# The Neural Basis of a Cognitive Map

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(Seek); electrophysiology animals: F9111, F9112, F9113, F9114 (Boreas), F9115 (Notus), F9116 (Eurus), F9117 (Zephyr); parallel/radial maze behaviour: G2101 (Neo), G2102, G2103, G2104, G2105, G2106 (Useless 3rd), G2107, G2108, G2109 (Arnie), G2110, G2111, G2112; parallel/radial maze mouse recordings: F9900 (Quebec), F9901, F9903; parallel/radial dwell time behaviour: G1001, G1002, G1003, G1004, G1005, G1006, G1007, G1008, G1009, G1010, G1011, G1012 and the parallel/radial maze rat recordings: G1801 (Leo), G1802 (Mike), G1803 (Don), G1804 (Raph), G1805 (Roger), G1806 (Splodge), G1807 (Mr Blue), G1808, G1809 (Speedo), G1810 (Lag), G1811 (Socks), G1812 (Decibel).

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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.

Roderick M. Grieves

First tier Matlab scripts for data extraction were provided by Sturla Molden (Centre for the Biology of Memory, NTNU), second tier processing scripts were written by Steven Huang (Centre for Cognitive and Neural Systems, Edinburgh), third tier custom, data analysis, presentation and statistical scripts were written by the author.

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The mouse electrophysiology data shown in Supplementary Figure 2 was acquired by the author using mice implanted by Tizzy Allison.

# Frequently Used Abbreviations

| Abbreviation | Expansion |
|---|---|
| HPC | Hippocampus proper |
| CA1-4 | Cornu ammonis regions of the hippocampus |
| EC | Entorhinal cortex |
| mEC | Medial entorhinal cortex |
| lEC | Lateral entorhinal cortex |
| PFC | Prefrontal cortex |
| mPFC | Medial Prefrontal cortex |
| PC | Place cell |
| HD | Head direction |
| BVC | Boundary vector cell |
| PoS | Postsubiculum |
| PaS | Parasubiculum |
| MPP | Medial perforant path |
| LPP | Lateral perforant path |
| DG | Dentate gyrus |
| VTE | Vicarious trial and error |
| C-D | Context dependent |
| PI | Path integration |
| Iso-D | Isolation distance |
| S/N | Signal to noise ratio |
| AP | Anterior posterior |
| DV | Dorsal ventral |
| ML | Medial lateral |
| S-R | Stimulus response |
| $M$ | Mean or average |
| $SEM$ | Standard error of the mean |
| $SD$ | Standard deviation |
| $d$ | Cohen's $d$ (Cohen, 1988) |
| $\eta_p^2$ | Partial Eta squared (Maher, Markey, & Ebert-May, 2013) |
| ~ | Approximately |
| * | Statistically significant at the .05 level ($p < .05$)[a] |
| ** | Statistically significant at the .01 level ($p < .01$) |
| *** | Statistically significant at the .001 level ($p < .001$) |
| ANOVA | Analysis of Variance |
| ANCOVA | Analysis of Covariance |

[a] Throughout this thesis analyses are considered statistically significant if the associated probability is less than 5% ($p < .05$).

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# Abstract

It has been proposed that as animals explore their environment they build and maintain a cognitive map, an internal representation of their surroundings (Tolman, 1948). We tested this hypothesis using a task designed to assess the ability of rats to make a spatial inference (take a novel shortcut)(Roberts et al., 2007). Our findings suggest that rats are unable to make a spontaneous spatial inference. Furthermore, they bear similarities to experiments which have been similarly unable to replicate or support Tolman's (1948) findings. An inability to take novel shortcuts suggests that rats do not possess a cognitive map (Bennett, 1996). However, we found evidence of alternative learning strategies, such as latent learning (Tolman & Honzik, 1930b), which suggest that rats may still be building such a representation, although it does not appear they are able to utilise this information to make complex spatial computations.

Neurons found in the hippocampus show remarkable spatial modulation of their firing rate and have been suggested as a possible neural substrate for a cognitive map (O'Keefe & Nadel, 1978). However, the firing of these place cells often appears to be modulated by features of an animal's behaviour (Ainge, Tamosiunaite, et al., 2007; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000). For instance, previous experiments have demonstrated that the firing rate of place fields in the start box of some mazes are predictive of the animal's final destination (Ainge, Tamosiunaite, et al., 2007; Ferbinteanu & Shapiro, 2003). We sought to understand whether this prospective firing is in fact related to the goal the rat is planning to navigate to or the route the rat is planning to take. Our results provide strong evidence for the latter, suggesting that rats may not be aware of the location of specific goals and may not be aware of their environment in the form of a contiguous map. However, we also found behavioural evidence that rats are aware of specific goal locations, suggesting that place cells in the hippocampus may not be responsible for this representation and that it may reside elsewhere (Hok, Chah, Save, & Poucet, 2013).

Unlike their typical activity in an open field, place cells often have multiple place fields in geometrically similar areas of a multicompartment environment (Derdikman et al., 2009; Spiers et al., 2013). For example, Spiers et al. (2013) found that in an environment composed of four parallel compartments, place cells often fired similarly in multiple compartments, despite the active movement of the rat between them. We were able to replicate this phenomenon, furthermore, we were also able to show that if the compartments are arranged in a radial configuration this repetitive firing does not occur as frequently. We suggest that this place field repetition is driven by inputs from Boundary Vector Cells (BVCs) in neighbouring brain regions which are in turn greatly modulated by inputs from the head direction system. This is supported by a novel BVC model of place cell firing which predicts our observed results accurately.

If place cells form the neural basis of a cognitive map one would predict spatial learning to be difficult in an environment where repetitive firing is observed frequently (Spiers et al., 2013). We tested this hypothesis by training animals on an odour discrimination task in the maze environments described above. We found that rats trained in the parallel version of the task were significantly impaired when compared to the radial version. These results support the hypothesis that place cells form the neural basis of a cognitive map; in environments where it is difficult to discriminate compartments based on the firing of place cells, rats find it similarly difficult to discriminate these compartments as shown by their behaviour.

The experiments reported here are discussed in terms of a cognitive map, the likelihood that such a construct exists and the possibility that place cells form the neural basis of such a representation. Although the results of our experiments could be interpreted as evidence that animals do not possess a cognitive map, ultimately they suggest that animals do have a cognitive map and that place cells form a more than adequate substrate for this representation.

Keywords: *cognitive map, place cells, shortcutting, trajectory dependent, place field repetition, multicompartment environment, spatial learning*

# Review

## Chapter 1

## Tolman's Cognitive Map

### 1.1 Tolman

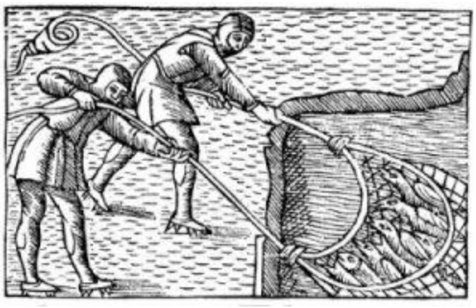

**Figure 1.1:** A wood cut commissioned in the mid-1500s by Olaus Magnus, Archbishop of Uppsala. The inscription depicts fishermen retrieving Swallows from a winter lake. The Archbishop recommends not trying to resuscitate the hibernating birds as they will likely die (Birkhead, 2009).

After observing the changes of season and the coinciding changes in bird populations, Aristotle came to the conclusion that in winter Redstarts annually transform themselves into Robins. Swallows and Kites, he claimed, spent the winter hibernating underground. The notion that animals would transform themselves in time for a change in season, or hibernate through the worst of the winter may seem a naïve one, but the truth would have been even less believable to Aristotle and his contemporaries. Mythical explanations for migratory phenomena such as these persisted at least as late as the 1500s (Birkhead, 2009)(see Figure 1.1). In reality, the tiny Redstarts and Swallows leave Greece in winter and migrate to sub-Saharan Africa, a distance of approximately 1000 miles[1]; meanwhile Robins migrate from northern latitudes into Greece for the winter. The larger and predatory Kites migrating from Greece can winter in areas south of the Sahara, a distance of nearly 5000 miles. Asides from the surprise that such small and seemingly fragile animals can fly these vast distances there is also the question of how

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[1] Assuming they fly directly over the Mediterranean, which many of them do; although passenger ships crossing the Mediterranean often harbour a small flock of migratory birds.

they navigate such large trips; Swallows have been known to return to the exact breeding spot they left the previous year. Some of the earliest studies concerning animal navigation were carried out not by psychologists but ethologists, observing such birds.

The study of how organisms are able to navigate their environment is in many ways the study of survival; animals often have to navigate to survive, be it an antelope navigating to the nearest watering hole or birds navigating thousands of miles back to their nesting ground. However, the processes underpinning this spatial navigation can be very complex. Edward Chace Tolman, among others, sought to understand these processes. He considered animal behaviour an ideal model for the processes which also presumably underlie human navigation. A discussion concerning cognitive maps, or indeed animal or human navigation would be impossible without mention of Tolman, for this reason this first chapter will focus largely, but not solely, on Tolman's work.

## 1.2 Tolman's Cognitive Map

Bayley and Gulliver (1908) suggested that human beings possess an internal representation of their environment; furthermore he suggested that this representation is based on surrounding landmarks and oriented using important geographical locations (Bayley & Gulliver, 1908). However, at the time psychology was still in its infancy, attempting to distance itself from its roots in philosophy and be taken seriously as a scientific approach to understanding the world. Many early psychologists felt the need to study scientific evidence in a way more in line with the classical sciences such as physics and chemistry. When it came to the study of behaviour, different stimuli could be controlled and measured accurately and their resulting effects on an organism's behaviour could also be measured accurately, the approach assumed at the time was to measure these two variables, the underlying processes or mental states of the organism were discarded as irrelevant. As it was, the implications of Bayley and Gulliver's (1908) suggestions were lost in a sea of early behaviourist psychological research, concerned with the behaviour of animals and men but concentrating on the relationship between stimuli and the responses they evoke:

*"In psychology our study, too, is sometimes concerned with simple responses of these types* [tapping the patella tendon or stroking the sole of a foot]*, but more often with several complex responses taking place simultaneously"* (Watson, 1919, p. 10)

Work by Tolman and others would eventually revisit the idea of internal representations or maps, however, this research met with heavy opposition from those researchers who followed the behaviourist train of thought:

*"We believe that in the course of learning, something like a field map of the environment gets established in the rat's brain. We agree with the other* [stimulus-response] *school that the rat running a maze is exposed to stimuli and is finally led as a result of these stimuli to the responses which actually occur. We feel, however, that the intervening brain processes are more complicated, more patterned, and often... more autonomous than do the stimulus-response psychologists."* (Tolman, 1948, p. 192)

The best way to understand the conflict which arose between these two schools of thought, and the resolution which was ultimately reached, if it can indeed be called that, is to examine those behavioural phenomena which Tolman (1948) highlighted as important and fundamental to understanding animal navigation. In Tolman's (1948) summary paper he himself outlined the five areas of research which he felt clearly and concisely demonstrated his theoretical position; latent learning, vicarious trial and error or VTE, searching for the stimulus, hypotheses and spatial orientation. Each of which will be discussed below.

Tolman (1951b) gives a wide and detailed data language which he uses to describe his behavioural theory and experimental results. A number of these expressions will be useful in the proceeding chapter. Tolman suggests that as animals explore their environment they form *hypotheses*, an example of a simple hypothesis may be; if a certain stimulus ($S_1$) is encountered, the correct response (R) will lead to a subsequent stimulus ($S_2$). For instance, if a rat finds himself in a particular environment such as a T-maze ($S_1$) upon navigating from the start arm to the left arm of this maze (R) he may find a food reward ($S_2$). If this process is repeated and the hypothesis proven correct more than once, Tolman (1951b) suggests that it becomes an *expectancy*, when the rat finds himself in the T-maze he may now expect to find food in the left arm and make the appropriate response to achieve it. Over time this expectancy may become a *belief*, the rat may begin to expect food on this T-maze as well as others in different contexts (Tolman, 1951b; Tolman & Gleitman, 1949b). In parallel to these processes, Tolman (1951b) also describes *cathexes*, or the associations between *needs* and *goals*. As the need for a particular resource or stimulus (such as food and water) increases, the rat will begin to start seeking it with more frequency. If a source of the stimulus is found (such as in a water bottle or food hopper) it will become a *goal* (G) and the cathexis now becomes a *demand* (a strong motivation for behaviour). Tolman (1951b) suggests that observable behaviour arises from the conflict and resolution of different cathexes and hypotheses. If the subsequent stimulus ($S_2$) of an expectancy is the goal object (G) of a parallel demand then the corresponding expectancy's response (R) will be initiated, this will continue until the need is reduced sufficiently for the response to be discontinued. This interplay between expectancy and demand is known as a *progression-readiness* and in Tolman's (1951b) terms, behaviour is the result of all present progression-readiness'. From this small sample of terms it is clear that for Tolman (1948, 1951b) a cognitive map is not merely an internal representation of the layout of an environment, it is also the collection of progression-readinesses associated with that environment. The research which Tolman (1948) used to support his cognitive map theory often provides evidence for only one or a few of these individual components, however, as we will see there were often competing explanations which did not require Tolman's (1951b) complex learning system.

## 1.3 Latent Learning

Latent learning describes the process by which animals learn in the absence of any motivation or reward and without obvious behavioural improvement, this improvement becomes apparent, however, when the animal is tested experimentally at some later point. For Tolman, the demonstration that rats could learn in the absence of any obvious S-R relationship was important both because it showed that learning could exist in the absence of motivation and because it showed that performance is not necessarily a measure of learning.

Tolman (1948; 1930a) describes such a study in which three groups of rats were trained on a complex maze consisting of 14 interconnected T-mazes. One group was trained to navigate the maze and find a food reward, a second group navigated the maze but no food was present, a third group of rats performed under similar conditions to the second group for 10 days after which a food reward was available on the maze. As expected the first (rewarded) group learned the task very well, the second (unrewarded) group did quite poorly but the performance of the last group (delayed-reward) was startling; the rats performed similarly to the unrewarded group for the first 10 days when they were also unrewarded, however, after this point their performance improved significantly until it was similar to the rewarded group, this sudden improvement in performance occurred in a matter of only one or two sessions (Tolman, 1948)(see Figure 1.2).

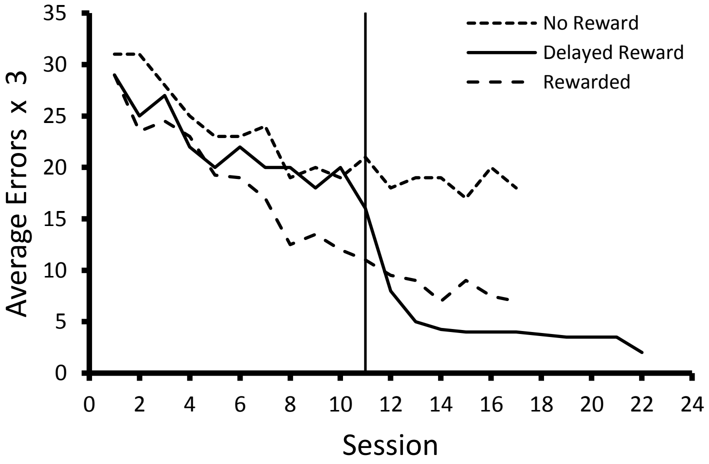

**Figure 1.2:** Showing the average number of errors for the three groups in Tolman and Honzik's (1930a) experiment. The vertical line marks the point at which the delayed reward group started receiving a food reward.

Similar results have been demonstrated on a number of apparatus (Blodgett, 1929; Spence & Lippitt, 1946; Thistlethwaite, 1951). Tolman's (1951b) explanation was that, even in the absence of food, the rats still formed an expectancy as to the layout of the maze – if they were placed on the maze and made a certain set of responses they would move to a particular area of the maze. When the food reward was introduced to the delayed-reward group it became the goal object of a demand and the rats then felt motivated to navigate to it by fulfilling the response component of the underlying expectancy. Although the animals had not displayed any signs of S-R learning (they were not exposed to the stimulus and response simultaneously) they had in fact formed an internal representation or 'cognitive map' of the maze environment which they were able to utilise when the motivation was applied at a later date (Tolman, 1948). The rats learned the layout of the maze, this learning was just not yet apparent, it was *latent*, not manifested in their behaviour until the application of the reward.

A number of researchers were unable to replicate Blodgett's (1929) and Tolman's (1930a) latent learning effect (Meehl & MacCorquodale, 1951; Meehl & Maccorquodale, 1953; Reynolds, 1945) but see (Blodgett, 1946). Furthermore, a number of S-R theorists, mainly Meehl and MacCorquodale (1953) building on the work of Hull (1950), were able to give an alternative explanation for the latent learning effect. Meehl and MacCorquodale (1953) argue that a change in the rat's motivation can account for the corresponding change in performance. They suggest that in latent learning experiments the delayed reward group acquires a habit for navigating to the end of the maze, as can be seen by a slight drop in errors at the beginning of training in all groups (Tolman, 1948). However, on day 11 after exposing the delayed-reward group to the maze environment and the food reward this habit becomes multiplied, thus these rats, when later placed in the maze, feel more motivated even though they are similarly deprived (Estes, 1954). Meehl and MacCorquodale (1953) were able to formulate this relationship mathematically, using Hullarian principles and theory. However, this and similar S-R theories regarding latent learning have largely been forgotten or contested (Deutsch, 1956; Jensen, 2006; White, 1943). A broader criticism is that the associative learning of the kind proposed by Hull (1950), is not merely built on S-R relationships, there may also be S-S, R-R and more complex hierarchical, S-(R-S) relationships (Adams & Dickinson, 1981; Rescorla, 1990). Thus, showing that learning can occur in the absence of an S-R relationship does not mean the animals are not learning in an alternative, associative method (Prados & Redhead, 2002). Furthermore, as Mackintosh (1974) pointed out, it is impossible to know whether the animals in the delayed-reward group truly experienced no reinforcement, he suggested that as rats encountered blind alleyways, or were picked up by the experimenter, they may have experienced sufficient negative and positive associations to form a bias for the correct path through the maze.

## 1.4 Vicarious Trial and Error (VTE)

When navigating through a maze with choice points, or when having to make some important behavioural choice, rats often hesitate and shake their head from side to side, looking back and forth between the options. Alternatively, the rat may make a motion to choose one of the options but again, hesitate and reconsider. This type of behaviour is known as Vicarious Trial and Error (VTE) (Muenzinger, 1938; Tolman, 1938; Tolman, 1939, 1951a). Tolman (1948) was interested in the phenomena of VTE for a number of reasons which will be described below, but in general terms it suggested that rats were attending to their environment. It suggests that the animals do not merely decide on a set of responses at the start of the maze and then commit to them until they find the food or are stopped, they actively decide on behaviour whilst solving the task.

VTE can be observed in a number of different tasks and under a number of different circumstances, however, the example Tolman (1948) gives, attributed to Lashley, consists of an elevated jumping-off stand, in front of the stand the rat is given two choices, doorways or trapdoors (Tolman, 1948; Tolman & Minium, 1942)(see Figure 1.3). These doorways are distinguished in some way by colouring or patterning such that they can be interchanged, but regardless of location the same one is always held correct. If the rat jumps at the correct doorway it opens and allows the rat access to some food, whereas the incorrect doorway is held shut, if the rat jumps at this one he falls into a safety net below. It is worth noting, for the sake of further discussion, that one of the key features of this task is the fact that the doorways swap sides randomly, in this way the rats presumably are conflicted as to whether to pay attention to the spatial cues (is it the left door that is always rewarded?) or the visual ones (is it the black door that is always rewarded?).

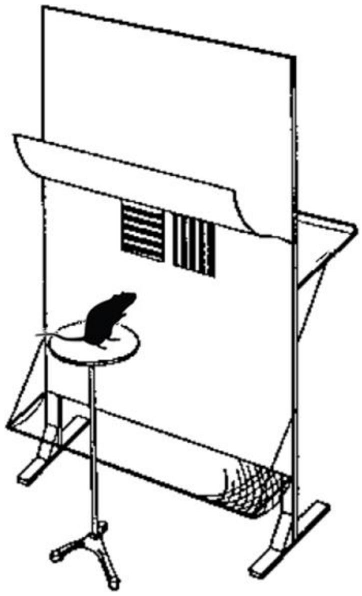

**Figure 1.3:** The Lashley jumping task (Tolman, 1948). Rats are placed on a jumping stand and must jump through one of two distinguishable trapdoors to a food reward.

A number of interesting observations were made using the above apparatus, the first was that rats often looked back and forth between the two options (VTEing); it was also found that this VTEing occurred much more frequently just before a rapid increase in the rat's performance and then decreased once the animal had learned the task at hand (Tolman, 1948). Looking more closely at the discriminations the rats were making Tolman (1948) showed that when the discrimination was easy the rats made more VTEs than when the discrimination was difficult, however, as the animal's performance increased VTEs decreased for the easy discrimination and increased for the difficult one (Tolman, 1948; Tolman & Minium, 1942).

Tolman's (1948) explanation for these phenomena concerned not only the rate of learning but also the type. For him VTEs were concerned both with the discrimination of different stimuli and the discrimination of task contingencies. When first learning the discrimination, the behaviour of the rats was not indicative of them trying to make a discrimination – the rats were not sampling the choices in order to tell which was which – rather the animals were attempting to learn the *rules* or context at hand. At this stage, if the discrimination was easy (if the doorways were obviously different) the rats were able to form a hypothesis or expectancy, they learned quickly and attended readily to the doorways, thus

VTEing more. As they learned the discrimination, because the doorways were readily discriminable and the correct response was easy to determine, the rats needed to VTE less. However, if the discrimination was more difficult (for instance if the doorways were different shades of grey), the rats would learn at a slower rate, did not find the discrimination obvious and so would VTE less. As the rat's performance increased under these conditions they would start to attend more to the discrimination at hand, and because this discrimination was more difficult they would need to VTE more. To Tolman (1948), VTEing was evidence that the rats were generating some internal representation of the task, as their behaviour suggests an active selection and comparison of discrete stimuli not just a passive participation. Building a catalogue or map of the task or environment's contingencies and stimuli in this way (as expectancies) is a key feature of Tolman's (1948) cognitive map theory. Later research confirmed that the hippocampus plays a role in VTE behaviour, with lesioned animals VTEing less and learning at an impaired rate (Hu & Amsel, 1995).

The Lashley jumping task is the same apparatus used by Maier and Murphy (1939) to study experimentally induced neurosis in the rat. Among other findings, Maier (1939) showed that when the task was made impossible (neither door was rewarded, or both were rewarded randomly) rats either formed their own contingency, always choosing a particular door or side, or would VTE indefinitely, becoming transfixed on one of the doorways. As Maier's (1939) rats were forced to make more difficult or impossible discriminations the frequency of fixations would increase, rats would attempt to escape the apparatus or they would fall into conflict-induced seizures (Maier & Longhurst, 1947; Maier & Murphy, 1939) but see (Morgan & Morgan, 1939). In terms of Tolman's expectancy theory, the rats in Maier's (1939) experiment probably did not know what stimuli to attend to, could not understand the rules behind the task, and could not form a hypothesis or expectancy. As such they were similar to those rats in Tolman's (1930a) task who were given a difficult discrimination, their learning was very slow (or not at all in this case) and because the stimuli were difficult to discriminate (in this case the stimuli were meaningless) the correct response was impossible to distinguish and the frequency of VTEing decreased to nothing.

However, it remains unclear how distinct Tolman's (1948) explanation of VTEing is from Hull's (1950) drive theory. There seems to be no reason why rats cannot VTE in order to determine the magnitude of differing 'reaction potentials' (S-R preferences, based on a number of different factors such as previous experience, motivation, incentive and inhibition) and ultimately compare these to choose a doorway. Indeed Tolman's (1949, 1951b) progression readinesses have been likened to Hull's (1950) reaction potentials and an alternative explanation for VTEing has been suggested based on these principles (Taylor & Reichlin, 1951) but see (Austin, 1953).

## 1.5 Searching for the Stimulus

Another argument Tolman (1948) presents concerns the way rats behave and learn after experiencing an aversive stimulus such as an electric shock. Early reports suggested that rats appeared to 'look around' after being shocked as if trying to identify where the stimulus originated, this period of active observation was subsequently shown to be important in learning the association between shock and source.

Tolman (1948) describes a series of experiments designed to assess whether rats could learn an avoidance reaction in a single trial (Hudson, 1950) but see (Suboski, Greenner, & Spevack, 1967). In this experiment, rats were placed in a housing cage, at one end of the cage there was a food dish where the rats could feed. Behind the food dish the wall of the cage was made distinguishable by decorating it with a striped pattern. When the rat approached and touched the food dish he would receive an electric shock. Immediately after receiving the shock and for hours, days and even weeks afterwards, when placed in the cage the rats would show the same avoidance behaviour (burying or avoiding the food bowl). Hudson (1950) showed that the rats would respond to the aversive stimulus and did indeed learn the association in a single trial; however, he also noticed that immediately after receiving the shock many of the animals would appear to look around their surroundings as if trying to find a source with which to associate the pain. This led Hudson (1950) to the next phase of the experiment; here rats were placed in the same cage as before, except that when the animal was shocked the lights immediately went out while the food bowl and striped wall were removed. When light was returned Hudson (1950) found that many of the rats no longer showed any aversion to the food bowl, some of the animals came to associate the shock with some other feature of their environment and only a few of the animals learned to avoid the food bowl as did the previous group.

These results suggest that the seeking behaviour observed immediately after the electric shock is in fact an important period of learning and association. Tolman (1948) viewed this similarly to the phenomena of VTE, he proposed that in searching for the stimulus rats were attending to their surroundings and actively building associations between experience and environmental features. To Tolman the rats were actively selecting the relevant stimuli with which to form a cognitive map. Specifically, in the dark they were unable to combine the maze environment ($S_1$), the response (R, touching the food dish) and the secondary stimulus ($S_2$, the shock) to form an expectancy.

## 1.6 Hypotheses

When a rat attempts to solve some discrimination or other task requiring a choice, they will very often cycle through a series of different behaviours or responses. For instance a rat having to choose between the two different doorways in the Lashley jumping task described above, may, for a short time always select the door on the left, the door with the darkest colour or the door opposite to the one chosen previously. Tolman viewed these brief periods of consistent and systematic trial and error as a method for testing different hypotheses or solutions to the task. Based on what it knew so far, the rat was formulating a hypothesis or solution to the task before trying it out, if the solution failed after a number of consistent trials a new hypothesis was formulated and the process repeated.

The example Tolman (1948) gives is the experiment carried out by Krechevsky (1932), here rats navigated through four connected compartments, between each compartment there were two doors which the rats were able to move through (Figure 1.4). The doors were signalled by colour (or rather light vs dark) and the rats were rewarded for various contingencies, with different rats rewarded for different sequences of dark or light door. Krechevsky (1932) observed that when learning the task rats would often make seemingly systematic errors, for instance always choosing the doors on the left or always choosing the dark coloured door. This type of information is not an easy one to analyse, even by today's standards[2], so the analysis for this experiment was carried out on a mostly case by case basis (Krechevsky, 1932; Tolman & Krechevsky, 1933). However, Krechevsky (1932) came to the conclusion that the rats were in fact systematically testing different potential solutions to the task at an above-chance level.

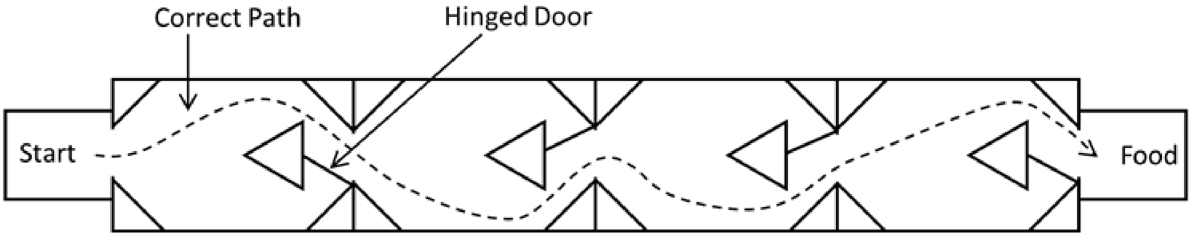

**Figure 1.4:** Krechevsky's (1932) 'hypotheses' task. Rats navigate from a start box to a food reward, via four connected compartments. In each compartment the rat must choose between a left or right doorway according to a sequence configured by the experimenter previously.

Tolman could have described these behaviours as 'fixation' (Tolman, 1951b), whereby rats will often persist in trying the same behaviour even when it does not result in reward. Indeed hypothesis-testing may appear as a sequence of fixation periods; in terms of Maier's (1939) results where rats became fixated on the doorway in an impossible jumping task the explanation would be that the rat exhausted all conceivable hypotheses and fell into an inert fixation phase. Whether Tolman considered these possibilities is unknown. Ultimately

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[2] Although it is becoming more common, as computational modelling and machine learning builds more and more on the behaviour of animals, to model, predict and categorise different navigational strategies.

Tolman and Krechevsky came to define these behavioural patterns under the same umbrella term; means-end-readiness (Tolman & Krechevsky, 1933). The rats are hungry and *ready* to find food so they are prepared to use and try different *means* in order to find that food. Although the individual means they use, such as always selecting doors on the left, remained termed hypotheses.

For Tolman (1948, 1951b), the hypothesis testing observed in tasks such as this one are strong evidence for his expectancy theory. After a period of systematic testing the rat begins to make the correct response whenever he is placed on the apparatus. This suggests that he has formed an internal representation of the stimuli, responses and goals found on the apparatus; all of which are important components of a cognitive map.

## 1.7 Spatial Orientation

In the early 1900s many of the experiments carried out using rats were concerned with the most basic principles of navigation, from a traditional empiricist standpoint these experiments were crucial as assumptions have to be accounted for experimentally. At this time the S-R approach to animal navigation was also reducing many complex behaviours to simple processes, sometimes at the expense of overall validity. The contemporary perception of many, including some researchers, was that animals were simplistic, unsophisticated and even machine-like. The slow accumulation of surprising results, which were indicative of complex behaviour, led Tolman and others to carry out their highly influential experiments. A series of seemingly innocuous experiments demonstrate this relationship well.

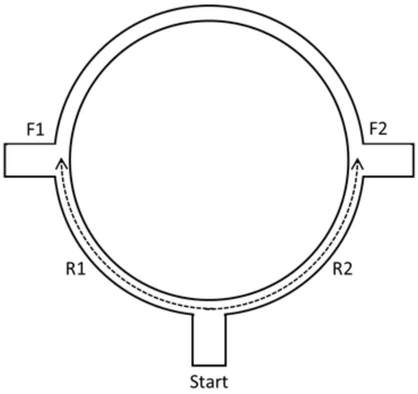

**Figure 1.5:** The maze used by De Camp (1920). Rats start at the bottom of the ring, food rewards are found at F1 and F2, rats can take routes R1 or R2 freely.

De Camp (1920) trained rats on a ring shaped maze, the layout of which can be seen in Figure 1.5, the rats started from a start box at the base of the ring (start) and reward sites could be found along the left (F1) and right (F2) sides of this ring. Rats were trained in two counterbalanced groups but for simplicity we will describe one here. The animals were trained to navigate from the start box to goal location F1, the opposite goal location, F2, was not rewarded. During this training the rats were allowed to navigate around the ring however they wanted, using the short route, R1, or the long route, continuing past R2. De Camp (1920) found that the rats would initially explore the ring and use both possible paths (R1 and R2) to the food reward, but very quickly they would begin consistently using the shorter, direct path, R1. When the reward shifted, to F2, De Camp (1920) again found that the rats began to explore both possible routes, but once they were aware of the new reward location they very quickly adjusted to using the new shorter route, R2. In effect, no matter the location of the food reward the rats sought out and ultimately preferred the route to the reward location which constituted the shortest travelling distance. Tolman and Sams (1925) followed up on this experiment with a similar design. In their task rats were provided with two routes from a start location to a food reward. Both routes were of the same distance but rats had to pass through a holding chamber before reaching the reward, in these chambers the rats were delayed for a set length of time. Tolman and Sams (1925) found that when rats were delayed for a longer length of time on one of the routes they showed a strong preference for the route with the shorter time delay. Completing, in a fashion, this series of experiments, McCulloch (1934) showed that when rats were trained to pull bowls of food within their reach using attached lengths of string, rats preferred to pull pieces of string which provided less resistance.

Together these experiments highlighted an interesting and important feature of behaviour, which is now known to be restricted not just to spatial navigation; 20 years before Zipf's (1949) 'principle of least effort' was proposed Tolman and his contemporaries were confirming that, when solving a task animals in general will assume the behaviour, path or technique which requires the least amount of effort. Given two options, rats will prefer the one which requires travelling less distance, takes less time or generally requires less effort to achieve. In many ways this finding sets up a contradiction waiting to unfold in the animal literature; rats clearly prefer the response which requires the least amount of effort, or in other words, rats prefer to gain the maximal reward for the minimum energy expenditure – a finding which is in agreement with the S-R school of thought. However, in many cases, as we will see, this principle requires the rat to have an overall representation of its surroundings, a cognitive map, for it to make an informed and sometimes inferential response[3].

With these findings in mind we come to possibly the strongest and most longstanding or Tolman's (1948) arguments. This began with a relatively innocuous behaviour observed in traditional, complex mazes, presumably originating as a by-product of the frustration and impatience of the laboratory rat. Tolman (1948) notes that a number of researchers, anecdotally, reported rats escaping from mazes and making their own way to the goal location[4]. Anecdotal evidence on its own is not enough to formulate an argument, so Tolman, Ritchie and Kalish (1946a) designed an experiment to assess exactly this behaviour. The task they designed can be seen in Figure 1.6. In training, rats navigated from a start location to a circular platform and from there they navigated a series of turns down an alleyway to a food reward. During the

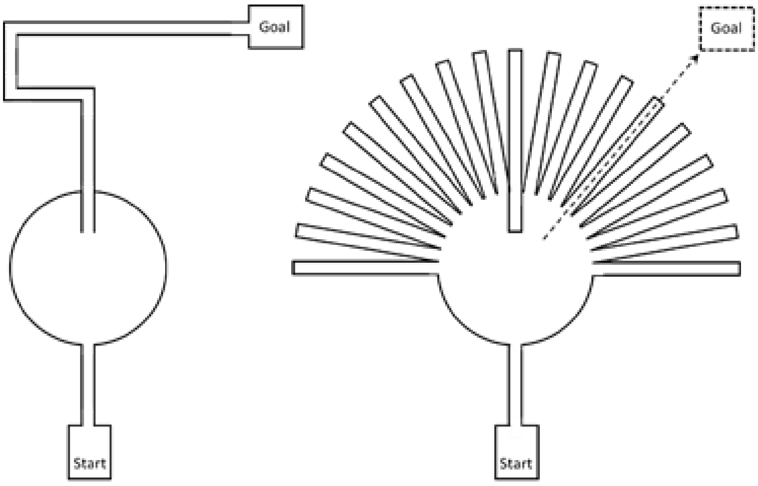

**Figure 1.6:** The 'sunburst' maze used by Tolman, Ritchie and Kalish (1946a). Rats are initially trained to navigate from a start box to a food reward (left). In testing, the rats are given a choice of 18 alternative alleys, one of which leads to the previous location of the reward chamber (right), this is labelled with an arrow.

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[3] A potential hypothesis is that the principle of least effort will on some level be of a much lower priority in the mouse when compared to rats. If this were true it would explain much of the difficulty experienced by researchers attempting to train mice on tasks in which rats excel. This could be tested by comparing the performance of rats and mice in De Camp (1920), Tolman and Minium (1942) and McCulloch's (1934) tasks.

[4] Indeed mazes designed with rats in mind must always take this into account and usually make it as difficult as possible for the rats to make their own paths – because *they will*.

experimental phase, this alleyway remained but was blocked at the circular platform, the rats instead had to choose between 18 alternative alleyways, each leading away at different angles to the platform. One of these alleyways led to the previous spatial location of the food reward. If the rats had built an internal representation of the task during training, they should be aware of the location of the food reward relative to the circular platform, despite the fact that they made a series of turns when navigating there. In light of the principle of least effort, the rats should now, upon finding the original route blocked, seek the shortest route to the food reward – the route leading to where the food was previously located. When Tolman, Ritchie and Kalish (1946a) tested their rats in this way they found that a significant number of the animals did in fact choose this route, suggesting that they had in fact acquired:

*"…not merely a strip-map to the effect that the original specifically trained-on path led to food but, rather, a wider comprehensive map to the effect that food was located in such and such a direction in the room."* (Tolman, 1948, p. 204)

For Tolman the ability to make a spatial inference, a previously unrewarded response based on acquired spatial knowledge, demonstrated that rats are in fact capable of not only learning the layout of an environment as they explore it but also that they can use this internal representation to make novel and strategic responses. However, Tolman, Ritchie and Kalish (1946a) were criticised for placing a light near the location of the food reward throughout the experiment, it is possible under these conditions that the rats merely navigated to the light source as a 'beacon' (Bennett, 1996; O'Keefe & Nadel, 1978); a distal cue which is used for navigation from a distance, after which the animal may or may not utilise a more local search strategy. However, Tolman, Ritchie and Kalish (1946a) considered the position of the light an important spatial cue and crucial for the rat's ability to make a spatial inference and take the shortcut. A further discussion on shortcutting in rats, humans and other animals will be made in later chapters.

## 1.8 Tolman Revised

The cognitive map theory lays the foundation for much of the topics discussed throughout this thesis and as such provides a satisfactory basis from which to continue. However, in terms of spatial navigation it appears to be only half correct. It certainly seems true that S-R theories cannot account for a number of complex behaviours such as latent learning and shortcutting (despite attempts at reformulation and failures of replication), however, it is equally true that under certain conditions rats do not appear to utilise any navigation strategy as complex as a cognitive map. Gradually a number of researchers began to reduce the two approaches to their most basic principles and found that in many ways the two theories are built on very similar core concepts (MacCorquodale & Meehl, 1954; Restle, 1957; White, 1943):

*"...this common core of meaning has not been enough emphasized; both the S-R psychologists and the 'field theorists' have often failed to realize the extent to which they were actually saying the same thing in different words."* (White, 1943, p. 164)

Indeed the resolution of these two different theories was in a form not dissimilar to the resolution of theories in other fields; both it would seem are correct depending on the circumstances. This approach was perhaps anticipated by Tolman (1948) as he suggested that rats may utilize 'narrow' cognitive maps with reduced information under certain circumstances:

*"...narrow strip maps rather than broad comprehensive maps seem to be induced: (1) by a damaged brain, (2) by an inadequate array of environmentally presented cues, (3) by an*

*overdose of repetitions on the original trained-on path and (4) by the presence of too strongly motivational or of too strongly frustrating conditions."* (Tolman, 1948, p. 206)

Researchers assuming the S-R approach often performed their experiments on over trained rats and in environments devoid or lacking in extramaze cues. Whereas supporters of theories such as Tolman's (1948) often concentrated on the rate and form of initial learning, in environments rich in extramaze cues. Here, Tolman (1948) was beginning to suggest spatial navigation may in fact form a spectrum, with these differences in training methods resulting in poor or rich cognitive maps.

Restle in (1957) summarised the research concerning spatial navigation to this point and suggested an alternative explanation, substituting Tolman's (1948) 'narrow strip map' for a S-R method of navigation. In this view, navigation results from the competition, resolution and combination of kinaesthetic or sequence-based information (the basis for S-R learning) with multiple environmental cues (the basis of a cognitive map). This revision is based on a number of important observations; although simple mazes, such as the T-maze, can be learned in the absence of complex additional information such as visual, olfactory, tactile and auditory cues (Blodgett & McCutchan, 1947), more complex tasks generally require these cues for learning to occur at a realistic rate (Honzik, 1936; Tsang, 1934). However, once such a task is learned these cues can be removed without disturbing performance to any great degree (Zoladek & Roberts, 1978), although as the task becomes increasingly complex visual cues are likely still needed to prime this sequence learning (Hunter, 1920). Restle (1957) suggests that in a simple environment, kinaesthetic information is available immediately; through trial and error exploration the rat may find the reward and subsequently learn the sequence of responses which resulted in attaining it. In this case learning can progress in the absence of any cues other than kinesthesis. However, in a more complex environment this form of learning may be ineffective and the rat will attend to external cues relevant to navigation, if they are available. Under these conditions, although the rat is using external information, kinaesthetic information (the sequence of responses being made) is still learned and can eventually substitute any need for external cues (Ritchie, Aeschliman, & Pierce, 1950) but see (Scharlock, 1955). This pattern of learning explains why rats trained on the same apparatus, the T-maze, can be shown to utilise a strong place preference (Blodgett & McCutchan, 1947; Blodgett, McCutchan, & Mathews, 1949; Galanter & Shaw, 1954; Tolman & Gleitman, 1949a; Tolman, Ritchie, & Kalish, 1946b, 1947; Waddell, Gans, Kempner, & Williams, 1955) or a strong response preference (Hill & Thune, 1952; Scharlock, 1955) depending on the circumstances and cues which are available.

The idea that rats may not always utilise a cognitive map as described by Tolman (1948) does not mean they do not or cannot generate, recall and use such an internal representation. In many ways a S-R form of navigation is merely a reduced view of Tolman's map, the only difference being the number and complexity of associations concerned and the flexibility of these associations in terms of context and spatial inference. In reality, rats navigating a maze are likely utilising every available and relevant form of information including kinaesthetic and visual cues; their performance most likely reflecting a proportion of these relevant cues.

The dense and overbearing 'terminological wilderness' of Tolman's learning theories combined with the vague and often misleading definitions associated with it (MacCorquodale & Meehl, 1954; White, 1943) meant that researchers were not quick to adopt it as a substrate for behavioural terminology. However, Tolman's (1948) 'cognitive map' is a concept widely discussed and presented in current day research despite the fact that the term is a loaded one (Bennett, 1996), for the purposes of this thesis we will define 'cognitive map' as (Tolman, 1948) originally intended; the internal representation of an animal's environment and corresponding context based on the association of cues (not all of which may be spatial) with spatial locations and or responses. Similarly, Hull's (1950) strict and inflexible mathematical postulates proved too restrictive outside laboratory settings. This was compounded by the fact that much of his theory remains scattered in countless unpublished manuscripts, notebooks and unfinished books, lacking an overall concrete view of the theory (Koch, 1954). However, as will be discussed below, S-R theories have similarly survived, transformed, and still play a major role in describing spatial navigation behaviour.

## 1.9 Summary

Tolman (1948) presented a number of experiments which he suggested undermine the S-R theories of navigation and learning; latent learning, spatial orientation, hypotheses, vicarious trial and error and searching for the stimulus. Some of the experiments were replicated, some were found to be inimitable. Furthermore, researchers favouring S-R theories were able to offer alternative interpretations of the results. Restle (1957) reviewed this literature and offers a contemporary view that rats utilise all forms of navigational cue, in varying intensity, depending on the task demands and surrounding environment. Both a complex form of navigation utilising extra maze cues and a simpler form of navigation relying mainly on kinaesthetic information appear to underlie spatial navigation, the strength of each of these depending on the proportion of relevant and trustworthy cues available.

# Chapter 2

## The Hippocampus as a Cognitive Map

### 2.1 O'Keefe and Nadel (1978)

In 1978 O'Keefe and Nadel sought to unify the older S-R and cognitive mapping theories under a new and improved theory, based now on extensive electrophysiological, histological and pharmacological studies as well as the behavioural studies continuing from the work described previously. After Restle (1957) and MacCorquodale and Meehl's (1954) persuasive arguments, suggesting that Tolman's (1948) cognitive map could largely be reduced to S-R relationships, the cognitive map as a concept suffered a loss of interest in the research community. However, O'Keefe and Nadel (1978) again suggested that spatial navigation is indeed based on a dichotomous pairing of cooperating systems and their work was successful in revitalising cognitive map theories. In this chapter we will focus on the behavioural implications of their seminal theory and the subsequent revisions to it. Central to their argument, O'Keefe and Nadel (1978) introduce two foundation navigation systems, based on those forms of navigation described above but using new terminology and with more evidence linking the two as a cooperative system of navigation. The authors suggest that space is represented in the brain in two different ways; an egocentric taxon system which operates in taxon space and an allocentric locale system which operates in locale space.

### 2.2 Taxon Navigation

O'Keefe and Nadel's (1978) taxon system relies heavily on sensory data and is primarily involved in the execution of motor routines, in this way it is comparable to the earlier S-R theories of navigation. However, it is more similar to a process first described by Darwin (1873) and Murphy (1873), originally named dead reckoning after the deduced or 'ded' reckoning historically utilised by sailors to estimate their position. This process consisted of frequently measuring speed and heading, these two pieces of information combined with a previously calculated position could be used to estimate the ship's current position. This process was functional, but over time inaccuracies in measurement would inevitably accumulate and lead to uncertainty in any estimations. In current spatial navigation research this process has come to be known as inertial navigation or Path Integration (PI) because assessing dead reckoning usually consists of showing that animals can return directly to a starting point after a complex outbound path, an ability that seems to demand integration in the mathematical sense of the word (Mittelstaedt & Mittelstaedt, 1982; Mittelstaedt & Mittelstaedt, 1980; Shettleworth & Sutton, 2005). O'Keefe and Nadel (1978) define their taxon system as operating on an internal representation of space (taxon space) which is based on relationships (vectors) relative to the animal and as such can be understood as egocentric. In practice this system acts to accumulate previous movements, the distance and orientation of each is recorded as a series of vectors which can then be used to compute simple, novel geometric responses (Figure 2.1).

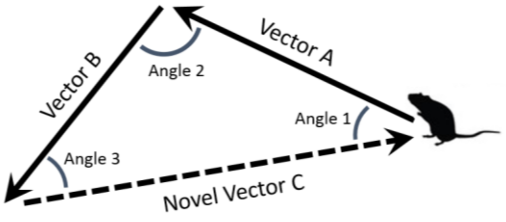

**Figure 2.1:** Diagram showing the accumulation of active movements and a possible computed novel response based on this information.

For O'Keefe and Nadel (1978) the taxon system is based largely on eventual goals, with perhaps intermediate subgoals, the system works to decode stimuli and provide the animal with the sequence of responses necessary for navigating to this goal. For this reason it is largely inflexible; upon discovering an obstruction a taxon system would not be able to spontaneously offer an alternative route (although this does not mean the system cannot be 'aware' of different routes to the same goal under normal circumstances). This system does, however, provide a number of advantages; its simplicity allows for sequenced routes to be accessed and utilised much more quickly than a detailed cognitive map. Physiologically, O'Keefe and Nadel (1978) also suggest that such a system may reside in a different part of the brain, this compartmentalisation of spatial navigation functions could also provide advantages in terms of optimised neural processing. A taxon system of navigation requires the existence of an internal representation of both distance and orientation, these are widely researched in the much simpler navigation strategies of insects; the existence of each of these will be discussed below.

## 2.3 Distance

Honeybees use a 'waggle dance' form of physical communication to inform other bees as to the spatial location of a food reward, communicating its existence, distance and orientation from the hive (Frisch, 1965, 1967; Landgraf, Rojas, Nguyen, Kriegel, & Stettin, 2011; Seeley, 1995) as well as its quality (Stabentheiner & Hagmüller, 1991) and possibly scent (Reinhard, Srinivasan, Guez, & Zhang, 2004; Thom, Gilley, Hooper, & Esch, 2007) demonstrating not only a spatial memory for these parameters but also suggesting that bees can estimate distances and are aware of their orientation – two key parameters of a taxon system of navigation.

Heran (1956) and von Frisch (1967) suggest that honeybees can estimate the distance they have travelled based on the level of energy expended. A similar system could exist in rats and other animals, as we saw before with McCulloch's (1934) food bowl raising experiments, rats are able to distinguish between high and low energy activities. However, Esch and Burns (1995) were able to show that bees returning from a food source suspended in mid-air high above the ground communicated the distance travelled, through their dancing, as being far less than the distance to the same food source located in the same position but at ground level. To access the high altitude food source would require flying a greater distance and with much greater energy expenditure, thus the bees could not have been estimating or communicating distance based on energy expenditure. The authors suggest that the bees may be utilising an optic flow[5] method of estimating distance; when they are flying close to the ground objects move past at a faster rate than when they are flying high above the ground and visual landmarks are far away. This optic flow theory explains best why the bees communicated the distance to the high up food reward as being less even though it was actually further and more energy costly.

Dacke and Srinivasan (2008) further suggest that bees can sum the optic flow related to passing objects; they trained bees to find a food reward after passing a specific number of identical landmarks (vertical stripes) as they flew along a tunnel. Bees trained to find food rewards at specific stripes were far more likely to search for food rewards near that landmark indicating that they could distinguish this reward location from the others. The authors suggest that the bees may have used a visually driven odometer, summing the perceived stimuli and their corresponding optic flow to estimate distance, this was shown similarly by Si, Srinivasan and Zhang (2003). However, an earlier and extremely similar experiment, substituting vertical stripes for yellow tents in a more natural open meadow setting found evidence that bees have some additional form of distance measurement. When the distance of the tents from the home hive was varied bees were as likely to search for food at the reward location indicated by the tents as the reward location at a similar distance from the hive as the original (Chittka & Geiger, 1995). These and a number of experiments suggest that bees may indeed use optic flow as their primary estimation of distance (Srinivasan, Zhang, Altwein, & Tautz, 2000; Srinivasan, Zhang, & Bidwell, 1997; Srinivasan, Zhang, Lehrer, & Collett, 1996) as do ants (Ronacher & Wehner, 1995) but see (Ronacher, Gallizzi, Wohlgemuth, & Wehner, 2000).

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[5] Optic flow merely refers to the process whereby visual scenes and objects ‘flow’ across the field of vision and thus the retina as an animal moves through an environment.

Ants are renowned for their ability to participate in wide ranging foraging trips and after finding a source of food they are often able to immediately return to their nest by the fastest direct route possible, despite a winding and seemingly random outbound journey or the weight of their discovered food (Wehner & Srinivasan, 1981; Wehner & Wehner, 1990). It has been shown with a great degree of certainty that on these foraging trips ants orient using a celestial compass (Wehner & Lanfranconi, 1981). However, the method by which they estimate distance is not well understood. They probably do not utilise optic flow as they are able to navigate in the dark without access to chemical signalling (Thiélin-Bescond & Beugnon, 2005) or with their eyes covered (Ronacher & Wehner, 1995) the energy expenditure hypothesis also does not seem to apply to ants for the same reason as in bees; similar distances which require different energy expenditure are still estimated inaccurately (Wohlgemuth, Ronacher, & Wehner, 2001). Wittlinger, Wehner and Wolf (2006) provide an alternative explanation; they were able to show that desert ants (Cataglyphis fortis) are able to estimate distances travelled with great accuracy based on the number of steps taken. They trained ants to forage along a single alleyway for a food reward at a set distance (see Figure 2.2). By attaching stilts to the legs of desert ants or removing the lower portion of their legs they found that depending on the length of the ant’s legs (and thus the distance of its stride) the perceived walking distance was altered. Ants walking with a reduced leg length underestimated the distances they had travelled, whereas ants walking on stilts overestimated this distance. These results give convincing evidence that ants are able to sum

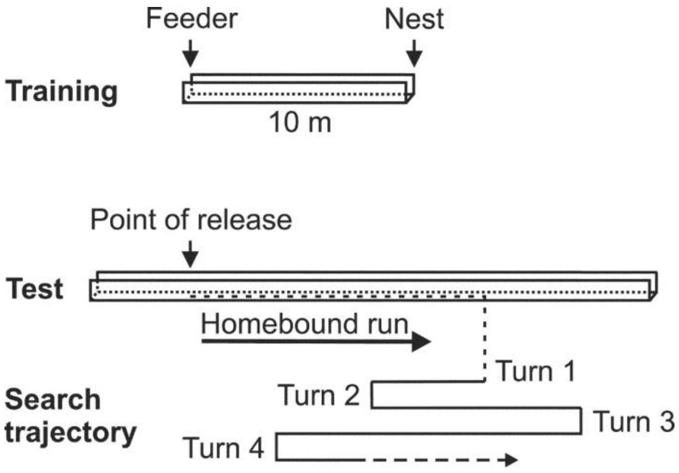

**Figure 2.2:** A schematic of the training and testing proceures used by Wittlinger, Wehner and Wolf (2006). Ants were trained to navigate from their nest location to a feeder 10m away. During testing the ants were removed from the feeder location to a parallel alleyway and the distance they travelled along this alley before executing typical nest searching behaviour (180 degree u-turns) was measured.

the proprioceptive information from their own movement to form an internal distance measurement, much in the same way bees sum optic flow parameters.

In human research Redlick, Jenkin and Harris (2001) suggest that, similar to foraging bees, humans are able to perceive distance through optic flow alone. Their subjects were placed in a virtual reality environment and asked to estimate a given distance in this environment based on visual information simulating the optic flow which would normally be induced by movement[6]. They found that participants were able to accurately estimate distances based on this information alone, although they were more likely to overestimate distances when the acceleration was small or the velocity was constant. This relationship corresponds with the real life acceleration threshold of the human vestibular system; a system which is also based on non-visual somatosensory and proprioceptive cues such as inner ear otiliths and semi-circular canals (Benson, Spencer, & Stott, 1986; Ivanenko et al., 1997) but see (Gundry, 1978). Similar results further support the view that humans can use optic flow to estimate distances and movement (Bremmer & Lappe, 1999; Harris, Jenkin, & Zikovitz, 2000).

