y-maze win-stay task

Unlike the spatial alternation paradigm used by Lee et al. (2006) where the rats learned the task on the first day, the rats used in this experiment reached plateau performance of $\sim 80\%$ correct by day 3 of training. This stretched learning phase allows the analysis of the association between the development of goal sensitive cells and performance improvement of the rats. Although, on average, the learning phase of the task was three days, different rats learned the task at different rates stretching from two to five days. The different learning rates partially

address the issue of dissociating the linear relationship between the rat's performance and the development of goal sensitive cells from a time dependent familiarity effect. As different rats achieved the plateau performance at different rates, the linear relationship can not be solely the result of their co-correlation with time. Thus the strong linear correlation between the rats' performance on the double Y-maze win-stay task and the observed percentage of goal sensitive cells during the learning phase suggested that the observed increase in goal sensitive cells is related to the learning process. However, common to all unit recording experiments, a conclusive casual relationship between the learning and the goal sensitive cells cannot be inferred from the data at hand. A stronger case can be established if the lesion of the structure induces a learning phase deficit of the win-stay task.

6.4.2 Number of cells active in the different areas

Ainge et al. (2007a) reported that more hippocampal cells were active at the start of the double Y-maze before the first choice point than the rest of the maze. We also observed a similar biased representation. One of the proposed explanation was that this mirrors the results observed from striatal cells in which they over-represent the start and the goal of the T-maze during the over-training phase of learning (Barnes et al. 2005; Jog et al. 1999), and may represent elements of procedural learning (Packard and McGaugh 1996) after over-training. We tested this hypothesis by comparing the distribution of active cells in each of the four areas during the learning phase (day 1–4) and the plateau/over-training phase (day 8–14) and failed to find any significant difference between the two distributions. We conclude that this over-representation at the start of the maze exists even at the beginning of training and thus cannot be attributed to over-training. Another explanation is that the biased representation is due to the hippocampus encoding each of the four trajectories independently, thus resulting an over- representation at the start of the double Y-maze where all four trajectories overlap. Given the above scenario and the assumption that every part of a trajectory is evenly represented, one would expect that the number of cells that are active at the start of the maze is twice as much as that after the first choice point, which is similar to what was observed in our experiment (see figure 6.7).

6.4.3 The development of goal sensitive cells

As summarised in the introduction, goal sensitive cells from the hippocampus have been reported under both win-stay (Ainge et al. 2007a; Ferbinteanu and Shapiro 2003; Ji and Wilson 2008) and win-shift (Ainge et al. 2007b; Frank et al. 2000; Ji and Wilson 2008; Wood et al. 2000) rules. These goal sensitive cells have been implicated to facilitate the resolution of the tasks by either encoding memory (e.g. retrospective encoding of previously visited goals), intended destination (prospective encoding) which may represent mental time travel similar to what was reported by Johnson and Redish (2007), or dis-ambiguation of overlapping trajec-

ries similar to the formation of multiple reference frames in one environment (Gothard et al. 1996). However, without a concurrent analysis of the rat's behaviour, it is difficult to establish a link between the neural code and the resolution of the task. For example, an intended destination can simply arise from a goal directed behaviour which does not help solving either a win-stay or a win-shift task. Trajectory dependent codes can simply arise from repeated exposure to the maze environment (Bostock et al. 1991; Hayman et al. 2003; Lever et al. 2002) and may not contribute to the performance of the task. Here we show that the proportion of goal sensitive cells recorded from CA1 of hippocampus is significantly higher on the first day the rat reaches asymptotic performance when comparing to the data recorded both one and two days prior to reaching asymptotic performance. This shows that the development of goal sensitive cells parallels the improvement in performance accuracy. A significant linear relationship is also identified when regressing the proportion of goal sensitive cells against trial accuracy (see figure 6.10). This correlation suggests that the emergence of goal sensitive hippocampal cells may underlie the rat's ability to accurately execute the win-stay task on the double Y-maze, hence supporting the interpretation that the goal sensitive firing aids task resolution. Ji and Wilson (2008) showed that, when encountering a novel task, the hippocampus contains more prospective encoding, but gradually shift to retrospective encoding with additional experience. Unfortunately, with the repetitive nature of the win-stay task, it is impossible to distinguish the difference between prospective and retrospective encoding. We thus are unable to determine whether it is the development of prospective or retrospective encoding that correlates with the rat's improved accuracy on the win-stay task. The linear relationship between performance and the proportion of goal sensitive cells disappears on the three days (the transition phase) after the rat has acquired the task but re-emerges again for the rest of the training days (the plateau phase). One pitfall for this analysis is that there were less data from the three day period and also the range of performance levels are smaller, which could make the regression analysis more susceptible to fluctuation of the proportion of goal sensitive cells. We address this issue by restricting the regression analysis of the plateau phase data to the same performance range as the transition phase. This restriction also reduces the size of the data set to a comparable level to the transition phase. A significant linear relationship still exists after this restriction, suggesting that the different level of linear relationship observed between the transition phase and the plateau phase was not due to the smaller data set in the transition phase. When comparing the regression result of the learning and the plateau phase, the regression line of the plateau phase appears to be a parallel shift of the line from the learning phase. This suggests that, given the same level of performance, the proportion of goal sensitive cells is lower in the plateau phase, which mirrors the observation that the average proportion of goal sensitive cells peaks on the day the rats acquired the task and starts declining thereafter. The decline is not statistically significant. However, when plotting the data from each rat separately, we note that the large error