For more complex organisms such as rats, humans and other mammals there are many self-motion cues other than optic flow that may be utilised to keep track of body movements. As well as the semi-circular canals of the inner ear (Bles, de Jong, & de Wit, 1984; Glasauer, Amorim, Vitte, & Berthoz, 1994) there are many other sources of internal or `idiothetic' information, provided by otiliths in the inner ear (Israel & Berthoz, 1989; Israel, Chapuis, Glasauer, Charade, & Berthoz, 1993), muscles and joints (called proprioceptive input, (Rieser, Ashmead, & Pick, 1988)), motor efferent signals and vestibular information generated as a result of changes in linear or rotational movement velocities (Mittelstaedt &

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[6] This visual information is nothing more than a repetitive, moving pattern, thus information derived from this does not represent the use of landmarks or other spatial information associated with a more complex system of navigation. Optic flow is merely used to estimate distance travelled regardless of the visual information available. Interestingly, navigation in virtual reality environments does not appear to be greatly disturbed (Chance, Gaunet, Beall, & Loomis, 1998) despite the absence of vestibular information.

Mittelstaedt, 1980; Sun, Campos, Young, Chan, & Ellard, 2004) for a review see (Angelaki & Cullen, 2008; Lackner & DiZio, 2005). Indeed it has been suggested that these physical cues may override visual cues such as optic flow (Harris et al., 2000) but both may be important when moving relative to other moving objects (Fajen & Matthis, 2013).

To investigate the properties of these nonvisual inputs Klatzky et al. (1990) asked participants to estimate walking distances whilst blindfolded. They gave participants a distance (between 4 and 12m) which they had to walk in an open gymnasium with no barriers or auditory cues. Participants were given distractor tasks to deter the use of step counting strategies, such as those utilised by the desert ants described above. Under these conditions, participants were able to reliably estimate the distance travelled and on average made no more than one footstep's equivalent of error. They also asked participants to walk a particular distance before turning 180 degrees and returning to their start location, participants were able to complete this task, making roughly 125cm of error when retracing a 4-10m path. A number of similar experiments confirm that human participants are able to retrace a trajectory and reliably return to their starting position (Bigel & Ellard, 2000; Corlett, Patla, & Williams, 1985; Elliott, 1986; Fukusima, Loomis, & Da Silva, 1997; Loomis, Da Silva, Fujita, & Fukusima, 1992; Mittelstaedt & Mittelstaedt, 2001; Rieser, Ashmead, Talor, & Youngquist, 1990; Steenhuis & Goodale, 1988) the majority of these experiments suggest that greater distances result in greater error and that delays do not interrupt this relationship, but see (Thomson, 1983).

Together, these results suggest that humans and other animals are likely to possess an internal representation of distance. Insects such as bees and ants appear to have a physiological basis for perceiving distance, perhaps even more directly than in larger animals (Frisch, 1967; Wittlinger et al., 2006). Humans certainly appear to be able to perceive and estimate distances travelled based purely on the information from structures in the inner ear, which give independent information of head orientation relative to gravity as well as linear acceleration. These two pieces of information, although the process by which they are combined to give an overall perception is still not fully understood (Ivanenko et al., 1997), appear to be enough for participants to estimate distance even in the absence of vision (Klatzky et al., 1990), similarly, vision appears to be enough information in the absence of any of these vestibular cues (Redlick et al., 2001).

## 2.4 Orientation

It is clear that mammals and probably many insects possess an internal representation of distance, however, this forms only half of the information necessary for a vestibular based, taxon navigation strategy; an organism must also have a representation of orientation to navigate. There is no doubt that insects are able orient themselves using a number of modal stimuli such as phototaxis or directional light orientation (Brines & Gould, 1979; Frisch, 1950) including orientation using polarised light from the sun (Krapp, 2007; Rossel, Wehner, & Lindauer, 1978; Wehner, 1997) or moon (Dacke, Nilsson, Scholtz, Byrne, & Warrant, 2003), the colour gradient of the sky (Rossel & Wehner, 1984) and each of these combined (Pfeiffer & Homberg, 2007). Insects can also use gravitaxis or an orientation relative to gravity (Hartman, 1979; Horn, 1975) for a review see (Jander, 1963). A tethered insect flying inside a drum with striped walls will tend to turn if the drum is rotated, in the same direction (Reichardt & Wenking, 1969; Zeil, Boeddeker, & Hemmi, 2009). If the drum is rotated clockwise the insect will similarly adjust its flight and turn in the clockwise direction, and vice versa. This automated response, utilising the process of optic flow described above, helps the insect maintain a straight heading even in windy conditions. These orientation techniques are very interesting but the question remains whether insects and other animals can utilise information such as this to actively navigate and whether animals have internal methods for determining orientation.

In a series of experiments, researchers were able to demonstrate that dung beetles (*S. zambesianus*) can utilise the polarised light resulting from moonlight interacting with the atmosphere (Dacke, Byrne, Baird, Scholtz, & Warrant, 2011; Dacke et al., 2003) to navigate when foraging at night. Specifically, the beetles use this cue to maintain a straight heading when rolling dung balls to a secure location, suggesting that they are able to orient themselves using this visual cue. In a follow up experiment (Dacke, Baird, Byrne, Scholtz, & Warrant, 2013), dung beetles were found to show the same straight headings even in the absence of sun or moonlight. However, when fitted with cardboard masks, preventing them from viewing the sky but still allowing them to view the ground level landscape, the beetles were impaired in their orientation and could no longer navigate in straight paths. The authors conclude that the beetles are able to use starlight alone to navigate, probably utilising the polarisation of this weak light source in the Earth's atmosphere. These results suggest that dung beetles possess a very complex orientation system which allows them to navigate in the absence of any cues other than celestial bodies. However, the results also suggest that these insects do not possess an internal sense of orientation; in the absence of any visual cues the beetles were unable to maintain anything resembling a straight heading (see Figure 2.3). It may be that the success of the dung beetles' celestial navigation system

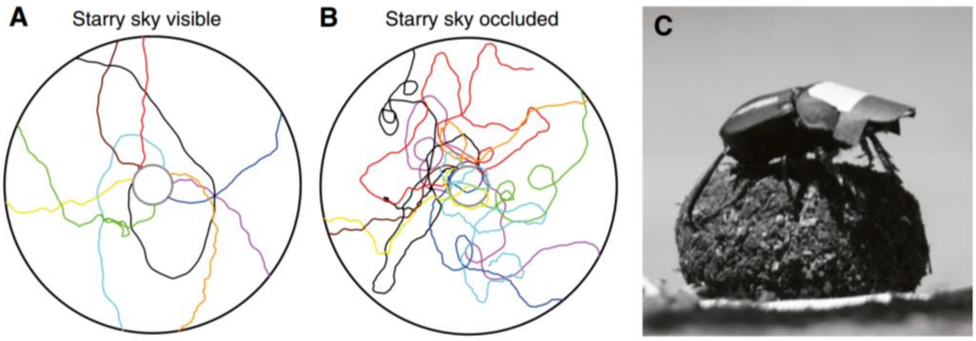

**Figure 2.3: A)** a series of example trajectories, recorded when dung beetles were navigating with the aid of light from the stars. The beetles typically roll their balls in a relatively direct path from the dung pile at the centre of the arena to the edge. **B)** A series of example trajectories recorded when dung beetles were navigating whilst wearing a cardboard head cap, preventing them from viewing the sky. Here, the trajectories are much longer and the level of cross-over is much higher. **C)** A photo of a dung beetle wearing a cardboard head cap.

has resulted in a loss of any internal sense of direction. In evolutionary terms, the arid areas where these beetles survive do not often experience cloudy nights, a dung beetle with no internal sense of direction would probably not be at a great disadvantage. Similar navigation systems have been proposed in amphibians (Ferguson, Landreth, & Turnipseed, 1965) and spiders (Norgaard, 2005) but not yet demonstrated in this way.

Muller and Wehner (2010) observed that in the presence of spatial landmarks Namibian desert ants (*Ocymyrmex*) can navigate with great accuracy to their nest site, which is nothing more than a small hole in the sand, and to reward locations. However, the ants can similarly navigate, albeit with an impairment, in the absence of any visual cues, relying on PI information alone. In this experiment ants did still have access to the sun as a compass cue, however, Muller and Wehner (1988) were previously able to show that without access to polarization or solar cues ants were able to navigate the final leg of a triangle with no impairment (see Figure 2.4). Under all conditions the ants made the same systematic and significant error when navigating this shape; the error angle **ε** was found to depend on the turning angle **α** and the ratio between the lengths of the two outbound paths, **a** and **b**. The authors provide a mathematical model for the ant's PI system which can account for this systematic error. Furthermore, they suggest that under normal conditions this error would not occur, in the wild ants tend to avoid making large angular turns, especially turns which create a bias in one direction (they prefer to alternate left and right turns), in the wild, ants

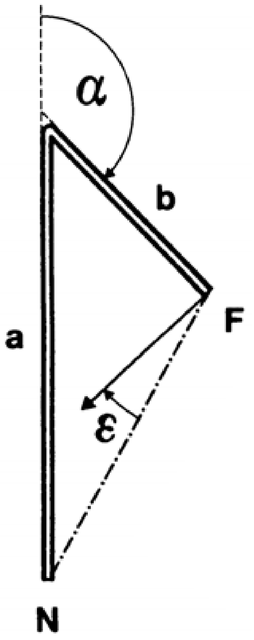

**Figure 2.4:** The triangle task used by Muller and Wehner (1988; Tolman & Minium, 1942) to assess orientation in the Namibian desert ant. The ant starts at the nest site (N), navigates along paths a and b, making turn α to a reward site (F) where it then has to make a rotation to orient itself to the nest. Shown is the typical orientation error (ε) made by ants displaced to a parallel and unfamiliar environment after reaching F. Similar tasks to this have been used to assess orientation in a number of animals, including humans.

would also have access to additional directional information from polarised light, the sun and from surrounding landmarks near the nest site.

Orientation based on celestial cues is particularly suited for insects; solar phenomena such as the pattern of polarized light and celestial bodies such as the stars and moon are at a visual range indistinguishable from infinity. Thus these cues are not subject to the effects of motion parallax and are well suited as a means for defining directions. Furthermore, the compound eyes of many invertebrates have an exceptionally large field of view, often able to perceive the entire celestial hemisphere (Stavenga, 1979). Evidence suggests that larger animals may also utilise these cues; invasive Burmese pythons (*Python molurus bivittatus*) displaced from their home territory in the everglades of South Florida have been tracked heading directly from their displacement site back to their home territory. The mechanism which the snakes use to navigate is still unclear; because the snakes were passively transported to their translocation areas they did not have access to PI information, however, they were able to maintain a direct and stable compass bearing for distances greater than 30km suggesting the use of celestial or polarisation cues (Pittman et al., 2014). Nevertheless, many animals, such as mammals do not have access to these cues as they do not have the physiological adaptations necessary for perceiving them. Most of these animals still have to navigate more complex routes than insects, over longer distances and under hostile conditions.

Similar to insects, mammals also appear to have an internal representation of orientation, but it is based largely on vestibular information. Etienne, Maurer and Saucy (1988) were able to show that golden hamsters (Mesocricetusa uratu) navigating into an arena to retrieve a food reward under infrared light can successfully navigate back to a home box location. However, the return journey is disrupted if the arena is rotated while the hamsters are retrieving the food, causing them to make ipsidirectional errors (over compensating in the clockwise direction when rotated counter clockwise and vice versa). In this experiment the hamsters were able to estimate orientation, they also perceived the rotation of the arena and the overcompensation for this appeared to lead to consistent angular errors. To investigate this effect further, Mittelstaedt and Mittelstaedt (1980) showed that mice could compensate for a rotational episode in the dark by internally monitoring changes in orientation. Mouse pups were placed in the centre of an arena and the behaviour of the mother was observed. Without intervention, female mice would accurately navigate to the pup and return to a home nest location. If the pup was rotated, relative to the arena, at a rate above the threshold required for vestibular perception, the mice were similarly unaffected and navigated back to the home location. However, if these rotations were performed at a rate slow enough to be imperceptible to the vestibular system the mice attempted to exit the arena at an angle which would be correct had the rotations not taken place. In a similar experiment Matthews, Ryu, and Bockaneck (1989) compared the performance of intact rats trained to find a water reward in one of six arms in a radial arm maze to that of labyrinthectomized rats with an obviously impaired vestibular system. When the rats were placed in an opaque start box at the centre of the maze and rotated, labyrinthectomized rats, presumably disorientated, were impaired at selecting the correct arm compared with a group of control rats. These rats performed significantly better when visual cues were present, although they were still significantly impaired, the intact rats' performance was unaffected by the presence or absence of visual cues. Together these results suggest that mammals have a constantly updating internal representation of orientation, they also provide strong evidence that this representation is reliant on the information arising from a functional vestibular system and that this system can compensate for a complete lack of visual navigation cues.

In order to better understand the orientation abilities of larger mammals such as humans, Worchel (1951) asked human participants to complete the third side of a triangle (see Figure 2.4), after leading them along two sides of a triangular path, participants had to return to the starting position. Upon signalling that they believed they were back at the starting point the distance between them and the actual start was measured and used to assess navigational error. Worchel (1951) found that blind and sighted (but blindfolded) participants performed similarly, with the congenitally and recently blind participants performing slightly, but not significantly worse than the blindfolded. All of the participants were able to return to the starting position with an error roughly half the length of the triangle's hypotenuse regardless of its size (i.e. completing a triangle with a 22m hypotenuse resulted in a mean error of 10ft for blind and 7ft for sighted participants). In further experiments Worchel (1951) found that all of the participants made larger errors when the number of paths was increased to form a more complex polygon or their length was increased. Similar experiments have found congenitally blind participants slightly worse than sighted in similar tasks (Rieser, Guth, & Hill, 1986) or not significantly impaired (Loomis et al., 1993) [7].

In a further investigation, Klatzky et al. (1990) asked blindfolded participants to complete the third side of a right angled triangle; the participants were led along two sides of the triangle and then asked to return to the starting point. To eliminate the possibility of counting steps, participants were required to complete a verbal task while navigating. Again, participants were able to accurately return to a starting position. However, Klatzky et al. (1990) also found that the errors participants made were proportional to the distances of the initial vectors they travelled, even though shorter distances were completed more quickly and so should have been less susceptible to interference or temporal decay. Specifically, unlike the PI system of the ant (Muller & Wehner, 1988) they found that the error in estimating the angle of return orientation did not change depending on the scale or shape of the triangle, which is expected given that the angles of a triangle do not change if the

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[7] A number of studies have found blind participants to be significantly impaired on spatial tasks; less able to produce tactual maps of a school campus (Casey, 1978), estimate Euclidean distances with greater error (Rieser, Lockman, & Pick, 1980) and have poorer knowledge of the locations of landmarks (Rieser, Hill, Talor, Bradfield, & Rosen, 1992). These effects are not directly related to the topics in this thesis, however, they do suggest that greater experience with spatial environments, specifically visual experience of spatial environments aids in building internal representations of new environments when they are encountered.

triangle is resized. The estimation of distance was effected, however, which led the authors to suggest that these distances were represented as scale independent representations of the paths, relying on the ratios between different distances and resulting in greater estimation error as these distances become harder to represent abstractly. As well as larger distances, participants also made significantly greater errors when they were expected to return to a starting position after navigating a greater number of paths, forming a complex shape rather than a triangle. These errors were particularly noticeable if these paths crossed, with many participants returning to a start position which would only be correct had this path crossing not occurred. This effect of ‘path crossing’ has also been observed in other studies (Loomis et al., 1993).

These results are similar to those of Lindberg and Garling (1981); in their experiment they led participants on a number of trajectories composed of between 2 and 6 paths. They found that as the number of paths increased the accuracy with which participants could identify the position of a reference point (their starting position) decreased, this effect was compounded if the participants were required to complete a distractor task; incremental subtraction while they walked. The finding that greater complexity in outbound paths leads to greater uncertainty in orientation relative to a starting position suggests that instead of simply keeping track of the start location’s heading and continuously updating this as navigation proceeds, participants may be storing an internal representation of their journey, this is supported by the ability of participants to retrace their journey relatively accurately when requested (Loomis et al., 1993).

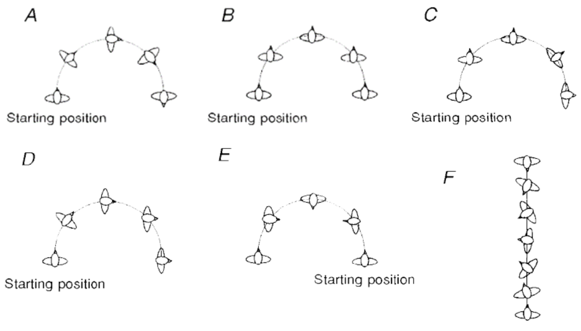

**Figure 2.5: A-F)** The different possible trajectories used by Ivanenko et al. (1997). Note that the trajectory and orientation of the participant are not always in agreement.

In an effort to further explore the different forms of information arising from the vestibular system and how this information may be interpreted by the brain, Ivanenko et al. (1997) tested participants on a "remote-controlled robot equipped with a racing-car seat" which was able to travel in linear and rotational trajectories, whilst keeping the participant facing the same or conflicting directions (see Figure 2.5). Participants were asked to point to the position of a stable visual cue which they were familiarised with before the experiment. Participants were blindfolded and wore headphones playing white noise, the only information available to them for estimating distance and orientation was their vestibular inertial system. Ivanenko et al. (1997) found that participants were able to reliably keep track of the cue's position, despite the variety of movements they were experiencing; unless their motion through space and direction did not correspond to the normal movement of the body during locomotion. The authors suggest that the brain efficiently combines linear acceleration information from otiliths and angular information from the semi-circular canals to accurately represent the body's movements through space, however, this process is disrupted if motion and direction provide conflicting information. One caveat to this experiment is that the consistent acceleration process of the seat did not recreate the rapid and brief acceleration that the body naturally has to decode. However, Takei, Grasso, Amorim and Berthoz (1997) similarly suggest that in a task requiring participants to walk two full revolutions of a circle, blindfolded, different sensory information or different processing modes are probably involved in estimating the shape and distance of the trajectory and in estimating the total angle of rotation. This is indicated by the finding that errors were not correlated between these estimations; the most likely explanation is that distance estimation is the result of proprioceptive input, whereas angular estimation is the result of vestibular inputs.

Together these results suggest that many animals have an internal representation of orientation, which is continually updated and adjusted based on vestibular information (Matthews et al., 1989) – resulting from both passive and active movements (Mittelstaedt & Mittelstaedt, 1980). This estimation is based on non-visual information (Klatzky et al., 1990), however, navigation with visual aids can be more precise (Matthews et al., 1989). As the distance and complexity of the outbound journey becomes more complex, estimation becomes less and less accurate as small errors accumulate (Lindberg & Garling, 1981). It would also appear that this information is combined in the brain, but with information from different sensory systems accounting for different navigational information (Ivanenko et al., 1997), possibly with a low degree of overlap (Takei et al., 1997).

## 2.5 Summary

These experiments show that both an internal representation of orientation and distance exist in a number of different animals, although these representations may be based on different sensory information. In terms of O'Keefe and Nadel's (1978) taxon navigation, this suggests that the information required to navigate based solely on idiothetic information is certainly accumulated by many animals as they navigate. Furthermore, this information is sufficient to make simple novel responses (such as returning to a start location after a number of outbound paths), although the longer this information is utilised the less reliable it becomes. This evidence is in agreement with the existence of O'Keefe and Nadel's (1978) taxon system of navigation.

## 2.6 Beacons

Before continuing to discuss the ethological evidence for the existence of O'Keefe and Nadel's (1978) locale system of navigation it is necessary to discuss a common, intermediate form of navigation which does not exclusively depend on a taxon or locale system. 'Beacons' are landmarks which can aid navigation by providing heading information (as an animal moves around the beacon it provides a stable polar point to orient with) and distance information (as an animal moves away from the beacon it grows smaller and this contraction of angular size provides a stable estimation of distance) (Bennett, 1996; Hogarth, Roberts, Roberts, & Abroms, 2000). The use of beacons can be viewed as a reduced form of locale navigation; instead of utilising an array of landmarks beaconing relies on the presence of only one. Although it does suggest an ability for visual and spatial learning, as the correct landmark and its association with an environment must be recognised, beaconing does not necessarily suggest the existence of a locale system of navigation or a cognitive map (Shettleworth & Sutton, 2005), that system is defined by the use of multiple landmarks and the relationships between each of them to determine location. Indeed evidence suggests that in rats an entirely different brain region may be responsible for beacon navigation than taxon and locale strategies (Devan & White, 1999; Save & Poucet, 2000).

A number of experiments have demonstrated that insects utilise proximal and distal landmarks for navigation (Collett & Kelber, 1988), however, they do not use the arrangement of these landmarks as a constellation for navigation. Rather insects navigate towards a single salient cue as a beacon before utilising a PI strategy of navigation (Bregy, Sommer, & Wehner, 2008) or they search for an area where the arrangement of landmarks produce a similar retinal pattern of stimulation (Collett & Kelber, 1988; Knaden & Wehner, 2005; Wystrach, Beugnon, & Cheng, 2011). Visual landmarks such as these are often given priority over PI information (Collett & Kelber, 1988; Knaden & Wehner, 2005), but when information from distal and local cues is conflicting, the information from distal cues is given priority, a finding consistent with the idea that smaller, local cues are probably less stable over time than larger distal cues (Collett & Kelber, 1988). Using the panoramic outline of distal cues in this way can be considered a beacon form of navigation as the animal is still not attending to specific landmarks and the relations between them, but rather a specific singular cue (Rumelhart, McClelland, & University of California, 1986).

This panoramic, view dependent form of navigation is supported by evidence that Namibian desert ants (*Ocymyrmex robustior*) navigating in a desert environment devoid of prominent landmarks perform ‘learning walks’. Learning walks have been observed in a number of invertebrate species and are thought to occur as insects attempt to familiarise themselves with the visual features of the surrounding environment that can be used to locate the area in future, in effect, actively storing in memory how different landmarks look

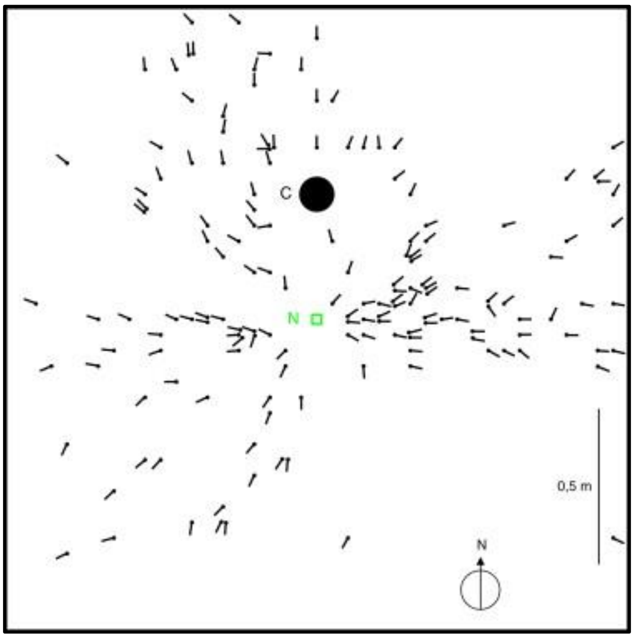

**Figure 2.6:** Orientation of ants navigating spiral search patterns around their nest site, the ants perform short stops and purposefully orient themselves (Müller & Wehner, 2010). N = the nest entrance, C = the black cylindrical landmark, small lines show the orientation of the ants and small black circles show the head end of the body at this time. It is clear that the ants are orienting themselves towards the nest entrance, not the cue. The ants are thought to be capturing visual information along with PI information to create a catalogue of known locations which they can use to navigate upon returning to the nest.

from different viewpoints (Becker, 1958; Collett, Graham, Harris, & Hempel-De-Ibarra, 2006; Lehrer, 1993; Nicholson, Judd, Cartwright, & Collett, 1999; Warrant & Dacke, 2010) see (Wehner, 1981) for a review. By learning the pattern of stimuli falling on the retina caused by the panoramic layout of visual cues, insects can match these stimuli and in this way identify certain areas of their environment. These learning walks are most prominent in naïve individuals (Zeil, Kelber, & Voss, 1996) and decrease in frequency over time which has been suggested as evidence of visual learning and memory (Collett & Collett, 2002). On their spiral learning walks, Muller and Wehner (2010) observed that ants stop and turn to face their nest entrance (see Figure 2.6) attending specifically to the visual cues that can be found there (Müller & Wehner, 2010). The frequency of these spirals decreases significantly over time, suggesting a visual learning process. When returning to the nest the ants navigate towards prominent landmarks near the nest site, using them as beacons. Once within the area of their learning walk the PI and visual information obtained when leaving the nest can then be used to locate the nest entrance (Wehner & Srinivasan, 1981). Other insect species have also been observed performing learning walks such as these; the nocturnal Namib Desert spider (*Leucorchestris arenicola*) has been shown to utilise visual information when attempting to locate a goal or nest site (Norgaard, Henschel, & Wehner, 2007; Norgaard, Nilsson, Henschel, Garm, & Wehner, 2008). If landmarks are available these spiders are able to return to their burrows even after passive displacement.

Similar to the learning walks of flightless invertebrates, newly hatched wasps and bees perform ‘inspection flights’ or ‘orientation flights’ (Becker, 1958; Lehrer, 1996; Zeil et al., 1996). These flights consist of an aerial inspection of a nest site before departing from the area (Capaldi et al., 2000; de Ibarra, Philippides, Riabinina, & Collett, 2009; Vollbehr, 1975; Zeil, 1993a, 1993b; Zeil, Boeddeker, & Hemmi, 2008; Zeil et al., 1996) or before departing from a relatively new reward site (Boeddeker, Dittmar, Stürzl, & Egelhaaf, 2010; Collett & Lehrer, 1993; Lehrer & Collett, 1994; Schöne, 1996). For newly hatched wasps these flights consist of circling at a constant angular velocity but at an increasing altitude around their nest when they start to participate in active foraging (Zeil, 1993a). Wasps adjust this flight to allow adequate fixation of the nest and closest significant landmark simultaneously. Wasps are probably using these flights to acquire visual ‘snapshot’ information regarding their nest site and the surrounding landmarks (Zeil, 1993a) this is supported by the observation that wasps make similar inspection flights upon returning to the nest (Zeil, 1993b). The behaviour of wasps who find landmarks have changed upon returning to their nest suggest that they follow the positioning of closest landmarks more strongly than those distal to the nest site and that they largely ignore unreliable contour information such as shadows (Zeil, 1993b). Evidence collected by Collett and Lehrer (1993) suggests that over time bees stop performing these learning flights, after which their subsequent search for the goal becomes more and more driven by the angular size of a significant landmark, utilising this cue as a beacon. Indeed it has been suggested that insects, as a general rule, may utilise distal landmarks as stable beacons or to provide directional information during navigation and homing (Graham & Cheng, 2009; Graham, Fauria, & Collett, 2003; Sturzl & Zeil, 2007; Zeil, Hofmann, & Chahl, 2003) whereas proximal landmarks are used to specify a locality, such as a remembered foraging route or the location of a goal site (Collett et al., 2006).

Convincing evidence of this landmark-panorama navigation strategy was presented by Collett and Rees (1997). By recording the flight patterns of wasps (*Vespula vulgaris*) and honeybees (*Apis mell-ifera*) as they approached a familiar reward site it was shown that these insects have a preferred flight path which they take when approaching the area. The authors suggest that these flight paths are intended to align nearby landmarks on the retina with a learned pattern of stimuli, directing the insects in to the correct spatial location (see Figure 2.7). The authors conclude that based on the behaviour observed in these insects, they navigate towards a conspicuous landmark, acting as a beacon. The relative size of this beacon on the insect's retina acts as an estimation of distance, with the insect comparing its current view with a stored visual record of the landmark from a number of distances. As the proximity to the landmark increases so does its speed of movement and position on the retina. When this movement reaches a threshold the landmark begins to be ignored, at which point the insect fixates on a new beacon, this sequence continues until the goal site itself acts as the beacon.

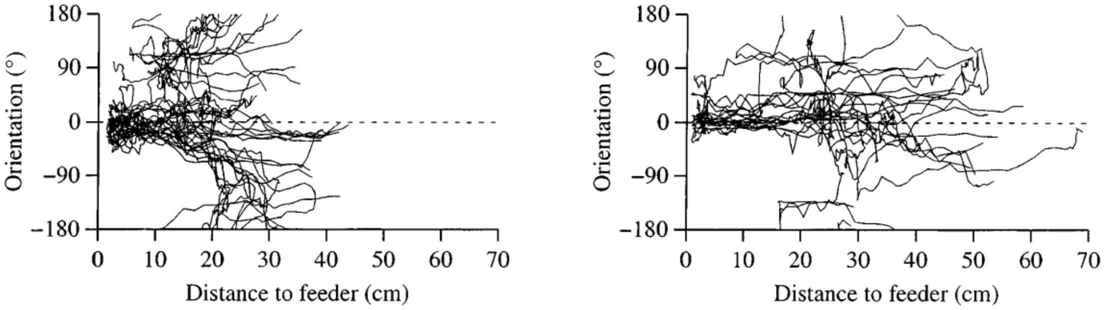

**Figure 2.7:** The flight patterns of two wasps, recorded as the insects approached a reward site marked by two landmarks. Shown is the angular deviation from the insects preferred path (shown by the dotted line) as the distance from the reward increases. It is clear from the recorded flight paths that as they near the reward the wasps' paths converge on a similar approach pattern, aligning the view of the landmarks in a consistent manner.

There is some evidence for a similar view dependent recognition system is humans; Diwadkar and McNamara (1997) found that participants were impaired at identifying an arrangement of objects if their viewpoint was changed, with a slight improvement when the viewpoint was exactly opposite; a phenomenon attributed to the similarity of the view when it is perfectly mirrored (Logothetis & Pauls, 1995; Vetter, Poggio, & Bulthoff, 1994) (see Figure 2.8). These results suggest that the participants' memory for the spatial arrangement was view-dependent, much like the guidance strategy utilised by wasps approaching a goal site. Simons and Wang (1998) found similar results in a setup similar to Diwadkar and McNamara (1997). They showed that participants were impaired at identifying a displaced object when the arrangement was viewed from a different angle. Interestingly, this effect was not observed when the participant also changed viewing orientation, suggesting different mechanisms are involved in spatial memory when movement is active and when movement is relative. Neither effect was altered by the introduction or removal of distal cues, although a more recent study suggests that spatial memory of this kind can be aided by stable distal cues (Burgess, Spiers, & Paleologou, 2004). Together these results suggest that, in human participants, the recognition of environmental changes may be view dependent, however, the recognition of landmarks may be controlled by an alternative mechanism. A possible explanation is that humans and possibly other mammals are, unlike insects, able to interpolate and extrapolate view independent representations of a spatial arrangement without actually experiencing the different views, the processes underlying this effect are still not well understood (Bülthoff & Edelman, 1992; Bulthoff, Edelman, & Tarr, 1995; Rock & DiVita, 1987; Ullman, 1989). The participants in this study appeared to recognise the object arrangement without the aid of distal cues, in contrast to insects such as bees and wasps which ignore local cues when local and distal cues provide conflicting information.

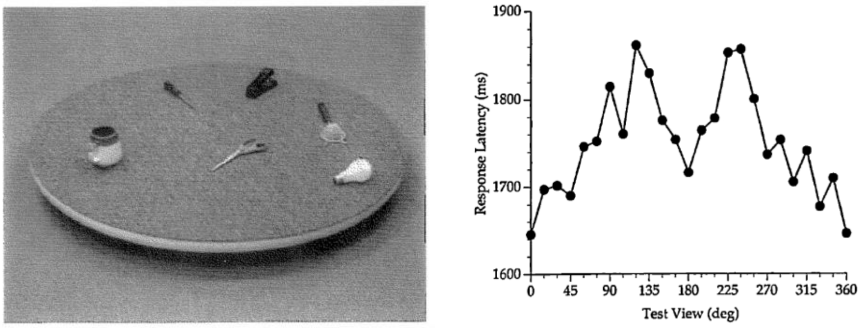

**Figure 2.8:** Left) An example spatial arrangement used by Diwadkar and McNamara (1997) during training. The objects are placed on a table top and the participants are permitted to view the arrangement for 30s. Right) The performance as measured by response latency (how quickly participants identified photographs from different viewpoints as the same arrangement or not) against angular rotation of the test image from the training view. The latency is low at 0° and 360° where the image is from the same view the participant experienced, the latency also drops around 180° where the arrangement is viewed from the opposite side to that experienced during training.

Overshadowing is an established classical conditioning phenomena, observed when alternative and competing stimuli are associated with an Unconditioned Stimulus (UCS) such as food. If one stimulus is more salient than the alternatives the association between this Conditioned Stimulus (CS) and the UCS will be strong, the association with the weaker, alternative CSs will be comparatively weak; their effect is overshadowed by the strong association (Jones, Gray, & Hemsley, 1990; Pavlov & Anrep, 2003; Rescorla & Wagner, 1972). Overshadowing can be useful in determining the relative strengths of different cues an animal utilises as it navigates. The removal of more salient cues will result in the greatest disruption to behaviour as their association with the UCS is the strongest (Etienne & Jeffery, 2004). Using these principles Redhead et al. (2013) found that landmarks acting as beacons overshadow geometric cues such as the shape of an environment. In a virtual water maze task, human participants were required to locate a platform marked by a beacon in a distinctively shaped pool. In environments with greater than 3 sides, participants were found to rely on the beacon for navigation, as measured by their escape latency when the beacon was removed. This association was strong enough that if the shape of the maze and position of the beacon gave conflicting information participants navigated to a location in the maze indicated as correct by the beacon rather than the actual trained platform corner. Redhead and Hamilton (2007) similarly found that in a virtual water maze task, a beacon cue overshadowed an arrangement of cues on the walls of the maze. During a test trial in which the beacon was removed, leaving only the landmarks to guide navigation, participants spent no more time in the platform area than would be expected by chance. Further evidence suggests that when given access to both an arrangement of landmarks and a beacon, rats preferentially use the beacon and a simpler, taxon based navigation strategy (Harvey, Brant, & Commins, 2009).

When given access to a beacon both humans (Redhead et al., 2013) and rats (Harvey et al., 2009) appear to preferentially utilise the beacon as a much simpler navigation strategy, but evidence suggests that they can also still utilise landmark information if a beacon is unavailable (Harvey et al., 2009). However, Wiener, Condappa, Harris and Wolbers (2013) suggest that this may not always be the case. They found that in a virtual cross section maze young human participants were able to utilise an allocentric place strategy; upon joining a previously learned route they were able to successfully navigate to the goal location. However, older participants were less flexible in this way, although they were able to learn a training route through the maze they consistently used a beacon strategy of navigation and were unable to utilise a place strategy when approaching intersections from novel directions (see Figure 2.9). The authors suggest that this impairment is due to the neurodegeneration of the hippocampus (as will be discussed later this is the brain region thought to be responsible for allocentric navigation strategies (Raz et al., 2005)), which would explain why these participants resorted to a much simpler navigation strategy more like the direction specific, response based strategy utilised by insects.

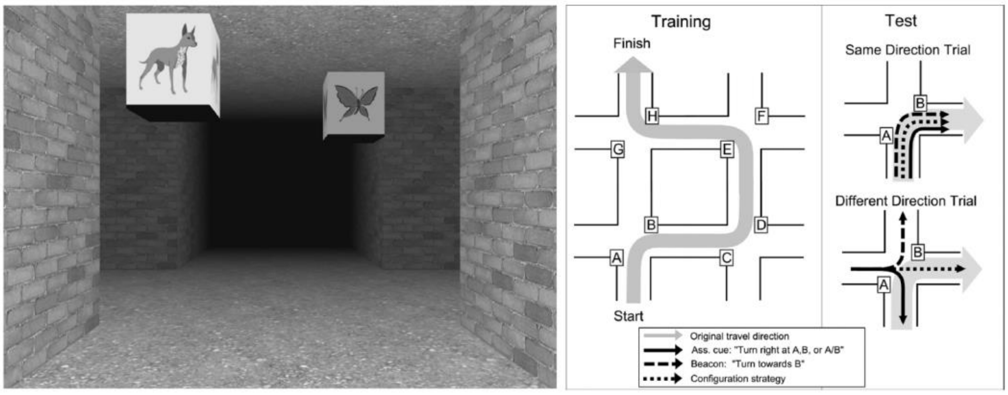

**Figure 2.9:** The virtual reality environment used by Wiener, Condappa, Harris and Wolbers (2013). Left) A screenshot of an intersection in the maze environment, intramaze cues can be seen at the intersection corners. Right) A schematic of an example training and testing protocol. In training the participants learn to navigate a particular route through the maze. In testing the participant starts at a novel location and their response is recorded. In this design associative responses (such as turning right when encountering cues A and B), beacon responses (such as turn towards cue B) and a configuration strategy (such as turn right relative to A and B) can be distinguished.

## 2.7 Summary

Insects clearly utilise beacons for much of their navigation; many insects have been observed taking learning walks or orientation flights where they focus on the location of goal or nest sites and the location of nearby landmarks (Müller & Wehner, 2010). Over time the frequency of these explorations decrease, at this point bees have been shown to start attending more to local cues, utilising the size and location of these cues as an indicator of their intended destination (Collett & Lehrer, 1993). At this point wasps have similarly been shown to approach reward sites from a particular direction, maintaining a consistent retinal pattern of stimuli and using landmarks as a sequence of beacons for guiding landing behaviour (Collett & Rees, 1997). Similarly, rats and humans have been shown to prefer beacon based navigation strategies to more complex allocentric strategies (Redhead & Hamilton, 2007), this effect is compounded when participants are older and are presumably suffering from neurodegeration in the brain regions responsible for allothetic navigation strategies (Wiener et al., 2013). Beacon strategies such as these do not constitute a locale or map based navigation strategy, although they clearly utilise visual cues such as landmarks (Bennett, 1996).

## 2.8 Locale System

In contrast to the taxon system, O'Keefe and Nadel (1978) define their locale system as operating on a Euclidian representation of space, where the positions of objects are defined by their relationship with other objects relative to the movements of the animal. This system can be seen as allocentric and can exist without information of the animal's current position, although this information is of course necessary for navigation. Where the taxon system is concerned with goals and the sequence of responses which lead to them, the locale system constructs maps through the gradual exploration of an environment, accumulating information to form a detailed representation of an environment which can include non-spatial information. Navigation based on such a map is considered highly flexible, can adapt to unexpected obstacles and is less likely to lead to disorientation. However, O'Keefe and Nadel (1978) suggest that such a system will probably be slower and more effortful to maintain and utilise. In contrast to the PI or taxon system, locale or map based navigation systems are more often studied in mammals such as rats or human participants.

## 2.9 Landmarks

We have seen that insects can use visual cues such as landmarks to navigate (Collett & Kelber, 1988), however, insects appear to utilise these in a different way to more complex organisms such as mammals. Rats are known to recognise different objects in their environment based on a number of characteristics (Ennaceur, 2010). Insects, however, appear to have a more basic approach to object recognition, comparing the pattern of stimuli falling on the retina to a library of previously recorded images (Dyer & Vuong, 2008), they are able to interpolate and average between known viewpoints to produce novel images (Avargues-

Weber, Deisig, & Giurfa, 2011; Dyer & Vuong, 2008) but this system is less well developed than in rodents (Ennaceur, 2010), birds (Watanabe, 2001) and primates (Logothetis & Pauls, 1995; Perrett, Oram, & Ashbridge, 1998). In contrast to the all or nothing, PI or landmark navigation of insects (Bregy et al., 2008) rats and humans have been shown to average the information from each to determine a heading (Bodily, Daniel, & Sturz, 2012; Hamilton, Rosenfelt, & Whishaw, 2004), suggesting a more systematic approach to navigation (Maaswinkel & Whishaw, 1999). This is consistent with the view that insects have far less cognitive resources to utilise for spatial navigation and are probably not able to process this information in parallel as mammals do.

A number of experiments have been proposed as evidence of a map based navigation strategy in insects, however, the results can often be explained in terms of a much simpler mechanism (Bennett, 1996). Old worker bees caught at their nest site, fed concentrated sucrose solution and released far from their hive at random locations are able to navigate back to their nest, something young bees are unable to do (Gould, 1986a; Gould & Gould, 1994). This suggests that the older bees have some internal representation of the surrounding environment. However, as discussed above, bees and other insects often perform learning flights around their nest site, for the purpose of imaging landmark panoramas and landmarks which can be used as beacons (Collett & Collett, 2002). It is entirely possible that older bees are simply more likely to have explored their release site in the past and are able to follow a previously experienced path back to their nest (Wehner, 1981).

These possibilities were tested in a well-known experiment, itself not published in a peer reviewed journal; bees were trained to find a food reward on a boat moored in the middle of a small lake (see Figure 2.10). Upon returning to their nest, bees conducted waggle dances to communicate the reward locations to other bees in the hive. Gould and Gould (1982) report that these other bees ignored the waggle dance and did not visit the reward location, they suggest that these bees compared the location information in the dance to an internal representation or map of the surrounding environment and concluded that a reward location in the middle of the lake was unlikely (Gould, 1990; Gould & Gould, 1995). In the six days of training no bees visited the feeder in the lake, but bees did follow waggle dances for a feeder located a similar distance away from the nest on dry land. Furthermore, a more recent experiment has shown that bees will follow the directions in a waggle dance if the communicated location is on the other side of a body of water, suggesting that it is not the presence of water itself that discourages following the directions (Tautz et al., 2004). A number of alternative explanations have been made for the results of the original lake experiment (Shettleworth, 2009), bees may have attempted to locate the lake feeder but their optic flow system for determining distance (Tautz et al., 2004) may have led to disorientation over the flat featureless lake surface (Dyer & Seeley, 1989; Frisch, 1967) but see (Gould & Towne, 1989). However, results from a more recent replication of the lake experiment (see Figure 2.10) suggest that bees do in fact follow waggle dances communicating the location of a lake feeder. Wray et al. (2008) recorded the behaviour of bees observing these implausible waggle dances compared to dances for an equidistant feeder on land. Both dances recruited the same number of bees, these bees were equally likely to follow the dance instructions, left the hive after a similar length of time and a similar number of recruits were found at both feeder sites. The authors conclude that in light of these results Gould's (1982) lake experiment should not be taken as evidence of cognitive mapping in insects.

In a similar experiment, Gould (1986b) trained bees to find food at a feeder location (see Figure 2.11), these bees were then caught at the entrance to their hive and displaced to another, presumably novel, location some distance away. If, upon their release, the bees were disoriented they would depart from this new location in random directions. If they were not aware that they had been displaced they would probably fly on the bearing they would normally take from the hive to their usual reward site. If they had only route specific landmark memory but had previously experienced this new site on some past foraging trip,

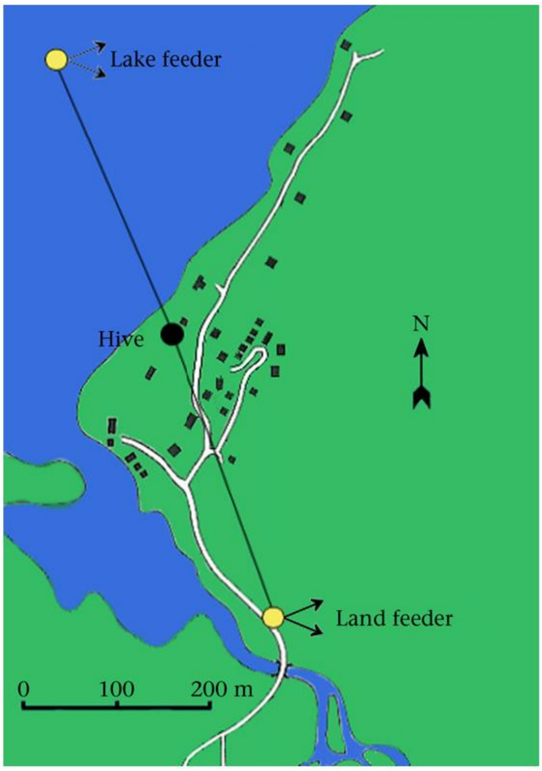

**Figure 2.10:** An above view of the training area used in Wray et al.'s (2008) replication of Gould's (1982) lake experiment. Bees were as likely to follow waggle dances indicating the location of either feeder, their behaviour did not indicate any difference in interpretation of these dances.

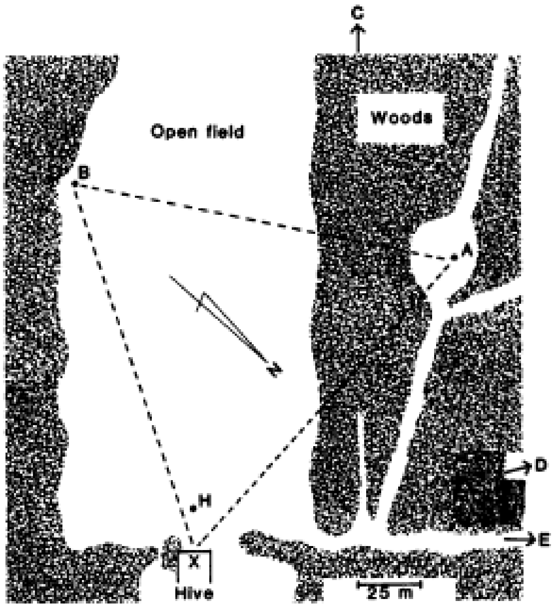

**Figure 2.11:** The experimental area used by Gould (1982). Bees were trained to find a food reward at feeder location A. They were then displaced, from the hive entrance, to location B without access to visual cues and released. Under these conditions, bees were found to fly directly from B to A. Similar results were obtained from a second hive where bees were trained to site B and displaced to site A.

they would be able to fly directly back to their hive and then continue on to their usual feeder location. However, if the bees had a cognitive map of the area, they would be able to fly directly to their usual feeder site utilising what would be a novel route or shortcut. Gould (1982) reports that bees did in fact fly in a heading directly towards their usual feeder location. However, again a number of subsequent experiments failed to replicate Gould's (1982) findings (Dyer, 1991; Wehner & Menzel, 1990). For instance, Menzel et al. (1990) found that bees displaced from their hive to a location along a training route flew in a direction consistent with a compass bearing from their hive to the feeder not in a direction that would actually lead them there; Menzel et al. (1998) similarly found that bees displaced from one feeder location to another flew in the compass direction consistent with the direction of the hive from the first feeder not in the true direction of the hive; Wehner et al. (1990) found that displaced bees could fly in a direction corresponding to their hive or a nearby feeder when displaced from their hive to a training location, however, if the bees were released halfway along a trained route the bees would fly off in random directions seemingly unable to align their PI and landmark information. Together these results suggest that bees may be able to utilise significant landmarks as beacons when navigating open spaces such as those used by Gould (1982), alternatively they can certainly utilise the sun to give them a compass bearing, but this is only useful in combination with their PI system, otherwise they may fly in the correct compass bearing but in a direction that takes them even further away from the nest (Menzel et al., 1998). Given the similarity between the navigation strategies of bees, wasps (Collett & Lehrer, 1993) ants (Nicholson et al., 1999) and spiders (Nørgaard, Gagnon, & Warrant, 2012) and the fact that the most likely insect to require and utilise a cognitive map is probably a social, flying insect like the bee (Frisch, 1967), there seems little evidence that insects possess a cognitive map (Bennett, 1996; Cruse & Wehner, 2011).

However, a number of ethological studies suggest that large animals do utilise a cognitive map for navigation. After observing the hunting, marking and navigational behaviour of wolves in the wild, Peters (1978) concludes that wolves must maintain a cognitive map of their territory. In wooded areas, often masked by snow, the use of beacon strategies seems unlikely for these animals, the complex winding, often unplanned paths the animals take when hunting also makes a PI system unlikely or at least very complex. Nevertheless, wolves have often been observed, after finding a source of food, returning directly to the distant location of their pups in order to feed them. The marking strategies of wolves may provide them with landmarks which they can use to navigate, however, the mechanism with which a wolf may recognise a particular marking site from any other are still unknown. Harrison, Fuller and Proulx (2004) report similar observations in Fishers (*Martes pennanti*), large weasels native to North America. These animals have a home range through which they have been observed taking, novel, direct paths between the nesting sites of prey animals (Powell, 1978), although it can never be certain wild animals are taking novel routes rather than stereotypical routes held in memory for a long period of time (Bennett, 1996). Elephants too have been recorded navigating distances over roughly 100km a month (Leggett, 2011) and frequently visit isolated and distant waterholes during these trips (Viljoen, 1989), however, their large working memory (Bates et al., 2008) may allow them to store a vast library of routes between known locations, this is supported by the fact that much of their navigation takes place in environments devoid of many stable landmarks, certainly landmarks which could be seen over such large distances. It has similarly been suggested that many primates utilise a map based navigation approach when foraging for food; moustached tamarin (*Saguinus mystax*) and brown-mantled tamarin (*Saguinus fuscicollis*) have been observed moving between foraging sites in the South American rainforest. The tamarins do this in such a way as to minimise the distance travelled between trees, even taking into account the timing that particular trees begin to fruit (Garber, 1988; Janson, Terborgh, & Emmons, 1981) leading some researchers to conclude that such a form of spontaneously efficient navigation must be map based (Garber, 1988; Milton, 1981) a conclusion supported by the speed at which these primates can learn to associate visual cues with a food reward (Menzel & Juno, 1982).

As described in the opening paragraphs to this thesis many migratory birds are known to possess remarkable navigational abilities (Thorup et al., 2007) which are supplemented by an impressive use of celestial and geomagnetic cues (Akesson, Morin, Muheim, & Ottosson, 2005) and possibly odour (Holland et al., 2009) allowing them to navigate in both the lateral and longitudinal axes (Chernetsov, Kishkinev, & Mouritsen, 2008). However, after over 50 years of intense research still very little is known about what cues birds actually use, or how they interpret them and use them to navigate (Holland et al., 2009). Blaser et al. (2013) sought to understand the navigation process of birds better, using domesticated pigeons, these birds are useful due to the ease with which they can be trained to navigate to specific areas over great distances. Blaser et al. (2013) trained pigeons to navigate from their home location to a feeding loft 30km away. During testing half of the

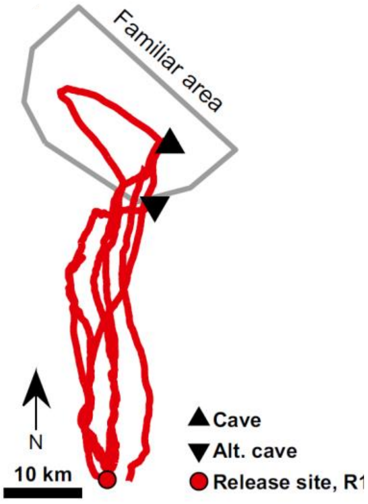

**Figure 2.12:** Overhead view of the paths taken by Egyptian fruit bats (Rousettus aegyptiacus) displaced from their usual territory by more than 40km. Upon being released the bats navigate directly back to their familiar area or resting cave (Tsoar et al., 2011).

pigeons were food deprived, half were well fed and all were released at a site equidistant from their home and food loft. The hungry pigeons were significantly more likely to navigate to the feeding loft, whereas the satiated pigeons navigated back to their home location. These results suggest that rather than just utilising some celestial cue to provide a compass heading and a rough bearing to a single location pigeons may maintain an internal representation of their environment, which they can use to return to specific important locations from novel starting points. Similar results have been found using Egyptian fruit bats (*Rousettus aegyptiacus*) fitted with a high resolution GPS tracking device. These bats forage at night before returning to a particular cave to rest. The bats consistently fly from their cave to a preferred tree night after night, although there are no prominent landmarks, sources of light or unique odour cues which can be used as beacons. Furthermore, when these bats were passively displaced by up to 40km they successfully navigated directly to their cave or preferred feeding site (see Figure 2.12), if they were displaced to an area where landmarks were not clearly visible (such as a deep natural crater 80km away) they were initially disoriented but then navigated directly once they left the crater’s boundary. The use of beacons seems unlikely as the forest environment was largely homologous, the bats could not have used PI information as they were passively displaced to the novel location, the authors conclude that the bats may be using some distant visual cue or odour cues from the ocean, however, utilising these cues to navigate to specific targets from a novel starting position would require a map based knowledge of the area (Tsoar et al., 2011).

These ethological studies provide good evidence for the existence of map based navigation strategies in a number of different species, however, in many of them the familiarity of the subjects with their habitat, the routes they take and their novelty are unknown. For this reason, much of the experimental evidence supporting the existence of a cognitive map can be found in research based on human participants or complex organisms thought to represent a good biological model for human navigation. These studies are usually also conducted under more controlled conditions. Some of the earliest evidence of map based navigation in the laboratory was collected using small rodents; Collett, Cartwright and Smith (1986), for instance, trained gerbils (*Meriones unguiculatus*) to find sunflower seeds in a particular spot on the floor of a black painted room with a single source of light in the centre of the ceiling. An array of landmarks was provided and the food was always found at a particular location relative to one, cylindrical landmark. The gerbils consistently searched at the correct reward location, and when the arrangement of landmarks was rotated they searched in the rotated reward position. Collett, Cartwright and Smith (1986) argue that because the gerbils foraged at a particular site, rather than an ambiguous area surrounding the cylindrical landmark, they must have utilised the array of landmarks to determine the correct direction and distance. This is supported by the finding that the size of the landmark did not influence the gerbils' estimation of distance to the reward, this is in contrast to insects which often use the size and expansion of stimuli over the retina as a cue for distance (Collett & Lehrer, 1993). Furthermore, if the light source was extinguished after the gerbils viewed the room but before they reached the food, they would continue on to the correct location, suggesting that they computed their outbound trajectory before the light was removed.