bar observed on the first day after task acquisition appears to be the result of differential rates of decline of the proportion of goal sensitive cells from different rats. One can also argue that this decline is caused by gradual deterioration of unit recording quality due to micro-movement of electrode tips over days. However, given that we only include data that meet our criteria and goal sensitive cells were found from recording data collected throughout the fourteen days of training, it is unlikely that recording deterioration contributes significantly to this trend. This pattern suggests that the hippocampus plays a more prominent role during the acquisition of the win-stay task and may be the reason why Ainge et al. (2007a) found minimum impairment after the lesion of the hippocampus as the rats in the experiment were already well-trained on the task at the time of lesion. As reported by Packard and McGaugh (1996), over-training shifts the rat's preference from a hippocampal mediated to a striatal mediated behaviour. The trend of decline in goal sensitive cells can thus be hypothesised as the evolution of task dependence upon the hippocampal structure. Additional experiments are needed to strengthen this interpretation. One experiment is to lesion the hippocampus of rats before any experience of the double Y-maze win-stay task and to show that the lesioned rats are impaired during the learning phase of the task. Another experiment will be to record from striatal neurons, and observe the temporal evolution of striatal codes during the learning and plateau (over-training) phase of the win-stay task. Both Jog et al. (1999) and Barnes et al. (2005) explored the temporal evolution of striatal code on a conditioned T-maze task but did not specifically examine whether striatal cells showed goal sensitive coding. It is possible that goal sensitive coding does not exist under the conditioned task as cells could choose more task relevant features to encode (Griffin et al. 2007). In van der Meer and Redish (2009) the authors found that ventral striatum cells temporally shifted their spatial representation to the reward site at the last choice point of a multiple T-maze during the earlier sessions when the rats spent longer time at the choice point, which suggests a form of learning correlated goal encoding. It will thus be interesting to compare the temporal development of goal sensitive codes between the hippocampus and striatum and determine how the information coded by the two structures interact with each other during task resolution.

6.4.4 Stability of hippocampal codes

It was shown that, when exposed to a new environment, hippocampal cells exhibited an initial period of firing instability which stabilises by day three (Frank et al. 2006, 2004). As the rats used in this experiment were not exposed to the double Y-maze prior to the recording experiment, this initial period of instability might contribute to the temporal development of goal sensitive cells. This concern is similar to what was discussed in section 6.4.1 and is partially addressed from the observation that different rats learned the win-stay task at a different rate as if the development of goal sensitive cells is related to the amount of experience a rat has on the

maze, the development of goal sensitive cells should not be correlated with performance but instead with the number of days it spends on the maze. We also calculated the mean coefficient of variation across days and found no significant changes of the measurements with time. We thus conclude that the firing stability of hippocampal cells did not significantly affect the development of goal sensitive cells. On a related note, Ainge et al. (2007a) showed that some of the hippocampal cells exhibited significant change in firing when the rat was traversing the same trajectory even within the same day by either starting or stopping firing. These changes were observed from rats that were very familiar with the task and the environment. We explored whether recording data collected during the learning phase of the task would contain more incidences of intraday significant changes in firing and found no significant changes across days. We thus conclude that such phenomenon does not contribute to the development of goal sensitive cells.