Morris (1981) was similarly able to show that rats can navigate without access to any local cues. In this classic experiment, rats were placed in a water filled pool (2m in diameter) containing a submerged platform which remained in the same spatial location relative to cues in the room. The water in the pool was made opaque using milk powder and no cues were given inside the pool, the only information available to the rats was that from distal cues surrounding it. Initially the rats, when placed at random starting points in the pool, swim until they find the platform and 'escape'. In further trials the rats take less and less time to swim to the platform, suggesting that they have learned its spatial location. Rats trained in the same way but with a platform which moves randomly around the pool do not show this improvement in performance, confirming that the rats are not able to locate the platform using some uncontrolled cue. Morris (1981) suggests that this task is most likely solved using a map based representation of space, or at least an allothetic navigation strategy; utilising the arrangement of distal cues and the relationships between them to find the platform (Wolbers & Wiener, 2014). In the case of the watermaze this view is now widely accepted (D'Hooge & De Deyn, 2001).

## 2.10 Summary

It is clear from the wealth of ethological and laboratory experiments that the existence of a cognitive map in insects is still, at best, controversial (Bennett, 1996). However, small animals and humans are able to navigate in ways which can only be explained by a map based approach. Many animals in a natural setting display navigation over great distances (Chernetsov et al., 2008), even in the absence of beacons or PI information (Tsoar et al., 2011). In controlled settings animals have been shown to utilise a number of landmarks simultaneously to navigate (Collett et al., 1986), even when distal cues provide the only available information (Morris, 1981). An alternative way to test whether an animal is utilising a map based strategy is to assess its ability to take a novel route or shortcut (Bennett, 1996; Tolman, 1948) but this topic will be covered in greater detail in the chapters supporting Experiment 1.

## 2.11 The Cognitive Map Revitalised

O'Keefe and Nadel (1978) provide a framework for animal navigation based on two contrasting navigation systems; taxon and locale navigation. The taxon system is inflexible due to its basis on a sequence of responses and information derived from internal sources.

The locale system is much more flexible owing to its basis on an internal representation or map, utilising the relationships between different cues and providing an animal with its position relative to these cues in a Euclidean representation of space. Evidence for each of these systems has been discussed, both in insects, where the taxon system appears to dominate navigation and may even be the only form available to them, and larger animals where both systems appear to operate simultaneously and are utilised depending on the information available at the time.

More recent theories surrounding spatial navigation and more specifically, spatial learning, are still built on the foundations provided by O'Keefe and Nadel's (1978) proposal. In many ways these new theories are even still the same dichotomous pairing of S-R and cognitive map that Restle (1957) proposed half a century ago (Evans, 2008). An example of this can be seen in the popular model-free and model-based reinforcement learning (RL) algorithms. These systems were primarily developed in order to improve the rate of machine learning, however, they have also proven useful in explaining, mathematically, many forms of learning observed in animals, including humans. Model-free systems represent a very basic form of learning, an agent, be it an animal or a machine, receives input from a number of sensory modalities, it is also motivated to receive some form of reward or stimulation and may or may not also receive some form of punishment. Using these inputs and motivations a model-free system can be viewed as similar to operant conditioning or S-R learning; a series of actions (or a 'policy') which lead to reward become more likely to be performed, actions which lead to punishment become less likely. This form of learning is relatively slow, especially for machines solving complex problems, for this reason model-based learning algorithms are often considered more valuable. These systems are thought to be more similar to those employed by human beings and can be viewed as an extension of the model-free system rather than an alternative (Fermin, Yoshida, Ito, Yoshimoto, & Doya, 2010; Haith & Krakauer, 2013). In model-based systems, the agent additionally works to build a model of the problem or task it is faced with (Daw, Niv, & Dayan, 2005; Johnson & Redish, 2005; Zilli & Hasselmo, 2008). In a spatial task this model could form a spatial map, but the model need not be spatial in nature, it could also include or be based on task demands, reward contingencies, experimental phases etc., features which Tolman (1948) suggested would also be important aspects of a cognitive map. The benefit of the model-based system is that once this model has begun to form the agent or animal can start to predict the outcome of particular behaviours before executing them, this model can also be retained and applied to other tasks in different environments, increasing the efficiency with which learning can occur in different contexts. Tolman also proposed this same idea when he suggested that animals could apply expectancies, hypotheses and perhaps even cognitive maps to different environments (Tolman, 1948, 1951b). The downside of a model-based system is that it requires greater effort, similarly to O'Keefe and Nadel's (1978) locale system of navigation, inaccurate models can also impair performance, similar to the way in which Tolman and Krechevsky observed rats using incorrect hypotheses when trying to solve a task (Krechevsky, 1932; Tolman, 1948). So we see that the findings and theories proposed by early behaviourists are still relevant today and are still influencing the genesis of new theoretical approaches.

Of course the behavioural aspects of O'Keefe and Nadel's (1978) book represent only a small part of their proposal, they were primarily interested in providing a neurobiological basis for these systems. The discovery of place cells in the hippocampus sparked a revitalisation of cognitive mapping theories. Similarly, the contrast between route and map-based systems sparked a growth of both behavioural and neurophysiological research on the PI systems used by animals to navigate. The physiological basis for these navigation systems will be discussed next.

# Chapter 3

## The Neural Basis of a Cognitive Map

As is clear from the title of O'Keefe and Nadel's (1978) book, *The Hippocampus as a Cognitive Map,* they consider the hippocampus to have an important physiological role in their proposed model of spatial navigation. This proposal was based on the observed effects of lesions and damage to this structure as well as the recent finding, at the time, of cells with spatially localised firing fields in the hippocampus. They also suggest that the structure of the hippocampus is ideally suited to perform the computations which would be necessary for delineating the relationships between spatial cues in an allocentric manner. We will briefly discuss the architecture of the hippocampus and other structures known to support spatial navigation which will be relevant to this thesis. Unless otherwise stated, it should be assumed that the findings reported here refer to the rodent brain, specifically that of the rat.

### 3.1 The Hippocampus

Owing to the ease with which human brains could be obtained, initial physiological and functional observations pertaining to the brain were made in that of the human. The first description of the human hippocampus in particular, was made by Arantius in 1587, who compared the protrusion on the floor of the temporal horn to a hippocampus, or sea horse (Lewis, 1923). Whilst making illustrations of this structure, Duvernoy in 1729 similarly likened it to a seahorse (Lewis, 1923), see Figure 3.1. Later, in 1732 Winslow likened the hippocampus to a ram's horn (Winslow, 1767), sometime after this, ram's horn was transformed to 'cornu Ammonis' after the Egyptian god Ammon (de Croissant de Garengeot, 1742; Lewis, 1923) de Garengeot's cornu Ammonis survives today in the names of four main histological divisions of the hippocampus: CA1, CA2, CA3 and CA4 (a neglected division of the gyrus dentatus). Together these four subdivisions form what is now often referred to as the hippocampus proper. The hippocampal formation, however, includes these regions as well as a number of associated regions; the subiculum, presubiculum, parasubiculum, and entorhinal cortex (Andersen, 2007). For the purposes of this thesis and the sake of simplicity we will refer to the Hippocampus Proper (HPC), Dentate Gyrus (DG), the Subiculum and the Entorhinal Cortex (EC) as distinct regions of interest.

**Figure 3.1:** A dissected lobe of the human hippocampus on the left, a seahorse is shown in the middle and a carving of the Egyptian god Amun or Ammon is shown on the right. The similarity in shape led many early anatomists to name to brain region after the animal, or specifically the Latin name for seahorse, Hippocampus, which itself means "Horse Caterpillar". Alternatively, some anatomists noted the similarity to Ammon's horns, which is where the name for the hippocampal subdivisions, cornu Ammonis, originated.

When dissected longitudinally (in the septal-temporal axis or sagittal plane) it is clear the HPC and EC communicate in a series of unidirectional connections forming a circuit or 'trisynaptic loop' (Andersen, 1975; Swanson, 1977; Witter, 2010). Unidirectional or non-reciprocating connections such as these are unusual in the surrounding cortex (Felleman & Van Essen, 1991) suggesting a specialised role for this synaptic loop. If we start at the EC where much of the neocortical input reaching the HPC starts; cells in the superficial layers II and III (layer I is also a superficial layer but it is mainly fibrous) give rise to axons which project to the granule cells of the DG via a major HPC input known as the perforant path, the DG does not project back to the EC. These granule cells then project to the pyramidal cells of CA2 and CA3 via the mossy fibres system, this projection is again unidirectional. The pyramidal cells of CA3 project on to the pyramidal cells of CA1 via the Schaffer collateral system, a major source of input to the CA1 region which again is not reciprocated. The pyramidal cells of the CA1 subfield project on from here to the subiculum, providing a major excitatory input, which again is unidirectional. The subiculum projects on to the presubiculum and parasubiculum, however, our loop is closed by the projections from cells in both CA1 and the subiculum which lead back to the deep layers (especially layer V) of the EC where information is relayed out of the loop and back to the cortex (Amaral & Witter, 1989; Andersen, 2007; Blackstad, 1956; Canto, Wouterlood, & Witter, 2008; Lorente De Nó, 1934; Witter, 2010). This loop can be clearly seen in Figure 3.2.

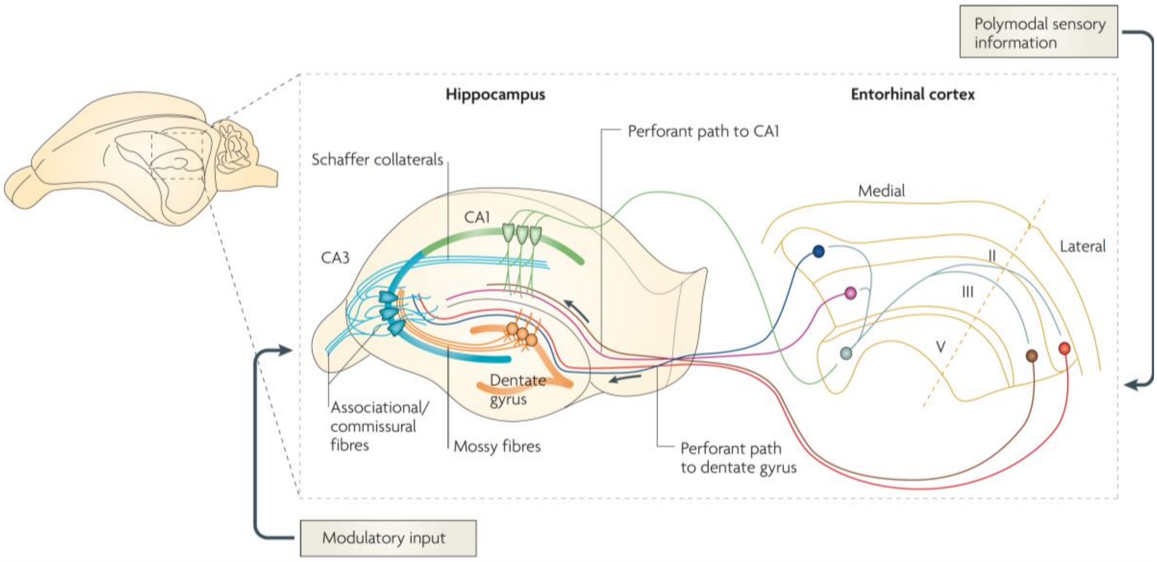

**Figure 3.2:** Diagram showing the circuitry which underlies the communication between the hippocampus and entorhinal cortex. Taken from (Neves, Cooke, & Bliss, 2008), Figure 1.

This brief description of the complex circuitry found in the hippocampus and surrounding brain regions is not intended to be an adequate anatomical survey of the region's properties and function. The HPC is widely researched and detailed descriptions of projections within and around the structure are well documented (Andersen, 2007; Duvernoy, 2005). Rather the nature of the trisynaptic loop and its unusual unidirectional structure is intended to emphasize that the HPC is organised in a unique and instantly recognisable way, even when viewed in the brains of different species.

## 3.2 The Hippocampus and Place Cells

Initial interest in the hippocampus was sparked by the observed impact of hippocampal damage, both accidental and intentional, on behaviour. One of the most influential cases in this respect was that of patient H.M. or Henry Gustav Molaison (Squire, 2009), who suffered from partial and later tonic-clonic epileptic seizures which were found to arise from structures in his medial temporal lobe (Corkin, 2002). As a treatment[8], in 1953 surgeons removed Molaison's hippocampal formation and a number of adjacent structures, including most of the amygdaloid complex and EC (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997; Penfield & Milner, 1958). What was left of his hippocampal tissue appeared atrophic and because the entire EC was destroyed it is unlikely Molaison's hippocampus retained any of its functions. As a treatment for epilepsy the surgery was a success, however, the resulting unusual side effects led to an intense study of Molaison's condition, essentially for the rest of his life and even long after his death. A number of these results came to define much of what cognitive neuroscience is today. After the surgery Molaison was afflicted with massive anterograde amnesia (Scoville & Milner, 1957) for both episodic and semantic memory (Gabrieli, Cohen, & Corkin, 1988) which stayed with him for the rest of his life (Milner, Corkin, & Teuber, 1968). However, his long-term memory was intact and his language skills were largely unaffected (Kensinger, Ullman, & Corkin, 2001), although there is still debate as to whether some of his problems with language were a consequence of the surgery (MacKay, Burke, & Stewart, 1998) or poor education (Schmolck, Kensinger, Corkin, & Squire, 2002). Tests of Molaison's spatial learning provided mixed results, he was able to recognise the floor plan of his house before the surgery (Corkin, 1984), draw a floor plan of the house he was living in after surgery (Corkin, 2002) and navigate easily around the nursing home he eventually lived in, but he was unable to use a physical map to navigate in unfamiliar

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[8] The word 'treatment' is used loosely here; however, the gigantic moral and ethical implications surrounding early experimentation on human subjects by removing not yet fully understood parts of the brain just to see what would happen are not the subject of this thesis.

surroundings (Corkin, 1984). Furthermore, he was impaired on a number of spatial tasks (Corkin, 1979; Morris, 1999; Teuber & Weinstein, 1956) for a review see (Corkin, 1984). A number of cases have shown similar impairments; after a severe case of herpes simplex encephalitis, patient E.P. suffered bilateral damage to his medial temporal lobe including the hippocampus, as a result he suffered extensive anterograde amnesia. He was still able to recall the spatial layout of his neighbourhood before the damage, however, was unable to learn new spatial layouts (Teng & Squire, 1999). Patient K.C. suffered a closed-head injury during a motorcycle accident where he suffered extensive brain damage including loss of volume in the HPC and parahippocampal cortex, with actual damage to the latter structure. Although the loss of hippocampal function was much less in this patient he still suffered from anterograde amnesia and was impaired in a number of spatial aspects; he was unable to recognise some spatial landmarks and features on printed maps although his spatial memory acquired before the accident was intact (Rosenbaum et al., 2000). Patient TT was a London taxi driver who suffered bilateral hippocampal lesions after contracting limbic encephalitis. His hippocampus was extensively damaged, however, the surrounding structures and the rest of his brain appeared to be unaffected. When navigating around a virtual London, he was generally able to navigate without any great difficulty, as he learned the layout of this city as a taxi driver 40 years previously the authors conclude that the hippocampus is not necessary for the retrieval of spatial memory, in agreement with previous research. However, TT did have difficulty when navigating small, less often used roads, suggesting that the HPC may be more heavily involved in retrieving remote spatial memories or representations of greater complexity (Maguire, Nannery, & Spiers, 2006). Recent studies seem to support this distinction between broad and detailed spatial representations (Rosenbaum, Cassidy, & Herdman, 2015; Rosenbaum et al., 2000). Together, these findings implicate the hippocampus as a structure which is crucial for the formation of new memories but not necessarily the storage and retrieval of old ones, this relationship appears to be the same for spatial memories and for information which O'Keefe and Nadel (1978) would consider part of a cognitive map.

Attempts to replicate the impairments observed in human patients with hippocampal damage in animals were initially unsuccessful. Following the important findings arising from the study of H.M.'s condition, the doctor responsible for his surgery repeated the procedure in monkeys, however, the results suggested that these monkeys could complete many tasks H.M. could not (Orbach, Milner, & Rasmussen, 1960). For instance, H.M. showed a significant impairment in delayed recall tasks (Cohen & Squire, 1981; Milner, 1972) however, monkeys with hippocampal damage were seemingly unimpaired (Deutsch, 1983). These disappointing results continued in research on primates (Cordeau & Mahut, 1964; Correll & Scoville, 1967) rats (Isaacson, 1972; Kimble, 1968) and cats (Flynn & Wasman, 1960), see (Deutsch, 1983) for a review. Theories arose to account for these apparent discrepancies, these mainly concentrated on the idea that there may be different kinds of memory, each relying on different brain regions in different ways. Declarative memory consists of knowledge which can be consciously recalled and is divided into episodic memory (for events and autobiographical information) and semantic memory (for factual information)[9]. Contrasting with declarative memory is procedural memory which can be recalled unconsciously and includes memory for learned habits or physical movements and skills (Andersen, 2007; Tulving, Donaldson, Bower, & Research, 1972; Winograd, 1975)[10]. With this knowledge it became much easier to design correctly equivalent tasks for the assessment of deficits in animals. For example, monkeys can learn to solve a visual discrimination task after hundreds of trials, however, this kind of learning is procedural and depends on the basal ganglia, not

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[9] Recent findings suggest that the CA1 subfield of the HPC may not be as heavily involved with declarative memory as the other CA regions and DG, possibly suggesting that CA1 is more involved with spatial memory (Coras et al., 2014).

[10] There is also working or short-term memory which, as the name would suggest, allows for the maintenance and manipulation of transitory information. This information is lost rapidly unless rehearsed continually or passed into long-term memory for storage. Working memory in humans is not dependent on a functioning HPC (Baddeley & Warrington, 1970; Drachman & Arbit, 1966; Jeneson & Squire, 2012; Milner, 1972).

the hippocampus. It was declarative memory that was impaired in H.M., he was unimpaired on procedural tasks and could even learn new ones after his surgery (Milner, 1962). Thus it must be declarative memory that is dependent on the medial temporal lobe. Only later research on numerous patients with damage to various brain regions were able to show that nondeclarative or procedural memory is in fact dependent on structures out with the hippocampus such as the basal ganglia, cerebellum, amygdala and neocortex (Squire, 2009). Eventually, tasks were developed for primates and other non-human species that were specifically sensitive to the kind of memory impairments caused by medial temporal lobe damage (for example, the one-trial, Delayed Non-Match to Sample task or DNMS) and animal models of human memory impairment became more common (Gaffan, 1974; Mishkin, 1978; Mishkin & Delacour, 1975). Researchers now had great interest in the hippocampus, the structure was further implicated in memory, including spatial memory and learning (Abrahams, Pickering, Polkey, & Morris, 1997; Feigenbaum, Polkey, & Morris, 1996; Maguire et al., 1998; Maguire, Frackowiak, & Frith, 1997; Nunn, Graydon, Polkey, & Morris, 1999; Nunn, Polkey, & Morris, 1998; Smith & Milner, 1981) and these effects were now replicable in animal models. Quickly, attention was directed towards the neurons within the HPC and how these cells may be related to the function of the structure as a whole.

When recording single, complex spiking (Fox & Ranck Jr, 1975; Ranck, 1973), pyramidal (Henze et al., 2000) neurons in the rat hippocampus, O'Keefe and Dostrovsky (1971) found that the firing rate of many CA1 cells was modulated by spatial location; although because of the wide number of effects found when the HPC is damaged they were initially unsure how such activity would present itself and so recorded a great number of cells whilst rats performed a variety of behaviours. Through a number of, albeit preliminary, tests they were also able to show that 2 of these cells also appeared to radically change their firing patterns when the surrounding environment was disrupted by removing the curtain surrounding the recording platform. The behaviour of the rats at this point also resembled exploration of a novel environment. Together these results suggested that cells in the HPC fire in specific areas of an environment and that this firing may reflect changes in the animal's surroundings. O'Keefe and Dostrovsky (1971) suggested that these 'place cells' function as the neural basis of a cognitive map, giving the animal an internal representation of specific places, orientation and other sensory features of the environment[11]. Later experiments confirmed the finding of spatially modulated place cells in the rat HPC (Best & Ranck Jr, 1982; Hill, 1978; Hill & Biology, 1979; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe, 1976; O'Keefe & Speakman, 1987; Olton, Branch, & Best, 1978; Olton & Samuelson, 1976; Olton, Walker, & Gage, 1978) and a number of further interesting characteristics were explored.

Place cells recorded as rats explore an environment fire maximally when the rat's head is in one specific region of the environment (see Figure 3.3). This area of high firing rate is known as that place cell's 'place field' (O'Keefe, 1979; O'Keefe & Conway, 1978; O'Keefe & Nadel, 1978), typically, firing outside of the place field is absent. Contrary to O'Keefe and Dostrovsky's (1971) initial report, place cell firing is usually independent of the rat's head

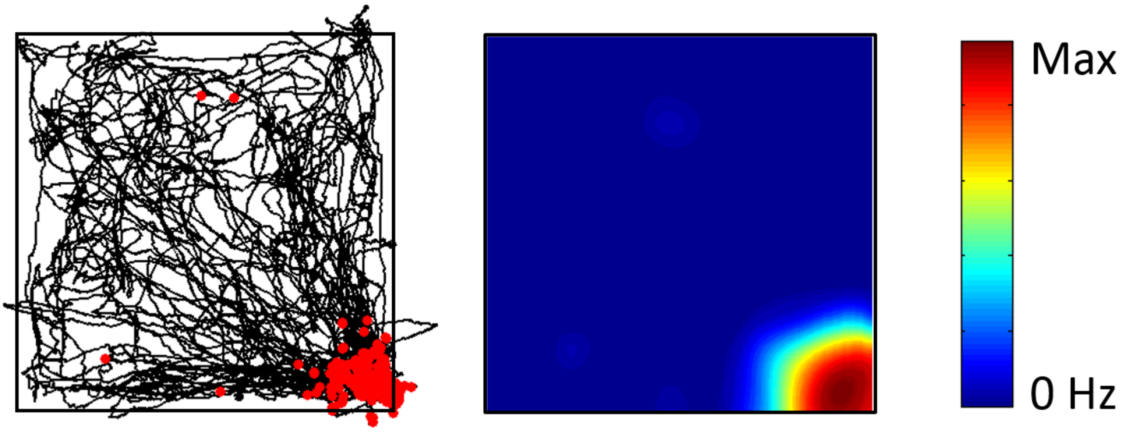

**Figure 3.3:** Plots showing the localised firing of a place cell in a square environment. Left) Cumulative position plot, the black line shows the tracked position of the rat, red dots show the position of each recorded action potential. Right) The same data shown as a firing rate map, the action potentials are binned and divided by binned dwell time to give firing rate (Hz). In these plots red and hot colours represent high firing rate, blue and cold colours represent low or no firing.

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[11] Many of the cells they recorded reportedly responded only when the animal was in a particular location, looking in a particular direction whilst the experimenter delivered tactile stimulation, suggesting an integration of a multitude of sensory modalities. However, such specificity is not commonly seen in modern recording setups where interference and noise are at a minimum and head direction can be recorded automatically and reliably.

direction, making spatial location the best, if not the only determinant of the cell's firing (Poucet, Lenck-Santini, Paz-Villagrán, & Save, 2003). In their 1978 book, O'Keefe and Nadel built much of their theory around these recently discovered cells and it is clear to see why. From their firing it would appear that place cells are encoding some representation of location, or at the very least a spatial component of the surrounding environment. Representations such as these are key to O'Keefe and Nadel's (1978) locale navigation which requires an awareness of allothetic 'location' relative to spatial cues. As research continued, place cells began to look more and more like a potential neural basis for a cognitive map and the finding of place cells in other brain regions implicated in spatial navigation such as the subiculum (Sharp & Green, 1994) and EC (Frank et al., 2000a; Quirk, Muller, Kubie, & Ranck, 1992) strengthened the view of these cells as crucial to spatial processes.

Place cells recorded simultaneously and therefore proximal in the brain, have place fields in different areas of an environment, suggesting that the population of cells as a whole can come to represent the entire surface of an environment (O'Keefe, 1976; Wilson & McNaughton, 1993). Indeed, after an initial period of exploration, the firing properties of this population can be used to accurately predict the location of an animal (Wilson & McNaughton, 1993). Furthermore, once the representation of an environment has formed it is stable across days (Muller, Kubie, & Ranck, 1987) and even weeks (Thompson & Best, 1990) (see Figure 3.4), although this stability is impaired in aged rats (Barnes, Suster, Shen, & McNaughton, 1997) and in rats with damage to their perirhinal cortex (Muir & Bilkey, 2001).

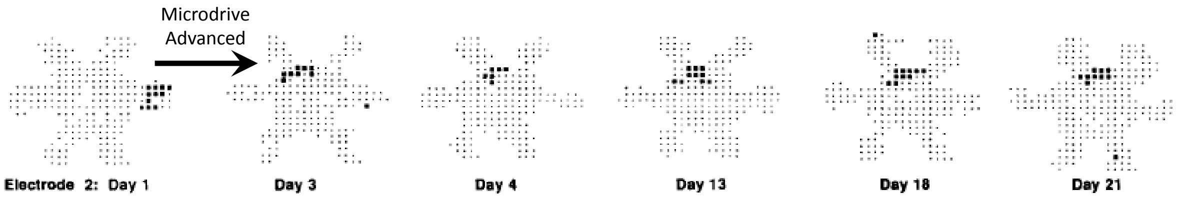

**Figure 3.4:** A place cell recorded in a six arm radial maze (Day 1), the microdrive was then advanced and a new cell discovered with a different firing field (Day 3), this cell was then maintained for a further 18 days. Each day is represented by a firing rate map of the spikes recorded on that day. Areas of high firing rate (3 standard deviations greater than the grand mean firing rate) are shown by black boxes, areas which the rat visited but where the cell fired below this level are shown by grey dots. Taken from (Thompson & Best, 1990), Figure 4.

Evidence suggests that, in rats at least, active exploration and experience of an environment is required before place cells form a representation of that environment – seeing an environment is not sufficient in itself (Rowland, Yanovich, & Kentros, 2011). If the environment is altered or completely novel the cells may completely change their firing relationship and represent this environment in a unique way (O'Keefe & Conway, 1978), this process of place field shifting between different environments is known as place field 'remapping' (Muller & Kubie, 1987) and is also impaired in aged rats (Wilson et al., 2004). Together, these results further support the idea that place cells may underlie spatial navigation and memory; place cells as a population uniquely represent entire environments and these specific representations are recalled whenever the animal encounters the environment in the future, suggesting that the HPC may be involved in the storage and activation of spatial maps in the brain.

Place cells encode even more information relevant to a locale system of navigation; in an environment the location of a place cell's place field is often dictated by the distal cues or landmarks surrounding the environment, if these landmarks are rotated the firing fields of place cells rotate correspondingly (Muller & Kubie, 1987; O'Keefe & Conway, 1978; Yoganarasimha & Knierim, 2005). This interaction between place cell firing and distal cues appears to represent information concerning the relationship between landmarks and the animal's position, a representation which is in agreement with O'Keefe and Nadel's (1978) proposed locale system of navigation and which could underlie a cognitive map. However, it has also been suggested that when local cues are emphasised the firing rates of place cells can come to encode non-spatial cue information or a conjunction of non-spatial and spatial information (Young, Fox, & Eichenbaum, 1994). In an experiment designed to replicate the (Collett et al., 1986) experiment with gerbils, if two landmarks indicate a goal location some place cells fire in specific relation to these salient cues, suggesting that behaviourally relevant stimuli can come to form a spatial reference frame for place cell firing (Gothard, Skaggs, Moore, & McNaughton, 1996). This has been shown in other experiments where place fields shift their firing location relative to a reward (Breese, Hampson, & Deadwyler, 1989) or a moving goal/start box (Gothard, Skaggs, & McNaughton, 1996). When rotating both local and distal cues (double rotation cue conflict) subpopulations of place cells in CA1 may follow either (Knierim, 2002; Shapiro, Tanila, & Eichenbaum, 1997; Yoganarasimha, Yu, & Knierim, 2006) but place cells in CA3 are more likely to follow local cues (Lee, Yoganarasimha, Rao, & Knierim, 2004), this relationship suggests that the visuospatial information from distal cues may enter the HPC via the postsubiculum and medial EC as a head direction signal (Goodridge & Taube, 1997) whereas spatial information from local cues may be interpreted similarly to object information, entering the HPC via the lateral EC (Yoganarasimha et al., 2006). Thus, the factors controlling hippocampal cell activity may be more complex than initially thought.

Regardless of the conflicting evidence surrounding visual cues, it is clear that they are important for the spatial selectivity of place cell firing. When visual and olfactory information is completely absent place fields are unstable, suggesting that place field firing cannot be maintained indefinitely by PI information alone (Save, Nerad, & Poucet, 2000). However, blind rats have similar place fields to sighted rats if proximal cues are provided (Cressant, Muller, & Poucet, 1997; Hill & Best, 1981) suggesting that PI can maintain place cell firing if it is updated frequently. These results suggest that without input from external cues such as proximal or distal landmarks (when an animal must rely on internal cues alone and thus PI) place cells are not able to reliably keep track of an animal's movements, as we saw before, PI is subject to an accumulation of errors and it would appear these errors are inherent in the firing activity of place cells. Findings from human patients with damage to the hippocampus or EC suggest that neither structure is necessary for PI in humans (Kim, Sapiurka, Clark, & Squire, 2013; Shrager, Kirwan, & Squire, 2008) despite findings that hippocampal activity, as measured using fMRI, is related to accurate PI in human participants (Wolbers, Wiener, Mallot, & Buchel, 2007). However, PI is dependent on a functioning HPC in rats (Kim et al., 2013; Maaswinkel, Jarrard, & Whishaw, 1999; Whishaw, Hines, & Wallace, 2001) although the parietal cortex may also play a role (Save, Guazzelli, & Poucet, 2001). One explanation of these contrasting results is that humans may be able to maintain or utilise spatial maps in working memory[12], where animals cannot. Thus, animals with HPC damage and an impaired long term memory may be analogous to an intact human exceeding the capacity of their working memory; they cannot rely on their long term memory because the information is not yet encoded but their working memory cannot hold the data and so it is lost.

## 3.3 Summary

In humans, both episodic and spatial memory are heavily dependent on a functional HPC (Corkin, 1984; Scoville & Milner, 1957). PI in rats is also dependent on the HPC (Save et al., 2000) although this may not be the case in humans (Kim et al., 2013). Cells which show remarkable spatial selectivity in their firing rate have been found in most areas of the HPC (Poucet et al., 2003) with differing characteristics (Maurer, Vanrhoads, Sutherland, Lipa, & McNaughton, 2005), these ‘place cells’ increase their firing rate in different areas of an environment and in different areas of different environments (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). As a neuronal population, these areas of high firing, or ‘place fields’, come to represent the entire surface of an environment (O'Keefe, 1976). The locations of these place fields are fixed relative to distal visual cues (Yoganarasimha & Knierim, 2005), although non-spatial and local cues may take precedence depending on the context (Knierim & Rao, 2003). O’Keefe and Nadel (1978) argue that these cells are the perfect substrate for an internal spatial representation or cognitive map, the features necessary for their locale system of navigation appear to be encoded in place cell firing; the firing of an individual place cell encodes spatial information, as a population place cell firing can come to represent the entire surface of an environment, this representation is stable over time and reflects the relationships between distal cues – all of these are features crucial to O’Keefe

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[12] Human subjects often report ‘seeing’ an internal representation of their environment when asked to perform PI tasks (Kim et al., 2013).

and Nadel's (1978) cognitive map. But as we will see, this system is probably dependent on a number of brain structures each harbouring an equally unique community of spatial cells.

## 3.4 The Entorhinal Cortex and Grid Cells

The EC can be divided into a number of different layers which are further subdivided into superficial (I – III) and deep layers (IV – VI) based on the presence of particular cell types, cell layers or white matter (Canto et al., 2008). The EC can also be divided along the mediolateral axis into the medial entorhinal cortex (mEC) and lateral entorhinal cortex (lEC) based on cytoarchitectonic criteria; these areas also communicate differently with the HPC and surrounding cortical regions (Burwell, 2000; Canto et al., 2008; Fyhn, Molden, Witter, Moser, & Moser, 2004) making this distinction functionally relevant. The EC provides the HPC with sensory information from the cortex both directly (Dickson, Magistretti, Shalinsky, Hamam, & Alonso, 2000; Witter, 1993) and indirectly via the perirhinal and postrhinal cortices (Burwell, 2000). Visuospatial information arising from posterior associational regions such as retrosplenial cortex projects to postrhinal cortex before entering dorsal DG via the mEC and Medial Perforant Path (MPP) (Canto et al., 2008; Dolorfo & Amaral, 1998). Whereas information from anterior associational regions such as the medial frontal cortex projects to the perirhinal cortex before entering the DG via the lEC and Lateral Perforant Path (LPP). These findings in combination with electrophysiological and anatomical results suggest that the function of the lEC and mEC may be dissimilar, despite their physiological similarity, proximal location in the brain and association with the HPC, for a review see (Kerr, Agster, Furtak, & Burwell, 2007; Sewards & Sewards, 2003).

Indeed the effects of damage to the mEC and lEC suggest a functional difference between these two regions. Lesioning the MPP and thus disrupting input to the HPC from the mEC results in spatial learning deficits and place learning impairments in a water maze task, whereas lesioning the LPP does not (Ferbinteanu, Holsinger, & McDonald, 1999). Burwell (2004) found that damage to neither the mEC or lEC impaired the spatial navigation performance of rats in a water maze task, however, damage to either region resulted in contextual discrimination impairments in a fear conditioning task. Hunsaker, Mooy, Swift and Kesner (2007) found that damage to the MPP affected spatial processing in an object exploration task, damage to the LPP affected both spatial and non-spatial processing in the same task. In an extensive series of experiments van Cauter et al., (2013) found that damage to the mEC resulted in spatial deficits in an object exploration and one trial object recognition task when a spatial displacement was introduced, but nonspatial object recognition was unaffected. Damage to the mEC was also accompanied by a mild spatial impairment in a water maze task and a substantial deficit in an assessment of path integration. Damage to the lEC, however, resulted in no spatial impairments, only nonspatial processing in the object exploration task (but not the single trial object recognition task). O'Reilly, Alarcon and Ferbinteanu (2014) found that mEC damage resulted in mild and temporary spatial impairment, similar to those observed after lesioning CA3. Further studies have failed to find any spatial learning deficits after damaging the EC (Galani, Weiss, Cassel, & Kelche, 1998; Hagan, Verheijck, Spigt, & Ruigt, 1992; Pouzet et al., 1999). These results represent a constellation of interactions and contrasting findings, however, the trend appears to implicate the mEC in spatial navigation and the lEC with nonspatial and contextual processing, although these associations may not be entirely confined to either structure. The mixed results from studies interfering with the perforant path as a way to 'disconnect' the mEC or lEC from the HPC also suggest that at this point spatial and non-spatial processing may be mixed, possibly in preparation for the formation of declarative memory in the HPC (Hunsaker et al., 2007; Van Cauter et al., 2013). As with the HPC, many studies seek to understand the function of the EC at the single cell level, this data has shed some light on the function of the EC and the information it may be processing, these studies largely agree that at the single cell level the mEC and lEC appear to satisfy very different functions and that the mEC at least may be heavily implicated in one or both of O'Keefe and Nadel's (1978) navigation systems.

Although early theories, based on physiological evidence, predicted cells in the EC would fire in a spatially modulated grid pattern (Calvin, 1998) early reports suggested that cells in the dorsal mEC were not well spatially modulated. Although they did show location specific firing which was also relatively stable over time (Quirk et al., 1992) this firing was not well localised, at least not in comparison to cells recorded in the HPC. However, evidence suggests that the firing patterns of cells in the HPC are correlated with the location of cells along the dorsal-ventral axis (Maurer et al., 2005), given the close communication between the superficial (dorsal) layers of the EC and CA3 (ventral and septal HPC) and the deep (ventral) layers of the EC with CA1 (dorsal and temporal HPC) (Moser & Moser, 1998) some researchers sought to understand whether a similar relationship would be expressed in the EC. This line of research led to the finding that neurons in the dorsolateral band of the mEC have much more spatially selective firing fields.

Unlike place cells in the HPC, cells in the mEC fire in multiple discrete and regularly spaced locations which form a triangular lattice or tessellated grid (see Figure 3.5). These ‘grid cells’ are found close to the border between the mEC and postrhinal cortex (Fyhn et al., 2004) in the dorsolateral band of the mEC (Hafting et al., 2005). Initial recordings were made in regions of the mEC which were more ventral (Barnes, McNaughton, Mizumori, Leonard, & Lin, 1990; Frank et al., 2000a; Quirk et al., 1992), here the firing of cells is still a grid structure but the spacing between fields is so great that early recording environments were not large enough to reveal the grid structure (Fyhn et al., 2004). Cells even more ventral, in the ventromedial band of the mEC, are largely non-spatially modulated with no visible grid structure to their firing (Fyhn et al., 2004). This relationship mirrors the form of inputs to the different regions; dorsolateral mEC, where grid cells can be found, receives spatial input from the postrhinal cortex and dorsal presubiculum, whereas ventromedial mEC, where grid cells are not as apparent, receives largely non-spatial inputs from the perirhinal cortex (Burwell, 2000). These results suggest that grid cells, like place cells, may be involved in spatial processing and navigation, preparing information before passing it to the HPC, performing an independent function, or both. Subsequent research has identified the existence of grid cells in the presubiculum and parasubiculum (Boccara et al., 2010) both of these structures project to the EC.

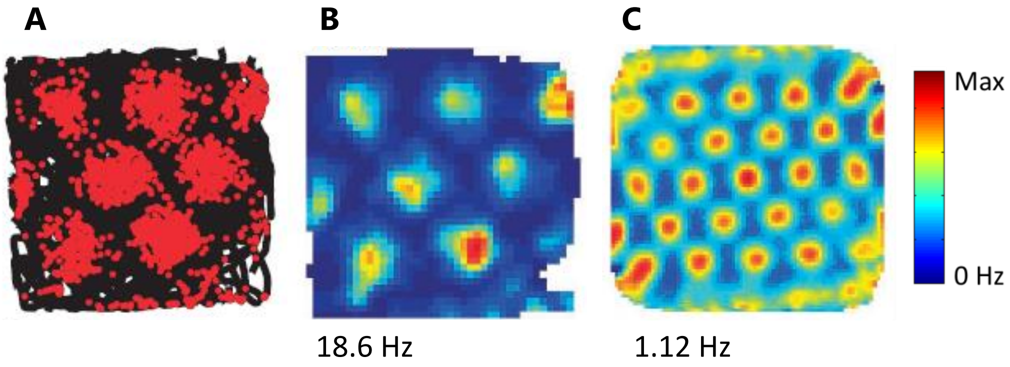

**Figure 3.5:** The periodic firing of a grid cell can be seen in a cumulative position plot (**A**), here black lines show where the rat was tracked as having moved, red dots show each recorded action potential. It can also be seen in a firing rate map (**B**), here position and spike information are binned and divided to give binned firing rate (Hz). A spatial autocorrelogram (**C**) also highlights the periodic nature in the firing rate map, these are produced by correlating the firing rate map with a duplicate of itself, the firing rate map is then shifted in 1 bin increments and the degree of correlation is recalculated after each shift, the red and hot colours represent a high degree of correlation, a peak correlation value always lies in the centre where the two ratemaps overlap perfectly. Taken from (Hafting et al., 2005), Figure 2.

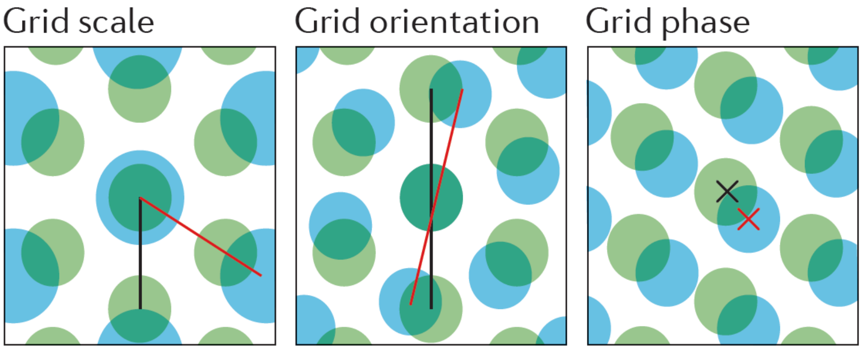

**Figure 3.6:** The different features of a grid cell's firing pattern; two stylised examples using green and blue to represent the firing fields of two different grid cells. Left) The scale, size or spacing of the grid is calculated as the distance between a central field and its neighbours. Middle) The orientation or angle of the grid is calculated as the angle from a vertical axis (usually dictated by the camera tracking the rat's movements) between two opposing fields in a hexagonal tile. Right) Phase or displacement is calculated as the distance between the field of one grid cell and the nearest field of the second. From Figure 1 in (Moser et al., 2014). Also see (Hafting et al., 2005) for a more detailed description of these features.

We have seen that, like place cells, the firing rate of grid cells is heavily spatially modulated, to understand how this information may be useful, how it is transferred between the HPC and EC and how it may ultimately be used to navigate we must explore some of the properties of grid cells. Hafting et al., (2005) report that the firing properties of grid cells are localised within the mEC, that is to say, grid cells recorded simultaneously and thus near to each other in the brain show similar firing properties, as measured using the features of their firing grid (see Figure 3.6). However, the spacing and size of individual firing fields in the dorsal mEC increases as recordings are made more ventrally with the field size increasing in proportion to the spacing. Regardless of recording location the grid phase and orientation of different grid cells is seemingly random, with each firing phase equally represented in local cell populations, suggesting that like place cells in the HPC grid cells as a population probably come to represent the entire surface of an environment (Hafting et al., 2005). Like place cells, the firing of grid cells is dictated by external cues; when distal landmarks are rotated grid cell firing fields rotate by a corresponding angle (see Figure 3.7). If the firing rate map for a rotated session is rotated to counter for the cue rotation it correlates highly with the firing rate map for a non-rotated session, suggesting that the phase and orientation of the grid pattern are indeed dependent on the location of external cues (Hafting et al., 2005). However, unlike place cells, grid cells do not appear to depend on extramaze cues to maintain a stable firing pattern. In complete darkness the grid pattern persists, orientation and spacing are undisturbed, although there is a significant drop in spatial correlation values suggesting that the grid phase may drift slightly in the absence of anchoring visual cues. The finding that grid cells are not as reliant on visual input as place cells, apparently continuing to fire in a perfect grid even in complete darkness, has led many to suggest that grid cells may be involved in the computations underlying path integration (Fuhs & Touretzky, 2006; Hafting et al., 2005; McNaughton et al., 2006). This is further supported by the finding that unlike place fields, the features of grid cell firing are unaffected by the geometric size and layout of an environment (Fyhn, Hafting, Treves, Moser, & Moser, 2005; Hafting et al., 2005). Furthermore, in rats, lesions of the mEC result in PI

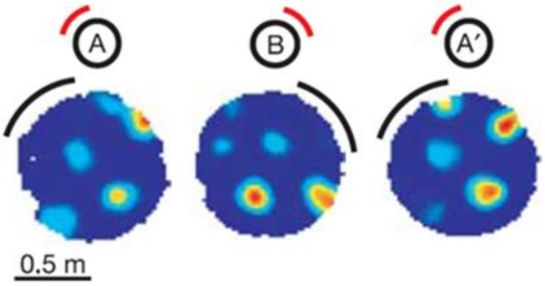

**Figure 3.7:** The firing of a grid cell in response to a rotated cue card. **A**) The cell firing in a grid pattern. **B**) The cell firing is rotated in response to the 90° rotation of the cue card. **A′**) The cell's firing returns to its original pattern when the cue card is returned to its original orientation. From (Hafting, Fyhn, Molden, Moser, & Moser, 2005) Figure 4.

impairments (Van Cauter et al., 2013) directly implicating the structure as one necessary for successful PI. Thus it would appear that grid cells may form the neural basis for PI or the taxon navigation system outlined by O'Keefe and Nadel (1978).

Unlike place cells, in new environments the firing of different grid cells remains coordinated, where the firing of place cells in different environments is orthogonal (statistically unpredictable) after remapping, the grid patterns of grid cells rotate and move together, maintaining a stable relationship between environments (Fyhn et al., 2005). Furthermore, a change in the phase and orientation of grid cell firing is associated with place cell global remapping in the HPC but not rate remapping (Fyhn, Hafting, Treves, Moser, & Moser, 2007) suggesting that rate remapping in the HPC may be mediated by contextual information, possibly from the lEC, which as we discussed above has been implicated in a number of contextual, non-spatial tasks (McNaughton et al., 2006). Indeed, recent research has found a significant drop in HPC rate remapping after damage to the lEC (Lu et al., 2013), leading some to suggest that activity in the lEC gates spatially modulated information from the mEC to the HPC (Hayman & Jeffery, 2008; Lyttle, Gereke, Lin, & Fellous, 2013).

The relationship between the HPC and EC, between place cells and grid cells, is a complex one and due to the relatively recent discovery of grid cells is, at this stage still preliminary. This is compounded by the retrospective back projections between the two regions, making a circuit rather than a straightforward sequence of processes. Popular theoretical models suggest that grid cell firing may be a first step towards the formation of place cell firing, by combining between 10-50 grids of physiologically realistic scales (as are found in different regions of the mEC) it is possible to compute a singular region of excitation or peak as found in HPC place cells (see Figure 3.8 for an example) (de Almeida, Idiart, & Lisman, 2009; Fuhs & Touretzky, 2006; Hayman & Jeffery, 2008; Monaco & Abbott, 2011; Rolls, Stringer, & Elliot, 2006; Savelli & Knierim, 2010; Solstad, Moser, & Einevoll, 2006), although input from lEC may also be necessary (Lyttle et al., 2013; Si & Treves, 2009).

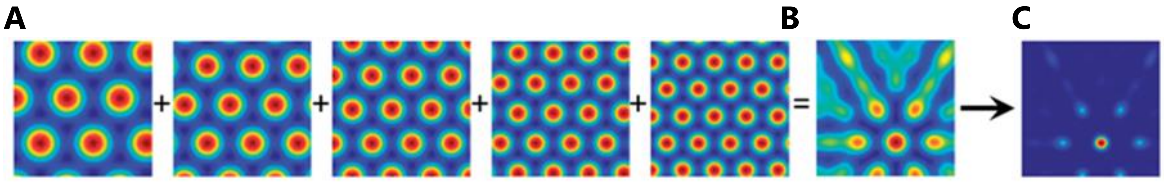

**Figure 3.8:** Showing how a series of firing grids with different scales, such as those of grid cells, can be combined to produce a single dominant firing field, such as those of place cells. A series of grids with differing scales (**A**) are summed to form a hexagonal output with a strong peak and a number of secondary peaks (**B**), this matrix can be filtered using a simple sigmoid modulation to produce an output not dissimilar to the single strong firing fields observed in place fields (**C**). In this final representation there are still weak secondary peaks, although place cells sometimes have multiple firing fields they are not observed to follow this hexagonal shape. However, when computed in the brain this final representation may actually have peaks far enough apart that they have not been observed in the laboratory. The size of the peak in **C** is dictated by the smallest scale of grid in **A**, this dependency could explain why cells in the HPC have different place field sizes depending on their location in the septotemporal axis, as the projections from the mEC to the HPC are also distributed non-linearly along this axis (dorsal mEC cells projecting to septal HPC cells and ventral mEC cells projecting to temporal HPC cells), the scale of grids in the mEC is in turn dependent on the location of the cell in the dorsoventral axis. Figure adapted from (McNaughton, Battaglia, Jensen, Moser, & Moser, 2006) Figure 6.

However, much experimental work has sought to better understand the relationship between the HPC and EC, often observing the impact on neural activity or behaviour after removing one region from the circuit. After inactivation of the HPC using Muscimol, phase precession in the mEC is intact and firing remains spatially modulated on a linear track (Hafting, Fyhn, Bonnevie, Moser, & Moser, 2008), bilateral lesions of the HPC have similarly little effect on the firing fields of grid cells although they become significantly more dependent on the orientation of the animal (Fyhn et al., 2004). A more recent study, however, found that temporary inactivation of the hippocampus with Muscimol, removing the flow of information from the HPC back to the mEC, abolishes the grid firing pattern. Until the effects of the Muscimol are washed out, grid cells lose their periodic firing patterns and their firing instead appears to become predominantly direction dependent (Bonnevie et al., 2013). One explanation could be that the HPC provides information on the contextual and spatial features of an environment, updating the firing of grid cells and correcting any accumulation of path integration errors. However, rather than observing less stable or less finely tuned grids Bonnevie et al., (2013) observed a complete absence of any periodic grid firing, suggesting that the HPC may be providing a more substantial input. Alternative models suggest that the HPC input may represent the significant excitatory drive needed to maintain grid cell firing, without it the only information left includes weak head direction signals from adjacent parahippocampal structures, in the absence of excitatory HPC input these weaker 'background' inputs result in the greater directionality of grid cells in the mEC (Bonnevie et al., 2013). However, the process by which information from place cells may be translated to a periodic grid pattern (if it is indeed grid cells which require place cell firing and not the reverse) is still not well understood. In contrast to inactivation of the HPC, damage to the EC has little effect on the spatial firing of place cells, they still form recognisable place fields, only the control of environmental cues appears to be affected (Van Cauter, Poucet, & Save, 2008) suggesting that the EC may provide the HPC with a stable spatial reference frame.

## 3.5 Summary

The EC plays a crucial role in spatial navigation, this is demonstrated by the finding that damage to the EC results in multiple spatial deficits (O'Reilly et al., 2014) and that spatially modulated 'grid cells' can be found in the mEC (Fyhn et al., 2004). The firing fields of these grid cells are arranged in a grid structure which extends over the entire environment, a number of spatial measures are used to assess the structure of these grids (McNaughton et al., 2006). These have shown that the orientation of a grid is dictated by distal cues but the phase is dictated by local cues such as boundaries (Hafting et al., 2005). This grid pattern of firing persists even when the animal is navigating in darkness and unlike place cell firing it remains relatively stable. This has led many to suggest that the activity of grid cells underlies PI (McNaughton et al., 2006) and is supported by findings that mEC damage results in PI impairments (Van Cauter et al., 2013). Alternatively, some models suggest that grid cell firing may be integrated to produce the single activity patterns observed in place cells (Hayman & Jeffery, 2008), however, damage to the HPC results in catastrophic disruption to the firing of grid cells, the grid pattern is lost and cells respond more strongly to directional information (Bonnevie et al., 2013) suggesting that it is place cell firing which is necessary for the formation of grid patterns. Damage to the EC, however, appears to have little effect on the firing of place cells, although the directional control of distal cues is disrupted (Van Cauter et al., 2008), later findings suggest that damage to the mEC results in spatial navigation impairments, damage to the lEC appears to affect mainly non-spatial processing (Van Cauter et al., 2013). These results suggest that the EC may provide the HPC with a spatial reference frame, supplying information regarding environmental cues, both distal and local, with the mEC responsible for distal cues and the lEC responsible for local and non-spatial cues. Furthermore, in the absence of cues (such as in darkness) the mEC functions as a path integrator, continuing to provide the HPC with a spatial reference frame despite the lack of environmental cues. However, further research is needed to better understand the functions of the mEC and lEC before this conclusion can be formalised.

## 3.6 The Head Direction System and Head Direction (HD) cells

Ranck, Jr. (1984) reported finding cells modulated by heading or direction in the dorsal presubiculum of the rat. Initial experiments in this area only reported finding cells which responded to auditory cues, but these rats were restrained and so spatial activity could not be assessed (Segal & Olds, 1973). However, Jeffrey Taube later confirmed Ranck's (1984) initial report (Taube, Muller, & Ranck Jr, 1987) and continued to head a pair of papers which provided a detailed description of the activity of these cells (Taube, Muller, & Ranck, 1990a, 1990b), which are known as 'head direction' cells. Head Direction (HD) cells fire maximally when an animal's head faces a particular direction in the azimuthal (horizontal) plane, this 'preferred direction' is independent of the animal's current behaviour or position (see Figure 3.9 and Figure 3.10). Different HD cells have different preferred firing directions, equally distributed, such that as a population there does not seem to be an overall preferred direction (Taube et al., 1990a). Like place cells the firing of HD cells has been shown to rely on the position of environmental cues (Goodridge & Taube, 1995; Taube, 1995; Zugaro,

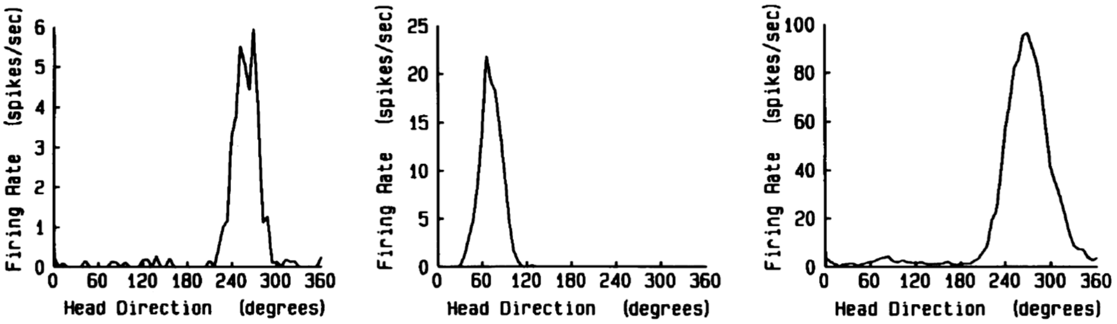

**Figure 3.9:** Showing firing rate plots for three head direction (HD) cells. The angle of the animal's head relative to the environment is shown on the x-axis, the firing rate (Hz) of the cell is shown on the y-axis. The firing rate of each cell peaks at a particular angle and forms a distribution around this value, this angle is known as the HD cell's 'preferred direction'. From (Taube, Muller, & Ranck, 1990a) Figure 3.

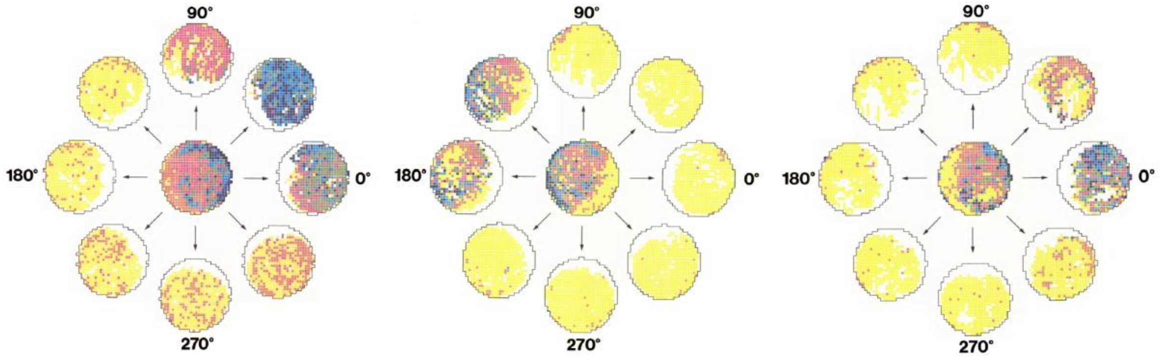

**Figure 3.10:** Showing the preferred firing direction of three HD cells recorded as a rat explored a cylindrical environment. In the centre of each plot is an unedited firing rate map (direction independent), around this are 8 maps filtered to show spike and position data recorded only when the rat was facing within 45° of this direction. From (Taube et al., 1990a) Figure 11.

Tabuchi, & Wiener, 2000) if these cues are stable (Knierim, Kudrimoti, & McNaughton, 1995) but can function based on PI alone (Mizumori & Williams, 1993; Yoder, Clark, Brown, et al., 2011) although the two are probably used in conjunction (Blair & Sharp, 1996). As with place cells, if distal cues are rotated or if the animal is moved between environments the preferred firing direction of all HD cells realign or rotate similarly (Skaggs et al., 1995) and the place fields of simultaneously recorded place cells also rotate in agreement or remap (Knierim et al., 1995). As in the experiments described above for assessing animals' internal representation of orientation, if an animal is rotated in the dark above the threshold for vestibular perception HD cells maintain their preferred firing directions, but if the rotations are imperceptible to the vestibular system the HD system can be slowly rotated out of place (Blair & Sharp, 1996), as we saw before, rotations at such a low speed also result in rotational navigation errors. These results suggest that the HD system may be receiving information from the vestibular system.

The influence of the vestibular system was elucidated relatively easily and as we saw above, evidence suggested a role of the vestibular system even before HD cells were known to exist. However, the connection between the HD and vestibular systems is still not entirely clear, it is better understood mainly because researchers searched backwards along the circuit basing their predictions on anatomical information. Head direction cells are found in a comparatively greater number of brain regions than grid cells and place cells. Ranck (1984) initially reported finding HD cells in the presubiculum, a structure which receives projections from a number of brain regions including the HPC, especially region CA1 (van Groen & Wyss, 1990) and projects to the EC, especially layers I and III of the mEC[13] (Caballero-Bleda & Witter, 1994; van Groen & Wyss, 1990), thus making it well situated as a spatial structure. Taube et al. (1990a, 1990b; 1987) reported finding HD cells in the Postsubiculum (PoS), a structure which projects largely to the mEC (van Haeften, Wouterlood, Jorritsma-Byham, & Witter, 1997) and receives large input from the Anterior Thalamic Nuclei (ATN) (Niimi, 1978; Wright, Erichsen, Vann, O'Mara, & Aggleton, 2010) a brain region

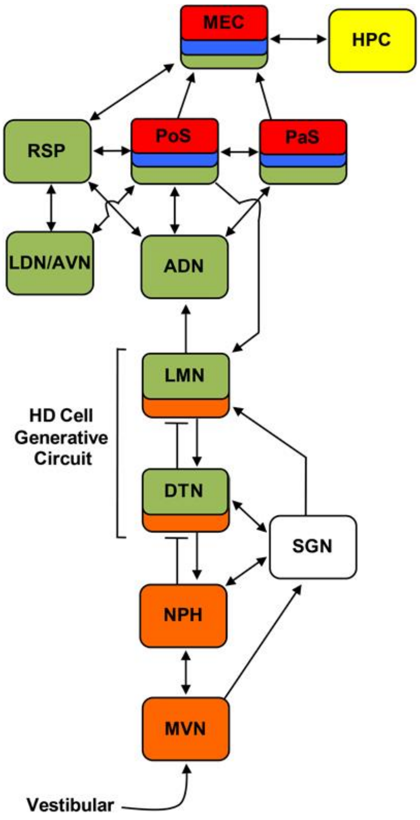

**Figure 3.11:** A simplified view of the head direction circuit. Colours signify the existence of particular cells, yellow (place cells), red (grid cells), blue (border cells), green (HD cells) and orange (angular velocity cells). Vestibular and angular information enters the dorsal tegmental nuclei (DTN) from the nucleus prepositus hypoglossi (NPH) and medial vestibular nuclei (MVN), it then enters the lateral mammillary nuclei (LMN) and then the anterodorsal thalamus (ADN) where it enters the medial entorhinal cortex (MEC) and laterodorsal nuclei (LDN) via the retrosplenial cortex (RSP), postsubiculum (PoS) and parasubiculum (PaS) before entering the hippocampus (HPC). From (Clark & Taube, 2012) Figure 2.

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[13] With parasubicular neurons projecting mostly to layer II.

which also contains HD cells (Blair & Sharp, 1995; Taube, 1995). The ATN in turn receives projections from the Retrosplenial Cortex (RSP) and large projections from the mammillary bodies via the Mammillothalamic Tract (MMT)(Wright et al., 2010), HD cells have been found in the RSP (Chen, Lin, Green, Barnes, & McNaughton, 1994; Chen, Lin, Barnes, & McNaughton, 1994) and Lateral Mammillary Nuclei (LMN)(Blair, Cho, & Sharp, 1998; Stackman & Taube, 1998). The LMN in turn receive projections from the Dorsal Tegmental Nuclei (DTN)(Clark & Taube, 2012) where HD cells are also found (Sharp, Tinkelman, & Cho, 2001). In both the LMN and DTN, with HD cells there are also neurons which are sensitive to angular velocity (Sharp et al., 2001) – this information is thought to be the antecedent to the head direction signal and can also be found in the nucleus prepositus hypoglossi and medial vestibular nuclei (Clark & Taube, 2012), visual information is also thought to enter the HD system via a number of possible pathways early on in the circuit (Yoder, Clark, & Taube, 2011). The arrangement of these brain regions and the propagation of this HD signal through the brain can be seen more clearly in Figure 3.11 and is supported by a series of comparative experiments (Bassett, Tullman, & Taube, 2007; Blair et al., 1998; Blair, Cho, & Sharp, 1999; Clark, Bassett, Wang, & Taube, 2010; Clark & Taube, 2011; Goodridge & Taube, 1997). Head direction cells have been reported in a number of downstream brain regions, most notably the striatum (Ragozzino, Leutgeb, & Mizumori, 2001; Wiener, 1993) and mEC (Giocomo et al., 2014; Witter & Moser, 2006).

Lesions of the PoS disrupt HD cell activity in the ADN (Goodridge & Taube, 1997) and LMN (Yoder & Taube, 2011), the PoS receives large input from the visual system, suggesting that this may be the point where HD cell firing becomes modulated by visual cues. ADN lesions do not effect place cell firing in the HPC, however, after PoS lesions place fields are less stable, suggesting that without this input from the HD system to the HPC via the mEC hippocampal representations may be more prone to PI error, or other errors attributable to an inability to internally represent HD (Calton et al., 2003). Alternatively, without HD information the mEC may be less able to provide the HPC with a stable reference frame, resulting in place field 'drift'. This conclusion is supported by the finding that mEC lesions result in largely the same effects (Brun et al.; Van Cauter et al., 2008), although the presence of HD cells in the mEC (Giocomo et al., 2014; Witter & Moser, 2006) means that disruption to the HD signal may also be responsible. Advanced techniques for inactivating either grid or HD cells in the mEC, but not both, will be needed to disambiguate the HD contribution to place cell firing.

It is not entirely clear where the HD signal originates or how; experimental and anatomical evidence strongly implicates the vestibular system. Indeed a number of models have been proposed which suggest that head direction may be calculated based on vestibular and directional information, this may also utilise distal cues in order to update itself (McNaughton, Chen, & Markus, 1991). One such model proposed by Skaggs et al. (1995; 1993) suggests that a network of head direction cells held in a stable state by a series of recurrent excitatory and inhibitory connections can account for the HD cell preferred firing directions. This model can be visualised in Figure 3.12. Head direction cells are shown as an outer ring, these cells have strong excitatory connections with neighbouring HD cells and strong inhibitory connections with distant HD cells; all of these connections are stronger than ones from outside the ring. This setup will give the HD cell network a resting state where a number of localised HD cells are active while the rest are suppressed. As the direction of the rat and its head change so do the inputs from 'rotation' cells (vestibular neurons or subsystems which have access to proprioceptive, or similarly basic perceptual information) and 'visual' cells (cells, systems or processes involved in processing or relaying visual information relating to environmental cues). Although these inputs have a weak effect on the network they are large enough to destabilise the resting state and cause the location of maximal excitation, or activity 'bump', to rotate around the HD cell ring, thus leading to different HD cells being active only when the animal is facing a specific direction. Similar attractor type models have since been proposed (McNaughton et al., 2006; Redish, Elga, & Touretzky, 1996), these are all based on the same excitatory and inhibitory connections between HD cells and even arrange the HD cells in a ring as shown in Figure 3.12 (Clark & Taube, 2012).

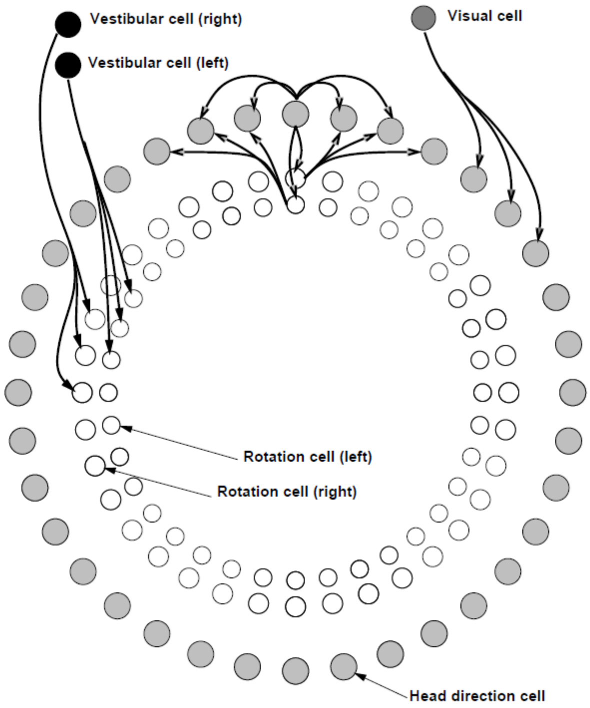

**Figure 3.12:** Head direction network model. The circles here represent cells of various types, although some are arranged in a ring this may not (and is probably not) the actual architecture of the cells in the brain. From (Skaggs, Knierim, Kudrimoti, & McNaughton, 1995) Figure 3.

## 3.7 Summary

Head direction cells can be found in a number of brain regions including the postsubiculum (Taube et al., 1987) and mEC (Witter & Moser, 2006), these cells fire maximally when an animal's head faces a particular direction in the horizontal plane (Ranck Jr, 1984). It is clear that the HD system provides animals with an internal representation, or 'sense' of direction. The compass-like firing of individual neurons provides clear directional information and the firing of HD cells appears to be modulated by little else (Taube et al., 1990a, 1990b). Thus it is likely they encode an animal's perceived directional heading with respect to its environment (Clark & Taube, 2012; Taube, 2007). This information appears to be important in downstream structures such as the mEC, where there are many HD cells and grid cells can be conjunctively modulated by head direction (Sargolini et al., 2006). In the

HPC the firing of place cells can similarly be influenced by head direction (Muller, Bostock, Taube, & Kubie, 1994). Disruption to the HD signal through damage to the postsubiculum causes instability in HPC place fields (Calton et al., 2003) and spatial deficits (Bett, Wood, & Dudchenko, 2012; Taube, Kesslak, & Cotman, 1992), disruption to the HD signal is also associated with an inability to navigate allocentrically (Gibson, Butler, & Taube, 2013). These effects are probably because the mEC is less able to provide a stable reference frame without cue-landmark, HD information.

## 3.8 Boundary Vector Cells

Early observations demonstrated that HPC place cell firing often appears to be determined, at least partly, by the geometric constraints of an environment. By elongating a square environment into a rectangle, place fields which were previously small and round can be seen to stretch in proportion to the walls, becoming long and distended (O'Keefe & Burgess, 1996). This led a number of researchers to formulate a model of place cell firing which employed a class of cells known as Boundary Vector Cells (BVCs), these cells would fire in relation to environmental boundaries and place cell firing would arise as a result of a threshold sum activity of a subpopulation of these BVCs (Barry et al., 2006; Burgess, Donnett, Jeffery, & O'Keefe, 1997; Hartley, Burgess, Lever, Cacucci, & O'Keefe, 2000). Since these models were introduced, cells which behave in the same way as the hypothesised BVCs (also known as border cells) have been found in a number of brain regions including the subiculum (Barry et al., 2006), presubiculum, parasubiculum (Boccara et al., 2010) and mEC (Bjerknes, Moser, & Moser, 2014; Solstad, Boccara, Kropff, Moser, & Moser, 2008). In both the models and reality these cells have a preferred firing direction, much like HD cells, but instead of firing maximally when the animal's head is facing this direction a BVC will fire when the animal encounters an environmental boundary in that direction from the animal (see Figure 3.13). This firing is driven by the memory of the boundary's position relative to the animal, based on PI information and not simply by perceptual cues such as stimulation

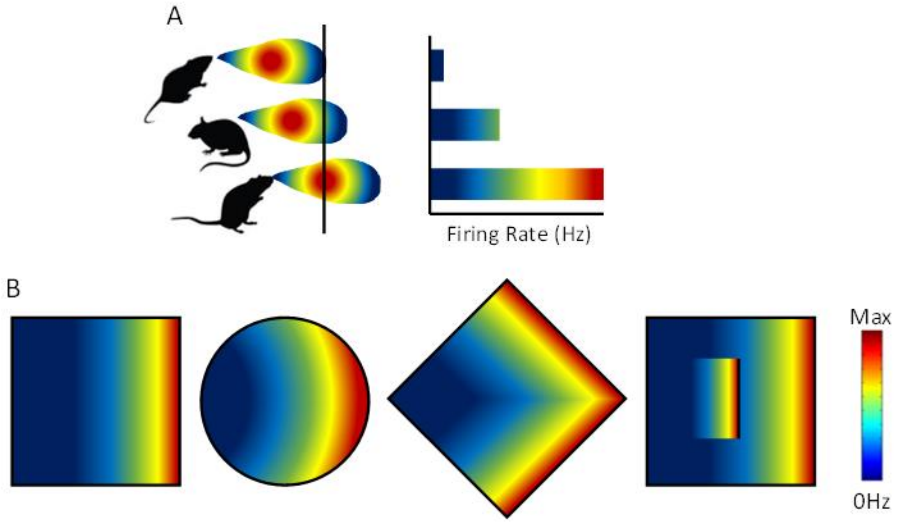

**Figure 3.13:** Showing the response, in firing rate, of a single BVC to environmental boundaries. **A**) as the animal moves near to the boundary the cell's firing rate changes such that at a particular distance from this boundary (and any others along the same dimension) the cell fires maximally. This firing is independent of the animals head direction or behaviour. **B**) The response of this BVC to different environments, it is clear that the cell fires maximally along the east wall of all of the environments. The last example shows that BVCs will fire maximally for all boundaries which meet this directional criteria. Figure adapted from (Lever, Burton, Jeewajee, O'Keefe, & Burgess, 2009) Figure 1.

of the whiskers, although visual information such as optic flow may be involved (Raudies & Hasselmo, 2012). This consistent firing is observed in every environment in which the cell is observed, if the animal's sense of direction remains the same in each (for instance if each environment is placed in the same curtain enclosure with the same distal cue card), although the preferred firing direction of BVCs is much more resilient to changes in the environment than place cell firing (Lever et al., 2009; Sharp, 1997). Environmental boundaries which can drive BVC firing in this way may be walls, low ridges or vertical drops and the colour, texture or odour of these does not seem to influence the cell's firing (Lever et al., 2009). The proposition that place cell firing may be the result of BVC input rather than that of grid cells (as we saw earlier there are models for deriving place fields from multiple grid patterns of different scales) has gained recent support. At 2.5 weeks of age, rat pups already have an internal representation of their environment in the form of stable place fields and a fully functional HD signal, however, at this age grid cells have still not fully developed their hexagonal grid pattern of firing (Bjerknes et al., 2014; Langston et al., 2010) and don't for another half week (Wills, Barry, & Cacucci, 2012). This evidence, in conjunction with a number of flaws in the grid cell model suggests that their input may not be driving place cell firing. However, before 2.5 weeks of age BVCs in the mEC are fully developed and their firing is stable (Bjerknes et al., 2014). This finding, in conjunction with the accuracy with which a number of BVC models can account for and even predict place cell firing in multiple environments suggests that BVCs may, at the very least, play a pivotal role in the formation and maintenance of HPC spatial representations.

## 3.9 The Neural Basis of the Cognitive Map?

We have seen in the preceding chapter that place cells are not the only spatially modulated cells in the brain, furthermore, many brain regions outside of the HPC appear to be involved in different aspects of spatial navigation. Retrospectively, the information which O'Keefe and Nadel (1978) outlined as important for their navigation systems is well represented in the brain; a taxon system of navigation requires a representation of distance and direction, both of which can be provided by HD and grid cells. Indeed a number of models exist which suggest that the HD system could easily perform the computations necessary for angular PI (Islam & Fukuzaki, 2010; Kubie & Fenton, 2009; McNaughton et al., 2006; Redish et al., 1996; Walters, Stringer, & Rolls, 2013) and experimental evidence to suggest that the two are closely linked (Golob & Taube, 1999; Valerio & Taube, 2012), similarly models have been proposed which implicate grid cells as the neural basis for PI (Burak & Fiete, 2009; Fuhs & Touretzky, 2006; Guanella & Verschure, 2006), and some models implicate all of the structures and cell types (Samu, Eros, Ujfalussy, & Kiss, 2009). In any case, the activity of place cells in the HPC appears to reflect the output of a PI system, wherever that may be (Barry & Burgess, 2014). A locale system of navigation, however, requires an internal representation of allothetic location, relative to environmental cues, such as landmarks; this information appears to be combined in the HPC and represented in the firing of place cells (Barry et al., 2006; O'Keefe & Nadel, 1978). Place cells, as O'Keefe and Nadel (1978) outlined, do appear to form a good neural basis for a cognitive map, as a population they are able to represent entire environments and this representation is stable over time. However, as we have seen, place cells do not operate in a vacuum; the activity of place cells is dictated by the activity of entorhinal grid cells and the HD signal perpetuated by the HD system. Boundary Vector Cells may also play an important role in both the formation of these HPC representations and in stabilising entorhinal representations. In current research, the strict, hippocampus centred spatial cognitive map proposed by O'Keefe and Nadel (1978) has been replaced with a more general cognitive map, more like the one originally proposed by Tolman (1948), this contains spatial, contextual and non-spatial information and resides in multiple brain regions (but still with the HPC at the centre). As we will see in future chapters, task demands and context play an important role in the formation of representations, or cognitive maps, in the HPC.

# Experiments

## Experiment 1

### Cognitive maps and spatial inference in animals

Published as Experiment 3 in:

> Grieves and Dudchenko (2013) Cognitive maps and spatial inference in animals: rats fail to take a novel shortcut, but can take a previously experienced one. *Learning and Motivation*, (44: 81-92).

### 4.1 Abstract

Rats ($N = 12$) were trained in a maze where they navigated from a central platform to a reward via an intermediate platform. Before training, half of the rats experienced this environment with a shortcut route available to use (pre-exposure group) the other half experienced the maze with this route present, but inaccessible (non-exposure group). During this exposure period no food rewards were present. After this exposure period the shortcut routes were left in place but made inaccessible, the rats then completed 11 training sessions. A probe test was then conducted in which the training route was made inaccessible and the shortcut route was reopened along with a previously open but unrewarded route and an equally novel one. We found that the rats given pre-exposure to the shortcut took this route significantly more than any other (70% of the time), the rats which were not given pre-exposure did not choose this route more than the others (17% of the time). These results, taken with previous experiments conducted in our lab (Grieves & Dudchenko, 2013) suggest that rats are unable to make a truly novel spatial inference and thus take a shortcut. However, rats are more likely to take a shortcut if they have experienced it in the past, even if it was not associated with a reward at that point.

## 4.2 Introduction

A central assumption in spatial cognition is that, with experience, animals build an internal representation, or map, of the outside environment that can be used for navigation (O'Keefe & Nadel, 1978; Tolman, 1948). One way of testing whether an organism uses this 'cognitive map' is to see whether it can take a novel shortcut between two spatial locations (Bennett, 1996; Singer, Abroms, & Zentall, 2006). The evidence for this ability, however, is mixed. One of the first attempts to show that rats were capable of making spatial inferences about their environments was conducted by Tolman, Ritchie and Kalish (1946a). They trained rats on an indirect route to a reward spatial location. They then blocked the maze's original route and replaced it with 18 alternative alleyways in a semi-circular formation. Tolman et al. (1946a) found that rats under these conditions were significantly more likely to choose the alleyway leading directly to where the food reward was previously located. This result led Tolman (1948) to suggest that the rats had formed;

> *"not merely a strip map to the effect that the original specifically trained-on path let to food but, rather, a wider comprehensive map to the effect that the food was located in such and such a direction in the room"* (p. 204).

Other experiments have provided mixed results, however. For example, Singer et al. (2006) found that rats failed to take a shortcut to a reinforced location in an enclosed maze with plain walls. However, in a different group of rats trained with distinctive maze walls, preference for a short-cut was found. In the water maze, Benhamou (1996) found that rats failed to find the submerged platform from a novel maze entry point, though evidence for this was found in a more open water maze environment (Eichenbaum, Stewart, & Morris, 1990).

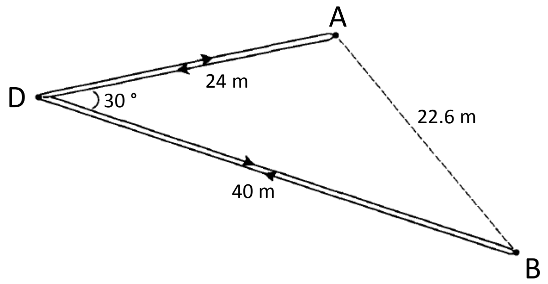

Figure 4.1: The setup used by Chapuis and Varlet (1987). Dogs start at position D, they are led to position A where they are shown a hidden piece of meat, they are then led to position B via position D where they are shown a second hidden piece of meat. The aim is to assess whether the dogs, when free to collect the food rewards, follow this same path or take a novel shortcut between A and B.

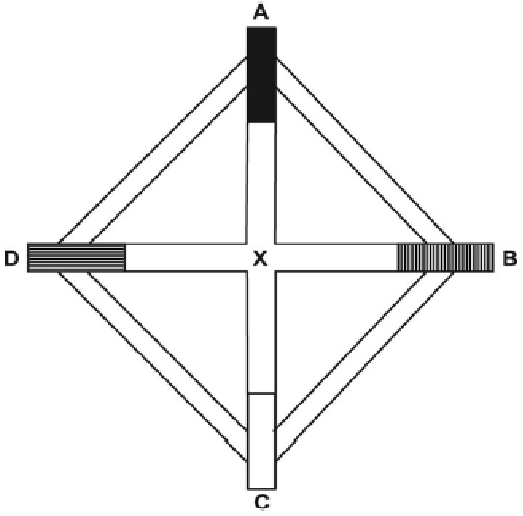

Figure 4.2: The maze used by Roberts, Cruz and Tremblay (2007). A-D refer to tactually distinctive reward or start locations, these are connected by alleyways which cross at point X, as well as diagonal alleyways connecting pairs of boxes.

The capacity for spatial inferences has also been assessed in other animals. Chapuis and Varlet (1987), for instance, tested the shortcutting ability of Alsatian dogs in an open meadow environment (see Figure 4.1). They led dogs from a starting position to the location of a food reward, then back to the starting position and then to a second food reward. On a subsequent test, dogs released from the starting position navigated to the nearest food and then straight to the second food location, without returning to the starting position. This novel short-cut between the two separately experienced reward locations suggests that the dogs had formed an overall representation of the environment. One criticism of these and other demonstrations of cognitive mapping (Chapuis, Durup, & Thinus-Blanc, 1987; Gould, 1986b; Tolman et al., 1946a) is that animals may solve the tasks by simply approaching familiar cues that are near the food location (Bennett, 1996).

In the Tolman et al. (1946a) experiment, for example, rats may have selected the short-cut alley because it led to a light near the goal location. Tolman argued that the light was an important orienting cue for the rats and did not consider that they may have used it as a navigational beacon. However, to investigate this critique, Roberts, Cruz and Tremblay (2007) tested rats in an enclosed plus-maze (see Figure 4.2). The maze had distinctive goal boxes at the end of each arm, and these were separated from the alleyways by curtains. In one experiment, rats were trained to find food in a single goal box for 30 days. They were then given a short-cut test, where the original alleyway was closed and two new, diagonal alleyways between the goal boxes were made available. The rats started from a goal box adjacent to the reinforced box, and one of these alleyways thus led directly to the reinforced goal box, while the other led to a box that had never been reinforced. In the first two trials on this test, rats did not choose the shortcut route significantly more than the alternative route. On subsequent test trials this shortcut route was preferred. This pattern of results raises the possibility that the use of the shortcut route required experience with that route (particularly as the rat was permitted to correct itself if an error was made), rather than reflecting a truly novel spatial inference.

In an attempt to address this ambiguity, we revisited this issue using an approach that had been previously developed by Hazen, Lockman, and Pick (1978) for assessing spatial inferences in children. They led children through a series of 4 or 6 specially constructed rooms, arranged in a 2 × 2 or 3 × 2 configuration, respectively (see Figure 4.3). Each room contained 4 doors, and was made distinguishable by a distinct toy placed in its centre. The children repeatedly experienced the same route through the rooms (e.g., room A > B > C > D) until they could correctly anticipate the toy in the next room. In the spatial inference test, the children were asked to identify the toy in an adjacent room through a door that had never been entered. For example, while the child was in room A, he would be asked about the toy in the adjacent room D. Hazen et al. (1978) found that the capacity to make such a spatial inference

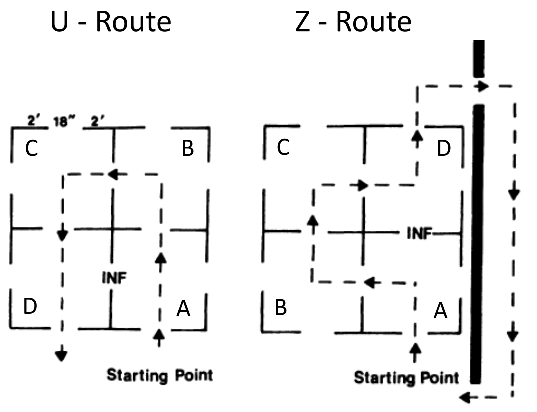

**Figure 4.3:** The 4 room maze used by Hazen, Lockman and Pick (1978). Children are led from the starting point through the rooms (A-D) each of which contains a distinctive toy. This path is either U-shaped (left) or zig-zag (right). INF marks the wall through which children are required to make a spatial inference – they are asked which room/toy would be found on the other side of the wall. For older children, a 6 room version of the same task was used.

appeared to improve with age and that the oldest children tested, 6-year-olds, made correct spatial inferences approximately 80% of the time in the 6-room maze. They also found that children under four years of age use a predominantly 'route like' motor program of navigation, possibly because they were unable to infer the locations of specific landmarks. In our experiments, using a similar apparatus designed for rats (Grieves & Dudchenko, 2013), we found that these animals were unable to make a spatial inference in a four compartment maze; when the training route (A > B > C > D) was blocked, rats were not more likely to take the direct doorway from A to D, suggesting that they were unaware of this shortcut and thus the overall layout of the maze. These results suggest that the capacity of rats to make a spatial inference is less than that of four year old children.

In subsequent experiments, we found that rats also failed to take a shortcut to a goal location in a three-platform maze even when intramaze cues were minimized and extramaze cues were made more conspicuous. One possibility, suggested by the results of Roberts et al. (2007) and earlier by Maier (1932), is that the rats require exposure to a shortcut route before it can be chosen. Maier (1932) allowed rats to explore a three-platform environment without any reinforcement. After a period of this training, the animals were then placed on one of the platforms with a food reward. When subsequently placed on one of the unreinforced platforms, Maier (1932) found that the rats could integrate these two experiences and navigate to the platform where they were rewarded. To test whether exposure to a shortcut route is necessary for its use, we conducted an additional experiment in which one group of rats received pre-exposure to a shortcut route, and a second group did not.

We trained 12 rats (6 per group) to navigate through a series of alleyways and platforms, arranged symmetrically so that rats would be rewarded only for moving through the maze in one direction. Before this training, one group of rats was allowed to feely explore the maze while a potential shortcut route was available (but no food rewards were present), the other group freely explored the maze but with these routes blocked by transparent barriers. The aim of this experiment was to clarify what conditions are required for rats to utilise shortcuts in their surroundings. Our previous findings (Grieves & Dudchenko, 2013) suggest that rats are unable to spontaneously utilise a shortcut route, thus we would expect that the rats not allowed to explore the shortcut before training would not utilise this route at an above chance level. However, it is possible that when given free exploration of the shortcut route before training rats are able to utilise it at a future date, this possibility was assessed using a second group of rats which were given exactly this kind of pre-exposure.

We found that after 11 training sessions where the shortcut routes were closed to all rats, the rats pre-exposed to the shortcut chose this route significantly more than 2 equivalent routes. However, as expected, the other group which received no pre-exposure, chose between these 3 routes equally. After these probe sessions, we then opened the shortcut routes and carried out a short period of training. The rats pre-exposed to the shortcut were also found to begin using this route significantly faster than the rats who did not receive any pre-exposure. These results suggest that rats are not able to make a truly novel spatial inference, but are able to utilise previously unrewarded routes to gain access to a food source. Furthermore, this experiment addressed potential issues in the previous experiments (Grieves & Dudchenko, 2013) and thus builds on the results reported there.

## 4.3 Methods

### 4.3.1 Subjects

Twelve male Lister–Hooded rats (Rattus Norvegicus, 250-300g) were the subjects of the present experiment. The rats were housed in three groups of four and kept on a 12 hour light/dark cycle. Training and testing were always performed during the light phase of this cycle. The rats were kept on a food restricted diet sufficient to maintain 90% (and no less than 85%) of their free-feeding weight. The rats' tails were marked with an ink marker, allowing each of the animals to be visually identified. Testing was usually performed 5 days a week during the usual working weekdays. In this experiment compliance was ensured with national [Animals (Scientific Procedures) Act, 1986] and international [European Communities Council Directive of November 24, 1986 (86/609/EEC)] legislation governing the maintenance of laboratory animals and their use in scientific experiments. Experiments underwent further ethical and procedural approval by the Named Veterinary Surgeon and Named Animal Care and Welfare Officer responsible for overseeing experiments in the host laboratory.

### 4.3.2 Apparatus

The room used for this experiment contained no deliberate extramaze or intramaze cues but did have features (such as lights or walls) which could aid navigation. Obvious landmarks were covered with white cotton sheets which, when combined with the white walls, created a largely homogenous environment. The maze used in this experiment consisted of open platforms. No effort was made to obstruct the rats' views of the other platforms or any potential extramaze cues in the room. Open-top alleyways connected the

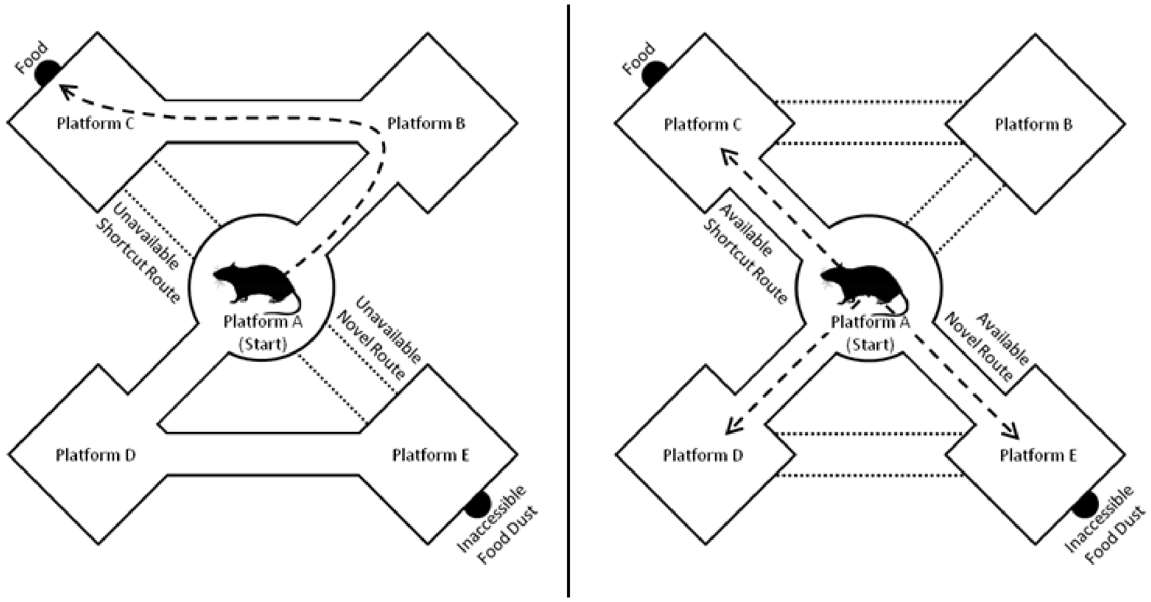

**Figure 4.4:** Showing the layout of the shortcutting maze for the half of the rats rewarded on Platform C. The rest of the rats were trained identically, their configurations, however, were symmetrically opposite to those shown here. Left) the configuration of the maze during regular training trials. Right) the configuration of the maze during probe trials. In both configurations unavailable routes were still present but blocked at either end by transparent walls. Present and available routes are shown with solid lines, present but inaccessible routes are shown with broken lines.

platforms, A > B > C, A > D > E, A > C and A > E (Figure 4.4). These had a wooden base and transparent 0.5 mm thick plastic walls (the four short alleys: H×D×L: 170mm × 130mm × 690mm; the two long alleys: H×D×L: 170mm × 110mm × 930mm). The square platforms were also constructed from wood (500mm square) and the round, central platform was constructed from an upturned plastic tub (450mm diameter). Equal numbers of animals were trained to find food at opposite ends of the apparatus, however, for simplicity one group will be described here. Platform A served as the start platform (Figure 4.4, left). Food bowls were affixed to the sides of Platforms C and E, rats could easily reach these but they were not visible from the rest of the maze. Chocolate puffed rice cereal was used as a reward and was found in the food bowl affixed to Platform C. Inaccessible chocolate cereal dust could be found in the opposite bowl affixed to the side of Platform E. Transparent plastic barriers (H×D×L: 210mm × 2mm × 297mm) were used to make alleys inaccessible when required.

### 4.3.3 Experimental Protocol

The 12 animals used in this experiment were divided into two groups of six. Both groups received five pre-training sessions on the apparatus over the course of five consecutive days. Each session lasted 10–15 min, such that each rat received a total of 55 min pre-training. One group was given pre-training with free access to the shortcut and the equivalent novel route. The second group was given pre-training with the shortcut and equivalent novel routes present but blocked using transparent barriers. No food or odour cues were present on the maze during these sessions.

After pre-training, these two groups were further subdivided such that three rats from each group were trained to find food affixed to Platform C (the layout described previously) and the remaining rats were trained to find it affixed to Platform E – training for these groups was identical, the only difference being that, from above, the task would appear to have been rotated 180°. This procedure was carried out in order to counterbalance any effects of uncontrolled spatial cues. Each rat was given a total of 110 training runs (over

11 sessions) on the experimental apparatus. A run consisted of a rat successfully navigating from the start platform, A, to the rewarded platform, C, where a food reward was available. Once the rat had completed a run, it was given approximately 5 seconds to consume the food reward before being returned to the start platform. The apparatus was cleaned with scented detergent each day and the order in which the rats were run each day was randomized. No more than two days were allowed to pass between training days. The time taken to complete each run was recorded by an experimenter in the experimental room, this experimenter changed position randomly after each run so as not to serve as a spatial landmark.

### 4.3.4 Shortcut Probe

After 11 sessions with the platforms in their training configuration (and immediately after the last 10 trials), a probe session was conducted in which the trained upon alleyways were made inaccessible and the shortcut and equivalent novel route were opened (Figure 4.4, right). This was done using the transparent barriers described previously. For half of the rats, the alleyway from Platform A to C served as a shortcut to the food reward, and the opposite alley leading to Platform E served as an equivalent novel choice because it was only ever present with the shortcut route. The alley leading to Platform D remained open and acted as a familiar but previously unrewarded choice. For the other half of the rats, the mirror opposite alleyways held the same purposes and configuration. The choice of alleyway made by the rat was measured and recorded via a ceiling mounted CCTV camera and television screen in an adjacent room. Rats were permitted two choices. There were no food, or olfactory cues present on the maze during the probe trials.

### 4.3.5 Post Probe Training

Once the shortcut probe was completed, the rats were trained for a further 6 days (90 runs in total) following the exact same protocol as during training but with all of the routes open on the maze. Thus, the rats could freely use either the shortcut or the indirect, training route to access the food.

### 4.3.6 Data Analysis

Data were collected and initially analysed in Microsoft Excel, statistical tests were performed using dedicated statistical software (SPSS version 20, IBM).

## 4.4 Results

### 4.4.1 Training

One of the rats in the group given pre-exposure to the shortcut route and trained to find food in the configuration shown in Figure 4.4 failed to complete training or learn the task[14]. The data from this animal have been omitted from any further analyses.

*Rats learned the layout of the maze and the task demands*

A four-factor univariate ANOVA (trial time, experiment group, reward site and session) confirms that across the 11 training sessions, the time taken for the rats to run from the start platform to the food bowl decreased significantly [$F(10,121) = 18.67$, $p < .001$, $\eta_p^2 = .71$], there were no other significant main effects or interactions [$p > .60$, $\eta_p^2 < .10$ all tests],

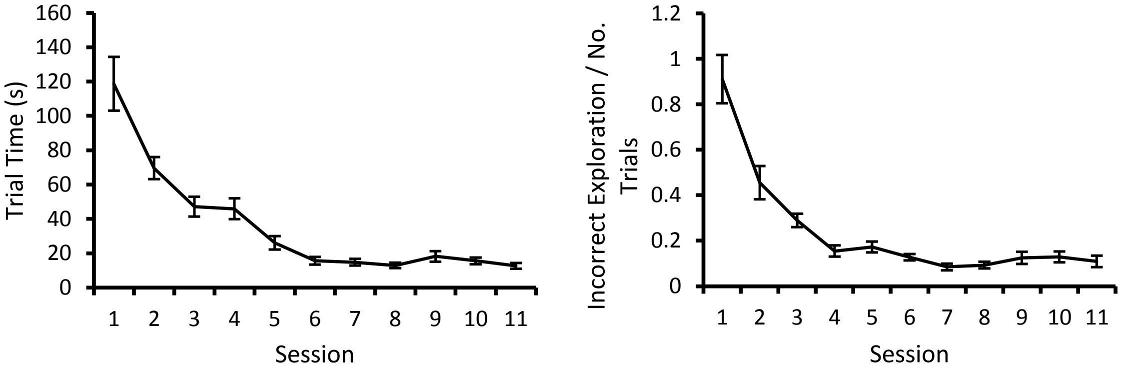

**Figure 4.5:** Performance improvements in both time and errors. Left) showing average and SEM trial times for all rats over the 11 training sessions. Right) showing number of trials in which rats navigated to the incorrect end of the maze over the 11 training sessions, expressed as a ratio to the number of trials completed (the rats may have explored the incorrect half of the maze more than once per trial).

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[14] This rat was consistently and significantly overweight, it's likely this animal was simply unmotivated to learn the task.

thus the counterbalanced groups were equivalent. A four-factor univariate ANOVA (incorrect exploration rate, experiment group, reward site and session) also confirms that the number of times the animals explored the incorrect half of the maze decreased significantly with training [$F(10,121) = 26.17$, $p < .001$, $\eta_p^2 = .77$], there were no other significant main effects or interactions [$p > .70$, $\eta_p^2 < .06$ all tests], thus the counterbalanced groups were again equivalent. These results can be seen in Figure 4.5.

### 4.4.2 Shortcut Probe

*The location of the food reward during training did not influence the rats' choices in the probe trial*

A Chi-Square (Fisher's Exact) test looking at the relationship between where the rats were trained to find food and their choice of routes in the probe test show that which end of the maze the rats were trained to find food had no significant effect [$X^2(22) = 1.16$, $p > .05$, Cramer's $V = .69$]. These spatially counterbalanced groups were combined for further analyses.

*Rats failed to select the shortcut route more than the alternative routes unless pre-exposed to it*

In the shortcut probe, 4 of the 5 animals given pre-exposure to the shortcut route chose this route as their first choice. One rat chose the novel route. If the rats were selecting routes in the probe session by chance, the probability associated with the observed choices of the shortcut route is .04. The likelihood that the rats chose the shortcut route with a higher underlying probability is greater: the observed results are 1.87 times more likely with a 40% chance of taking the shortcut; 6.3 times more likely with a 60% chance, and 10 times more likely with an 80% chance. None of the animals who were not given pre-exposure to the shortcut route chose this route. All 6 of the animals chose the novel route.

If we consider both choices made by each animal in the probe session, the 5 animals given pre-exposure to the shortcut alleyway chose the shortcut 7 times (70%), the equivalent novel route 3 times (30%), and did not use the familiar, training route at all (0%) (see Figure 4.6). This distribution is statistically significant [$D(10) = 1.368$, $p = .032$]. However, the six animals which were given no pre-exposure to the shortcut chose it and the familiar route twice each (~17%) and the equivalent novel route 8 times (~66%). This distribution is not statistically significant [$D(12) = 1.155$, $p = .109$].

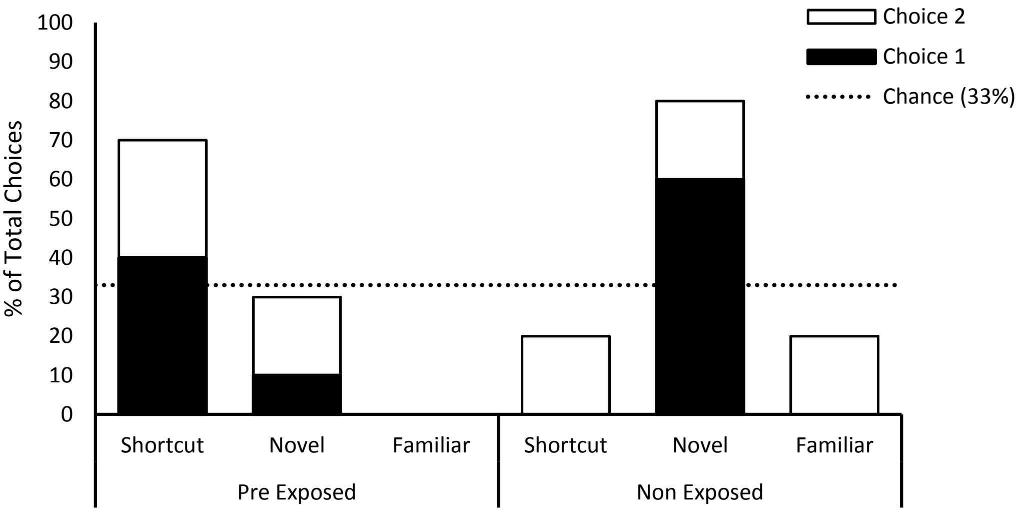

**Figure 4.6:** Results of the shortcut probe for both the pre-exposed and non-exposed groups. Values indicate the percentage total number of time the rats as a group selected each route (both the first and second choices are combined here but can be distinguished based on filled or clear bars). It is clear that the pre-exposed rats chose the shortcut route the most, whereas the non-exposed rats chose the novel route the most.

### 4.4.3 Post Probe Training

*Both groups learned to use the shortcut route with training*

A four-factor univariate ANOVA (trial time, experiment group, reward site and session) does not highlight any significant main effect in the time rats took to navigate from the start platform to the food reward during the post-probe training [$p > .05$, $\eta_p^2 < .25$, all tests], however a four-factor univariate ANOVA testing the rate at which the rats started using the shortcut route (shortcut use, experiment group, reward site and session) confirms a main effect of experiment group [$F(1,66) = 27.13$, $p < .001$, $\eta_p^2 = .39$], session [$F(5,66) = 69.92$,

$p < .001$, $\eta_p^2 = .89$] and a significant interaction between group and session [$F(5,66) = 8.44$, $p < .001$, $\eta_p^2 = .50$]. No other main effects or interactions reach significance [$p > .40$, $\eta_p^2 < .15$, all tests]. Thus, the counterbalanced groups were equivalent and the pre-exposed group was significantly faster at utilising the shortcut route after the shortcut probe. These effects can be seen in Figure 4.7.

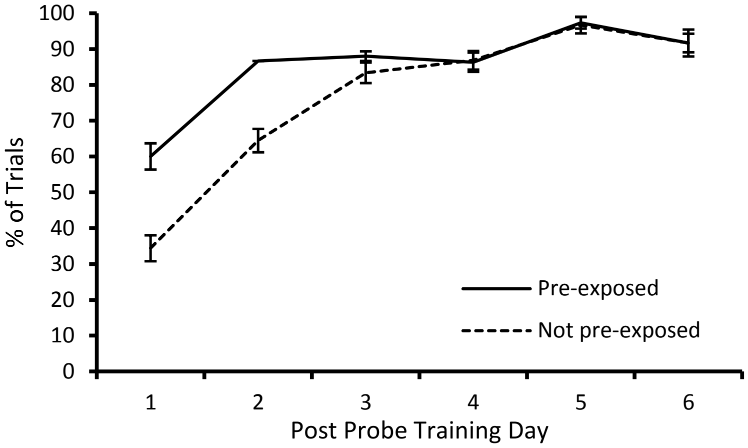

**Figure 4.7:** Post-probe performance. After the shortcut probe, shortcut routes were opened and the rats were free to choose them. The rats were then given a further six days of training. This figure shows the percentage of trials in which rats in the pre-exposure and non-exposure groups chose their shortcut route on each training day during this period. The animals in the group given pre-exposure started using their shortcut route significantly faster.

## 4.5 Discussion

The current experiment was primarily designed to test the capacity of rats to take a novel, direct route to a goal location that had only been reached previously by an indirect route. Half of the rats were given pre-exposure to this route, for the other half this route was truly novel. We found that rats selected the shortcut route, but only if they had experienced it in the past. This experience did not have to be rewarded, suggesting that the rats learned the layout of the maze latently (Blodgett, 1929; Jensen, 2006). In a previous experiment, inspired by Hazen et al.'s (1978) work with children, we trained rats to run through a series of four square environments, themselves arranged in a square (Grieves & Dudchenko, 2013). After this, the trained-upon route was blocked, and rats were given the choice of a direct route to the goal location, and two alternatives. Comparable numbers of rats selected each of the three routes, suggesting that there was no preference for the shortcut to the goal. In a second experiment, the environments were platforms and thus visible from one another, but rats again failed to take a shortcut following training. The current experiment addressed a number of limitations in those experiments, first, it could be argued that the rats were capable of taking the shortcut route, but preferred to sample a route leading to a novel location. In the current experiment, however, the novel and shortcut routes were sampled equally (or not at all) and were visually identical. Second, in our previous experiments the decisions rats made may have been influenced by previous maze experiences which biased them towards the use of intramaze cues. To address this possibility, naïve animals were used in the current experiment. Third, in our previous experiments shortcut routes were added to the maze configuration for use in probe trials and the trained on routes were removed. It might be argued that the animals no longer treated the situation as being the same environment. However, in the current experiment all of the alleyways remained in place, but were simply blocked with a transparent barrier when required. The finding that no animals chose the route that led to a platform that had never been reinforced in training (Platform D) in the probe session suggests that the overall environment was recognized as being the same during this session. When taken together, a more parsimonious explanation of these results is that, without pre-exposure to a shortcut, rats are unable to make a spatial inference.

In this view, the observed results may lend some support to Bennett's argument (Bennett, 1996; Bennett, 1991) that rats are unable to form cognitive maps or make spatial inferences using cognitive maps. He suggests that previous studies in the field of cognitive mapping, such as those of Tolman (1948), Chapuis and Varlet (1987) and Gould (1986b), have never fully excluded the possibility that instead of taking novel routes using an internal representation of their environment, organisms simply navigate towards conspicuous landmarks or beacons and then use local and recognizable landmarks to more accurately locate a resource. This theory is supported by studies that have failed to find evidence for shortcutting or cognitive mapping (Dyer, 1991; Randolf Menzel et al., 1990; Thompson &

Thompson, 1949; Wray et al., 2008) or have found simpler explanations for results supporting the existence of cognitive mapping (Bennett, 1996; Bennett, 1991; Dyer, 1991; Gibson, 2001).

For instance, Tolman, Ritchie and Kalish's (1946a) influential shortcutting experiment has been heavily criticised for including a light source above the reward location. Indeed, Gentry, Brown and Kaplan (1947) performed a series of in-depth experiments designed to replicate Tolman, Ritchie and Kalish's (1946) results. Large cohorts of animals (between 20 and 100 rats per cohort) were trained under the same conditions as those in the original experiment (but the experimenters tried two different light intensities), with the trained on route in place during testing and with this route removed completely. Gentry, Brown and Kaplan (1947) consistently observed, under all of these conditions that rats predominantly chose the routes immediately adjacent to the trained on route. Only under one of the conditions did any rats choose the 'shortcut' route at all; when the trained on route was removed completely, but even here less than 5% of the 22 rats chose the shortcut. These results are in direct contrast to those of Tolman et al. (1946a) who found that the majority of their rats selected the route which led to the reward location. In a further test, Gentry, Brown and Lee (1948) trained 80 rats on a maze composed of 8 T-mazes (Figure 4.8). After leaving a start platform the rats navigated through the mazes to a reward location, this was arranged such that the direction in which the rats left the start platform was in the opposite direction to the true location of the reward site. In testing, the original, training route, was blocked and 10 alternative alleyways were available instead – one of these led directly to the spatial location of the food reward during training. To replicate the design of Tolman, Ritchie and Kalish (1946) a light source was placed so that the reward location was between it and the start platform. In this experiment, the rats again showed a preference for the routes adjacent to the trained on alley (52.5% of rats, alleyways 2 and 3 in Figure 4.8, right) with only a small number of rats navigating towards the light source and the food (5% of rats, alleyway 8 in Figure 4.8, right).