6.4.5 Future directions

We have shown that there is a strong linear relationship between the development of hippocampal goal sensitive cells and improving win-stay performance from rats on a double Y-maze. This provides support for the hypothesis that these goal sensitive cells support task resolution. Several experiments have been proposed throughout the discussion that will further our understandings of this phenomenon. I will propose two additional experiments that address some short-comings of the experiment.

The first experiment aims to completely decouple the effects of environment familiarity from the development of goal sensitive cells. Smith and Mizumori (2006b) provide some evidence that the contextual encoding from the hippocampus only forms when the context becomes task relevant. A similar idea can be incorporated by first exposing rats to the double Y-maze under similar behavioural conditions with no memory demand. One of the viable designs is to bait all four goal boxes with rewards and allow rats to choose any of the four trajectories to obtain rewards. This removes memory demands from the task and can also serve as a control to dissociate familiarity effect from the development of goal sensitive cells. After a few days of experience, the rats can then be given the win-stay version of the task. The temporal evolution of the hippocampal code should address both the effect of memory demand and familiarity on the development of goal sensitive cells.

The second experiment is designed to address whether it is the prospective or retrospective encoding or both that is developed with learning. As discussed earlier, prospective encoding is more related to the intended destination or mental time travel (Johnson and Redish 2007) whereas retrospective encoding reflects memory components. As it has been shown that hippocampal lesion in human impairs the ability to imagine new events based on previous experiences (Hassabis et al. 2007), it will be informative to explore how the development of the

two types of encoding correlates with the rat's performance. To distinguish prospective and retrospective encoding, one needs to have a task for which the rewarded location for the current trial is not completely dependent on the previously visited one. A win-shift version of the task on the double Y-maze where rats need to visit each of the four goal boxes at least once to complete a block of trials fits this criterion and thus can be used to explore the correlation between behaviour and the development of both prospective and retrospective encoding.

Chapter 7

Conclusions and future directions

Cognitive map theory predicts that the most coherent environmental information should be used to determine the allocentric orientation of place representations (O'Keefe and Nadel 1978), and place learning does not require the presence of reward signals (Keith and Mcvety 1988). The most coherent cue hypothesis has been explored behaviourally (Biegler and Morris 1996b; Roberts and Pearce 1998), though inevitably the experiments required the use of reward signals to encourage the rats to perform the tasks. The theoretical part of this thesis implements a model of the head direction cell network with additional units that represent cues in the environment. These units are capable of resetting the encoded head direction of the network, resembling the cue control observed in the experiments (O'Keefe and Conway 1978; Taube et al. 1990b). By using a simple architecture and Hebbian learning projections, we showed that such a model is able to select the most coherent set of cues when resolving conflicting orientation information. We then explored this phenomenon experimentally by exposing rats with recording electrodes targeting place and head direction cells to repeated cue conflicts. A subset of the cues always maintained a fixed relative relationship with each other between conflicts. The CA1 place cells and entorhinal head direction cells remained controlled by the external cues after repeated conflicts, and simultaneously recorded place cells also exhibited coherent place fields between conflict sessions. However, the stable set of visual cues did not exert significantly greater control over either the place cells or the head direction cells after conflict. This result argues against the hypothesis that place and head direction cells automatically consider relative stability between cues in conflict resolution and raises doubts as to whether rats use the most coherent set of environmental cues automatically for orientation. However, the experiment did find a trend whereby additional conflict experience appeared to encourage the use of the 'stable cues' for orientation, which suggests that encoding of relative cue stability does occur but takes time. Thus the governing mechanism might be more complicated than the one used in the model. One possible scenario is that the main responsibility of the allocentric orientation representation provided by head direction cells (Yoganarasimha et al. 2006) is mainly