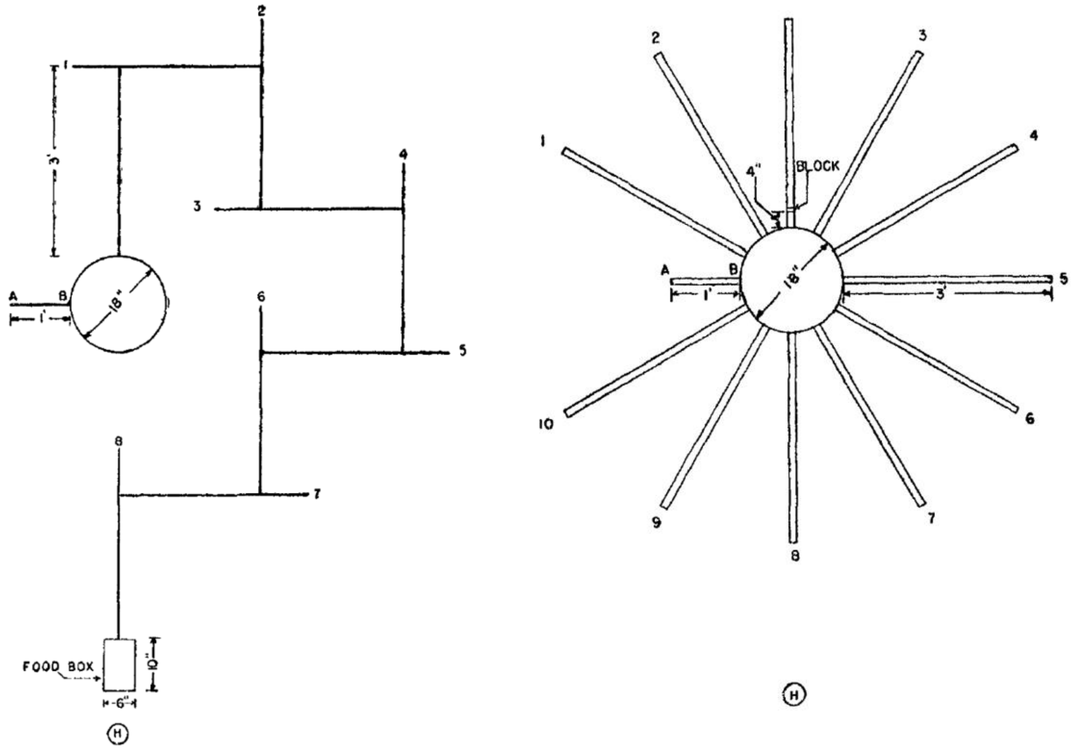

**Figure 4.8:** The mazes used by Gentry, Brown and Lee (1948) during training (left) and testing (right). Rats started on a round platform and navigated through 8 T-mazes to a food reward. In testing they were given 10 alternative alleyways to choose, one of which (alley 8 in figure) led directly to where the food reward was located previously. A light source was suspended above the maze in both conditions, at location H.

Together these results suggest a number of things; the light used by Tolman, Ritchie and Kalish (1947) probably did not influence the choices made by the rats, however, the effect observed in their experiment does not appear to be replicable in other laboratories. It would appear that rats may in fact choose paths leading in the same direction, initially, as the trained on route rather than choosing paths leading in the same direction as the food reward, similar results have been reported elsewhere (Grieves & Dudchenko, 2013). In Gentry, Brown and Kaplan's (1947) experiment, because the rats did not necessarily have to attend to their environment after leaving the round platform, the discrimination of the greatest behavioural salience is the selection of alleyway leaving the round platform. During testing the rats attempt to follow this association by choosing alleyways adjacent to the training path, the constellation of extramaze cues and the spatial bearing of the food reward appear to remain unlearned. Why only the rats in Tolman, Ritchie and Kalish's (1946) experiment chose the shortcut route at a greater frequency remains unclear. In Gentry, Brown and Kaplan's (1948) experiment the rats, presumably, had to attend to their environment more, as they had to solve a series of T-mazes before reaching the food reward. However, under these conditions the rats still appear to find the choice of alleyway from the start platform the most salient behavioural discrimination, possibly because the animals were over trained and were utilising an egocentric strategy of navigation (based on turns and responses rather than cue based navigation). It would be interesting to observe rat's choices in a test such as this when in testing they have had to make an allothetic discrimination based on extramaze information. Under these conditions, animals should attend to their environment more during training, navigate using distal cues and thus may be more likely to take a shortcut during testing.

Certainly, our only evidence of shortcutting suggests that latent learning (Thistlethwaite, 1951) of the environment occurred during the pre-exposure sessions. Another explanation is the type of reasoning described by Maier (1932) who showed that rats are able to integrate two discontiguous experiences in order to navigate to a particular goal location. In any case the utilization of the shortcut in the current experiment does not represent what we might consider to be 'true' spatial inference as the shortcut was no longer novel. The current results instead provide support for previous findings that suggest that rats need prior experience, or exploration, of a shortcut in order to utilize it in a practical setting. Roberts et al. (2007) showed that although rats initially failed to take a shortcut more than an equivalent novel route, their performance improved when given an opportunity to correct themselves and explore the novel routes. Furthermore, Chapuis et al. (1987) exposed golden hamsters (*Mesocricetus auratus*) to two unconnected maze areas each baited with a food reward. They then allowed one group of hamsters to explore a long route connecting the two areas. In the probe test, they found that this group utilized a shortcut more quickly and more prevalently than the control group. Both groups improved in performance on the second test. Chapuis et al. (1987) suggested that free exploration of the new route connecting the areas was crucial for the formation of a 'unified' cognitive map even though this exploration should not have provided the experimental group with any advantage in terms of spatial information. The maze areas were connected in the current study, but the results suggest that shortcuts are the product of learning, not spatial inference.

Returning to our initial motivation for this work: if rats are not able to make novel spatial inferences, their performance is similar to that of human infants below the age of four years. In the Hazen et al. (1978) study, although 6-year-old children were able to make spatial inferences, those of a younger age were not. The developmental theory suggested by Piaget (1952) considered the ability to make these spatial inferences and take shortcuts an important developmental aspect of psychomotor development – one which it would appear, rats fail to achieve, or which they are unable to demonstrate in the same way. From a rodent perspective, these results are surprising as there is evidence that rodents have the capacity for vector addition to reach a goal location in the dark (Etienne et al., 1998). One might expect that the rats could have used the learned vectors (A > B, B > C, and C > D) to calculate the novel vector A > D (Kubie & Fenton, 2009). The reason for the differences in results is not clear; although one possibility is that the use of vectors is perhaps easier in an open arena situation as opposed to a situation where a previously impossible route is abruptly made available. This again would suggest that experience with potential routes is essential for their subsequent use.

From a neurophysiological standpoint, the observed lack of capacity to take a novel, direct route to a goal location is also surprising. The rat brain exhibits a robust representation of location and direction (Moser, Kropff, & Moser, 2008; O'Keefe & Nadel, 1978; Taube, 1998) and this circuitry underlies the capacity to maintain orientation in the absence of landmarks (Parron & Save, 2004; Taube & Burton, 1995; Wallace & Whishaw, 2003). In previous work, conducted using a similar apparatus, Dudchenko and Zinyuk (2005) showed that head direction cells maintain a similar firing direction from one box to the next. If the head direction system provides a unitary directional reference, one would anticipate that it could be used to calculate a goal vector. Furthermore, previous research (Alvernhe, Van Cauter, Save, & Poucet, 2008) has shown place cell remapping in both CA1 and CA3 subregions of the hippocampus in response to a novel shortcut route, although these routes were 'instantaneous' (such as a new open doorway) rather than the extended alleyways used throughout the present study. The lack of spatial inference observed in the current experiment, however, may suggest that these neural representations of space may represent a more piecemeal encoding of environments (Derdikman et al., 2009; Spiers et al., 2013) and that any linkage of representation between environments is incidental. Indeed, results obtained with human participants suggest that simple navigational strategies may be sufficient and can appear, to an observer, to have the complexity of a cognitive map reliant on detailed neural representations (Gibson, 2001).

The current experiments make two contributions. First, our results suggest that rats are unable to make a novel spatial inference, even under conditions that are favourable, presumably, for the formation of a unitary representation. Second, we show that rats can select a shortcut route when they have been given previous exposure to it. This implies that the use of a shortcut reflects learning, as opposed to inference.

# Experiment 2

## Does Place Cell Firing Encode Goals or Routes?

## 5.1 Abstract

Rats (*N* = 8) were trained to navigate from a start box to three goal locations via four distinct routes. Two of these routes led to the same goal location. We assessed prospective context-dependent activity in the start box of our maze, as well as a number of additional maze areas. If this activity is dependent on the trajectory the animal is planning to take, then prospective firing should discriminate the four trajectories in the maze start box – although two of the routes lead to the same place the trajectories are distinct. However, if this firing is dependent on the goal that the animal is planning to navigate to, then we should observe cells which show similar prospective firing for the two trajectories which lead to the same goal location – although the trajectories are different they lead to the same place. We recorded a total of 386 place cells, 146 (37.82%) of these were identified as firing in a context dependent manner in at least one of our four areas of analysis ($p < .05$ as tested by an ANCOVA assessing firing rate and destination, with velocity and positon as covariates). Concentrating on the two goal sharing trajectories, we observed 27 (96.43%) cells that showed trajectory dependent prospective firing and only 1 (3.57%) which showed goal dependent prospective firing. We also observed an overrepresentation of the maze start box in terms of hippocampal place fields. During training we observed that rats found the two routes leading to the same goal more difficult than any of the others, we also found that these trajectories were overrepresented by trajectory dependent place cells, suggesting that the hippocampus may recruit additional neural resources for more difficult discriminations. Together these results suggest that instead of forming a global, map based representation, the hippocampus may represent an animal's environment, or at least its future behaviour, in the form of individual trajectories.

## 5.2 Introduction

As we discussed in previous chapters, hippocampal place cells appear to form the neural basis of a cognitive map (O'Keefe & Nadel, 1978; Tolman, 1948). Place cells fire almost exclusively when the animal's head is in a particular area of its environment and these areas of high firing rate are known as 'place fields' (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). Different place cells fire in different areas of an environment such that as a population the firing of these cells comes to cover the entire surface of an environment (Muller et al., 1987). The activity of place cells in different environments appears to be statistically unpredictable, they 'remap' and fire maximally in different areas of different environments, suggesting that place cells form unique representations for these environments (Bostock, Muller, & Kubie, 1991). These representations form quickly and are stable for days (Muller et al., 1987) or weeks (Best & Thomson, 1984) after initial exposure to an environment. Furthermore, place cell firing appears to reflect features of an animal's environment such as the relation between distal cues (O'Keefe & Speakman, 1987; Shapiro et al., 1997) and geometric boundaries (O'Keefe & Burgess, 1996), features which are considered crucial to an allothetic, map based method of navigation. This is supported by the finding that the hippocampus (HPC), where place cells reside in the brain, is crucial for many features of spatial learning (Barnes, 1988; Jarrard, 1983; Jarrard, 1993; Morris et al., 1982; Nadel, 1991; O'Keefe & Nadel, 1978; Olton, Walker, et al., 1978; Sutherland, Kolb, & Whishaw, 1982). Place cell instability is accompanied by performance impairments in a radial arm maze (Agnihotri, Hawkins, Kandel, & Kentros, 2004; Kentros et al., 1998), mice foraging randomly for food have relatively unstable place fields, after training on a goal-directed task this stability increases in mice who learn the task successfully, the mice that do not learn continue to have unstable place fields (Liu et al., 2003). The place fields of ageing rats are very different to those of young animals, they are larger and less stable, these older animals are correspondingly impaired in spatial learning (Rosenzweig, Redish, McNaughton, & Barnes, 2003; Wilson, Ikonen, Gallagher, Eichenbaum, & Tanila, 2005; Wilson et al., 2004) see Figure 5.1. These findings have led many to suggest that the activity of place cells at the ensemble level, forms spatial representations which are used in spatial navigation (Maren & Holt, 2000; O'Keefe & Nadel, 1978). Indeed, if the hippocampal representation does not match the current task or environment, behaviour is impaired (Lenck-Santini, Muller, Save, & Poucet, 2002; Lenck-Santini, Rivard, Muller, & Poucet, 2005; Lenck-Santini, Save, & Poucet, 2001a; O'Keefe & Speakman, 1987).

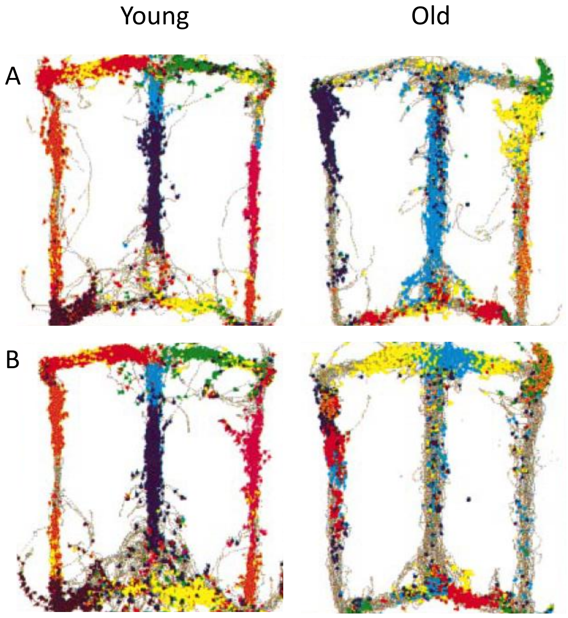

**Figure 5.1:** Figure showing the instability of place fields in older animals. Both a young (left) and old (right) rat experienced the same maze in the same environment at two different time points (rows A and B). The route of each rat is shown by a grey line, the coloured dots show where the recorded ensemble of place cells fired, with a different colour used for each cell. The young animals' representation is more evenly distributed and stable between sessions.

However, like spatial location, place cell firing has also been found to reflect many additional features of an animal's environment. When an animal is moved between different environments in different locations, place cells 'remap'; the position of their place fields changes, cells may become inactive or previously silent cells may begin to fire (Bostock et al., 1991; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005) for a review see (Colgin, Moser, & Moser, 2008). However if the features of an environment are changed but not its location, place cells 'rate remap'; the position of place fields is maintained while the firing rate of these fields changes (Leutgeb, Leutgeb, Barnes, et al., 2005). This finding suggests that the firing of place cells may encode two different kinds of data, a spatial representation which is distinct for different environments and an episodic or contextual representation which is distinct for the same environment under different conditions (Leutgeb, Leutgeb, Barnes, et al., 2005). Place cells recorded in an environment as its shape is slowly changed, maintain a similar firing position between the environments (Lever, Wills, Cacucci, Burgess, & O'Keefe, 2002), but with experience in two apparatus place cells develop distinct representations (Muller & Kubie, 1987), suggesting that contextual information may be incorporated into spatial representations after their initial formation. Indeed a number of different forms of information appear to be incorporated into these spatial maps; the firing of place cells is modulated more strongly by head direction when the current task emphasises orientation such as in a radial arm maze (McNaughton, Barnes, & O'Keefe, 1983; Wiener, Paul, & Eichenbaum, 1989) than in a cylindrical environment where the animal forages for scattered food rewards (Breese et al., 1989; Muller et al., 1994; Muller et al., 1987), but directional modulation can be similarly observed in a cylinder when the task emphasises orientation (Markus et al., 1995). Changing the odour or colour of an environment whilst retaining its shape can cause some, but not all place cells to change their firing (Anderson & Jeffery, 2003; Lever et al., 2002), suggesting that not all place cells are influenced by all environmental cues equally. Fear conditioning (Moita, Rosis, Zhou, LeDoux, & Blair, 2004) or a change in navigation strategy (Ferbinteanu, Shirvalkar, & Shapiro, 2011) can similarly result in the remapping of place cells.

Much like colour and odour, changes in the task demands whilst retaining the environment geometry are also enough to cause a change in the firing of place cells (Ainge, Tamosiunaite, et al., 2007; Allen, Rawlins, Bannerman, & Csicsvari, 2012; Markus et al., 1995; Wood et al., 2000), suggesting that hippocampal neuronal activity can encode information about locations, their significance and the task demands at each of them. Similar to the manipulation of environment location or shape, this rate remapping appears to develop with experience and is incorporated into an already existing spatial map (E.R. Wood and P.A. Dudchenko unpublished findings). Previous research has shown that the firing rate of place cells at the start of a maze or in a location where multiple trajectories overlap, is often modulated not just by location but also the animal's intended destination or future trajectory (Ainge, Tamosiunaite, et al., 2007; Allen et al., 2012; Ferbinteanu & Shapiro, 2003; Shapiro, Kennedy, & Ferbinteanu, 2006; Wood et al., 2000) but see (Lenck-Santini, Save, & Poucet, 2001b). Wood et al. (2000) showed that on a continuous T-maze (or a figure 8 maze) 66% of CA1 place cells with fields along the central stem of the maze were modulated by the future destination of the animal, with some cells consistently firing significantly more when the rat was about to turn left or right. Frank et al. (2000a) similarly showed that in a W-shaped maze 36% of CA1 place cells, 33% of superficial layer EC cells and 36% of deep layer EC cells fired differently depending on either the previous (retrospective coding) or future (prospective coding) position of the animal (Ferbinteanu & Shapiro, 2003). Concentrating on just the latter, prospective firing, Ainge et al. (2007) showed that on a concatenated or double-Y maze, where rats leaving a start box have a choice of four trajectories to four different goal locations, 46% of CA1 place cells displayed firing, at the maze choice points, which was significantly related to the final destination of the animal. However, in each of these cases it is unclear whether this prospective, differential firing is related to the trajectory the rat is planning to execute or the ultimate goal location it is planning to navigate to, or how either of these forms of information may be extracted or incorporated in hippocampal representations. This is compounded by the fact that both forms of information are represented in the hippocampus.

Goal locations are represented by place cell firing in a number of ways; place cells fire in goal locations as hungry rats wait for a food reward (Hok et al., 2007; Lenck-Santini et al., 2002), they can also fire in relation to a goal location rather than a fixed spatial reference frame (Gothard, Skaggs, Moore, et al., 1996), or they may fire in anticipation of an uncollected food reward (Holscher, Jacob, & Mallot, 2003). This goal firing appears to be unrelated to decreased inhibition or increased excitability, walking speed or other goal-related behaviour (Hok et al., 2007; Mizumori, 2008). Furthermore, goal locations have been found to be over represented in maze arenas (Gothard, Skaggs, Moore, et al., 1996; Holscher et al., 2003; Kobayashi, Tran, Nishijo, Ono, & Matsumoto, 2003) and in a water maze task (Hollup, Molden, Donnett, Moser, & Moser, 2001). Although other studies have reported equal representation of goal locations (Lenck-Santini et al., 2002; Lenck-Santini et al., 2001a) and in a plus maze environment place cell firing is not affected by moving a goal (Speakman & O'Keefe, 1990). Trajectory information is also often reflected in the firing of place cells; during goal-directed navigation in an open arena hippocampal activity has been shown to reflect an animal's future trajectory in brief sequences of activity (Pfeiffer & Foster, 2013). Many place cells are active in any given environment and as the animal explores or completes a task it will pass through a number of these place cells' place fields. During periods of slow wave sleep after exploring a new environment place cells have been observed to replay the activity of the previous day, with cells active in the environment reactivating during sleep (Wilson & McNaughton, 1994), this phenomenon has also been observed during quiet awake states (Foster & Wilson, 2006). This hippocampal 'replay' is thought to play an important role in memory consolidation during sleep and retrieval during awake states (Carr, Jadhav, & Frank, 2011; Derdikman & Moser, 2010), which is supported by the finding that disruption of replay events in the HPC greatly impairs spatial learning (Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009). Crucially, during replay, cells have been shown to reactivate in the same sequence as during spatial exploration (Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994), suggesting that the formation or retrieval of spatial memory in the hippocampus may be based on sequences or trajectories to a goal location (Foster & Knierim, 2012; Pfeiffer & Foster, 2013; Redish & Touretzky, 1998). Further observations suggest that at a choice point, when a rat is required to make a decision between two trajectories, place cells with fields along each of these potential trajectories fire non-locally and in sequence (van der Meer & Redish, 2010). These 'look ahead' events are so robust that when the position of the animal is decoded based on place cell activity it appears as though the animal is moving along each of these trajectories in turn (Johnson & Redish, 2007). This activity is thought to underlie decision making and forward planning; as the rat considers a trajectory, and on some level considers the outcome of taking it, the place cells representing it fire in sequence (van der Meer & Redish, 2010). These results give further evidence that the hippocampus represents environments in terms of its substituent trajectories.

Given the current uncertainty regarding the nature of prospective hippocampal rate remapping, we sought to better understand the behavioural correlates associated with this phenomenon. It is thought that this form of rate coding is important for the disambiguation of spatial contexts, allowing for the formation of distinct episodic memories for the same environment (Griffin, Eichenbaum, & Hasselmo, 2007; Griffin & Hallock, 2013; Hasselmo & Eichenbaum, 2005; Smith & Mizumori, 2006b), thus it important to understand what form of information drives this context dependent firing in the HPC. In a previous experiment (Ainge, Tamosiunaite, et al., 2007), rats were given the choice of four distinct routes to four spatially dissociated goal locations (see Figure 5.2). They found that the firing rate of many place cells was associated with the animal's final destination, they termed these place cells 'splitter cells'. Splitter cell firing observed at the choice points in this task could be the result of future trajectory based planning and decision making, with the rat considering the route and sequence of responses it is about the make. Conversely, this firing could reflect the anticipation of a goal location or the retrieval of a hippocampal (or otherwise) representation of that goal. We redesigned the maze used in the Ainge et al. (2007) study so that instead of four distinct routes and goals the rats were given the choice of four distinct routes to three goals, with the two central routes leading to the same goal location. Tasks such as this have been shown to be, at least partly, dependent on an intact HPC (Ainge, Tamosiunaite, et al., 2007) especially if a delay is introduced between trials, such as in our task (Ainge, van der Meer, Langston, & Wood, 2007). In this apparatus, trajectory dependent and goal dependent prospective rate coding in the start area of this maze could be distinguished. If firing is goal dependent many splitter cells would be expected to fire similarly in the start area of the maze when the rat is navigating to the central goal box, despite taking two distinct routes to get there. Alternatively, if firing is route dependent very few splitter cells would be expected to fire in this way, cells would fire differently in the start area of the maze when the rat is navigating to the central goal box, despite ultimately navigating to the same goal location. Our results provide clear evidence for this latter form of prospective coding; the firing rate of virtually every splitter cell we recorded was modulated by the rat’s future trajectory, not future goal.

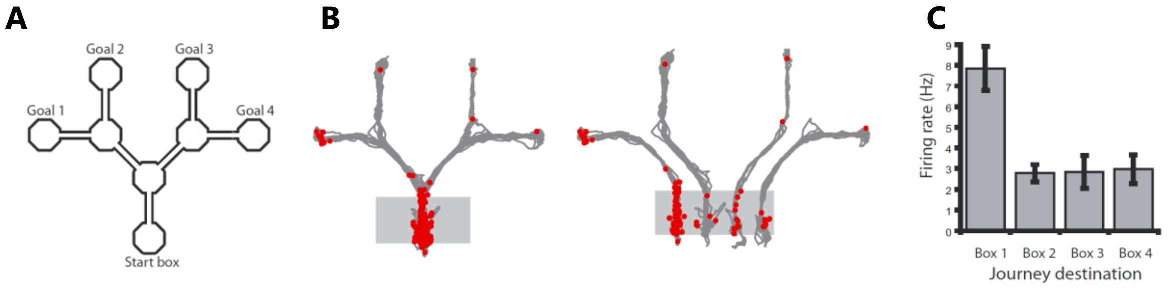

**Figure 5.2: A**) A schematic of the double Y maze used by Ainge et al. (2007). Rats are trained to navigate from the start box to each of the goal boxes in blocks of 10 trials. **B**) A cumulative position plot showing the firing of an example place cell on this maze. Grey lines show the positions where the rat was tracked as having visited, red dots show the locations at which the cell fired. Position and spike data for the four different trajectories are shown separately in the figure to the right. **C**) Plot showing the mean and SEM firing rate of the place cell in the start box when the rat was about to navigate each of the four goal box trajectories. From this plot and the position plot in **B** it is clear this cell fired significantly more in the start box when the rat was navigating from the start box to goal box 1 than when he was navigating to any other goal box.

## 5.3 Methods

### 5.3.1 Subjects

For the behavioural portion of the experiment 12 male, Lister hooded rats, with an average weight of 300g were used as subjects, a subset of 8 of these animals were subsequently used in the electrophysiological portion of the experiment at which point they weighed approximately 400-450g. A further 8 naïve animals, with an average weight of 300g, were used to test an alternative training protocol, these animals were not included in any other parts of the experiment. All animals were housed in groups of four in standard cages, but housed individually in custom designed cages post-surgery. The animals were maintained under a constant 12 h light/dark cycle and any testing was performed during the light phase of this cycle. Throughout testing, rats were food deprived such that they maintained approximately 90% (and not less than 80%) of their free-feeding weight or the weight which would be achieved when granted ad lib feeding. For no less than 7 days after surgery and 1 day before, animals were granted ad lib access to food. Animals were given free access to water at all times when in their home cages. Testing was usually performed 5 days a week during the usual working weekdays. In this and the subsequent experiments, compliance was ensured with national [Animals (Scientific Procedures) Act, 1986] and international [European Communities Council Directive of November 24, 1986 (86/609/EEC)] legislation governing the maintenance of laboratory animals and their use in scientific experiments. Experiments underwent further ethical and procedural approval by the Named Veterinary Surgeon and Named Animal Care and Welfare Officer responsible for overseeing experiments in the host laboratory.

### 5.3.2 Recording Device

We used microdrives based on a modified tripod design (Kubie, 1984); these drives each supported and advanced a bundle of 8 tetrodes which could be utilised for recording both single unit activity and local field potentials. In brief, the drives were composed of a mill-max connector for attachment to the recording system, three drive screws for lowering the electrode tips and three drive 'feet' which were secured to the animal's skull. These components were secured together using shaped acrylic polymer.

Each tetrode was composed of four HML coated 17 µm 90% platinum 10% iridium wires (California Fine Wire, Grover Beach, CA) twisted together in a tight bundle and annealed by treatment of 230°C hot air using a variable temperature hand held electric heat gun (GHG660LCD, Bosch) applied at various angles for between 7-10 seconds. Each drive supported and advanced 8 of these tetrode bundles such that the individual electrode compliment of each drive totalled 32 channels. In some drives an additional, thicker, Formvar coated 25µm Nickel Chromium tetrode was included for added strength and rigidity; these tetrodes were never used for recording purposes. Using tetrodes instead of sterotrodes markedly increases cell yield as well as the reliability of the captured single unit data, specifically signal quality, cell isolation and characterisation (Gray, Maldonado, Wilson, & McNaughton, 1995; O'Keefe & Recce, 1993).

For additional support and to allow attachment to a microdrive assembly, the tetrodes were threaded through a thin-walled stainless steel cannula (23 Gauge Hypodermic Tube, Small Parts Inc, Miramar, FL). The length of the electrode bundle was then strengthened using superglue[15], which was also allowed to adhere the wires to the inside of the tetrode cannula. The tetrodes were cut simultaneously so that a maximum length of 3mm was left protruding from the end of the cannula. This 3mm tip formed the majority if not the entirety of the material which was implanted in the brain, having only wire advancing through the brain allows for much less mechanical resistance from the brain tissue. The day before surgery and again immediately before surgery the tip of every electrode was gold plated (Non-Cyanide Gold Plating Solution, Neuralynx, MT) in order to reduce the impedance of the wire from a resting impedance of typically 0.7-0.9MΩ[16] to a plated impedance in the range of 200-300 kΩ (250kΩ being the target impedance). Testing was conducted using an impedance meter (Bak Electronics, IMP-1 metal electrode, Sanford, FL). See Figure 5.3 for a visual example of an electrode bundle tip.

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[15] The use of superglue is reported here but this was not the case in future experiments and its use is under no circumstances advised.

[16] Resting impedance as measured when electrical contact is made with gold solution. This is usually much higher, approx. 1.5MΩ but can be reduced greatly simply by first reversing the polarity of the plating process, thus cleaning the ends of the wires of any oils, debris or oxidised material instead of plating them.

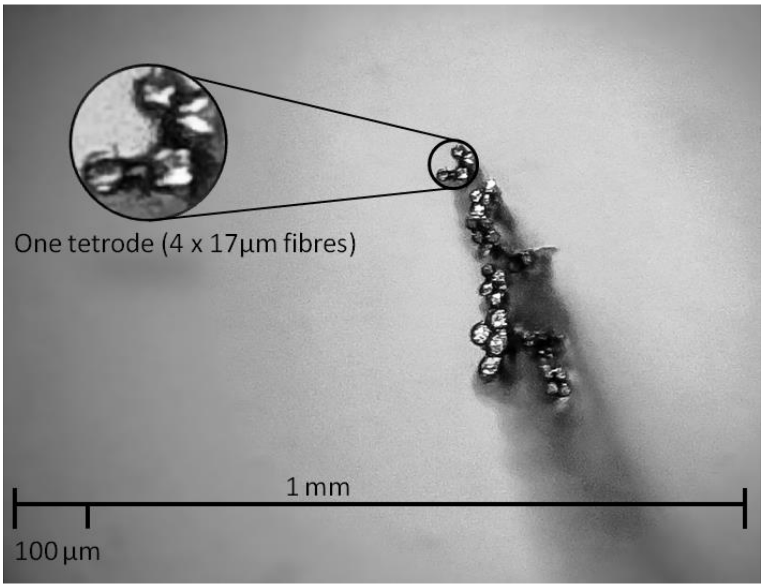

**Figure 5.3:** Showing a high magnification view of a prepared electrode tip. Before surgery the electrode is cut using sharp scissors (ToughCut, or preferably CeramaCut Iris Scissors, Fine Science Tools GmbH., Heidelberg, Germany) so that each tetrode tip forms a rectangular or diamond shaped flat surface which will be oriented perpendicular to the cells intended for observation. The exposed wires in each tetrode are ideally separated by no more than the thickness of the Teflon coating (~3µm) but different tetrodes may be separated from each other by relatively greater distances. Seven tetrode 'groups' can be identified, the 8th is out of view (this microdrive was not used for this reason), a tetrode composed of the much greater diameter Nickel Chromium wire can also be seen at the bottom left of the bundle.

Delrin mill-max socket (Mill-Max Mfg. Corp, Oyster Bay, NY), incorporated into the microdrive assembly (two 9 x 2 pin lengths of socket) allowed connection and communication between the unit recording system and the microdrive. Each wire in a tetrode was wrapped around one pin in the mill-max socket and secured using highly conductive silver paint (Electrolube, Derbyshire, UK), arranged so that signals from each tetrode could be distinguished and separated by the recording system from the others. The Teflon insulation was partially removed from this end of the wire, combined with the wrapping and silver paint this allowed secure and continuous conductivity. When this wrapping process was complete for all of the wires the entire mill-max component was coated with non-conductive nail varnish, dental cement (Simplex Rapid cold cure acrylic, Associated Dental Products Ltd., Kemdent), spray acrylic (Electrolube, Derbyshire, UK) or a combination of these in layers.

The actual drive mechanism of the microdrives consisted of three screws imbedded in drive 'feet'. The screws used were 12.7mm (1/2") long #0-80 UNF stainless steel hex socket head cap screws (Precision Technology Supplies, UK). These screws have 80 threads per inch, one full turn equates to a total advancement of 310µm, in practice they were typically turned in 1/8 increments or less (approx. 38µm)[17]. The feet were composed of a metal nut with matching specifications, super glued to a section of Amphenol Socket (Amphenol Ltd., Single Row 2mm PCB Header Socket, Wallingford, CT), encased in super glue, further encased in the dental cement described previously and internally lubricated with petroleum jelly.

An outer metal cannula or 'electrode sheath' (18 Gauge Hypodermic Tube, Small Parts Inc., Miramar, FL) was lowered over the tetrode cannula and electrode bundle during surgery, this rested on the surface of the animal's brain, surrounded by petroleum jelly. This provided long term protection for the electrode bundle, prevented dental cement or other surgical solvents from entering the brain, prevented the skull from reforming around the electrode bundle and ensured accurate direction of the tetrode cannula. Two wires attached to the central pins of the mill-max connector

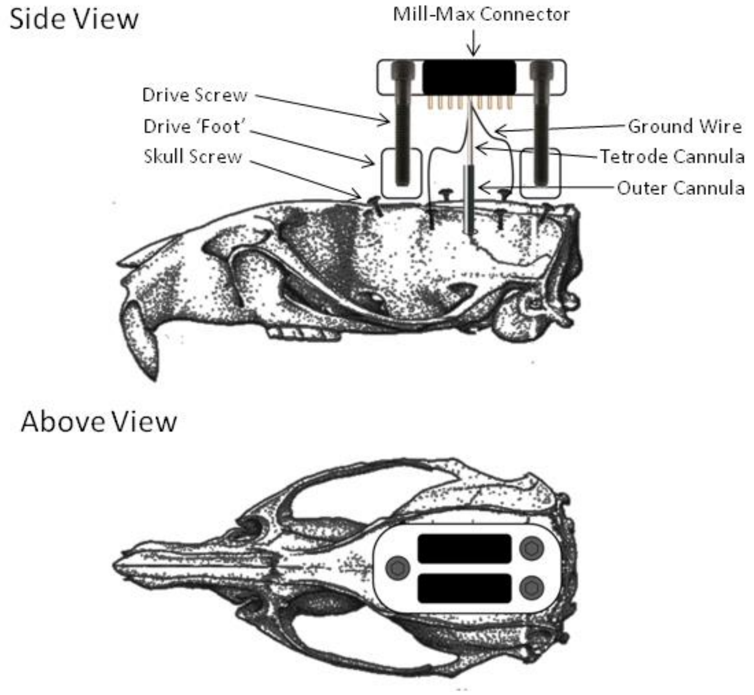

**Figure 5.4:** Showing a schematic representation of the construction and placement of the microdrive assembly over the animal's skull. Key components of the drive are labelled. During surgery, dental cement was layered around the base of the drive feet and skull screws until the top was level with the top of the outer cannula. This cement was then smoothed to remove any sharp edges which would be uncomfortable for the animal. In total the drive assembly weighs approximately 3.4g after these steps.

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[17] For comparative scale, the Stratum Pyramidale layer of CA1 (where pyramidal cell bodies are located and where the vast majority of our place cell single unit recordings most likely took place) is approximately 50-100µm, or approximately 5 cells thick (Andersen, 2007; Hussein & George, 2009). In practice the electrode bundle depresses the brain tissue as it advances, resulting in a much slower advancement through the brain than expected.

were also attached to two skull screws, located above each hemisphere and advanced completely through the skull. These wires acted to ground the animal and the microdrive assembly, protecting both from static build-up and greatly reducing interference from outside electromagnetic sources. A diagram showing the overall construction and placement of the microdrive assembly can be found in Figure 5.4.

### 5.3.3 Surgery

Animals were anaesthetised using an Isoflurane inhalation anaesthetic (Abbott Laboratories Ltd.) delivered using medical oxygen. Oxygen was maintained at 1.5L/min throughout surgery, Isoflurane was maintained at 1.5ml/h with the exception of the initial incision, drilling and final suturing when it was raised to 3ml/h. Once anaesthetised the incision site was shaved and disinfected, eye moisture was maintained using artificial tears (Viscotears, Alcon, Fort Worth, TX), hydration was maintained by administration of 2.5ml 5% glucose and 1ml 0.9% saline, animals were also given an anti-inflammatory analgaesia (small animal Carprofen/Rimadyl, Pfizer Ltd., UK). Body temperature was monitored and heat was applied using a small animal thermostatic heat blanket. Breathing was also monitored throughout surgery.

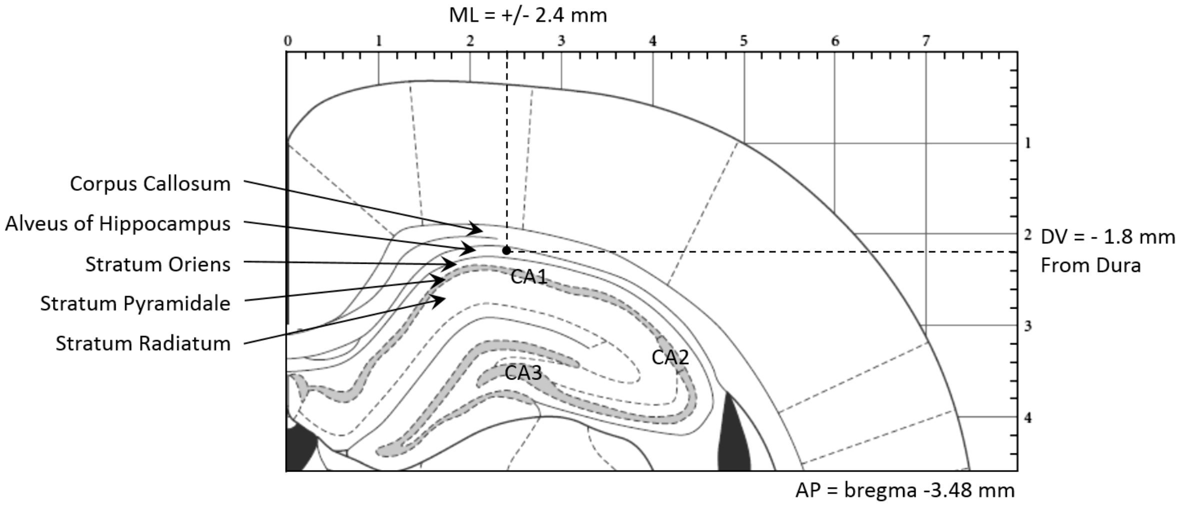

**Figure 5.5:** The coordinates and positioning of our recording electrodes. Shown is the stereotaxic brain atlas section corresponding to our AP coordinate, the correct ML and DV are shown by dotted lines, where these intersect is where the electrode tip is placed during surgery. After surgery and a brief rest period the electrodes are lowered into the pyramidal cell layer or stratum pyramidale.

The animal was then placed in a stereotaxic frame where the position of the skull was fixed using stereotaxic ear bars. An incision was made above the dorsal midline suture of the skull and the skull surface was cleaned of any tissue. The position of the skull was adjusted, if necessary, so that it was flat in the anterior-posterior plane until the height of bregma and lambda were within <0.1mm. A hole was drilled above the implant site, large enough for the outer cannula to rest inside (approx. 2-3mm) and 7-8 guide holes were drilled at various points for the skull screws (0.9mm diameter, stainless steel, Fine Science Tools GmbH., Heidelberg, Germany). The dura membrane was pierced and the electrode tip was lowered to our CA1 coordinate (-3.5mm AP from bregma, + 2.4mm ML from the midline, -1.7mm DV from dura surface, see Figure 5.5). The drive assembly was anchored to the skull screws and bone surface using the dental cement described previously. This cement was smoothed and any sharp edges were removed. If required, the incision site was sutured at the front and/or rear to aid wound closure. Animals were given at least 2 hours recovery in their home cage, heated to body temperature. At least one week of recovery time passed before screening or experiments and the animal had to have recovered its pre-surgery weight, whichever came latest.

### 5.3.4 Unit Recording

Single unit activity was observed and recorded using a 32-channel Axona USB system (Axona Ltd., St. Albans, UK). The mill-max connectors built into the rat's microdrive were attached to the recording system via two unity gain buffer amplifiers and a light, flexible, elasticated recording cable. The recording cable passed signals through a ceiling mounted slip-ring commutator (Dragonfly Research and Development Inc., Ridgeley, West Virginia) mounted on a moveable ceiling track to a pre-amplifier where they were amplified 1000 times. The signal was then passed to a system unit; for single unit recording the signal was band-pass (Butterworth) filtered between 300 and 7000 Hz, for local field potentials the signal was low-pass filtered (Chebyshev, 50 Hz notch, 0.1dB ripple) between 0 and 500 Hz.

Both signals were digitized at 48 kHz and could be further amplified 10-40 times at the experimenter's discretion.

The DACQ (Axona) software permits continuous or threshold-filtered viewing of single unit activity as a digital oscilloscope. In this mode, the presence of single unit activity was assessed during screening procedures. However, for more detailed screening or during recording, activity was recorded and analysed off-line. During recording the DACQ software captures 1ms waveform windows (0.2ms before spike peak and 0.8ms after), only spikes breaching a user-defined threshold are captured in this mode. The time at which these spikes occur is also recorded. Spikes with amplitude greater than 30% of the maximum possible gain in the final 0.4ms of the spike window (0.4ms after spike peak onwards) or with amplitude greater than 80% of the maximum or less than 80% of the minimum possible gain at the start or end of the spike window were rejected as noise artefacts. A 1.88ms spike lockout was also applied.

The position of the animal was continually recorded using one or two infra-red LED's fixed to the unity gain amplifiers attached to the rat's microdrive. A ceiling mounted, monochrome; infra-red sensitive CCTV camera tracked the animal's position within its field of view. This position information, along with the exact time at which every spike occurred allows for the spatially modulated firing of cells to be mapped, visualised and analysed.

### 5.3.5 Screening

Rats were screened for single unit activity and for the presence of theta oscillations once or twice a day, 5 days a week. Screening was conducted in the metre square, open environment described below. If no single unit activity of any kind was detected, or if the drive was to be advanced in search of new cells, tetrodes were advanced by up to 38μm. At least 4 hours (typically 6) were allowed to pass between advancing screws and assessing or recording activity. If single unit activity of any kind was detected or suspected, the animal completed a session of the experimental protocol[18].

### 5.3.6 Apparatus

We used two main pieces of maze apparatus, the first was an open field environment used for screening as well as the pre-maze session open field recordings. The second was the main experimental maze, where we sought to record the differential firing of hippocampal place cells.

Our open field environment consisted of a large, wooden, 100cm x 100cm (width x length) square enclosure with 25cm high wooden walls. This enclosure was painted black and elevated 80cm from the floor. When in use this enclosure was placed on top of the maze apparatus, so that the extramaze cues for each were identical. No intramaze cues were used in this enclosure, which was also cleaned regularly with detergent and rotated by random increments of 90° between each session.

Our maze environment was constructed entirely from wood and consisted of seven octagonal enclosures (25 x 25cm, width x length) with 25cm high walls, which formed the important parts of the maze such as goal boxes, start box and choice points. Alleyways connected these enclosures; these were 20cm long x 10cm wide with 10cm high walls. This maze was elevated 60cm from the floor on wooden stools. From the start box the rats could only navigate through a central alleyway to an initial choice point, here the rats could choose to navigate left or right. From here the rats could navigate on to one of two secondary choice points where they could again choose to navigate left or right. Initially moving left and then right or initially right then left would both bring the animals to the same central goal box. A floor plan of the maze can be seen in Figure 5.6. From the start box animals

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[18] If cells were present but none were identified as pyramidal, animals still completed a session of the experimental protocol. Pyramidal cells may have been silent in the screening enclosure but active on the maze, similarly, the high firing of an interneuron can easily mask the relatively low firing of a pyramidal cell. Furthermore, recording all cells in this way eliminates the possibility of biasing our population sample towards ideally spatially modulated cells.

could choose between 4 different routes but only 3 different goal locations. Only one doorway to the central goal box was ever open at any one time, the other was blocked using a transparent Perspex barrier. This allowed us to direct the animals towards using one of the central routes when needed. If boxes 1 or 3 were rewarded the barrier was placed in the door to box 2 on the opposite side of the maze, this ensured that if the rats were able to see the barrier their choice at the secondary choice points would remain unbiased, or at least unbiased towards the correct box.

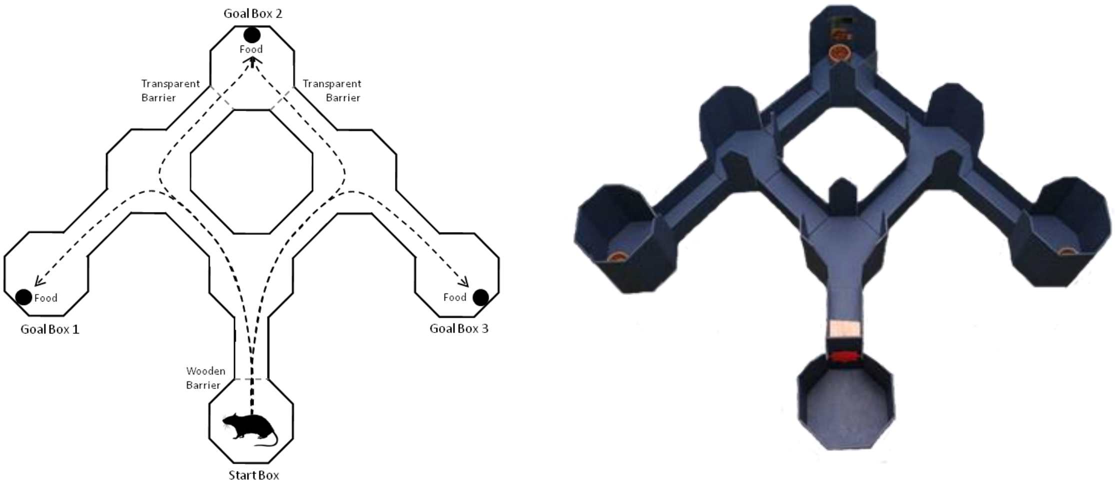

**Figure 5.6:** Showing a floor plan of the main maze apparatus or ‘Y-T-maze’ on the left and a photo of the maze on the right. Rats start in the box positioned at the bottom of the figure, four routes are available to the animal shown by dashed lines, but only three goal locations are available.

In order to facilitate discrimination of the boxes the maze was placed between polarising distal cues; a large white sheet ran along the left side of the maze, a large window blackout shutter ran along the right side of the maze and an upwardly directional light source emitted from the wall directly in front of the maze. Furthermore, similarly sized, simple objects were placed in each goal box, these included; a small grey elephant statue, a small white opaque bottle with cork stopper and a small black and red box with slanted lid. Two dimensional cues were also placed on various walls; the block which kept rats in the start box was decorated with an orange fluorescent star, the start box and each goal box also had Latin alphabet characters in different reflective colours attached to the walls opposite the entry door or doors. Heavy ceramic dishes were placed in each goal box, directly beneath these reflective letters.

### 5.3.7 Behavioural Training

The rats were trained on the maze task for at least 10 days pre-surgery; at this point the performance on this task reaches asymptotic levels[19]. Training followed a win-stay lose-shift procedure almost identical to that employed in previous experiments using the double-Y maze (Ainge, Tamosiunaite, et al., 2007). A trial started when the experimenter raised the wooden block holding the animal in the start box, the animal was then allowed to navigate through the maze to a goal box - animals were not permitted to navigate backwards through the maze at any point. If the goal box was correct and thus baited, the rat was allowed to eat the food reward (CocoPops, Kellogs, Warrington, UK) for a minimum of 3 seconds. The rat was then lifted by the experimenter, placed back into the start box and allowed to finish consuming any carried food reward. If the goal box was incorrect the food well would not be baited, the animal was returned to the start box and held there using the wooden barrier for a minimum of 3 seconds.

In this maze there are 3 potential goal sites but 4 available routes, ultimately we wished for rats to use each route the same total number of times. This was achieved by baiting each goal box in turn, the order of which was randomised each day. Rats completed trials as described above until they entered the correct goal box. They were then permitted a further 11 trials, in which they could make errors or correct choices. After these trials the food was moved to a new location and the process was repeated[20]. A schematic of the experimental procedure is shown in Figure 5.7. During these sessions the trial duration, number of errors made before discovering the rewarded location at the beginning of each

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[19] Four animals were trained for 24 days on the task (last 14 days data not shown), from this data the minimum asymptotic training schedule was established.

[20] When the food is moved we expect the rats to make at least one error – as they don't know the food has been moved they should return to the previously rewarded location expecting to find it there.

block and the number of errors made after discovering the food were recorded. The trajectory chosen on each trial was also always recorded.

#### 5.3.7.1 Training Without Barrier

To address a potential criticism, that we may have biased the rats' navigation strategy to a route based one, we trained an additional 8 naïve rats on the same task described above. However, instead of blocking one of the entrances to the middle goal box with a transparent barrier we left both entrances open. Whenever the central goal box was baited, the rats were free to use either trajectory or entrance to gain access to this goal box. We hoped that the rats would sample both trajectories at a roughly equal frequency without needing to direct their behaviour. These rats were trained for a total of 12 sessions.

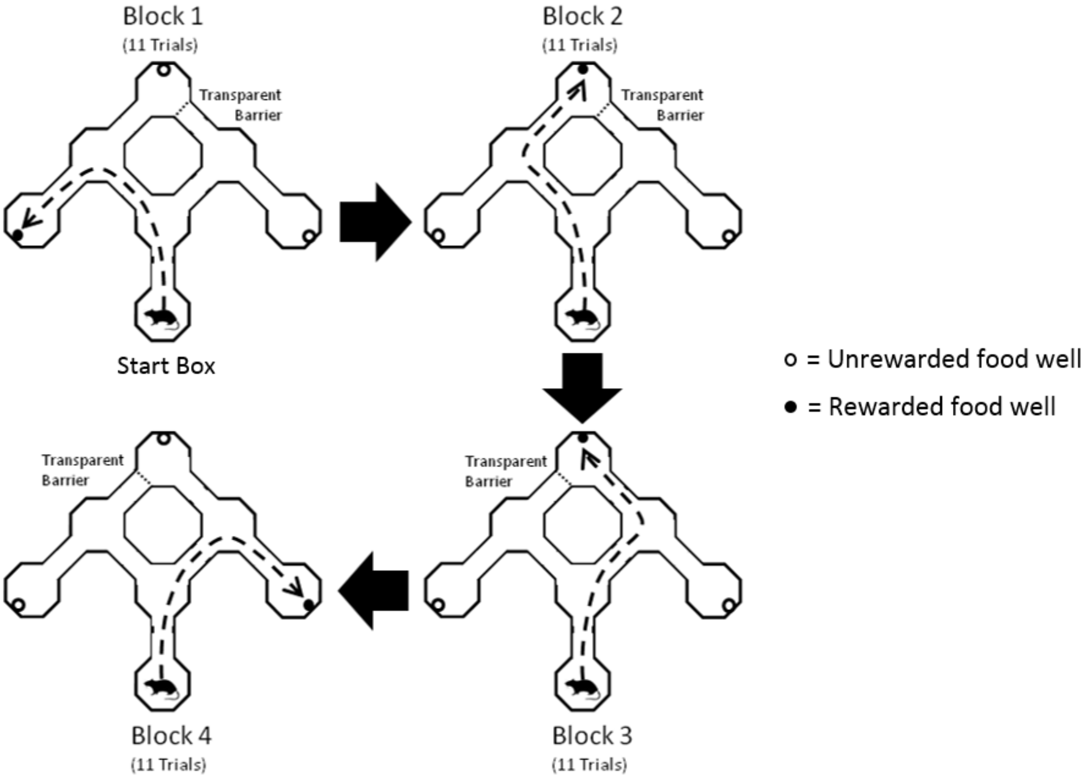

**Figure 5.7:** A floor plan of the maze apparatus and a flow diagram of the experimental procedure. One goal box was rewarded. The rat completed trials until it found this location. It was then allowed 11 further trials in which it should make the same response and return to the reward. The food then moved to a new goal box and the process was repeated until all four goal boxes had been utilised. This process was completed in one recording session, without unplugging the animal.

### 5.3.8 Recording Place Cells

After surgery, the pre-training protocol was continued, with some minor changes. When the rats were run after surgery for the purpose of recording single units they were attached to the recording system using the cable and mill-max connector described above. They were then placed in the square, open field environment which was mounted on top of the maze. The animals were recorded while they foraged for pseudo randomly scattered food rewards (CocoPops, Kellogs, Warrington, UK), this was continued for at least 10 minutes and until they had significantly explored the open field area (typically this took approximately 15 minutes).

Once the open field recording was completed the rats were placed in the start box of the maze without unplugging them from the recording system and the open field environment was removed. The rats were allowed a 60 second rest period in the start box. This allowed time for the animals’ spatial representation to adjust and update to the new, but familiar, environment - especially as the extramaze cues remained unchanged. The experimental protocol remained the same as before, except that after discovering the reward location, instead of a further 11 trials rats had to make at least 10 correct trials before the reward location was changed. Whenever rats were returned to the start box they were also held for approximately 6 seconds, this was to allow sufficient time to record any differential activity which may be present there.

Animals were often screened the day after a maze recording session. If the activity was deemed to be significantly different to that observed previously (based on the configuration of high firing putative interneurons, the signal to noise ratio of expected cells and the spatial modulation characteristics of screened place cells) another session was recorded on the maze. However, if the observed activity was similar the drive assembly was advanced using the drive mechanism. In practice screws were more often turned immediately after a maze recording session. No attempt was made to identify or characterise cells across days, the same cells may have been recorded more than once[21].

### 5.3.9 Data Analysis

#### 5.3.9.1 Cluster Cutting

As mentioned above putative single unit activity was recorded in the form of 1ms long spike windows with a resolution of 48kHz, at this resolution each window contained 50 amplitude samples[22]. The time and position at which each spike occurred was also recorded. This data was analysed offline using custom Matlab scripts. The dimensionality of the waveform information was reduced to two primary features, calculated from the 1ms sample waveforms; energy and first principle component. The energy of a signal *x* is defined as the sum of squared moduli given by the formula:

$$\varepsilon_x \triangleq \sum_{n=0}^{N-1} |x_n|^2$$

The first principle component is the linear combination of the standardized original variables and accounts for the greatest possible variance in the dataset. These values were used in combination with peak amplitude, time at peak and width of waveform to analyse and discriminate the activity of different single units. Peak amplitude is defined as the maximum amplitude reached during the sample window. Time at peak is defined as the time at which the waveform reached peak amplitude and is normalised to give a time point within the 1ms waveform window. Width of waveform is defined as the length of time between a spike's peak and its trough (see Figure 5.8 for a visualisation). Klustakwik (Kadir, Goodman, & Harris,

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[21] We did attempt to record cells showing differential activity for a number of days, however, the stability of our tripod drive design did not permit reliably holding the same cells for more than one day. This suggests that the number of cells we recorded more than once was probably quite low.

[22] We would expect 48 samples, 50 samples suggests a resolution of 50kHz. Why this discrepancy arises is unclear, the system may bracket each window with added neutral voltage samples.

2013) spike sorting algorithms were used to initially distinguish and isolate separate clusters given the features described above. The clusters were then manually checked and potentially refined using the manual cluster cutting GUI, Klusters (Hazan, Zugaro, & Buzsaki, 2006). As well as the previously mentioned features, manual cluster cutting also made use of spike auto and cross-correlograms (Examples of these can also be seen in Figure 5.8).

#### 5.3.9.2 Position Data and Firing Rate Maps

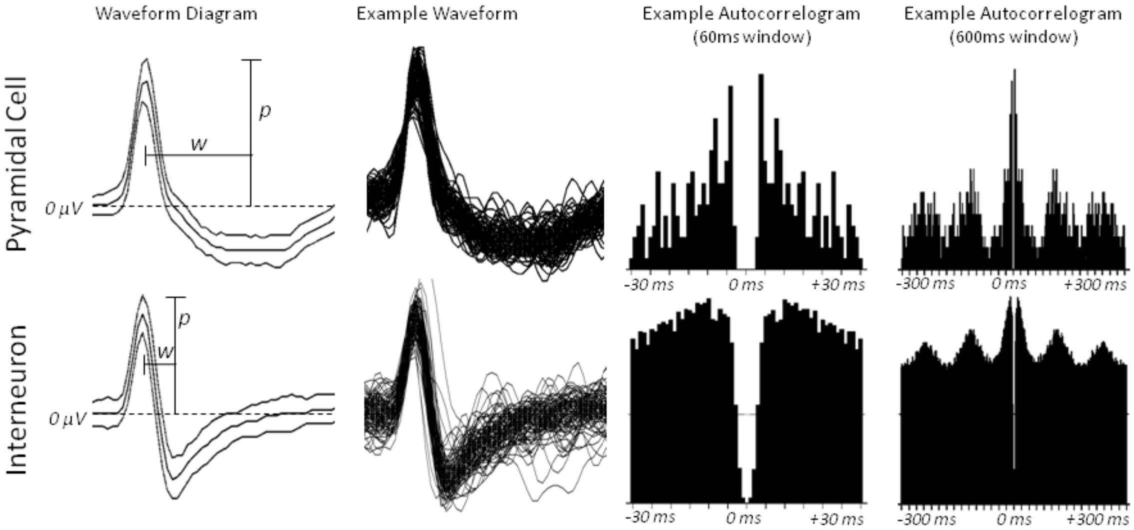

**Figure 5.8:** Showing waveform characteristics for an example pyramidal cell (top row) and interneuron (bottom row). The far-left column contains labelled diagrammatic waveforms showing the *M* and *SD* of 100 random samples, *w* labels the width of waveform, *p* labels the peak amplitude. The middle-left column shows the actual waveform, again composed of 100 random samples. The middle-right column shows the spike autocorrelogram cut to a 60ms window (30ms before and after spike peak) based on all spikes. The far-right column shows the spike autocorrelogram cut to a 600ms window (300ms before and after spike peak) based on all spikes. From these figures it is clear how pyramidal cells and interneurons can be discriminated based on their firing characteristics. Interneurons have a much steeper and shorter waveform, the absence of complex spiking also gives their spike autocorrelogram a 'V' shaped refractory period (at 0ms) and a gradual slope from here to asymptotic levels, however, both cell types may be theta modulated; this can be seen here in the 600ms spike autocorrelograms, identified by the presence of 5 peaks.

As the rat navigates an environment, the infra-red LEDs used for tracking are inevitably obscured at many time points. Position information is necessary for analysing spike data; therefore, for these points the position of the rat must be estimated based on known information. For this purpose we used a nonlinear recursive estimator or Kalman filter (Kalman, 1960) which has a number of advantages over a linear filter technique (Zaknich, 2005). Maps showing the distribution of spikes in the form of firing rate were then produced in order to better visualise the spatial modulation of each cell's firing, or lack thereof. These maps were also used to calculate a number of spatial measures which will be described below as well as to distinguish and count place fields. We generated rate maps using an algorithm described previously (Leutgeb, Leutgeb, Moser, & Moser, 2007). Briefly, the environment being mapped was divided into 2.5 x 2.5cm bins and the average firing rate within each bin was calculated by dividing the distance between the centre point of the bin and every recorded spike by the same measure for every recorded position data point. However, these distances were weighted by a Gaussian such that spikes and position data outside the bin had an effect on the calculated firing rate which approximated zero. The Gaussian kernel used is given by:

$$g(x) = \exp\left(\frac{-\mathrm{x}^2}{2}\right)$$

The algorithm for calculating firing rate is given by:

$$\lambda(x) = \sum_{i=1}^{n} g\left(\frac{s_{i-x}}{h}\right) \Bigg/ \int_{0}^{T} g\left(\frac{y(t) - x}{h}\right) dt$$

where *Si* represents the positions of every recorded spike, *x* is the centre of the current bin, the period [0 T] is the recording session time period, *y(t)* is the position of the rat at time *t*, and *h* is a smoothing factor, which was set to 2.5 cm. Bins in which the rat did not explore within 5cm of the centre were regarded as having never being visited.

#### 5.3.9.3 Spatial Firing Measures

Using the firing rate maps described above, we calculated a measure of spatial firing for identifying spatially modulated cells (place cells). Spatial information content (Skaggs et al., 1993) is defined as:

$$Information\,content = \sum P_i(R_i/R)\log_2(R_i/R)$$

where $i$ is the bin number, $P_i$ is the probability for occupancy of bin $i$, $R_i$ is the mean firing rate for bin $i$, and $R$ is the overall average firing rate.

#### 5.3.9.4 Place Fields

For clusters identified as place cells, firing rate maps were used in order to count the number of distinguishable place fields which were present in each environment. Custom Matlab scripts were used to isolate areas of firing over 20% of the maximum firing rate (peak firing rate in firing rate map). Areas of firing less than 1Hz were excluded. For open field sessions only firing which occurred within the walls of the square box was included[23]. Regions of firing meeting the above criteria which also had an area greater than 9 contiguous[24] pixels (1 pixel was approximately 2.5cm square) were considered place fields. The size, position, dimensions and firing rate properties of these fields were then extracted.

#### 5.3.9.5 Discrimination of Cell Types

During the cluster cutting stage described above every effort was taken to remove clusters which were noise, interference or mechanical artefacts generated during the

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[23] Cells often fire when the rat's head is not within the wall boundaries or when he is purposefully looking outside of the enclosure at the surrounding environment. Coupled with the small length of time spent there (firing rate is calculated as spikes divided by time) there are often anomalous regions of high firing rate outside of the enclosure boundaries. In the maze environment the rats' behaviour is more directed and consistent so there are far fewer of these anomalous areas, however, they were not removed from this environment due to the complexity of the maze's shape.

[24] Contiguity is defined here as sharing at least one side

recording process. Remaining clusters were further classified using custom Matlab scripts. Automated classification followed a number of criteria, a cell was classified as a place cell if:

- Firing rate was greater than 0.1Hz but less than 5Hz;
- Width of waveform was greater than 250ms;
- Spatial information content was greater than 0.5b/s.

or an interneuron if:

- Firing rate was greater than 0.1Hz;
- Width of waveform was less than 250ms.

How width of waveform can be used to discriminate between pyramidal cells and interneurons can be understood visually in Figure 5.8 on page 137. Interneurons were further subdivided into low firing and high firing based on a cut-off firing rate of 5Hz. Remaining units were classified as high firing pyramidal neurons (if satisfying the criteria for a place cell but firing rate was too high) and pyramidal cells (if satisfying the criteria for a place cell but spatial information content was too low). These criteria were assessed independently for open field and maze sessions. After automatic sorting of clusters in this way a second round of manual discrimination removed any clusters which were not recognisable as any form of single unit. This discrimination was based on the presence of a refractory period, the consistency of firing over the course of the recording session and the shape of the cluster's waveform.

#### 5.3.9.6 Cluster Quality

We used three primary measures to assess cluster and signal quality; isolation distance (Iso-D), $L_{\text{ratio}}$ and signal to noise ratio (S/N). Isolation distance and $L_{\text{ratio}}$ are described to great detail in (Schmitzer-Torbert, Jackson, Henze, Harris, & Redish, 2005) and in (Schmitzer-Torbert & Redish, 2004) respectively. Briefly, Iso-D and $L_{\text{ratio}}$ both make use of a measure known as Mahalanobis distance; this quantifies the distance between the spikes of a cluster and spikes of noise in n-dimensional space and is specifically suited to computations where the dimensions are correlated measures (if the dimensions are uncorrelated the mahalanobis distance is equivalent to the Euclidean distance between the centre of a cluster and the noise spikes).

$L_{\text{ratio}}$ makes use of this distance information to calculate the probability that spikes out with the cluster should be included in the cluster. This is arranged such that spikes occurring at the centre gain a probability of 1 and spikes occurring outside the cluster boundary gain a probability which approaches 0. Under these conditions, noise or artefact spikes which occur within or near the centre of a cluster have a large impact on the cluster's $L_{\text{ratio}}$. Such noise spikes will raise a cluster's $L_{\text{ratio}}$ from zero, closer to 1. In this way, a low $L_{\text{ratio}}$ denotes that a cluster is not only noise free but also has a boundary of uncontaminated space surrounding it.

Iso-D is based on more geometric foundations and as such is easier to understand; the isolation distance of a cluster is calculated as the squared mahalanobis distance of the $n_c^{th}$ closest noise spike, where $n_c$ denotes every spike in the cluster and noise refers to all other clusters recorded on the tetrode. This corresponds to the radius of the smallest ellipsoid which contains an equal number of noise and cluster spikes. In this way, a large Iso-D denotes that a cluster is well separated from the other clusters recorded on the tetrode (including any noise). Iso-D cannot be established if there are fewer noise spikes than spikes in a cluster.

Rather than operating to measure the quality of a recorded cluster, signal to noise ratio indicates how far above or below the background noise a cell's mean waveform peaked. This indicates how strong the signal was and how likely it is we recorded the occurrence of every spike. As the signal and noise are both measured across the same impedance we defined signal to noise ratio by the following:

$$Signal\ to\ Noise\ Ratio = \left(\frac{\left(\sqrt{}\mu_{signal}\right)^2}{\left(\sqrt{}\mu_{noise}\right)^2}\right)^2$$

where μ is the mean of the waveform amplitude. For noise we used the existing noise cluster which is present on every tetrode. A ratio of 1 indicates that a waveform peaked at the same amplitude as the background noise, higher numbers indicate a signal peak greater than that of the background. It should be noted; however, that this noise cluster is composed of waveforms in which at least one of the four tetrode channels achieved a great enough amplitude to trigger the recording system. This biases the noise sample to a level above that of the true background noise, which makes our S/N measurement more conservative. For every cluster we calculated its signal to noise ratio on all four tetrode channels, the highest of these was used in further analyses.

#### 5.3.9.7 Context Dependent (C-D) Firing

In order to assess C-D activity in the maze sessions we divided the maze into 14 parts corresponding to the different boxes and alleyways. Spike and position data were analysed for all maze areas, however, we tested for the presence of C-D firing in only a subset of these. These areas are the only four where there are overlapping trajectories and can be seen in Figure 5.9. Furthermore, a cell had to be 'active' in a maze area for it to be considered a C-D cell; we defined active as firing >1Hz on average in the maze area on at least one of the accumulated goal trajectories (when all of the individual trajectories to a goal are combined).

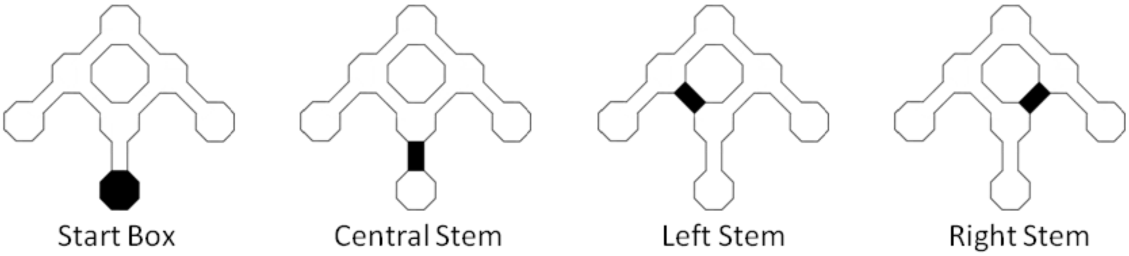

**Figure 5.9:** Showing the four maze areas were we analysed firing rate data for the presence of differential activity. These maze areas are the only four in which we can be sure to find overlapping trajectories which ultimately lead to different goals. For instance, in the start box the rats are constrained within the relatively small area at the beginning of every trajectory, however, over the course of the session the rats leave this box and navigate each of the four possible trajectories through the maze. We can separate these different trajectories and analyse place cell firing in the start box, any changes in firing rate are most likely due to the difference in planned trajectory.

For maze analysis; trajectory position data were plotted, the locations of the first and second choice points were manually defined. These three areas were then used to automatically identify the location of the other maze locations based on the shape and dimensions of the maze. The locations of the maze areas were then normalised and linearised so that the distance from the start box, through each of the intermediate maze areas to the goal box was equal for each of the four trajectories. Spike and position data were assigned to one of these maze areas, based on proximity to the area locations. Individual trajectories were then isolated (during recording, digital inputs were used to mark the beginning and end of each trajectory), grouped into the four possible routes and the data for each were combined, this process can be seen more clearly in Figure 5.10. For individual clusters, firing rate was calculated in each of the maze areas shown in Figure 5.9

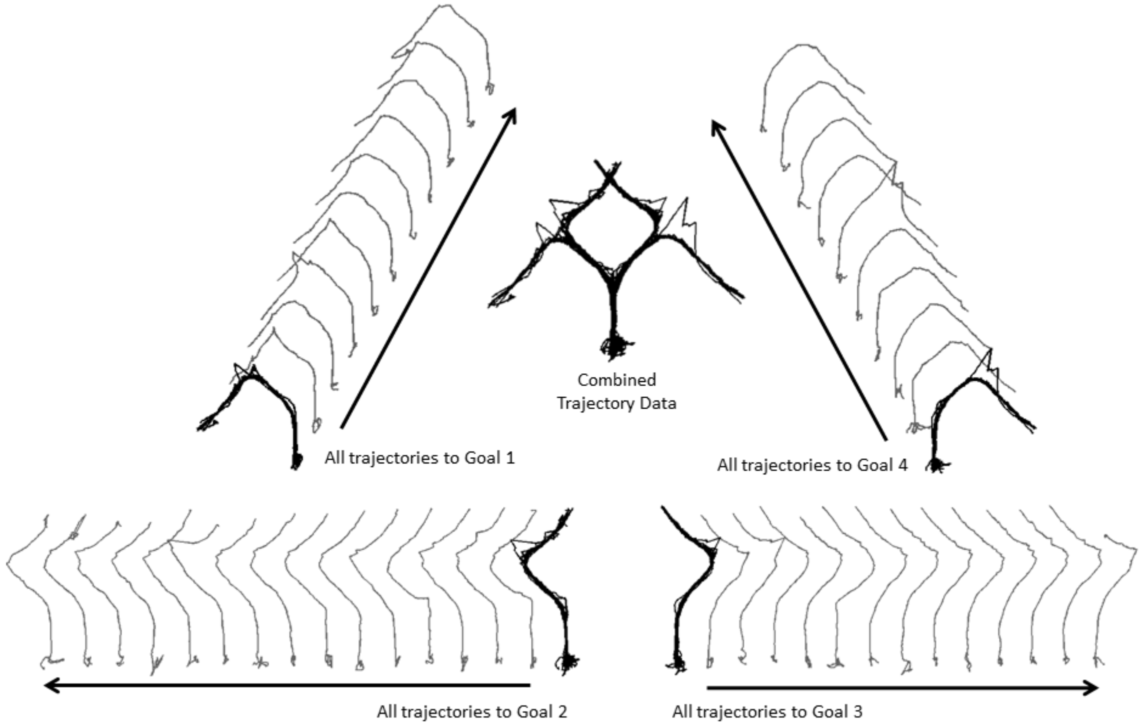

**Figure 5.10:** A representative day's data analysis. Showing every trajectory to each goal box, individual trajectories are plotted in grey, all of the trajectories to each goal are plotted together in black and all of the trajectories to all four goals are plotted together in the centre of the figure where the shape of the maze becomes obvious. Note that in the last trajectory to Goal 3 the rat was unable to enter the goal box because of the transparent barrier; as the rat did not know that the food had moved or that the trajectory was actually blocked when he was in the start box this trajectory can be included in differential data analyses. Errors made after these 'error' trials were not included in any analyses.

for each of the four routes. Firing rate was calculated as the total number of spikes divided by the total amount of time (Hz). For each maze area we also calculated the average x-coordinate occupied by the animal (binned into approx. 2.5cm square bins), average y-coordinate occupied by the animal (binned into approx. 2.5cm square bins) and the average velocity of the animal (calculated as total distance travelled divided by total time spent in the area).

For each of the four maze areas identified in Figure 5.9, an ANCOVA was performed to identify the effect of intended destination on firing rate. Average binned x-coordinate, average binned y-coordinate and average velocity were included as covariates. If intended destination was not found to have a significant effect on firing rate[25] the cell was not considered to fire differentially, but if firing rate was found to be significantly modulated by intended destination, post-hoc tests were performed. Multiple comparisons were carried out to further define the significant firing rate distribution; these consisted of six pairwise comparisons of estimated marginal means[26]. The six results of these tests were reduced to a binary and then converted to a decimal representation; such that the 64 possible combinations of significant and non-significant results were numbered 1-64.

#### 5.3.9.8 Ensemble Analysis

As well as testing trajectory dependent activity at the single cell level, we also looked to see whether ensemble place cell activity could be used to accurately determine the animal's trajectory. If place cells show trajectory dependent activity at the ensemble level, then we would expect trajectory determination to be equally accurate for all four routes, as each would be discriminable using the ensemble. However, if cells show goal dependent activity at the ensemble level then we would expect trajectory determination to be

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[25] ANCOVA tests were considered significant when $p < .05$.

[26] Multiple comparisons were made in SPSS v.19. A Sidak correction method was employed.

significantly less accurate for the two central routes, as these would be less distinct at the ensemble level.

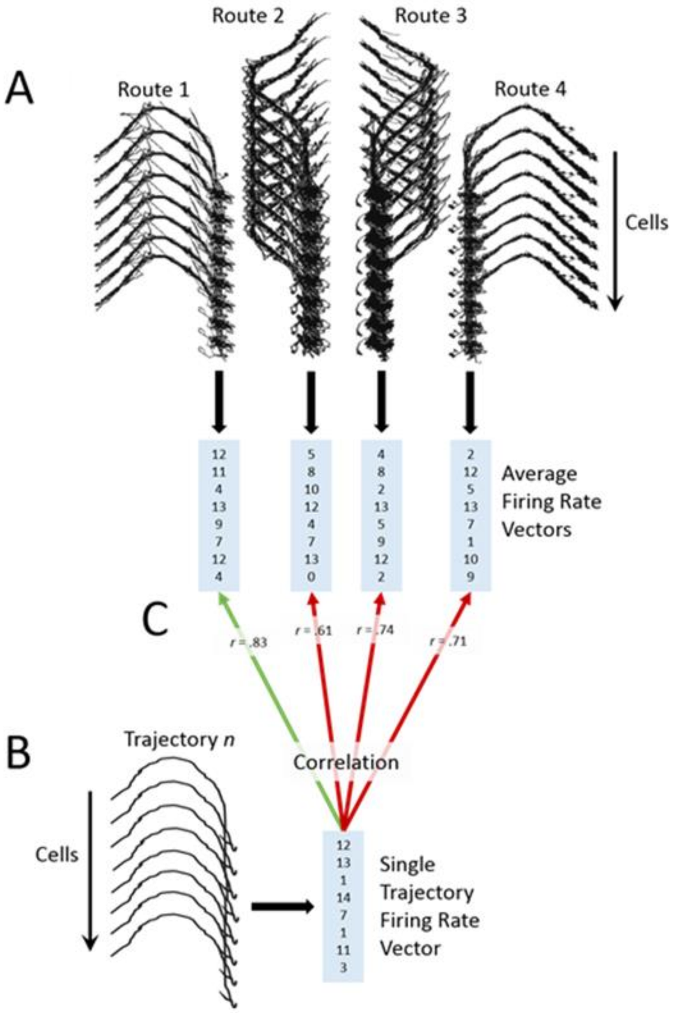

**Figure 5.11:** Schematic showing ensemble analysis procedure. **A**) For every cell in the ensemble (*n*) the cell's average firing rate in the maze area (for example the start box) is calculated for each route, using every recorded trajectory along that route. This generates four average firing rate vectors, one for each route, *n* cells long. **B**) For every trajectory recorded in this session, the firing rate of every cell is calculated in the same maze area, but using data from only this one trajectory. This generates a trajectory firing rate vector which is *n* cells long. **C**) The level of correlation between the trajectory firing rate vector and each of the route vectors is calculated and the route with the highest correlation is selected as the 'decoded' one. In this example the trajectory correlates most highly with the route 1 vector, which is a successful or correct decoding, selecting one of the other three route vectors would represent incorrect decoding.

We took ensembles of place cells (containing a minimum of 6 simultaneously recorded place cells) and calculated the average firing rate of each cell in each area of the maze when all trajectories to each goal are combined (i.e. all of a single cell's spikes which occurred in the start box when the animal was navigating to goal 1, divided by the total time spent in the start box when the animal was navigating to this goal). These average firing rates were arranged into four vectors or 'sets', *n* cells long, one for each route. We then did the same for individual trajectories and then calculated the correlation between these single trajectories and each of the trajectory sets. The animal's destination was 'decoded' as belonging to the set with which the single trajectory correlated most highly. This decoding was then assessed for the number of correct and incorrect groupings, if the central routes were represented more similarly (due to goal dependent firing at an ensemble level) then we would expect a greater frequency of decoding errors for these two routes. A schematic of this procedure can be seen in Figure 5.11.

#### 5.3.9.9 Perfusion and Histology

At the end of the experiment or if a rat's microdrive became detached the animal was anaesthetised using the Isoflurane inhalation anaesthetic described previously and injected intraperitoneally with a lethal dose of a pentobarbital agent (0.7ml Euthatal, Merial Animal Health Ltd., Essex, UK). When fully unresponsive to external stimuli the abdomen was medially incised to expose the ribcage which was itself incised and retracted to expose the heart. The blood was purged and replaced with 0.9% saline solution followed by a 4% formalin (10% formaldehyde) solution. The brain was then extracted and stored in 4% formalin for at least 7 days prior to any histological analyses. The brains were sliced to give 32µm sections on a thermostat regulated freezing microtome at -20°. These slices were mounted on microscope slides, Nissyl stained with a 0.1% cresyl violet and coverslipped. A slice best representing the electrode track was then imaged in tiles using a high resolution microscope mounted camera which were combined using ImageJ software (ImageJ, NIH, Bethesda, http://imagej.nih.gov/ij/, 1997-2014).

## 5.4 Results

### 5.4.1 Histology

*Recordings were made in CA1*

Electrode tracks were identified in 7 out of the 8 animals (see Figure 5.12), in these 7 animals all recordings were made in the CA1 region of the HPC. The electrode track for F6207 was lost due to necrotic tissue damage, likely the result of an infection at the implant site. However, part of the electrode track can be seen in the cortex above the HPC and appears to have descended at the correct ML and AP coordinates. Given that the other 7 animals were all found to be implanted to the correct coordinates and that this rat contributed only 9.95% of the cells included in our final multiple comparison analysis, his data were not removed from our analyses.

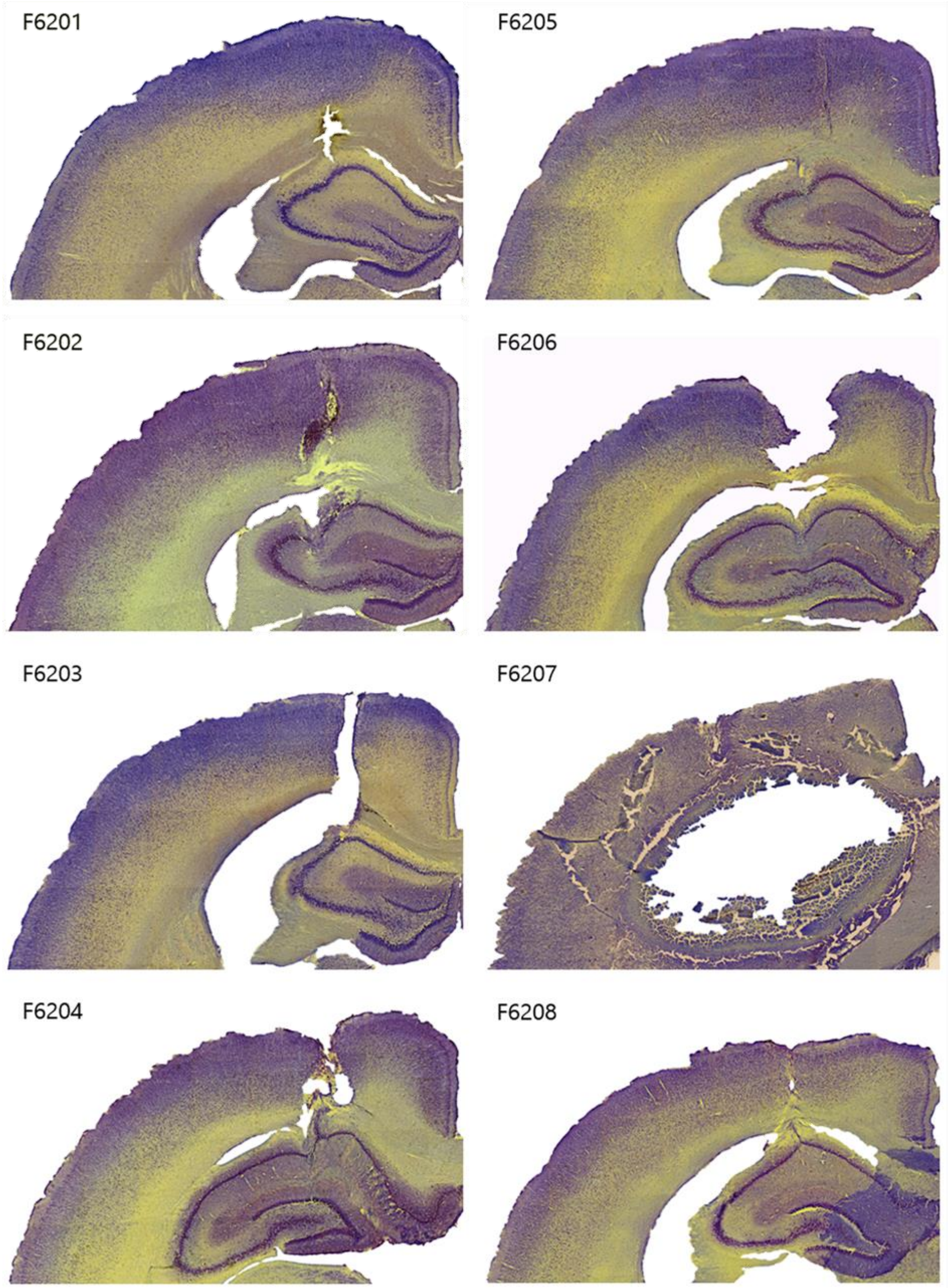

**Figure 5.12:** Showing histological sections for all eight implanted animals (one slice per rat). Rat ID numbers are given at the top left of each image. Each slice shows the electrode track at 2.5x magnification. All electrode tracks have a confirmed end point at or below the CA1 stratum pyramidale except for rat F6207 – this rat suffered necrotic tissue damage specific to the hippocampus shortly before the brain was extracted. Part of the electrode track can be seen above where the hippocampus would have been and it appears to descend at the correct ML.

### 5.4.2 Behavioural Training

*Rats learned the layout of the maze and the task demands*

Rats were trained for a minimum of 11 sessions on the maze before surgery. A two-factor univariate ANOVA (error frequency and session) confirms that over the course of the training they did not significantly improve the number of errors they made before finding the food [$F(9,110) = 1.70$, $p > .09$, $\eta_p^2 = .12$]. A second two-factor univariate ANOVA (run time and session) also confirms that the time they took to complete trials before finding the food also did not change over the course of the training [$F(9,110) = 1.12$, $p > .30$, $\eta_p^2 = .08$]. These results are shown in panels B and A, respectively, of Figure 5.13 below.

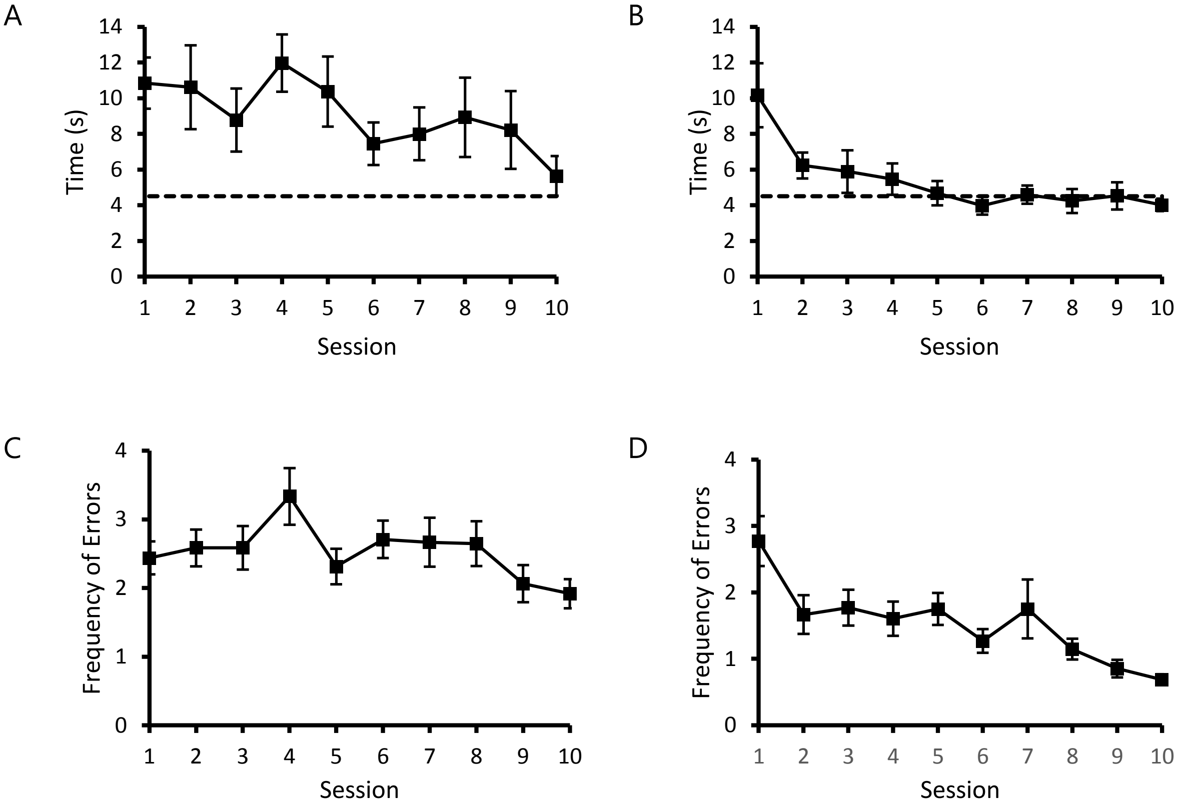

**Figure 5.13:** Average and SEM values per goal (11 trials) are shown. Dashed lines in A and B show the length of time in which rats could be expected to comfortably complete a trial (1.35m at 0.3m/s)(Hoydal, Wisloff, Kemi, & Ellingsen, 2007). In panel D, the frequency of errors expected if the rats were choosing randomly would be 8.25 (75% of 11). Panel **A**) the length of time taken for the rats to navigate from the start box to a goal box before they knew the location of the food reward. Panel **B**) the length of time taken for the rats to navigate from the start box to a goal location once they were aware of the correct goal location. Panel **C**) the number of errors made by the rats before they were aware of the correct goal location. Panel **D**) the number of errors made by the rats once they were aware of the food reward's location.

However, a two-factor univariate ANOVA (error frequency and session) suggests that the number of errors the animals made after finding the food did significantly decrease over the course of the training [$F(9,110) = 4.92$, $p < .001$, $\eta_p^2 = .29$]. A second two-factor univariate ANOVA (run time and session) also suggests that the time the rats took to reach the food reward once they knew where it was also decreased with training [$F(9,110) = 4.24$, $p < .001$, $\eta_p^2 = .26$]. These results are shown in panels D and C, respectively, of Figure 5.13 below.

A three-factor univariate ANOVA comparing the effect of training session on rats' runtimes when they were running with and without knowing where the food was located confirms that the rats navigated from the start box to a goal box significantly faster once they were aware of the reward location [$F(1,240) = 35.59$, $p < .001$, $\eta_p^2 = .12$]. Looking at all sessions combined, the rats needed an average of 9.08 (*SD* = 6.19) seconds to complete a trial if they were not aware of the food location but only an average of 5.38 (*SD* = 3.48) seconds once they were aware which goal was rewarded. Alternatively, on average the rats took approximately 41% less time to navigate through the maze once they knew where the food was located. This effect can be seen when comparing panels A and C in Figure 5.13.

### *Rats found the central routes much harder to learn and navigate than the outer ones*

During training the animals made a significantly greater number of errors when navigating the two central routes to goal box 2 (*M* = 19.95, *SD* = 6.42) than the outer ones to goal boxes 1 and 3 (*M* = 10.58, *SD* = 5.76) [$t(119) = 6.38$, $p < .001$, $d = 0.77$, paired samples t-test]. A three-factor univariate ANOVA (frequency of errors, session and destination) confirms a significant main effect of route destination (outer route or central route)[$F(1,240) = 40.98$, $p < .001$, $\eta_p^2 = .16$], session [$F(9,240) = 4.21$, $p < .001$, $\eta_p^2 = .15$] and a significant interaction between the two [$F(9,240) = 1.98$, $p < .05$, $\eta_p^2 = .08$]. These results can be seen in Figure 5.15.

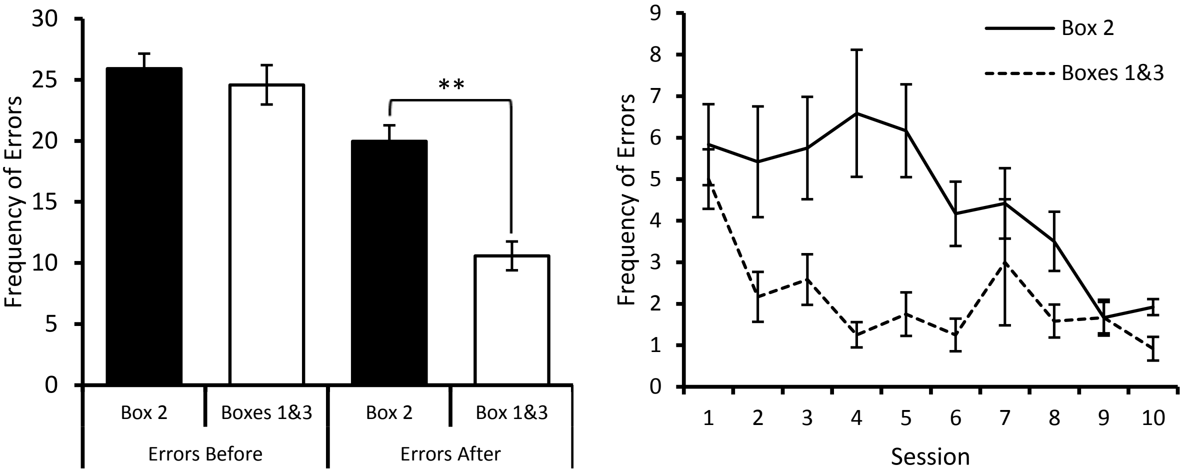

**Figure 5.15:** Showing behavioural training data. Left) the average and SEM total number of errors made when navigating the two routes to Box 2 and the routes to Boxes 1 and 3. This is shown for both errors made before finding the location of the food reward and after. After finding the food the rats made significantly more errors when navigating the routes to Box 2 (the central two routes). Right) the average and SEM number of errors made when navigating the two routes to Box 2 and the routes to boxes 1 and 3. This is shown only for those errors made after finding the food reward. Throughout training the rats frequently made significantly more errors when navigating to Box 2.

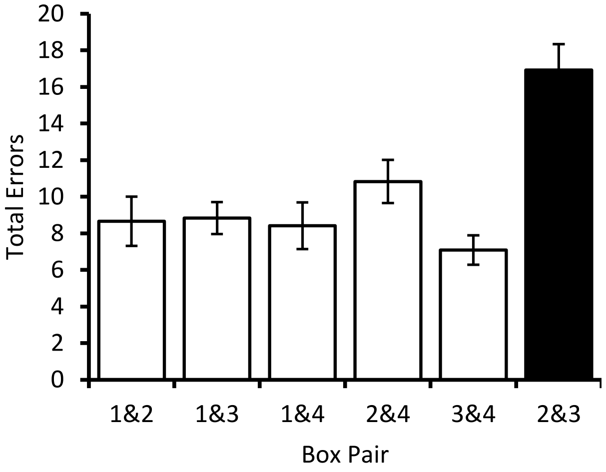

**Figure 5.14:** Showing a breakdown of post-reward errors. Average and SEM total values are shown. For example, the first bar shows the average number of times the rats were rewarded for taking route 1 but instead navigated route 2 in addition to the average number of times the rats were rewarded for taking route 2 but instead took route 1.

We sought to define the nature of the errors which rats made after finding the location of the food reward. An error where the rat takes route 1 to Box 1 when route 2 to Box 2 is rewarded can be interpreted as a similar form of navigation error as taking route 2 to Box 2 when route 1 to Box 1 is rewarded (the four routes and three boxes can be seen in Figure 5.6. Both result from a form of spatial confusion during which the rat appears to be temporarily unable to discriminate the two spatial locations or routes. Figure 5.14 shows the distribution of post-reward errors when grouped into the six possible pairs of these confusion errors. From this figure it is clear that the rats confused routes 2 and 3 (both to Box 2) significantly more than any route pairs [$F(5,66) = 9.14$, $p < .001$, $\eta_p^2 = .41$, univariate ANOVA, errors and box pair], post-hoc multiple comparison tests confirmed routes 2 and 3 were confused significantly more than any other route pair [$p < .01$, in all cases, with Sidak correction].

#### 5.4.2.1 Training Without Barrier

*Without the transparent barrier, rats did not alternate between the two trajectories to goal box 2*

We attempted to train 8 naïve animals to perform our task without using the transparent barrier. Without this barrier to direct their behaviour none of the animals adequately alternated between the two trajectories to goal box 2 (the middle goal box), and this alternation did not improve with training. This was assessed using a two-factor univariate ANOVA (alternation rate and session) [$F(11,84) = 1.23$, $p > .28$, $\eta_p^2 = .14$]. Without adequate alternation, rats would not sample these trajectories sufficiently to perform our

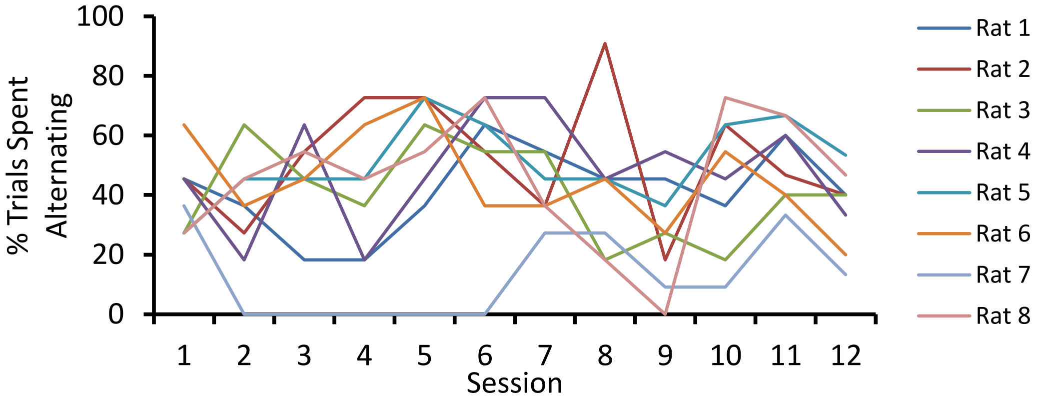

**Figure 5.16:** Figure showing training data for 8 naïve rats when the transparent barrier was not used. Lines represent the percentage of trials which the rats spent alternating. For example, if a rat used both trajectories equally, it would spend 100% of its trials alternating, if it used only one trajectory it would spend 0% of its trials alternating. None of the rats adequately alternated at a level which would provide enough trajectories for statistical analysis, nor was their behaviour generally consistent and it did not appear to improve over the course of these 12 sessions.

firing rate analyses reliably, thus, we did not train these animals any further. This data can be seen in Figure 5.16.

### 5.4.3 Single Unit Activity

#### 5.4.3.1 Cell Identification and Firing Properties

We recorded and analysed a total of 641 clusters. In the maze environment 599 (93.45%) of these were identified as cells based on the criteria described previously, 386 (64.45%) of these cells were identified as place cells and 146 (37.82%) of these place cells were identified as splitters in one of our areas of firing rate analysis. In the open field environment 578 (90.17%) of these clusters were identified as cells and 321 (55.54%) of these cells were identified as place cells.

*Place cells over represent the start area of the maze*

Similarly to what was reported in Ainge et al. (2007) we found that place cells are far more likely to show activity in the initial areas of the maze than later ones, this is shown by a significant negative correlation between the distance from the start box and the number of place cells which remain active [$r(12) = -0.57$, $p < .05$], we also found a similarly negative correlation between the number of place cells showing splitter activity and the distance from the start box [$r(12) = -0.73$, $p < .01$]. These effects can be seen in Figure 5.17.

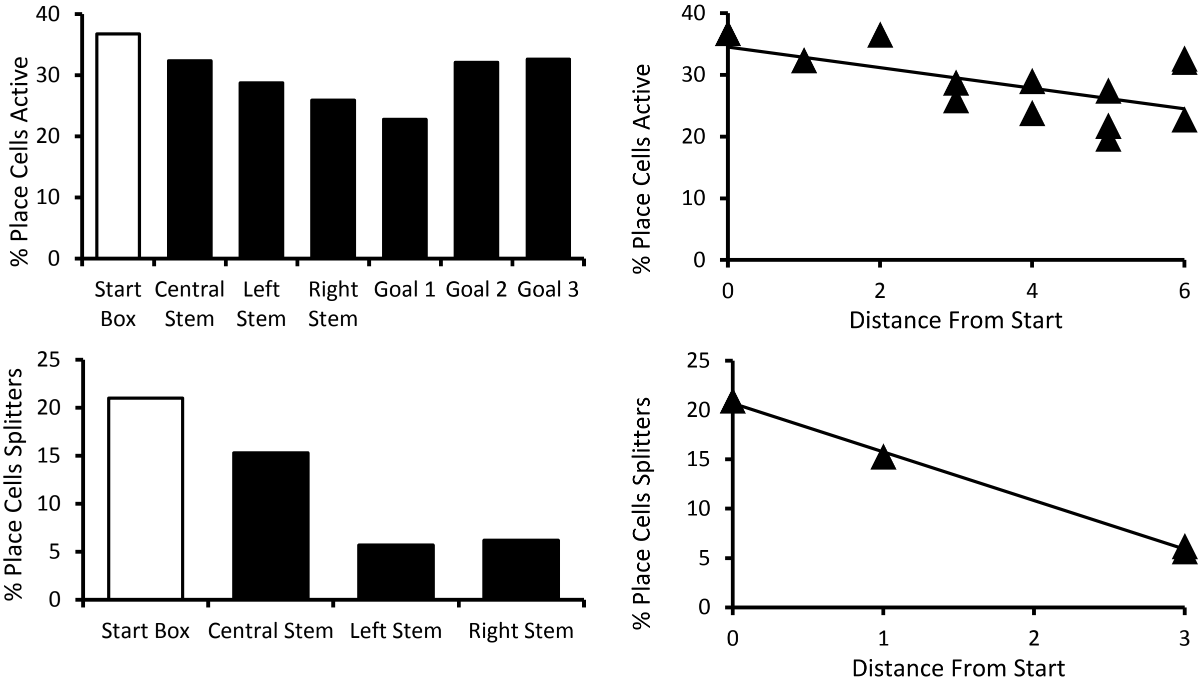

**Figure 5.17:** Showing the distributions of active place cells and splitters. Top left) The percentage of all place cells which were active (fired >1Hz) in each of the primary maze area. Top right) The percentage of all place cells which were active in all 14 maze areas, this is plotted against the distance of the maze area from the start box. It is clear that as the distance from the start box increases, the percentage of place cells which are active decreases. Bottom left) The percentage of all place cells which meet the criteria for a splitter cell in each of the 4 maze areas analysed for splitter activity. Bottom right) The percentage of all place cells which meet the criteria for a splitter cell in each maze area is plotted against the distance of the maze area from the start box. Again, it is clear that as the distance from the start box increases, the percentage of place cells which are splitters decreases.

We recorded a total of 810 place fields in our maze environment (2.10 fields per cell) and 1116 fields in our square box environment (3.48 fields per cell). By counting individual place fields we also found a much higher proportion of these in the start box of the maze compared to the other areas, this relationship did not form a linear trend as described above [*r*(12) = -0.46, *p* > .10], however, the probability of observing such a distribution by chance is very low [$X^2$(13, *N* = 810) = 147.14, *p* < .001][27]. The probability of observing the distribution of place fields we found in the square box environment is also very low [$X^2$(8, *N* = 1116) = 117.32, *p* < .001][27], although the relationship here is less clear. All correlations are Pearson's correlations, these results can be seen in Figure 5.18.

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[27] Chi square probability, assessed using: http://graphpad.com/quickcalcs/chisquared2/

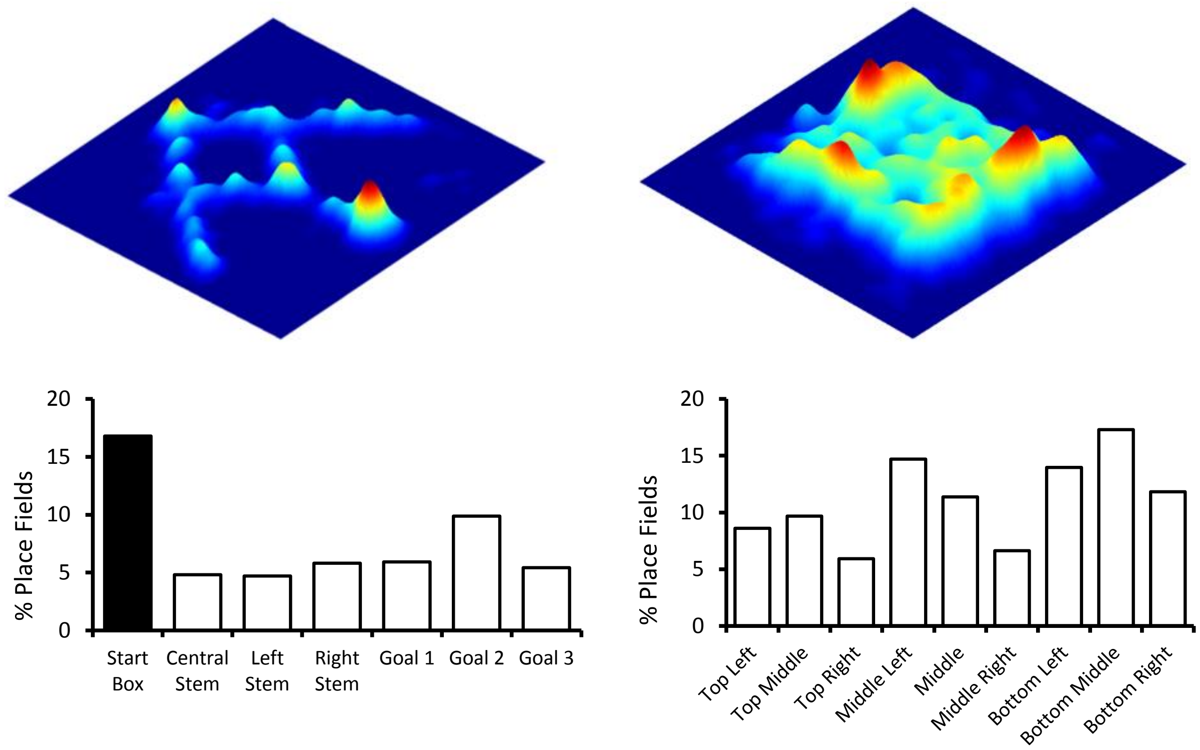

**Figure 5.18:** Left) Showing a three dimensional 'heat map' of all place cells recorded in the maze, below this is a plot showing the percentage of all place fields which occurred in each maze area of interest. Right) The same as left but for the square box environment.

### *Cells show different firing characteristics in the open field and maze areas*

The place cells we recorded showed a number of firing characteristics which differ between the open field and maze environments[28]. Cells exhibited a significantly higher firing rate (total spikes divided by total time) in the maze sessions ($M$ = 1.23 Hz, $SD$ = 0.55) than in the open field sessions ($M$ = 0.78 Hz, $SD$ = 0.04) [$t$(644.79) = 6.93, $p < .001$, $d$ = 0.55]. Peak firing rate, defined as the highest value recorded in the environment's firing rate map, also differed significantly between environments with a much higher peak firing rate in the maze sessions ($M$ = 14.15 Hz, $SD$ = 0.61) than in the open field environment ($M$ = 9.98 Hz, $SD$ = 0.43) [$t$(669.56) = 5.59, $p < .001$, $d$ = 0.43]. Place cell firing in the maze sessions was also much more spatially tuned than in the square box sessions as measured by spatial

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[28] Due to the large sample size small differences between groups is likely to prove statistically significant, for this reason please refer to Cohen's $d$ values given with statistical results for a measure of effect size – for this measure .2 would be considered a mild effect, .5 moderate and .8 strong (Cohen, 1988).

information content (*M* = 1.71 b/s, *SD* = 0.04; *M* = 1.45 b/s, *SD* = 0.04, respectively) [*t*(704.19) = 4.19, $p < .001$, *d* = 0.32].

We also observed a higher number of place fields per cell in the square box (*M* = 4.75, *SD* = 2.5) than in the maze (*M* = 3.32, *SD* = 1.43) [*t*(429) = 7.18, $p < .001$, *d* = 0.70]. When these values are adjusted to express the number of fields per $m^2$ area, we see that there is actually a significantly higher number of fields per $m^2$ in the maze environment (*M* = 6.65, *SD* = 2.87) than in the square box (*M* = 4.76, *SD* = 2.51) [*t*(430) = 7.28, $p < .001$, *d* = 0.70]. Place fields were also significantly larger in the square box environment (*M* = 56.97 pixels or ~620cm$^2$, *SD* = 83.79) than in the maze (*M* = 40.62 pixels or ~442 cm$^2$, *SD* = 37.36)[29] [*t*(1924) = -5.19, $p < .001$, *d* = -0.24]. All tests are independent samples t-tests.

### *Cluster quality did not impact firing rate ANCOVA outcome*

A number of factors associated with cluster quality could influence the outcome of our firing rate ANCOVAs. If a cluster is poorly isolated, missing spikes or wrongly including noise spikes it could appear that a cell's firing is modulated by intended destination when in fact it is not. We assessed a number of measures of cluster quality against the outcome of firing rate ANCOVAs; signal to noise ratio (S/N), isolation distance (Iso-D) and $L_{\text{ratio}}$. Specifically we tested the strength of correlation between each of these quality measures and ANCOVA *F* statistic, the results of these tests (bivariate Pearson correlations) can be seen in Table 1, in summary, none of these measures had a significant impact on ANCOVA *F* statistics in any of the four maze areas tested for C-D activity.

Furthermore, we compared the distribution of these three measures between splitter cells and place cells in our population sample. Exact Kolmogorov-Smirnov, independent samples tests confirm that the observed distribution of splitter cell isolation distances did not deviate significantly from that of the wider place cell population [*D* = 1.34, $p > .05$] nor

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[29] For a sense of scale, the octagonal compartments used in our maze have a surface area of ~512 cm$^2$.

did the distribution of $L_{\text{ratios}}$ [$D = 1.01$, $p > .20$] or signal to noise ratios [$D = .89$, $p > .40$]. Cells with an isolation distance less than 10 were excluded from these analyses as our splitter cell criteria restricted these to the place cell population. Combined, these results suggest that the observed splitter activity was not merely a result of poor cluster quality. The distribution of these measures can be seen in Figure 5.19.

Table 1: Cluster quality did not influence ANCOVA results

| Dependent Variable | Independent Variable | df | *r* | *p* |
|---|---|---|---|---|
| Start Box ANCOVA observed *F* Statistics | S/N | 151 | .057 | > .40 |
| | Iso-D[a] | 144 | -.029 | > .70 |
| | $L_{ratio}$ | 151 | -.014 | > .80 |
| Central Stem ANCOVA observed *F* Statistics | S/N | 135 | .163 | > .05 |
| | Iso-D[a] | 128 | .052 | > .50 |
| | $L_{ratio}$ | 135 | -.028 | > .70 |
| Left Stem ANCOVA observed *F* Statistics | S/N | 111 | .185 | > .05 |
| | Iso-D[a] | 104 | -.025 | > .70 |
| | $L_{ratio}$ | 111 | -.043 | > .60 |
| Right Stem ANCOVA observed *F* Statistics | S/N | 97 | -.018 | > .80 |
| | Iso-D[a] | 90 | .156 | > .10 |
| | $L_{ratio}$ | 97 | -.062 | > .50 |

**Table 1:** Showing bivariate Pearson correlation results, assessing the influence of signal to noise ratio (S/N), isolation distance (iso-D) and $L_{ratio}$ on the outcome of firing rate ANCOVAs in all four maze areas. An adjustment for multiple statistical tests was not included.

[a] Incalculable Iso-D values (n = 7) were not included, however, $L_{ratios}$ and signal to noise ratios are included for all clusters.