responsible for maintaining present heading using path integration but which cues are used by this system as a reference is determined by another system. A likely candidate is retrosplenial cortex. It is shown recently that lesions of the retrosplenial cortex affects the rat's ability to choose a subset of the available cues to guide navigation (Wesierska et al. 2009) and some directionally modulated cells recorded from the structure encode local views of cues (Chen et al. 1994a; Cho and Sharp 2001), which allows a more egocentric (i.e. split) representations to form. The more egocentric encoding of orientation is more suitable to emphasise only a subset of cues, but complicates the computation of inter-cue stability, which might explain why more experience is needed for the 'stable cues' to gain greater control of place and head direction cells. The result suggests that hippocampal place cells do not automatically choose to encode the allocentric frame of the surrounding environment and may switch between different types of reference frames depending on the task at hand. In the last experiment, we recorded CA1 place cells while the rat was learning a double Y-maze win-stay task (Ainge et al. 2007a) and found that the development of goal sensitive cells was strongly correlated with the performance of the win-stay task. This suggests that the emergence of goal sensitive activity is dependent on the demands of solving the task rather than on the experience of navigating on the double Y-maze. On the other hand, it is unclear whether hippocampus is the origin of the goal sensitive code as lesion studies also implicate other structures' involvement in spatial win-stay tasks (see chapter 1). For example, several structures such as the anterior thalamic nuclei (ATN) or the mammillary bodies (MB) have been implicated in the DMP version of the water maze task (Santín et al. 1999; van Groen et al. 2002a). Also, with the win-stay task, whether the goal sensitive codes represent a prospective or a retrospective encoding also cannot be determined with present experimental design. Additional experiments are needed to clarify these issues. This thesis explored the evolution of the firing of place and head direction cells when the rat encounters environmental changes or is learning a new task. We found that, even when the motivation is not involved, place cells don't always encode the allocentric information of the environment. On the other hand, the firing of place cells appears to become more correlated with behaviour when the rat is learning the rule of the task to obtain rewards. This demonstrated the dynamics of hippocampal codes and its ability to encode different types of environmental information that is required to perform certain tasks.

7.1 Future directions

Cue control of place and head directions by conflicting distal cues

As discussed previously, selecting the subset of cues with the greatest relative stability appears to require more conflict experience. As our experimental design did not explicitly test the experience dependent effect of cue control, an experiment that gives rats more conflict experience

while monitoring place and head direction cells is needed to provide stronger support to this observation. If the 'stable cues' do eventually gain significantly greater control over the orientation of encoded head directions, a demonstration that this translates to the ability of rats to use the cues to guide navigation will then be necessary to show that the encoded cue preference can be used to guide navigation. This can be achieved by using a task that requires the use of the 'stable cues' to find reward locations. For example, a place preference task would fit this purpose (Hok et al. 2007).

Development of prospective goal cells

Currently two additional experiments are ongoing in the lab to address issues raised in the double Y-maze experiment. The first experiment aims to completely decouple the effects of environment familiarity from the development of goal sensitive cells. Smith and Mizumori (2006b) provide some evidence that the contextual encoding from the hippocampus only forms when the context becomes task relevant. A similar idea can be incorporated by first exposing rats to the double Y-maze under similar behavioural conditions with no memory demand. One design is to bait all four goal boxes with rewards and allow rats to choose any of the four trajectories to obtain rewards. This removes memory demands from the task and can also serve as a control to dissociate familiarity effects from the development of goal sensitive cells. After a few days of experience, the rats can then be exposed to the win-stay version of the task. The temporal evolution of the hippocampal code should address both the effect of memory demand and familiarity on the development of goal sensitive cells. The second experiment is designed to address whether it is the prospective or retrospective encoding or both that is developed with learning. As discussed earlier, prospective encoding is thought to be more related to the intended destination or mental time travel (Johnson and Redish 2007) whereas retrospective encoding reflects memory components. As it was shown that hippocampal lesions in humans impair the ability to imagine new events based on previous experiences (Hassabis et al. 2007), it will be informative to explore how the development of the two types of encoding correlates with the rat's performance. To distinguish between the development of prospective vs. retrospective encoding during the learning phase of the task, one needs to have a task for which the rewarded location for the current trial is not completely dependent on the previously visited one. In a win-shift version of the task on the double Y-maze where rats need to visit each of the four goal boxes at least once to complete a block of trials, the next rewarded goal is always different from the previously visited goal within the block (as it is a win-stay task and the rat can only be rewarded in a goal once within a block of trials). Thus data collected from a rat performing the win-shift task would allow us to examine the development of both prospective and retrospective encoding at the same time as we only need to group the firing rate of place cells either according to the goal that the rat previously visited or the goal that the rat would be visiting next.

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