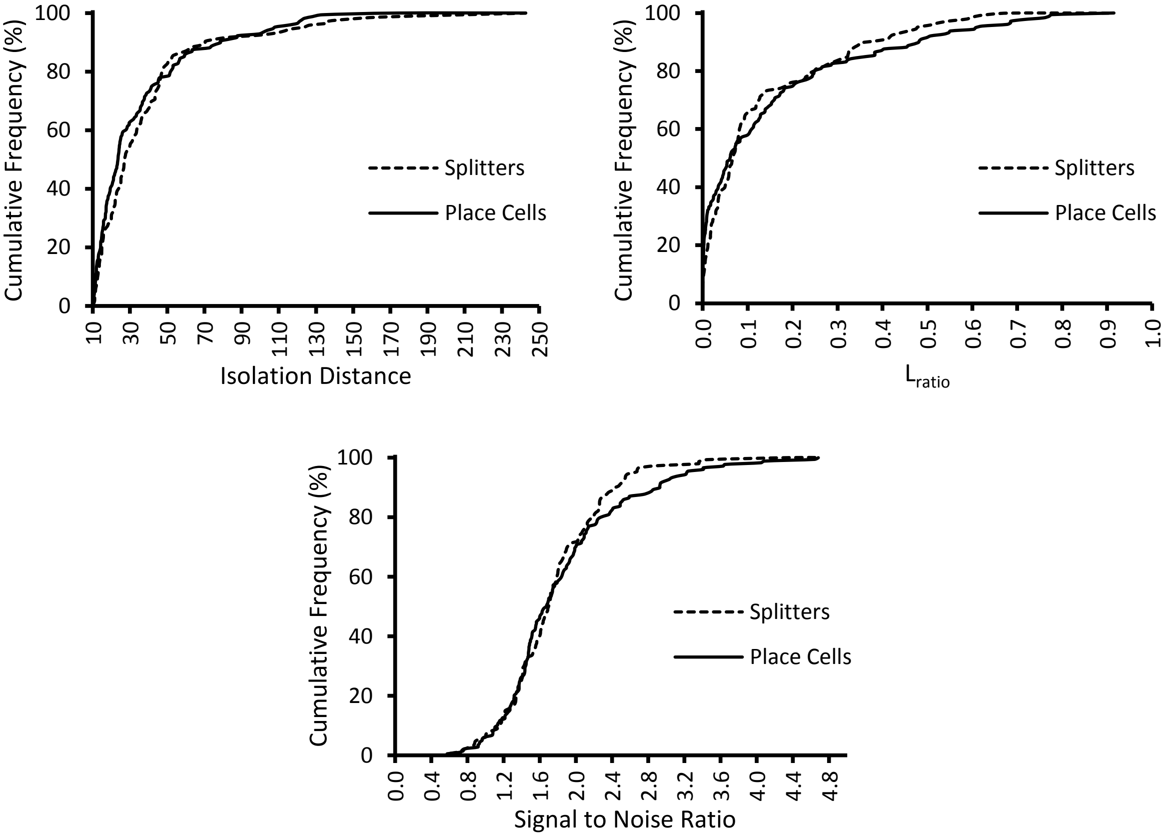
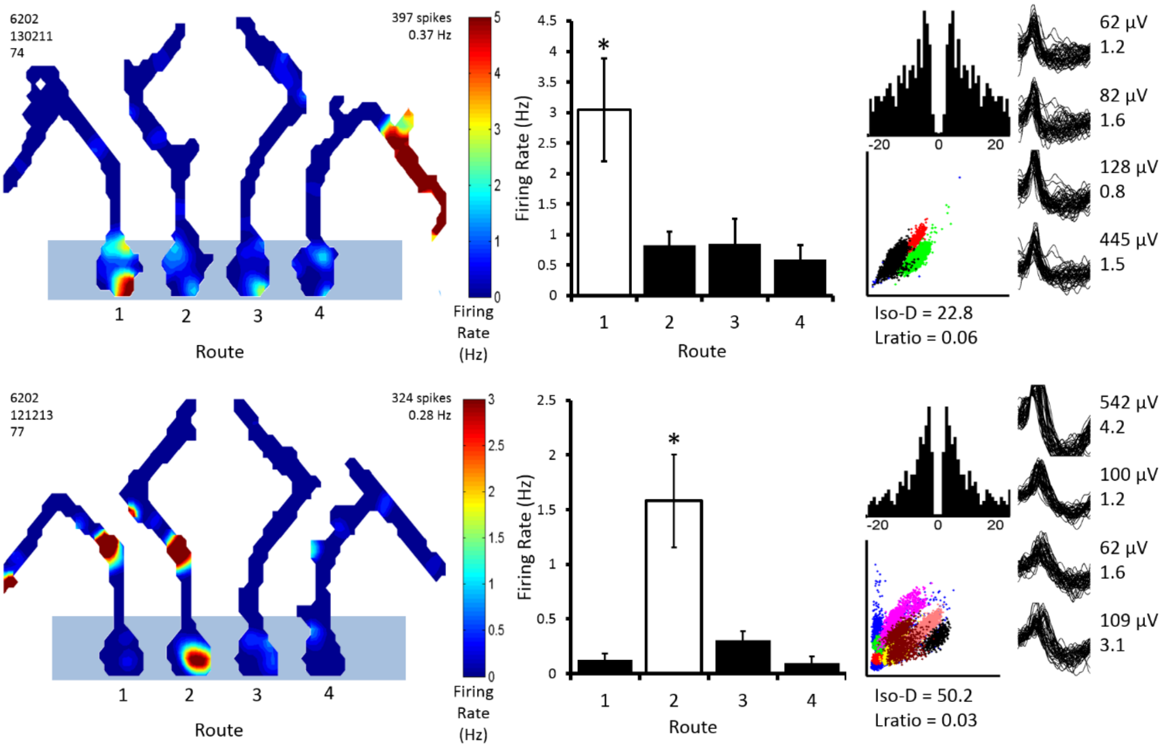


**Figure 5.19:** Recording quality assessment. Top left, top right, bottom; showing the observed cumulative distribution of isolation distance values, $L_{ratios}$ and signal to noise ratios, respectively, for both place cells and splitters. Percentages are of the total number of cells in each population. Distribution analyses were carried out on original data, however, the Kolmogorov-Smirnov test works on the basis of comparing empirical cumulative distributions, which would be similar to the cumulative frequency distributions shown here.

#### 5.4.3.2 Goal Sensitivity

Based on the criteria described above, we recorded a total of 386 place cells during the maze sessions, 146 (37.82%) of these cells were identified as splitters based on the firing rate ANCOVA results, 140 (96.55%) of these cells showed this splitter activity in the start box or central stem and were analysed by multiple comparisons, 46 (31.51%) showed splitter activity in the left or right stems and were analysed based on their firing preference. Even with the appropriate correction, the multiple comparison analyses carried out here are demanding in terms of a significant relationship. However, 40 cells showed a pattern of comparative *F* values consistent with the five categories of primary interest; those cells which show significantly different firing for one particular trajectory (such as one of the central two) and those which fire for the two central routes equally. Representative examples of these cells can be seen in Figure 5.20.



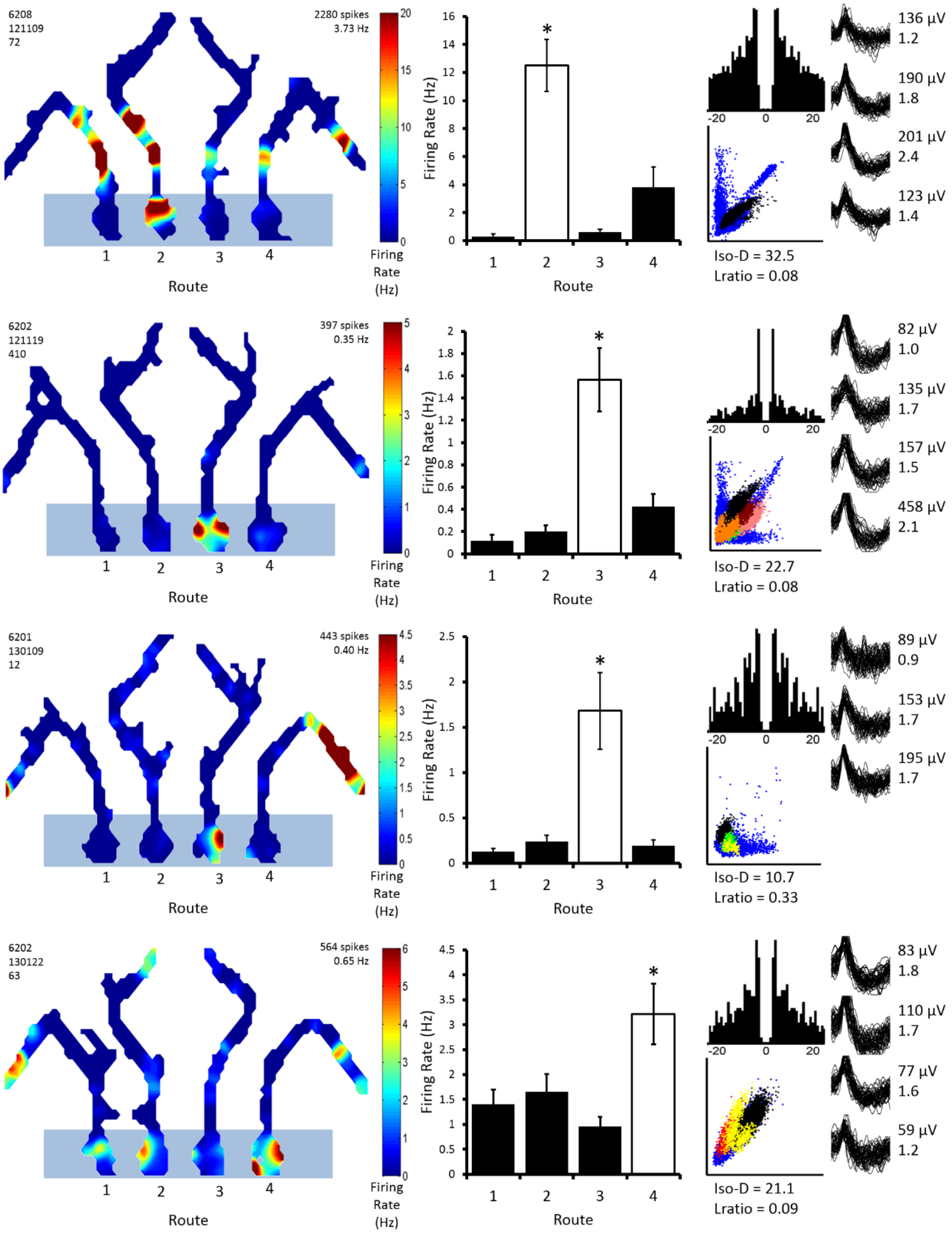


**Figure 5.20:** Showing example splitter cells (one cell per row). The left column shows the cell's firing rate map for the maze session, divided into the four different trajectories. The rat number, date, electrode and cluster are given (top left), total spikes and overall firing rate are also given (top right). The middle left column shows a bar graph with the mean and SEM firing rate in the maze start box on each of the four trajectories. Middle right column shows a 20 ms spike autocorrelogram, and the session cluster properties (energy on channel 1 vs one of the other active channels) the example cell's cluster is coloured black, isolation distance and $L_{ratio}$ values are included. The right column shows the cell's recorded waveforms – each composed of 100 random waveforms, the spike peak amplitude and signal to noise ratio are also given.

* trajectory mean deviates significantly from the others at the .05 level as confirmed by multiple comparisons employing a Sidak correction.

We used ANCOVA as a measure of the relationship between intended destination and firing rate, these tests also included velocity and deviation in the X and Y planes as covariates (each assumes one degree of freedom and it's associated fraction of the overall explained variance). For our population of splitter cells the greatest proportion of the overall variance was explained by intended destination (32.74%), the proportion of the overall variance explained by each of the covariates was much lower (Figure 5.21, left panel) [$F(3,740) = 343.59$, $p < .001$, $\eta_p^2 = .58$]. The statistical power attributed to intended destination (85.95%) was also much higher than the included covariates (Figure 5.21, right panel) [$F(3,740) = 328.55$, $p < .001$, $\eta_p^2 = .57$]. Multiple comparisons confirm that the variance explained by, and statistical power attributed to journey destination was significantly greater than any other variable ($p < .001$ in all tests, multiple comparisons with a sidak correction).

After combining the start box and central stem multiple comparison results, we found that 12 cells showed a significant preference for route 2, 15 for route 3 and only one cell fired similarly for both of the central routes, the probability of observing this pattern of results by chance is very low [$X^2(2, N = 28) = 12.04$, $p < .002$][30]. The majority of these cells are coding specifically for one of the central trajectories (27 or 96.43%) but only one demonstrates equal coding for both trajectories (1 or 3.57%), thus cells showed trajectory, not goal, dependent firing. These results can be seen in Figure 5.22. For the 64 possible outcomes of the multiple comparison tests, an average of 2.23 cells fell into each category. Multiple comparisons could not be conducted on the left and right stem data as the outcome is bimodal, however the preference of cells here (the preferential trajectory being the one with the highest mean firing rate) shows a similar distribution, but this is not statistically significant [$X^2(3, N = 46) = 2.35$, $p > .50$][30]. These results can also be seen in Figure 5.22.

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[30] Chi square probability, assessed using: http://graphpad.com/quickcalcs/chisquared2/

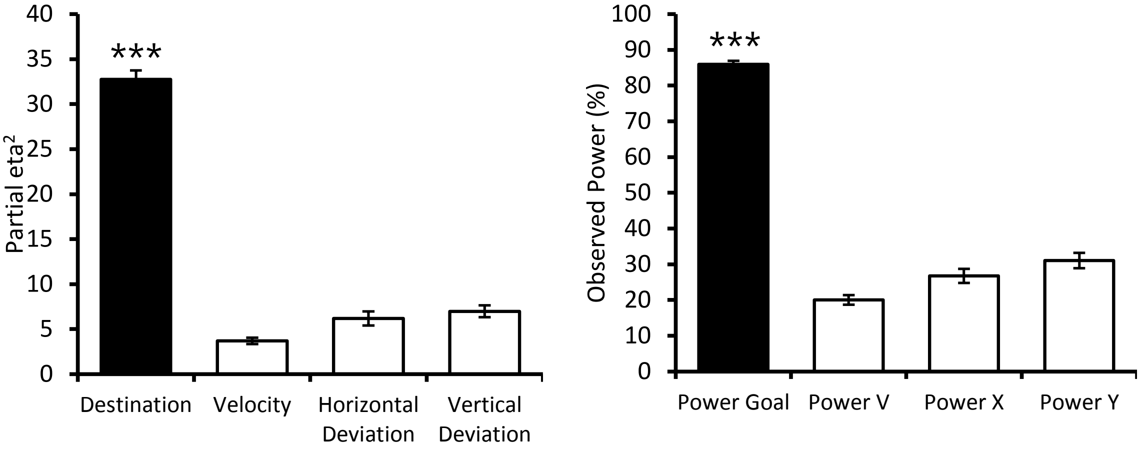

**Figure 5.21:** ANCOVA variance and power distributions. Left) showing the mean and SEM percentage of variance ($\eta_p^2$ x 100) explained by intended destination and each of the covariates in our splitter cell population. Right) showing the observed power attributed post-hoc to intended destination and each of the covariates in our splitter cell population. By definition, the cells included here were found to be significantly modulated by intended destination (ANCOVA resulting in a *p* value < .05).

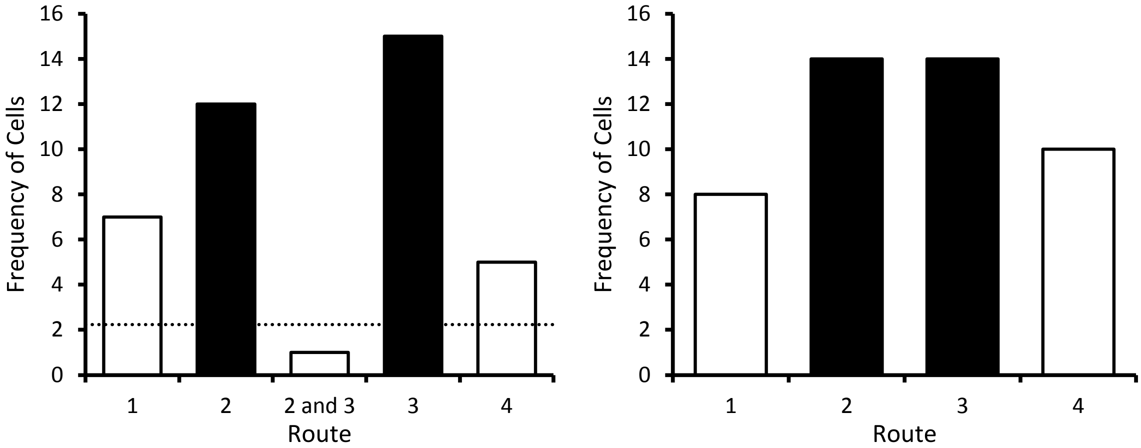

**Figure 5.22:** Showing the distributions of trajectory dependence. Left figure shows the combined multiple comparison results for the start and central areas, the dotted line represents the asymptotic level of cells per multiple comparison result. Right figure shows the route preferences of splitter cells in the left and right stem, preference was defined as the route on which the cell fired highest. Recall that during training animals made significantly more errors when navigating routes 2 and 3 (Figure 5.15).

### 5.4.3.3 Ensemble Analysis

We performed an ensemble analysis looking to test the accuracy with which an animal's trajectory could be identified based on the average firing rate of place cell ensembles. We analysed 25 ensembles independently, these were contributed by 6 different rats and consisted, on average, of 11.36 cells (SD = 1.14), ensembles had to contain at least 6 cells, our largest ensemble contained 27.

Generally, route average firing rate vectors correlated more highly with correct trajectory firing rate vectors and lower with incorrect trajectories, however, this effect is not statistically different for any single route in the start box [$p > .05$ all tests, independent samples t-tests], but when all correct and incorrect correlation values are combined the overall effect is significant (mean correct = .74, *SD* = .25, mean incorrect = .64, *SD* = .29) [$t(3.62) = 195.27$, $p < .001$, independent samples t-test]. In the start box, trajectories were correctly sorted approximately 48% of the time, which is an above chance level [$t(24) = 5.64$, $p < .001$, $t(24) = 3.80$, $p < .001$, $t(24) = 3.94$, $p < .001$, $t(24) = 5.66$, $p < .001$, respective one sample t-tests], this was consistent regardless of the route [$F(3,96) = 0.45$, $p > .70$, $\eta_p^2 = .01$, two-factor univariate ANOVA].

In the central stem, the correlation between routes and their correct trajectories are also consistently higher, but again there is not a statistically significant difference [$p > .05$ all tests, independent samples t-tests] unless all of the correct and incorrect values are combined (mean correct = .74, *SD* = .27, mean incorrect = .63, *SD* = .31) [$t(194.49) = 3.53$, $p < .001$, independent samples t-test]. Again, trajectories were correctly sorted approximately 45% of the time, which is an above chance level [$t(24) = 4.61$, $p < .001$, $t(24) = 3.60$, $p < .001$, $t(24) = 2.90$, $p < .001$, $t(24) = 3.80$, $p < .001$, respective one sample t-tests], and again this was consistent regardless of trajectory [$F(3,96) = 0.39$, $p > .75$, $\eta_p^2 = .01$, two-factor univariate ANOVA].

In the first choice point, the last area of the maze in which all four trajectories can be found but also the first area where they begin to diverge, routes also correlate higher with correct trajectories but this effect is statistically significant for every trajectory [$t(98) = 4.30$, $p < .001$, $t(98) = 4.05$, $p < .001$, $t(98) = 4.40$, $p < .001$, $t(49.83) = 4.67$, $p < .001$, independent samples t-tests]. The trajectories were correctly sorted approximately 54% of the time and each route was sorted at an above chance level [$t(24) = 5.28$, $p < .001$, $t(24) = 4.74$, $p < .001$,

$t(24) = 5.45$, $p < .001$, $t(24) = 5.71$, $p < .001$, respective one sample t-tests], this level was again consistent regardless of the route [$F(3,96) = 0.31$, $p > .80$, $\eta_p^2 = .01$].

These results indicate that at the ensemble level, in the start box, central stem and first choice point, cells represent the two central routes, 2 and 3, as distinctly as routes 1 and 4, which allows them to be distinguished based purely using ensemble firing rates. Thus, ensemble firing is trajectory dependent not goal dependent.

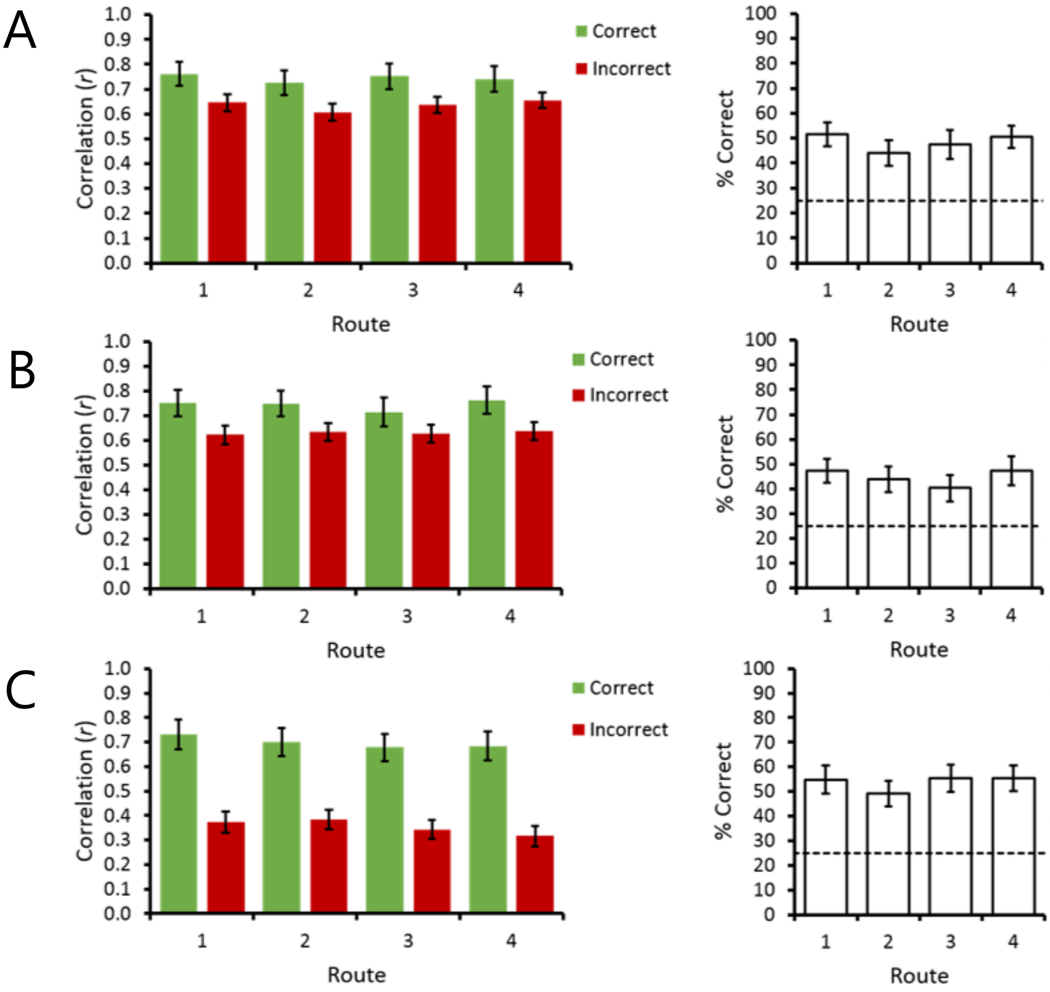

**Figure 5.23:** The results of the firing rate ensemble analysis. Showing the mean and *SEM* ensemble correlation between each route firing rate vector and the correct and incorrect trajectory firing rate vectors (left) and the mean and SEM percentage of trajectories which are correctly sorted using this analysis for each route (right), the dotted line shows chance level (25%). This is shown for the start box data (A) the central stem data (B) and the data in the first choice point (C). Routes consistently have a higher correlation with correct trajectories than with incorrect ones, this value is no lower or higher for the central trajectories than for the outer ones. The analysis also sorts trajectories correctly, based on the strength of correlation, approximately 50% of the time, regardless of maze area or route, suggesting that the two central routes to the middle goal box are as easily distinguished from each other, based on ensemble firing rates, as the two outer routes which lead to completely different goal boxes.

## 5.5 Discussion

In this experiment, rats were trained to navigate from a start box to three spatially dissociated goal locations using four distinct trajectories, two of these routes led to the same goal location. Prospective, context dependent place cell firing in the start area of the maze was predominantly trajectory dependent, goal dependent firing was observed in only one cell.

### 5.5.1 Trajectory Dependent Activity

We observed context dependent firing, as described previously (Ainge, Tamosiunaite, et al., 2007; Frank, Brown, & Wilson, 2000b; Wood et al., 2000), however, our results demonstrate that this firing is associated with the animal's future trajectory not with its final destination. This association was preserved, even when the effects of velocity and trajectory deviation were removed. Furthermore, we extended this analysis to assess the firing properties of place cell ensembles. We found that at an ensemble level, the firing rate of place cells was sufficient to decode the animal's trajectory at an above chance level, regardless of which route it was taking, this indicates that the ensemble firing of place cells carries sufficient information to distinguish the two central routes to the shared goal location and is thus also trajectory, not goal dependent.

One criticism may be that during training and single unit recording we used a transparent barrier, so that only one trajectory to the central goal box was open at any time. This may have biased the rats' representation or navigation strategy towards a route based system. However, when a second, naïve group of rats were trained on the same task but without the barrier, the majority of these animals formed a strong bias for one of the two central routes. Thus, given the choice, rats appear to simplify the task to a form with the minimum number of trajectories to learn, suggesting that even in the absence of a barrier, rats choose to solve the task in terms of trajectories, not goals[31]. This finding supports those of previous experiments demonstrating that place cell firing encodes more than spatial location (Ainge, Tamosiunaite, et al., 2007; Allen et al., 2012; Ferbinteanu & Shapiro, 2003; Shapiro et al., 2006; Wood et al., 2000) and that this firing can differentiate between more than two choices (Ainge, Tamosiunaite, et al., 2007) but importantly, it expands on these findings by clarifying that in mazes such as these, context dependent firing is in fact trajectory dependent. This finding has implications in both how we view the HPC in terms of spatial memory storage and retrieval and how it may come to represent context.

As we saw before, the HPC represents spatial information in terms of trajectories in a number of different ways. At choice points place cell firing becomes nonlocal; cells which fire along the rat's possible future trajectories fire in sequences corresponding to these trajectories, suggesting that as the rat considers and compares these choices neurons in the HPC are required to inform these representations. These 'look ahead' sweeps occur extremely quickly, within approximately 150ms (Johnson & Redish, 2007), so it seems unlikely that this form of anticipatory firing would result in enough spikes to account for the large differences in firing rate we saw in our maze, given the relatively long time periods spent in each maze area. However, Johnson and Redish (2007) suggest that if the animal's representation sweeps along one trajectory more than the others, this would be visible at the single cell level as prospective firing. This is supported by the finding that prospective firing observed in tasks dependent on the hippocampus (Ainge, van der Meer, et al., 2007; Griffin et al., 2007) is less prevalent than in tasks which are less dependent on an intact HPC (Wood et al., 2000), possibly because forward sweeps are more frequent in a hippocampus dependent task (Johnson & Redish, 2007). In our experiment we observed more prospective firing specific to the two central routes to the central goal location, rats also found these routes the most difficult during training, making significantly more errors when navigating

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[31] Similar navigation has been suggested in baboons, who simplify a complex jungle environment to a limited number of favourite routes (Byrne, 2000).

them. Future experiments interested in linking forward sweeps to prospective firing should identify whether the frequency of forward sweeps also increases with task difficulty.

Johnson and Redish (2007) also report that many look ahead episodes do not reach a goal location but instead only represent part of the rat's future trajectory[32], future research using our maze, or its four goal equivalent, the double-Y maze (Ainge, Tamosiunaite, et al., 2007), should explore whether look ahead episodes in the start box represent the animal's full trajectory or merely it's trajectory to the next choice point. Previous research has shown that at crucial choice points rats pause and VTE (Muenzinger, 1938; Tolman, 1948), they make small, fast head movements directed at each potential choice point. It is possible that in the start box a representation of the animal's trajectory to the next choice point is initiated, once at the choice point the animal VTEs and the next portion of the representation is initiated. Such a strategy could reduce the error associated with a taxon navigation strategy; at each choice point the animal pauses and the next trajectory sequence is extracted from a cognitive map. The use of a cognitive map would allow for the correction of any navigation errors up to that point, but by extracting trajectory information the animal does not have to constantly maintain this representation, a process which is computationally expensive and effortful (O'Keefe & Nadel, 1978).

It has been suggested that the context or task dependent firing observed in tasks such as the one reported here (Ainge, Tamosiunaite, et al., 2007; Wood et al., 2000) may be the result of rate remapping (Leutgeb, Leutgeb, Barnes, et al., 2005). Some researchers suggest that this remapping may result from a change in spatial reference frame; the rat may have multiple maps for each of the stages of a task (Redish, 1999; Redish & Touretzky, 1997). Multiple maps would allow an animal to efficiently maintain a representation of its current location and future goals, depending on the context or task demands. Evidence for this multiple map hypothesis can be found in relatively early place cell literature. Markus et al.,

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[32] Although they suggest that this may be because the ensembles they were recording did not contain the cells responsible for representing the last part of the trajectory.

(1995) report that on a platform environment, many place cells change their firing locations when the task is changed from one of random foraging to a specific, goal directed one. The platform environment remained the same, the only change was in the task demands, suggesting that the place cells were conforming to two different representations, reflecting not only the spatial features of the environment but also the non-spatial features of the task. Wible et al. (1986) similarly showed than in a Delayed Non-Match to Sample (DNMS) task, place cell firing was correlated not only with the animal's position but often with the phase of the experiment and the location of the reward; many place field locations also changed when the goal position changed, suggesting that different maps may have represented each phase of the task. Similar results in a DNMS task were also found by Hampson, Heyser and Deadwyler (1993). In an odour discrimination task where the rat's goal was dictated by sets of different odours, Eichenbaum et al. (1987) found that the firing of place cells was as related to the rat's location as it was to the rat's behaviour, with many cells firing differentially depending on the odour presented to the animal and thus its trajectory to the goal. Similar results in odour discrimination tasks have also been found (Cohen & Eichenbaum, 1995; Eichenbaum & Cohen, 1988). It is clear from these results, as it is from those described previously, that place cell firing can depend on more than the spatial features of an environment and the current task demands also play an important role. It is also clear how these results can be explained by the activation of different cognitive maps (Redish, 1999; Redish & Touretzky, 1997; Touretzky & Redish, 1996). In these experiments the firing of place cells appears to change rapidly from one representation to another (Wible et al., 1986), with perhaps some cells maintaining the same firing pattern while others change (Markus et al., 1995). However, in our experiment we observed many cells which changed their firing pattern in one maze compartment (for example, the start box) but maintained a stable representation in a separate maze area (see example cells 2 and 3, Figure 5.20). Similarly, we found no relationship between a cell's preferred trajectory in one area of the maze and its preferred trajectory in another[33]. It is unclear how, or if, a multiple map hypothesis can account for this simultaneous change and maintenance of firing pattern. It seems reasonable that a separate reference frame may come to represent each trajectory, especially as our animals were well trained and our task was designed such that within a block of trials the rats knew exactly where they were navigating to next. However, it seems unreasonable that rats utilise separate maps in the start box of the maze but the same map later in the environment. This 'stable field' phenomenon may warrant future research, of particular interest is whether these stable place fields develop sooner than differential ones and whether the locations of these fields are related to the preferred trajectory of differential cells. More basic research may investigate whether differential firing is affected by lesion or inactivation of the lEC, as this has been shown to impair rate remapping; specifically the kind observed when the shape or colour of an environment is changed (Leutgeb, Leutgeb, Barnes, et al., 2005; Lu et al., 2013). If differential firing is indeed a form of rate remapping, damage to the lEC should disrupt this activity in the HPC (the impact on differential activity in the mEC would also be of interest).

An alternative to the multiple map hypothesis, the 'buffer' hypothesis suggests that retrospective firing (differential firing related to the rat's past behaviour) reflects the maintenance of the animal's previous trajectory in a form of episodic working memory or buffer (Baddeley, 2000; Catanese, Viggiano, Cerasti, Zugaro, & Wiener, 2014). In a continuous T-maze task where prospective and retrospective firing could be distinguished, Catanese et al. (2014) observed both forms of coding in the same maze area. This simultaneous prospective and retrospective coding (by different cells with fields in the same location) is in disagreement with the multiple map hypothesis as both maps would have to be active at the same time. These results may provide an explanation for why the continuous T-maze task is

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[33] Admittedly we recorded very few cells which fired differentially in multiple maze areas at a rate strong enough to be positively categorised after multiple comparisons, furthermore, a comparison is statistically difficult because the distributions in the start areas of the maze are quadmodal whereas they are bimodal at later choice points. Data not shown.

dependent on an intact HPC only when a delay period is present (Ainge, van der Meer, et al., 2007); without a delay animals do not need to hold their previous trajectory in memory, this is only the case when they are delayed at a point in the maze. Under these conditions the HPC would be required to maintain this memory over the delay. It is generally suggested than the manual displacement of an animal from a goal to a starting position disrupts retrospective activity (Catanese et al., 2014), however, if the differential firing in the start area of our maze is retrospective (representative of the animal's previous trajectory) rather than prospective (reflecting the planning of a future trajectory), the observation of differential activity in the start area of the maze and stable fields later in the environment would not be surprising. However, this view does not explain why rats with hippocampal lesions are not impaired in a double Y-maze task when they are delayed ~15s in total (Ainge, Tamosiunaite, et al., 2007).

Nevertheless, an experiment could determine the nature of the differential coding in the start box; if the rat was cued at the first choice point as to which goal was baited then prospective firing should not occur until after the presentation of this cue, thus any differential activity observed in the start box would have to be retrospective. As far as the author is aware no experiment has shown conclusively that manual displacement disrupts retrospective firing. Regardless of the specific coding observed in the start box of our maze, future research may wish to explore what happens to this coding if the rat is delayed for longer periods than used here (6s). An example experiment may delay the rat for >60 seconds in the start box and observe the activity of place cells in the start box to determine if they continue to fire in a trajectory dependent manner. If this firing decreases or is disrupted over the course of this delay it would be interesting to determine if the rat's performance is similarly impacted. Similar experiments may require the rat to solve a task before exiting the start box, thus, presumably, disrupting any differential firing associated with the double Y-maze environment. If prospective firing reflects the planning of future trajectories one would expect an impairment in this planning when differential firing is interrupted.

### 5.5.2 Hippocampal Overrepresentation

In this experiment we observed three forms of over-representation, the first was a generally increased level of activity in the start area of the maze, as shown by an increased number of place cells active (firing >1Hz), an increased number of place fields and an increased number of cells showing significant trajectory dependent firing in the early areas of the maze. During recording we ended individual trials before the animal began to eat the food reward, this was to eliminate eating artefacts/noise from our recordings but it may have reduced the reliability with which we can detect goal related firing. However, we recorded the animal's movements in the goal boxes up to the food well, activity during eating cannot reliably be identified as goal specific, it may simply reflect some reward association (Dupret, O'Neill, Pleydell-Bouverie, & Csicsvari, 2010). Furthermore, we observed a linear decrease, throughout all of the maze areas, in the frequency of active cells from the start box to the goal locations.

Previous research has reported place field over-representation of goal locations; Holscher, Jacob and Mallot (2003) found that the firing of place cells was increased in baited arms of a radial maze when compared to non-baited ones, Gothard et al. (1996) observed many 'goal/landmark-related cells' which fired in the vicinity of a reward site situated in an open field and cued by two mobile landmarks, Kobayashi et al. (2003) also observed a greater number of place fields surrounding goal locations in an open field task where the animals were trained to find food at several specific locations, Hollup et al. (2001) also observed a greater number of place fields surrounding a platform location in a watermaze task. Over-representation of goal locations has been observed in a number of additional experiments (Dupret et al., 2010; Hok et al., 2007; Markus et al., 1995). However, this over-representation was not observed by Lenck-Santini et al. (2002; 2001a) in a Y-maze task, or

Ainge et al. (2007) in a double Y-maze task similar to ours. One possibility is that in open field environments place cells over-represent goal locations but in enclosed mazes such as a Y-maze or our maze, goal over-representation is not as relevant. Why this would be the case is unclear but it could reflect a difference in navigation strategy. Rats in enclosed alleyways may be more likely to use an egocentric navigation strategy, those in open field environments such as the watermaze can usually only use an allocentric strategy and thus the location of the goal may be more behaviourally relevant. Experiments in the plus maze can be designed such that animals can only use an egocentric or allocentric navigation strategy, future research could explore whether goal over-representation is more prevalent under an allocentric protocol. Another possibility is that in open field environments, such as the water maze, animals can use a visual matching navigation strategy such as those seen in insects (Collett & Lehrer, 1993; Collett & Rees, 1997; de Ibarra et al., 2009); as all visual cues can be seen from all locations within the maze animals can move around the environment until the cues line up with a stored visual representation of their positions at the goal. It's possible that under these conditions place cells in the HPC come to represent this visual scene like spatial view cells in the primate (Georges-François, Rolls, & Robertson, 1999; Robertson, Rolls, & Georges-François, 1998; Rolls, 1999) and human HPC (Burgess & O'Keefe, 2003; Ekstrom et al., 2003).

The second type of overrepresentation we observed was an increased number of trajectory dependent cells coding specifically for the two routes to the central goal box. We also know from our training data that the animals found these two routes the most difficult to navigate; they made significantly more errors when they were navigating these routes and they confused these two routes more than any other route pair. One explanation could be that although we do not see goal specific firing in the HPC another brain region is responsible for this form of future planning or decision making - we will discuss the potential of the Prefrontal Cortex (PFC) to fulfil this position shortly. Because the two central trajectories lead to the same goal location this second brain region may have difficulty in planning the correct trajectory at a particular time. Alternatively, when stimulating the HPC to initiate the correct contextual representation, this input may be so similar between the two trajectories that the incorrect representation is often initiated. If rats find it difficult to discriminate two distinct, well experienced trajectories because they lead to the same location, it is not surprising that they are unable to make a spatial inference and take a novel shortcut route between two known locations. The finding that there are more trajectory dependent cells coding for the two central routes also suggests that the HPC may recruit additional neural resources in the face of a difficult discrimination. The HPC has been implicated in the discrimination of structurally similar spatial environments (Aggleton & Pearce, 2001; Sanderson, Pearce, Kyd, & Aggleton, 2006), the similarity of our two central routes could require greater hippocampal resources to discriminate, which is why we see an increase in trajectory specific firing. Increasing neural activity in response to a difficult discrimination has also been reported previously; Gao et al. (2010) found an increase in the complexity of hippocampal activity in response to a more difficult auditory discrimination in the guinea pig, Hu et al. (2005) also found greater HPC neuronal activity during a difficult visual discrimination task than during an easy one. Surprisingly, there is not a great deal of research focusing on hippocampal place cells, context-dependent firing and discrimination difficulty. Future experiments could seek to explore this further. Place cell prospective activity could be recorded while animals make two distinct discriminations, one difficult and one easy (see Figure 5.24). The aim would then be to simply assess the frequency with which cells are 'recruited' to represent these

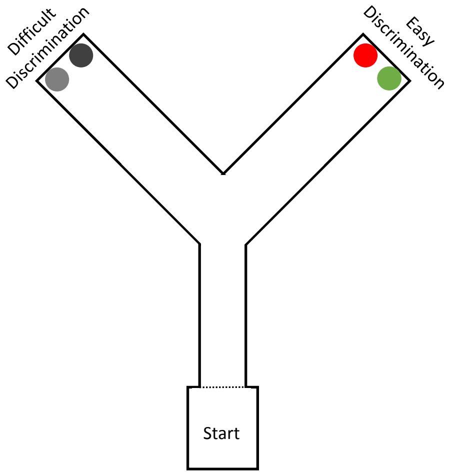

**Figure 5.24:** Dual discrimination Y-maze. Rats start at the bottom and navigate to the ends of the arms. One arm contains a difficult discrimination (between two similar odours, objects etc.) the other contains an easy discrimination. Rats alternate between the arms. The prediction is that more place cells will fire prospectively in the start box for the items in the difficult discrimination than the easy discrimination.

discriminations in the HPC. Such an experiment could also identify whether prospective firing is purely trajectory dependent, or whether it includes information about the response the rat will make at the goal location.

The third type of overrepresentation that we observed concerns the number of place fields recorded in each of our environments. The number of fields observed, per cell, in the open field environment was on average lower, however, when adjusted for surface area, the number of fields observed per cell in the maze was actually found to be disproportionately higher than the open field. Why we saw this increase in the number of place fields is uncertain, however, one possibility is that we observed place field repetition or 'path equivalence' (Derdikman et al., 2009; Frank et al., 2000a; Singer et al., 2010). In path equivalence, place cells fire in multiple areas of an environment where the animal is performing the same behaviour, such as turning left or running straight ahead. However, previous research has only demonstrated this phenomenon in parallel compartments or alleyways; in our maze the alleyways symmetrically opposite are not parallel, nor are the areas of the maze where the animal is likely to perform the same action or behaviour. Future research should look to determine whether the place field overrepresentation of our maze is a result of path equivalence, an equivalent phenomenon or whether the greater number of fields is driven by an alternative stimulus, such as the increased number of walls and boundaries. Previous research suggests that place cell firing is largely dictated by the geometric boundaries of an environment

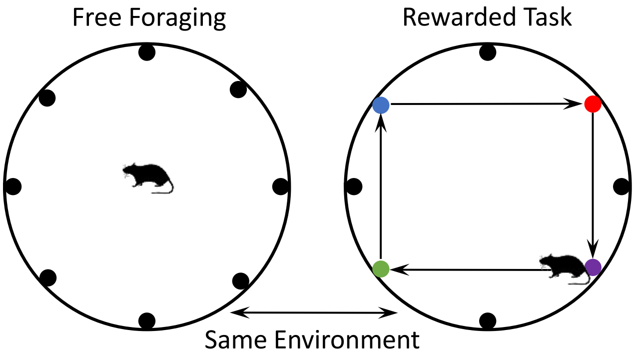

**Figure 5.25:** Task effects on place field frequency experiment. Place cells are recorded as rats freely explore and forage in an open field environment such as a cylinder (left). Place cells are also recorded as these animals solve a spatial task in this same environment (right). In this case the animals must visit a well near the outer wall in order to receive a food reward and also stimulate the release of a randomly scattered food reward. The animal must visit the wells in a specific order. As the animal retrieves the scattered food rewards between visiting wells it must hold in memory the most recently visited one, thus introducing a spatial memory component and encouraging the rat to explore the entire environment. A higher frequency of place fields may be expected when the animals are required to solve a task.

(Barry et al., 2006; Hartley et al., 2000) and thus, the frequency of place fields may have increased here in response to the increased number of boundaries. Alternatively, this increased number of place fields could reflect a greater level of hippocampal activation, as the rats were expected to solve a task in the maze whereas they merely foraged for scattered food in the open field. Future research could easily assess this possibility; Markus et al. (1995) showed that place cells may often change the location of their firing fields when a task is introduced to a familiar environment, however, they did not report on the frequency of place fields. A similar experiment could record place cells while animals forage in an open field environment and while they complete a (preferably hippocampal dependent) task in this same environment. The aim would be to assess whether there is a higher frequency of place fields expressed during the task than during the foraging period whilst maintaining the same extra-maze cues and boundary complexity (see Figure 5.25 for an example). A similar task has been employed previously (Bower, Euston, & McNaughton, 2005) and did find evidence of hippocampal overrepresentation of some journey elements, however, again this study did not concentrate on the frequency of place fields.

### 5.5.3 Interpretation

Episodic memories are autobiographical in nature, such as those for specific events or life experiences. This memory is often described as consisting of ‘what, where and when’ information, as it includes spatiotemporal relations (what and where) but with a wider temporal arrangement (when and which) (Norman & Eacott, 2004; Tulving, 1983; Tulving et al., 1972). In humans, the involvement of the hippocampus in the formation of episodic memory is widely recognised (Eichenbaum & Cohen, 2001; O'Keefe & Nadel, 1978; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991; Vargha-Khadem et al., 1997) as is its involvement in spatial memory (Abrahams et al., 1999; Abrahams et al., 1997; Corkin, 1979; O'Keefe & Nadel, 1978; Smith & Milner, 1981; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). This latter function persists in nonhuman species such as the rat

(Eichenbaum & Cohen, 2001; Morris et al., 1982; O'Keefe & Nadel, 1978) as evidenced by the detailed literature on place cells in the rodent HPC. The involvement of these cells in episodic memory processes has not yet been shown (Smith & Mizumori, 2006a), if indeed they are involved. However, the results reported here provide indirect evidence for the involvement of place cells in both spatial navigation and in the formation of episodic memory.

An important feature of episodic memory is context; place cells remap and fire differently in different environments, providing an animal with orthogonal representations for the different environments it may encounter. However, often animals need to differentiate between contexts in the same environment. Under these conditions place cells may also remap, but often they modulate their firing rate, thus maintaining the same place fields in the same locations but with a slightly different overall representation (Ainge, van der Meer, et al., 2007; Anderson & Jeffery, 2003; Hayman, Chakraborty, Anderson, & Jeffery, 2003; Markus et al., 1995; Wood et al., 2000). This rate remapping is thought to allow animals to form distinct representations for different contexts within the same environment, informing important features of episodic memory, mainly the 'when' and 'which'. This context processing view of the HPC is supported by the finding that if the HPC is damaged rats are unable to associate an aversive stimulus to contextual stimuli (Kim & Fanselow, 1992; Matus-Amat, Higgins, Barrientos, & Rudy, 2004; Phillips & LeDoux, 1992) similar results have been found using mice (Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998) for a review see (Myers & Gluck, 1994). Damage to the HPC or EC also results in reduced sensitivity to contextual changes (Freeman, Weible, Rossi, & Gabriel, 1997; Penick & Solomon, 1991; Wilson, Watanabe, Milner, & Ainge, 2013; Wilson, Langston, et al., 2013) and tasks involving contextual discrimination are associated with increased neuronal activity in the lEC (Wilson, Langston, et al., 2013). One view suggests that the prospective differential firing observed in tasks such as ours is a contextual coding process, allowing the animal to differentiate different trajectories even when starting from the same location; this allows the animal to access the correct memories associated specifically with that trajectory in the environment and ultimately make the correct sequence of responses (Balaz, Capra, Hartl, & Miller, 1981; Blanchard & Blanchard, 1972; Fanselow, 1986; Godden & Baddeley, 1975; Smith & Mizumori, 2006a). A more formal model built on this view has been suggested by Gaussier et al., (2002) in which the PreFrontal Cortex (PFC) provides a spatial planning input to the HPC which modulates place cell firing in a contextual manner (Hok et al., 2013; Hok et al., 2007; Hok, Save, Lenck-Santini, & Poucet, 2005). This is supported by the finding that in a cylindrical arena task where the reward and goal locations are spatially dissociated (Hok et al., 2007), cells in the medial PreFrontal Cortex (mPFC) fire similarly to place cells, albeit with less spatial information. These cells also over represent the goal location, suggesting that the prefrontal cortex is involved in the processing of intended goals (Hok et al., 2005), although this function is no longer required in over trained animals (Hok et al., 2013) suggesting that at this point it may migrate to a third brain region responsible for automated behaviour such as the striatum (Pennartz, Ito, Verschure, Battaglia, & Robbins; Rauch et al., 1995; Rauch et al., 1997), or the PFC may innervate the striatum directly (Alexander, DeLong, & Strick, 1986; Ferry, Ongur, An, & Price, 2000; McDonald, 1991). In this framework the HPC contains a cognitive map of an animal's environment, but goal related information is represented in the PFC. Once the animal has decided which goal location to visit, trajectory information is extracted from a contextually relevant cognitive map in the HPC, based on the animal's previous experiences in that context. This is then passed to structures with behavioural control, such as the striatum, so that the appropriate response can be initiated. Future research could look to find an association between the activity in the mPFC and the HPC. Specifically, research should assess if there is goal related prospective activity in the mPFC and if this reflects the trajectory dependent firing in the HPC. If navigational errors are attributable to a decision making or goal planning error, mPFC and HPC activity should both always reflect the animal's final destination, however, if navigational errors result from a contextual or mapping error in the HPC the firing in these two structures should be very different during error trials.

# Experiment 3

## Place Field Repetition in a Multicompartment Environment

### 6.1 Abstract

Hippocampal place cells fire when an animal is in a particular area of an environment and are generally thought to support spatial cognition (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). Recently, Derdikman et al. (2009) showed that in a hairpin maze composed of a series of parallel alleyways, place cells (and grid cells) tend to fire in multiple alleyways and at approximately the same spatial location relative to the boundaries of each alleyway. Spiers et al. (2013) found similar "place field repetition" as rats explored a multi-compartment environment composed of 4 identical parallel boxes connected by a corridor. Derdikman et al. (2009) also reported that both grid and place cells show repeating firing fields only in alleyways facing the same direction, and this was dependent on the animal's running direction through the maze. Whitlock and Derdikman (2012) later showed that the head direction system remains unaffected by these repeating fields. Clearly, angular orientation information and the head direction system play a crucial role in place cell firing, even in environments where place field repetition is observed. In this experiment, we sought to replicate the findings of Spiers et al. (2013) but also to investigate the effects of angular head direction information on place field repetition. We recorded place cells whilst rats (*N* = 4) freely explored a maze composed of multiple, parallel, visually identical compartments, similar to that used by Spiers et al. (2013) (534 place cells), but we also recorded activity in this same maze after introducing a 60° angle between each of the compartments (755 place cells). We found a significantly higher frequency of place field repetition in the parallel maze when compared to the radial maze, as highlighted by a higher degree of inter-compartment correlation and a higher frequency of place fields per place cell. Furthermore, ensemble analyses suggest that there may be limited information available to differentiate the

compartments at a population level. Our results confirm those findings reported previously (Derdikman et al., 2009; Spiers et al., 2013) but also show, in a novel way, that place field repetition occurs only in the absence of distinct angular head direction information. These results are discussed in terms of a Boundary Vector Cell (BVC) model of place cell firing and we report such a model which predicts our observed results.

## 6.2 Introduction

As discussed previously, in a given environment a place cell may fire with superb spatial localisation, often firing maximally in some portion of the environment and largely silent in all other areas (O'Keefe & Dostrovsky, 1971). Different place cells fire maximally in different spatial locations, such that as a population they represent the entire surface area of an environment, this, and other features, have led to the suggestion that place cells form the neural representation of a cognitive map – an animal's internal representation of its surrounding environment (O'Keefe & Nadel, 1978; Tolman, 1948). A simple prediction is that the firing of place cells is dictated by visual cues in the environment (McNaughton et al., 1991; Zipser, 1985), this is supported by the finding that under certain circumstances place fields rotate in unison with rotated visual cues (Muller & Kubie, 1987; O'Keefe & Speakman, 1987), altering the angle (Fenton, Csizmadia, & Muller, 2000) or distance (O'Keefe & Burgess, 1996) between the animal and distal cues also has an effect on place fields. However, after careful experimentation it has become clear that visual inputs are not the only cues which exert control over place cell firing. Place fields remain relatively stable in complete darkness (Save et al., 2000; Zhang, Schönfeld, Wiskott, & Manahan-Vaughan, 2014) although prior experience of the environment with light may be necessary (Quirk, Muller, & Kubie, 1990) and the instability associated with navigation in darkness appears to be accompanied by an impairment in spatial learning (Puryear, King, & Mizumori, 2006). Nevertheless, blind rats still have relatively stable place fields (Save, Cressant, Thinus-Blanc, & Poucet, 1998). In light of these results it has been proposed that place cells rely on the integration of a variety of cues, some of which are visual and some of which are non-visual, such as Path Integration (PI)(Etienne & Jeffery, 2004; Mittelstaedt & Mittelstaedt, 1980); an internally generated and updated representation of an animal's position based on vestibular and proprioceptive information accumulated over time. A number of experiments have confirmed that place cell firing is, at least partly, influenced by PI information (Etienne & Jeffery, 2004; Gothard, Skaggs, & McNaughton, 1996; McNaughton et al., 1996; McNaughton et al., 2006; Samsonovich & McNaughton, 1997).

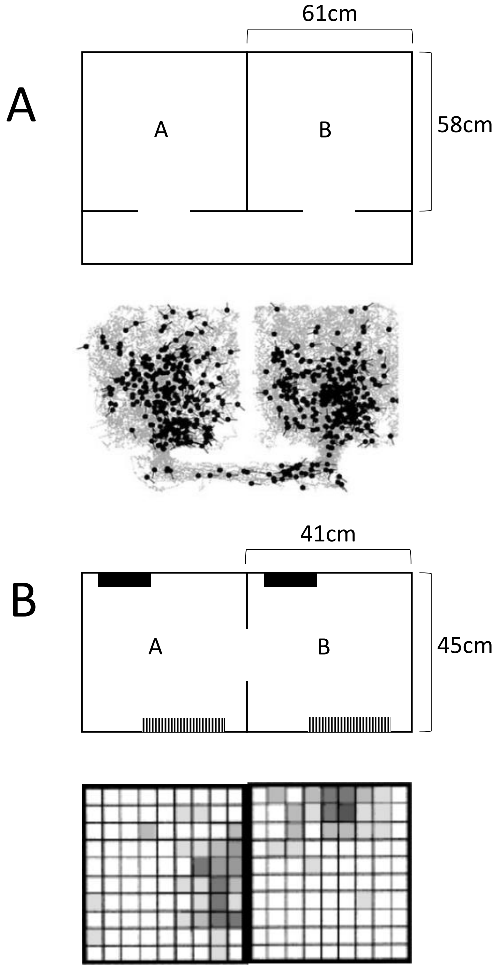

**Figure 6.1: A**) Schematic diagram of the maze used by Skaggs and McNaughton (1998). Two visually identical compartments are connected by a corridor. Below this is an example place cell recorded in the environment which shows repetitive firing. **B**) Schematic diagram of the maze used by Tanila (1999). Two visually identical environments are connected by a doorway. Below this is an example cell, showing the first session recorded in box A and B, in this case the cell does not fire repetitively, however, some cells maintained their representation for B upon returning to A.

Early experiments sought to determine if this PI information was sufficient to distinguish visually identical but spatially dissociated environments. Quirk et al. (1992) recorded cells in the mEC while rats explored two distinct but visually similar environments. They report that cells in the mEC are less likely to change their firing patterns than cells in the HPC, as reported by Muller et al. (1987) in a previous experiment. It is unclear whether Quirk et al. (1992) were recording putative grid cells, spatial non-grid cells or border cells which makes their results difficult to interpret. However, Skaggs and McNaughton (1998) were intrigued by the finding that place cells would fire differently in visually similar environments. To test the orthogonalisation of place cell maps in more similar environments, they recorded place cells while rats explored an environment composed of two identical compartments joined by a corridor (see Figure 6.1). However, they found that many place cells fired similarly in the two compartments, with place fields in identical locations in each compartment. The idea that the HPC may not consistently form orthogonal (statistically unrelated) representations for different environments, or form a consistent representation within an environment (some place cells showed repetitive firing, some did not) came as a surprise. Indeed it is difficult to understand how similar representations arise for different, albeit visually identical, compartments when the animal has access to PI information, accumulated as it moves from one compartment to the next. In a later experiment, Tanila (1999) recorded place cells while animals moved between two visually identical environments (A and B), unlike Skaggs and McNaughton (1998) a doorway was provided directly between the two compartments (see Figure 6.1). He found that although many cells formed a new representation for box B after moving from box A, cells were as likely to maintain their box B representation or return to their box A representation when the animal moved back to box A. There are a number of reasons why place cells may have represented this environment differently to that of Skaggs and McNaughton (1998). As we will see in later discussions, doorways represent a significant environmental feature in many tasks, it is possible that in moving directly between the compartments rather than via an intermediary corridor rats were more likely to form a global representation of the environment. Upon returning to box A, the observation that many place cells did not correct their representation may reflect a form of retroactive interference brought about by the rat’s experience in box B. In any case, the fact that many place cells fired similarly in the two compartments is again in contrast to the PI information available to the animal.

However, recent research suggests that this PI information may also repeat in environments such as these. As we saw in earlier chapters, grid cells are thought by many to form the neural basis of a distance metric, or PI system (Fuhs & Touretzky, 2006; McNaughton et al., 2006; Mizumori, 2008; Moser et al., 2008; Samu et al., 2009) although direct evidence of this relationship has still to be found. Derdikman et al. (2009) recorded both grid cells and place cells while rats ran back and forth along a 'hairpin' maze, consisting of a zig-zag path through space (see Figure 6.2). They found that in this environment grid cells lose their characteristic grid firing pattern and instead fire in similar locations in multiple alleyways. They also found that this was still dependent on the heading direction of the rat (cells would fire differently in north facing than south facing alleyways) and on the direction in which the rat was running through the maze (cells had a completely different representation when running left-right than when running right-left). We found similar results using a similar apparatus (see Supplementary Figure 1). The authors observed the same firing characteristics in place cells. Their conclusion was that instead of forming a global grid firing pattern, grid cells were reduced to responding purely to local cues – in this case the distance the animal had moved since turning into an alleyway. Due to the repetitive design of the apparatus this results in multiple firing fields at roughly equal positions in multiple

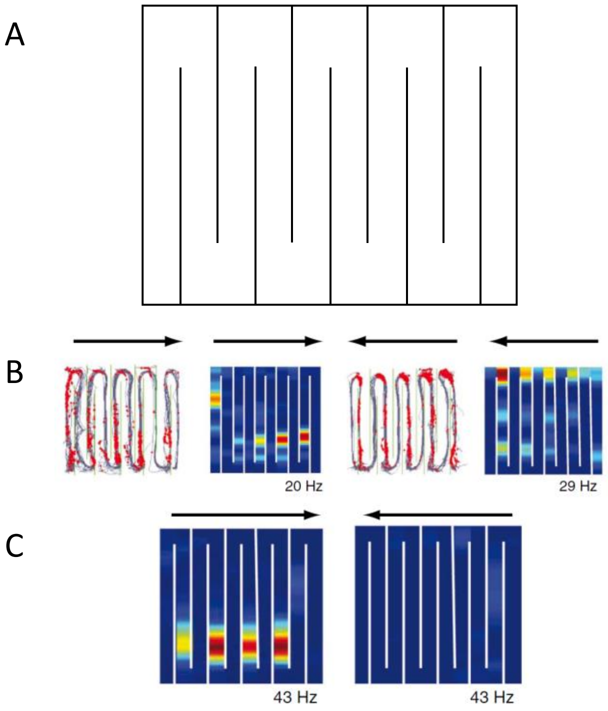

**Figure 6.2:** The apparatus used by Derdikman et al. (2009). **A**) Schematic of the maze; rats run from one end of a zig-zag alleyway to the other and back again continuously. **B**) An example grid cell firing rate map, the cell fires similarly in multiple alleyways, but only in alleyways facing the same direction and only when the animal is running in the same direction through the maze. Arrows indicate the direction of travel. **C**) An example place cell firing rate map, again this cell fires similarly in multiple alleyways but only in alleyways facing the same direction and only when the animal is running in a particular direction through the maze.

alleyways. The fact that place cells show this same phenomenon suggests that when the grid representation becomes fragmented in this way, entorhinal inputs to the HPC may influence the place cells there to fire in a similarly repetitive way. If grid cells do indeed form the neural basis of a PI system, these effects may also explain why animals are seemingly unable to differentiate between identical compartments even after consciously moving between them – the fragmented grid map is unlikely to be able to provide a global internal representation of the kind observed in open field environments.

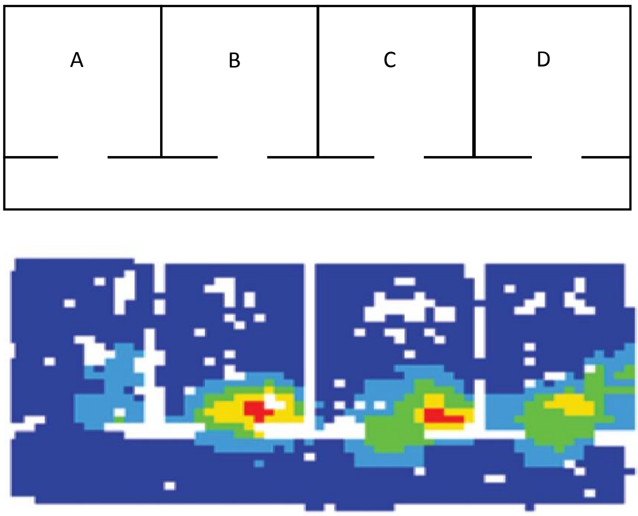

**Figure 6.3:** Top) Schematic of the four compartment maze used by Spiers et al. (2013). Rats forage for food rewards and are free to move between the compartments. Bottom) A firing rate map showing a place cell which has repeating place fields in the maze. Spiers et al. (2013) observed that the number of place cells with repeating place fields was much higher than would be expected by chance and was much higher than in previous multicompartment experiments.

With the insight of these grid cell recordings, Spiers et al., (2013) sought to understand whether animals in a multicompartment environment of a similar design to Skaggs and McNaughton's (1998) would find it easier or more difficult to differentiate numerous compartments, instead of the previously investigated 2 compartment apparatus. With a greater number of compartments it should be more obvious to the animal that it is moving between different areas, however, if grid cells 'reset' their representations as in Derdikman et al's. (2009) hairpin maze, then one might expect to see repeating place fields regardless of the apparatus' size. To test this, Spiers et al. (2013) recorded place cells while rats freely explored a four compartment maze (see Figure 6.3). They found that instead of firing in a global manner, with a single localised place field, a large proportion of place cells had repeating place fields in two or more compartments, suggesting that the firing of these cells reflected more local environmental cues such as the boundaries in the environment. When calculating the correlation between compartments, the distribution of resulting values was much higher than would be expected by chance. In further manipulations they found that these repeating fields could be disrupted by changing the size or colour of one of the compartments, such manipulations have previously been shown to induce firing rate changes in place cells (Lee et al., 2004; Leutgeb, Leutgeb, Treves, et al., 2005; Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004; Lever et al., 2002; Skaggs & McNaughton, 1998). Spiers et al. (2013) found that these changes occurred only in the compartment which was altered; place cells would continue to show repeating place fields elsewhere in the maze. The authors suggest that grid fields may reset in the doorway to each compartment, this is supported by the finding of place field overrepresentation of the doorways. Thus, within the compartments place cell firing is dictated by purely local cues and a change in one compartment does not affect the firing in any of the others.

It is clear that place cells in the hippocampus exhibit recurring firing patterns in environments comprised of repeating parallel compartments (Derdikman et al., 2009; Spiers et al., 2013), and partial remapping in environments with two parallel components (Skaggs & McNaughton, 1998; Tanila, 1999). This repetitive firing in similar environments provides support for the view that place cells are driven by local boundaries (Barry et al., 2006). In contrast, in studies using radial arm mazes (McNaughton et al., 1983; Mizumori, McNaughton, Barnes, & Fox, 1989; O'Keefe & Conway, 1978), repetitive place fields were not observed, despite the presence of similar elements in the apparatus – the arms of the maze. A likely difference between these differing types of recording environments is the orientation of the local environments. Place field repetition appears to occur when similar local environments are oriented in the same direction as one another, and does not occur (at least to the same extent) when similar environments are oriented in different directions (Fuhs et al., 2005). To test the effects of head direction or angular orientation information on place field repetition, we constructed a modular duplicate of Spiers et al's. (2013) multicompartment environment which could be arranged in a 'parallel' configuration (as used in the original paper) and an additional 'radial' configuration, where we introduced an angle of 60° between each of the boxes. We recorded place cells from rats freely exploring these environments each day and were able to replicate the findings of Spiers et al. (2013); a significant proportion of place cells in the parallel environment had repeating place fields, this effect was significantly higher than would be expected by chance. However, in the radial environment cells did not show the same level of repeating place fields and in fact place field repetition observed in this maze was not statistically higher than chance. The results of a Boundary Vector Cell (BVC) model are also reported, these predict precisely the pattern of results observed in our place cell data. Together these results suggest that the addition of angular head direction information greatly reduces the frequency of place field repetition, this finding is discussed in terms of a Boundary Vector Cell (BVC) model of place cell firing.

## 6.3 Methods

The methods used here were similar to those described previously, thus descriptions given below are brief and are included primarily to indicate deviations from those methods described above.

### 6.3.1 Subjects

Four naïve male Lister hooded rats, with a weight between 250-300g were used as subjects. The animals were housed in groups of four in standard cages, but housed individually in custom designed cages post-surgery. The animals were maintained under a constant 12 h light/dark cycle and any testing was performed during the light phase of this cycle. Throughout testing, rats were food deprived such that they maintained approximately 90% (and not less than 80%) of their free-feeding weight or the weight which would be achieved when granted ad lib feeding. For no less than 7 days after surgery and 1 day before, animals were granted ad lib access to food. Animals were given free access to water at all times when in their home cages. Testing was usually performed 5 days a week during the usual working weekdays. In this experiment, compliance was ensured with national

[Animals (Scientific Procedures) Act, 1986] and international [European Communities Council Directive of November 24, 1986 (86/609/EEC)] legislation governing the maintenance of laboratory animals and their use in scientific experiments. Experiments underwent further ethical and procedural approval by the Named Veterinary Surgeon and Named Animal Care and Welfare Officer responsible for overseeing experiments in the host laboratory.

### 6.3.2 Recording Device

In this experiment we used microdrives based on the same design (Kubie, 1984) as in Experiment 2; however some improvements were made on the design. As before, tetrodes were gold plated (Non-Cyanide Gold Plating Solution, Neuralynx, MT) in order to reduce the impedance of the wire. However, here we used a semi-automatic plating rig which delivered electrical pulses in 10μA, 1.8 μV increments which allowed plating from a resting impedance of typically 0.7-0.9MΩ  to a plated impedance in the range of 180-250 kΩ (200kΩ being the target impedance), much lower than in previous experiments. Tetrode bundles were no longer coated for structural support, as this was found to significantly decrease the cell yield of our microdrives, individual tetrodes were still heat annealed during construction. The dental cement used during surgery to fix the drives to the skull surface was mixed with powdered silver sulphate ($Ag_2SO_4$) (Sigma-Aldrich Co. LLC., Arklow, Ireland), this has been shown to give dental cement anti-microbial properties (Melo et al., 2013), this is the first time, to the authors knowledge, that silver sulphate additive has been used in this setting. In addition to the tripod microdrive design, half of the animals were implanted with pre-fabricated microdrives (Axona Ltd., St. Albans, UK). The tetrode construction, preparation and implantation remained the same as described previously.

### 6.3.3 Surgery

The surgical techniques in this experiment were identical to those described previously. Briefly, animals were anaesthetised using an Isoflurane inhalation anaesthetic

(Abbott Laboratories Ltd.), the animal was placed in a stereotaxic frame and the position of the skull was fixed using stereotaxic ear bars. An incision was made above the dorsal midline suture of the skull which was made flat in the anterior-posterior plane. A hole was drilled above the implant site and 7-8 guide holes were drilled for the skull screws (0.9mm diameter, stainless steel, Fine Science Tools GmbH., Heidelberg, Germany). The electrode tip was lowered to our CA1 coordinate (-3.5mm AP from bregma, + 2.4mm ML from the midline, -1.7mm DV from dura surface) and the drive assembly was anchored to the skull screws and bone surface using dental cement.

### 6.3.4 Screening and Single Unit Recording

The recording equipment and procedures utilised here were identical to those described previously. Briefly, single unit activity was observed and recorded using a 32-channel Axona USB system (Axona Ltd., St. Albans, UK). Microdrives were attached to the recording system where they were amplified and filtered according to the desired thresholds. Neuronal activity and the rat's position were recorded and then analysed off-line using custom Matlab scripts. Rats were screened for single unit activity and for the presence of theta oscillations once or twice a day, 5 days a week. In order to reduce the effects of generalisation between mazes and to guarantee pyramidal recordings in the first maze session, animals completed a session of the experimental protocol only when pyramidal (complex spiking) activity was observed during screening.

### 6.3.5 Apparatus

We used four main pieces of maze apparatus; an open field environment used for screening, a cylindrical environment used for characterising the stability of place cells and the two main experimental mazes, where we sought to record the repetitive firing of place cells. The cylindrical environment and the experiment mazes were placed inside a 500cm curtained enclosure with an opaque white curtain ceiling, together these curtains eliminated directional cues from unidirectional light sources or air currents. A 100cm x 50cm white sheet acted as a directional cue within this curtain enclosure, this was placed on the curtain wall opposite the maze goal boxes. The open field screening enclosure was situated in an area of the recording room out with this curtained area and separated from it by a white curtain running the length of the room.

Our open field environment consisted of a large, wooden, 100cm x 100cm (width x length) square enclosure with 25cm high wooden walls, painted blue. No intramaze cues were used in this enclosure, which was also cleaned regularly with detergent and rotated by random increments of 90° between each session. Our cylinder environment consisted of an 80cm round wooden base with 30cm high wooden walls – these walls were the same height as those on the maze and permitted animals to see extramaze cues. This environment was always placed facing the same direction relative to the white directional cue.

Our maze environments were constructed entirely from wood and consisted of four rectangular boxes (35 x 40cm, width x length) with 30cm high walls, painted blue. Two alleyways connected these boxes, one allowed for them to be arranged alongside and parallel to each other, the second allowed for them to be arranged in a radial configuration with a 60° between the boxes. Thus the exact same boxes were used in each maze configuration. These alleyways were 20cm wide with 30cm high walls and were also made entirely of wood and painted blue. Large wooden blocks could be used to close off boxes and make them inaccessible to the rats when desired. A floor plan of the two maze configurations can be seen in Figure 6.4. All of our environments were elevated by 80cm from the floor by wooden stools.

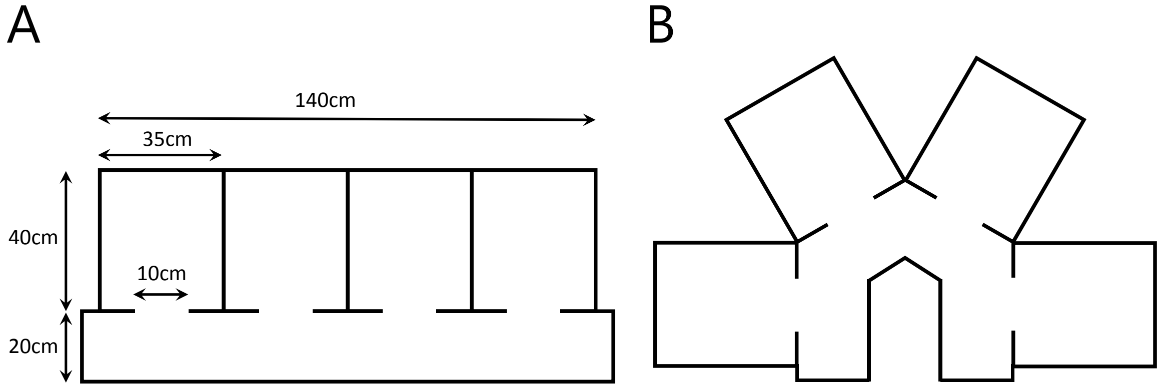

**Figure 6.4:** Maze compartment layouts. **A**) Schematic diagram of the parallel maze configuration. **B**) Schematic diagram of the radial maze configuration. A 100cm long white cue card was also suspended within the curtain enclosure, this was found roughly 1 metre from the alleyway of the maze (the south or bottom wall as depicted in this figure).

### 6.3.6 Procedure

During recording, rats were attached to the recording system via a flexible recording cable while they explored our maze and cylinder environments. Neuronal activity was recorded in our cylinder environment for a minimum of 8 minutes, the maze in either the parallel or radial configuration for a minimum of 18 minutes, the maze in its alternative configuration for a further 18 minutes and finally the cylinder environment for another 8 minutes. Between each of these environments, rats were removed to a small, tall sided, opaque cylinder where they were given access to drinking water for approximately 2 minutes (see Figure 6.5). In each environment rats freely foraged for scattered food rewards (Chocolate puffed rice cereal, ‘Coco Pops’, Kellogg’s, UK) – the wooden doors used during training were not used here, maze boxes were all always accessible. The maze and cylinder environments were cleaned with scented detergent between rats and the four maze boxes swapped positions between sessions and between rats.

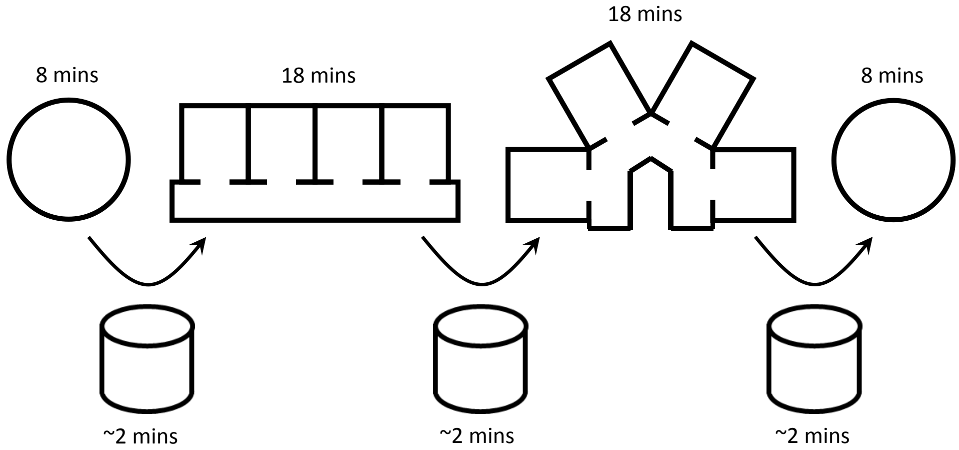

**Figure 6.5:** Schematic of the experiment 2 recording procedure. Place cells were recorded as rats explored a cylinder environment for a minimum of 8 minutes, the maze in its parallel configuration for a minimum of 18 minutes, the maze in its radial configuration for a minimum of 18 minutes and lastly the cylinder environment for a minimum of 8 minutes. The order of parallel and radial configuration was alternated. Between each of these sessions, rats were placed in a holding bucket where they had access to drinking water, this inter trial interval typically lasted approximately 2 minutes.

### 6.3.7 Data Analysis

#### 6.3.7.1 Cluster Cutting

Spike data were analysed offline using custom Matlab scripts, as described previously. The energy, first principle component, peak amplitude, time at peak and width of waveform were used to sort spikes using the Klustakwik spike sorting algorithms (Kadir et al., 2013). These clusters were then manually checked and potentially refined using the manual cluster cutting GUI, Klusters (Hazan et al., 2006).

#### 6.3.7.2 Discrimination of Cell Types

During the cluster cutting stage described above every effort was made to remove clusters which were due to noise, interference or mechanical artefacts generated during the recording process. Remaining clusters were classified using custom Matlab scripts. Units were classified as a place cell by automated classification if;

1) the firing rate was greater than 0.1Hz but less than 5Hz;

2) the width of waveform was greater than 250ms, and;

3) the spatial information content was greater than 0.5b/s.

Interneurons were identified on the basis of firing rate and waveform width (< 250ms). This categorisation was carried out on each environment independently. After this automatic sorting of clusters a second round of manual discrimination removed any clusters which were not recognisable as a single unit. This discrimination was based on the presence of a refractory period, the consistency of firing over the course of the recording session, and the shape of the cluster's waveform.

#### 6.3.7.3 Cluster Quality

We used the three primary measures of cluster and signal quality which have been described previously: isolation distance (Iso-D), $L_{ratio}$ and signal to noise ratio (S/N). We also calculated spatial information content defined as:

$$Information\ content = \sum P_i(R_i/R)\log_2(R_i/R)$$

where $i$ is the bin number, $P_i$ is the probability for occupancy of bin $i$, $R_i$ is the mean firing rate for bin $i$, and $R$ is the overall average firing rate. This was calculated using a single firing rate map produced for each environment in the same way as those described below.

#### 6.3.7.4 Repetitive Firing Analysis

Spike and position data were analysed using custom Matlab scripts; for each maze the position data for each compartment were extracted and adjusted to fill an area equivalent to the dimensions of the actual compartment.  This was required to compensate for optical distortion arising from the single CCTV camera tracking the animal's movements over such a large area. For compartments in the radial configuration the data were also rotated around the compartment centre to align them vertically before correlation. The firing rate in each compartment was calculated as the total number of spikes occurring within the compartment's boundaries by the total length of time spent there.

Position and spike data were processed as described previously. Firing rate maps were then produced for each compartment individually by dividing the compartment area into a grid of 3cm square bins (each compartment = 12 x 14 bins). The firing rate in each bin was calculated as the total number of spikes which occurred in that bin divided by the total length of time spent there. Bins in which the rats spent less than 0.1 seconds were treated as if they had not been visited. Bins were smoothed using a Gaussian filter defined by:

$$g(x) = exp\left(\frac{-x^2/\,2\sigma^2 - y^2}{2\sigma^2}\right)$$

The correlation between each compartment pair was calculated by pairwise Pearson product moment correlation coefficient such that for each maze a total of six correlation values could be obtained[34]. However, for the maze sessions, correlations were carried out only if a cluster satisfied the criteria for a place cell outlined above and only on compartment pairs in which the firing rate in one of the compartments exceeded 1Hz. For the cylinder sessions, the correlation was calculated only if the cluster satisfied the above criteria for a place cell in one or both of the cylinder sessions and contributed correlation values from one or both of the maze sessions.

#### 6.3.7.5 Shuffling

The correlations observed in the maze and cylinder environments were compared to correlations obtained from shuffled data. Shuffling followed one of two routes, the first was similar to that employed by Spiers et al. (2013) the second followed a Monte Carlo procedure. For the parallel maze, compartment rate maps were collected from cells which passed the above place cell criteria in the parallel maze session and contributed correlation values included in the parallel maze analyses. These rate maps were shuffled, paired

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[34] The six correlation or compartment pairs were compartments 1&2, 1&3, 1&4, 2&3, 2&4 and 3&4.

randomly without replacement and if the firing rate in at least one compartment exceeded 1Hz the correlation between a pair was calculated. The resulting distribution of correlation values served as our 'shuffled' distribution. For the Monte Carlo procedure the rate maps were chosen in pairs, at random, and the correlation between the pair calculated, this was done 100,000 times and the resulting distribution of these correlation values served as our 'Monte Carlo' distribution. This process was repeated for the radial maze and radial compartment rate maps and the cylinder environment and the cylinder rate maps. For the cylinder session, rate maps were collected from cells which satisfied the above criteria of a place cell in one or both of the cylinder sessions and contributed correlation values towards the parallel and or radial analyses.

#### 6.3.7.6 Spatial Autocorrelation

For our autocorrelation analyses, compartment firing rate maps (each 12 x 14, 3cm bins, width x height) were concatenated along the longest edge to produce a 48 bin wide combined rate map which was used to generate a self-normalised spatial autocorrelograms using custom Matlab scripts (see Figure 6.6). The combined rate map was correlated with itself before being shifted laterally by a distance of 1 bin (3cm), the correlation was then recalculated and the process repeated until the maps no longer overlapped.

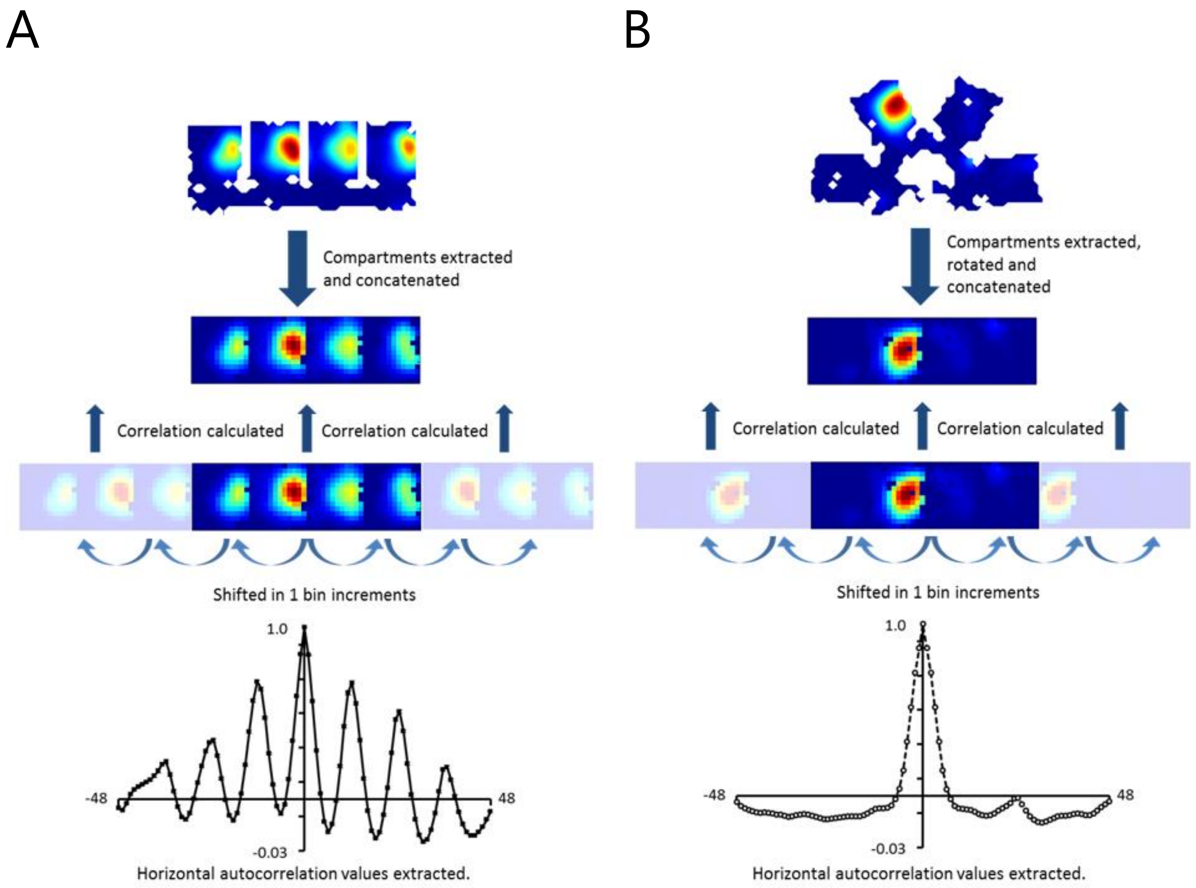

**Figure 6.6:** A schematic of the autocorrelation procedure for a single cell which was included in the parallel and radial correlation analyses. The procedure is outlined for both the parallel (**A**) and radial (**B**) environments. For both environments the process is the same: compartment rate maps are generated and concatenated to produce a map containing only the compartment data aligned horizontally. This map is then correlated with itself repeatedly as it is shifted in 1 bin increments in the horizontal plane. These correlation values can then be plotted to show the presence or absence of a periodic firing pattern, with the horizontal axis representing the extent of horizontal shifting (in bins) and the vertical axis representing the correlation value, which always peaks at 1.0, a perfect correlation, when the maps are perfectly aligned. The data for all cells included in these analyses can be seen in Figure 6.15.

#### 6.3.7.7 Neighbourhood Analysis

It is possible that although cells show repeating place fields in our parallel maze that they also modulate their firing rate based on the location of the compartment (for example, rate remapping). To assess this we ranked compartments according to their firing rate, this analysis has been described previously (Spiers et al., 2013). Briefly, we ranked compartments so that the compartment with the highest firing rate was scored a 0, compartments neighbouring this were labelled as having a distance from the maximum of 1, the compartment which was next furthest away was labelled with a distance of 2 and the compartment which the furthest away was labelled 3. If two compartments filled a position of equal distance, their values were averaged (see Figure 6.7). We then looked at changes in the firing rates of these ranked compartments across and within sessions. If rate remapping is observed in either maze configuration, firing rate should differ in relation to the compartment distance from the maximum in an informative way. If rate remapping is not present we would expect the maximum compartment firing rate at distance 0 to be relatively high, but firing in the distant compartments to be equivalent.

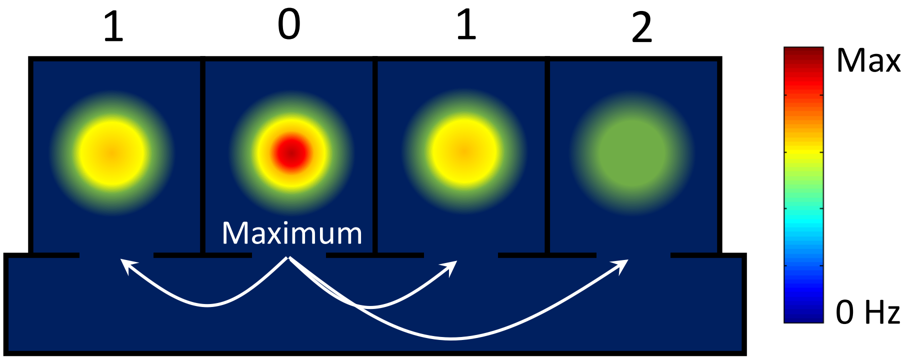

**Figure 6.7:** Schematic showing the firing of a hypothetical place cell which demonstrates rate remapping. The compartment with the maximum firing rate is labelled 0, the immediate neighbours are labelled as having a distance from the maximum of 1, the next furthest is labelled with a distance of 2 and a more distant compartment (if the maximum is in compartments 1 or 4) would be labelled as 3. In this example, rate remapping is present and firing rate declines linearly as distance from the maximum increases. For analysis, the firing rate of both compartments with a distance of 1 would be averaged.

#### 6.3.7.8 Place Fields

For clusters identified as place cells, firing rate maps were used in order to count the number of distinguishable place fields which were present in each environment. The rate maps were produced in the same way as compartment rate maps, except that they encompassed the entire maze session/area instead of a single compartment. Custom Matlab scripts were then used to isolate areas of firing over 20% of the maximum firing rate (peak firing rate in firing rate map). Areas of firing less than 1Hz were excluded. Regions of firing meeting the above criteria which also had an area greater than 9 contiguous[35] pixels (1 pixel

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[35] Contiguity is defined here as sharing at least one side

was approximately 2.5cm square) were considered place fields. The size, position, dimensions and firing rate properties of these fields were then extracted.

### 6.3.7.9 Compartment Morphing

If the repetitive firing observed in our parallel maze is the result of a BVC input to the HPC place cell population, we may expect that cells fire similarly (and repetitively) in the radial maze, but this firing may be locked to a global reference frame (relative to distal cues) rather than a purely local one. In this instance, rotating the radial maze compartments in order to calculate our correlation values may disrupt this relationship. To test the validity of this we also calculated our radial correlation values after morphing the radial maze compartments instead of rotating them. Morphing was carried out by repositioning radial compartment position and spike recording data to a vertical compartment of the same dimensions, such that each of these data points maintained its radial position as a proportion of the distance to the compartment perimeter along that radius (see Figure 6.8) this procedure has been reported previously (Leutgeb, Leutgeb, Treves, et al., 2005; Lever et al., 2002).

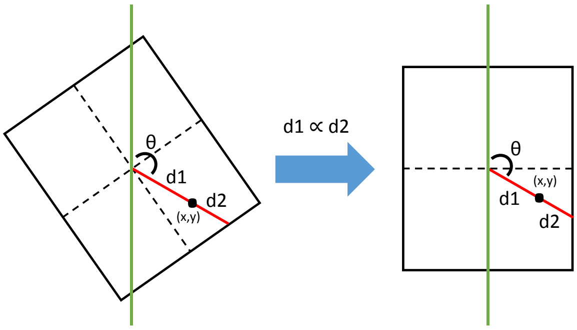

**Figure 6.8:** Schematic showing the radial compartment morphing process. Coordinates are repositioned within a vertical compartment, whilst maintaining their angle relative to the centre of the compartment (θ) and their proportional distance between the centre and the compartment perimeter (d1 ∝ d2) at angle θ.

### 6.3.7.10 Boundary Vector Cell (BVC) Simulations

We sought to model the firing of place cells in our maze environments using a BVC model of place cell firing. To generate BVC firing distributions the boundaries of the environments were mapped in terms of their vertices such that 1 pixel = approximately 0.25 cm in real space. These vertices were extended to give a vector of Cartesian coordinates, with a coordinate representing the position of the boundary every 0.25 cm. A grid of 'plausible' coordinates were then mapped within the polygon formed by these coordinates, the spacing in this grid was 2.5 cm[36]. For each of these coordinates, every visible boundary coordinate was mapped such that a catalogue of x,y coordinates and the boundary coordinates visible from each was available. To simulate a BVC's firing, a Gaussian matrix was positioned at each of these plausible coordinates in turn and the index of relevant boundary coordinates for that position was retrieved, these were used to extract the corresponding points in the Gaussian matrix and thus the cell's predicted firing rate. The Gaussian and other relevant formula are given below.

The firing of BVC *i* (tuned to preferred distance *di* and angle ω) to a boundary at distance ε and direction θ is given by:

$$Firing\ Rate(x,y) = gi(\varepsilon,\theta)$$

where;

$$gi(\varepsilon,\theta) =$$

$$\exp(-\frac{\left((X-xi)*\cos(\omega)-(Y-yi)*\frac{\sin(\omega)}{sigmax}\right)^2+\left((X-xi)*\sin(\omega)+(Y-yi)*\frac{\cos(\omega)}{sigmay}\right)^2}{2})$$

where *xi* and *yi* are the position of the rat relative to the centre of the Gaussian (*gx*,*gy*), given by:

$$xi = gx + di*\cos(\omega)$$
$$yi = gy + di*\sin(\omega)$$

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[36] The grid originally accounted for every plausible coordinate within the polygon, but this was found to be too computationally expensive when computing <1000 BVCs was required.

Sigmax and sigmay determine the Gaussian's angular tuning width and distribution around the BVC's tuning distance, these were set to 1.5 and 25 respectively. These values provide a relatively narrow Gaussian which is widely banded outwards from the rat. This Gaussian was further cut to a tuning 'cone' which was ω ± 7.5° wide (see Figure 6.9). At each position of the rat in the simulated environment, the firing rate of the BVC was calculated by linearly integrating the values of the above Gaussian at the points where the environment boundaries were visible to the rat. Thus, all boundaries visible to the rat 360° relative to its position provided an input to the BVC's firing rate, boundaries not visible to the rat had no

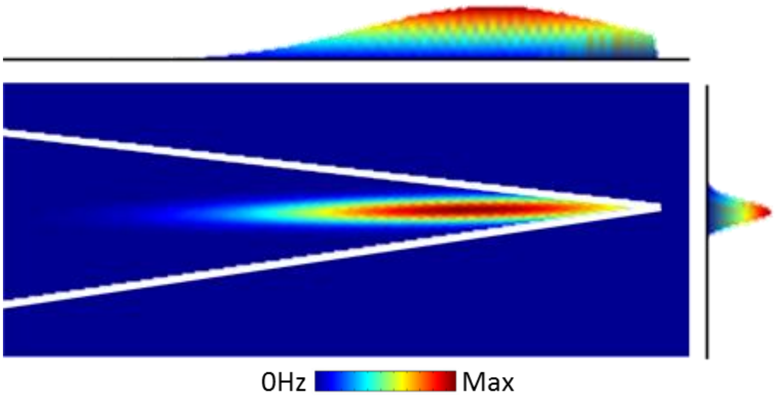

**Figure 6.9:** An example BVC tuning curve. Showing a side view (top), end profile (right) and above view (bottom left). The white lines shown in the above view define the edge of the tuning cone (15°).

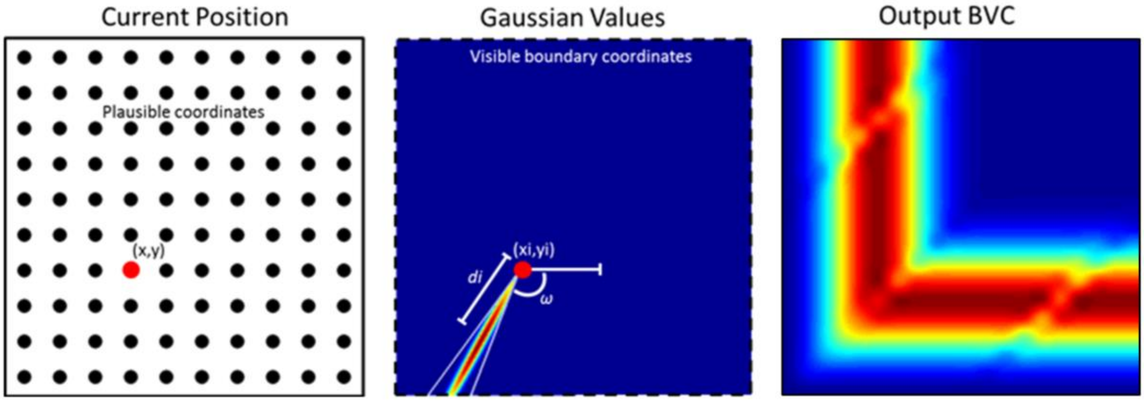

**Figure 6.10:** Boundary vector cell (BVC) simulation procedure. Left) A grid of plausible coordinates is mapped to the environment, for each of these points every visible boundary coordinate is found. Middle) For each of the plausible coordinates the Gaussian tuning curve is overlaid onto the environment and the corresponding visible boundary coordinate values are extracted from it. Right) The Gaussian values at each plausible coordinate are linearly integrated to give a single firing rate value which accounts for all visible boundaries in the environment at that point.

effect (see Figure 6.10). Each PC resulted from the threshold linear sum of 15 BVCs[37]. Examples of BVCs and place cells produced using our model can be seen in Figure 6.11.

We analysed these place cells in the same way as our real dataset, by calculating the level of correlation between the different compartment pairs. However, here we did not have access to position and spike data. Instead of creating compartment rate maps we extracted this data from overall maze firing rate maps, these were then rotated as images where required. With real place cells we also specified that a cell had to fire on average >1Hz in at least one compartment of a compartment pair before a correlation was calculated. Instead, a simulated cell's peak compartment firing rate had to exceed half of its overall maximum in at least one compartment per pair. This cut-off was also maintained throughout the shuffling procedures.

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[37] Our threshold was a binary filter of the BVC firing rate such that only the greatest 70% of the BVC firing rate was returned. A binary threshold was preferred as this eliminated anomalous values where boundaries parallel to the rat stimulated higher values than boundaries subtending the rat at the BVCs preferred angle – this is because parallel boundaries bisect the Gaussian along its length rather than width, thus resulting in a higher overall value. Although in practice, the method of transformation at this point had little effect on the resulting PC behaviour.

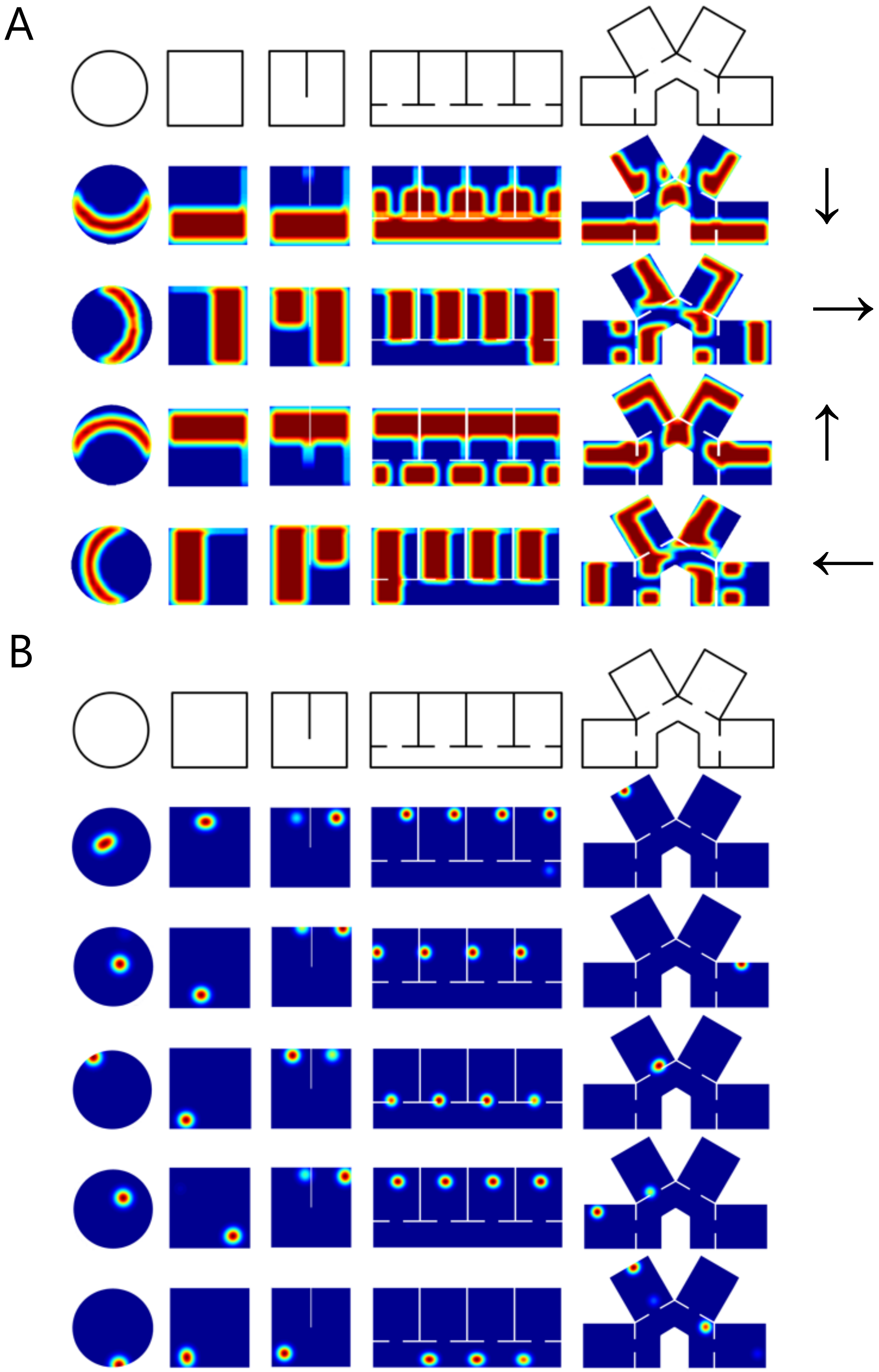


**Figure 6.11:** Example outputs produced by our BVC model. **A**) Four simulated BVCs (one per row) and their firing patterns in a number of different simulated environments. Each cell has a different preferred firing direction which is shown by an arrow on the right. **B**) Simulated place cells and their firing patterns in the same environments (a different cell is shown in each firing rate map).

#### 6.3.7.11 Perfusion and Histology

The procedure used for perfusion and histological examination were identical to those described above. Briefly, animals were injected intraperitoneally with a lethal dose of a pentobarbital agent (0.7ml Euthatal, Merial Animal Health Ltd., Essex, UK) and perfused with a 4% formalin (10% formaldehyde) solution. Brains were then sliced to give 32µm sections and Nissyl stained with a 0.1% cresyl violet solution. A slice best representing the electrode track was then imaged using ImageJ software (ImageJ, NIH, Bethesda, http://imagej.nih.gov/ij/, 1997-2014).

## 6.4 Results

### 6.4.1 Histology

Electrode tracks were identified in all four animals (see Figure 6.12), all recordings were made in the CA1 region of the HPC.

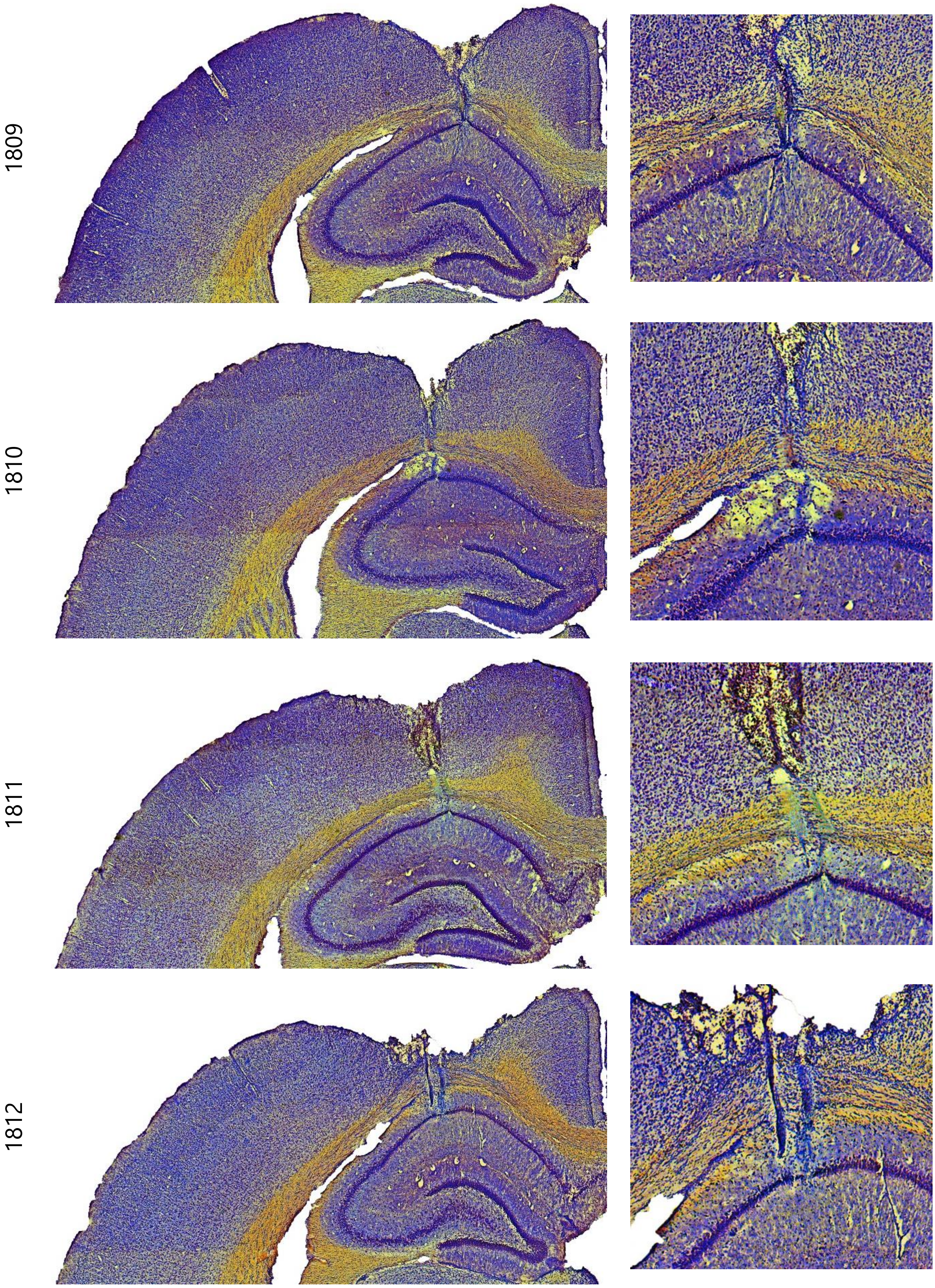


**Figure 6.12:** Showing histological sections for all four implanted animals (one per row), rat ID numbers are given on the left. The left column contains unilateral images of the hippocampus, showing the electrode track at 2.5x magnification. Images in the right column show the same image at approximately 10x magnification, where the intersection of the electrode track and pyramidal cell layer can be seen more clearly.

### 6.4.2 Place Field Repetition

A total of 1261 place cells were recorded in our parallel configuration, 534 (42.35%) of these were active in at least one compartment and thus included in our correlation analyses, yielding 2291 correlation values (4.29 per cell). A total of 1481 place cells were active in our radial configuration, 755 (50.98%) of these cells were included in our correlation analyses, yielding 2962 correlation values (3.92 per cell). Of these place cells 1134 were recorded in both configurations, 370 of which were included in the correlation analyses for both mazes. In our cylinder environments 1773 place cells were recorded, 554 (31.25%) of these were also included in our parallel or radial correlation analyses and thus included in our cylinder correlation analyses. For computational simplicity, we did not attempt to identify repeat recordings of the same cells, and thus the number of unique cells is lower.

*Recordings were stable throughout each session*

The correlation values observed between the cylinder sessions included in our analyses are, on average, very high (*M* = .60, *SEM* = 0.01), confirming that cells often fired similarly in the second cylinder session when the rat was returned there. Furthermore, the correlations observed in the cylinder environment (*N* = 554) differ significantly from shuffled [*N* = 545, *t*(1097) = 31.53, *p* < .001, *d* = 1.90] and Monte Carlo distributions [*N* = 49207, *t*(49759) = 39.07, *p* < .001, *d* = 1.69] as confirmed by very large effect sizes. The two shuffled distributions do not differ [*t*(49750) = -1.89, *p* > .05, *d* = -0.08]. All tests are independent samples t-tests. These distributions can be seen in Figure 6.16.

*Place field repetition was observed much more frequently in the parallel than in the radial configuration*

The average correlation value observed in the parallel compartments was significantly higher than that of the radial compartments [*t*(5251) = 29.49, *p* < .001, *d* = 0.82] assessed using an independent samples t-test. This result is accompanied by a strong effect size. This effect can be seen in Figure 6.13 and Figure 6.15. A number of example cells can be seen in Figure 6.14.

### 6.4.3 Shuffling

*Place field repetition in the parallel environment was much higher than would be expected by chance, this was not the case in the radial environment*

The correlations observed in the parallel maze ($N = 2291$) differ significantly from shuffled [$N = 1053$, $t(3342) = 22.34$, $p < .001$, $d = 0.83$] and Monte Carlo distributions [$N = 94996$, $t(97285) = 42.38$, $p < .001$, $d = 0.89$] as confirmed by large effect sizes. However, the two shuffled distributions do not differ [t(96047) = 0.50, $p > .60$, $d = 0.02$]. The correlations observed in the radial maze ($N = 2962$) differ significantly from the shuffled [$N = 1356$, $t(4316) = 3.26$, $p < .001$, $d = 0.11$] and Monte Carlo distributions [$N = 87889$, $t(90849) = 4.84$, $p < .0001$, $d = 0.108$] but each of these tests is accompanied by a low effect size. The two shuffled distributions do not differ significantly [$t(89243) = -0.69$, $p > .49$, $d = -0.02$]. All tests are independent samples t-tests. These results can be seen in Figure 6.16.

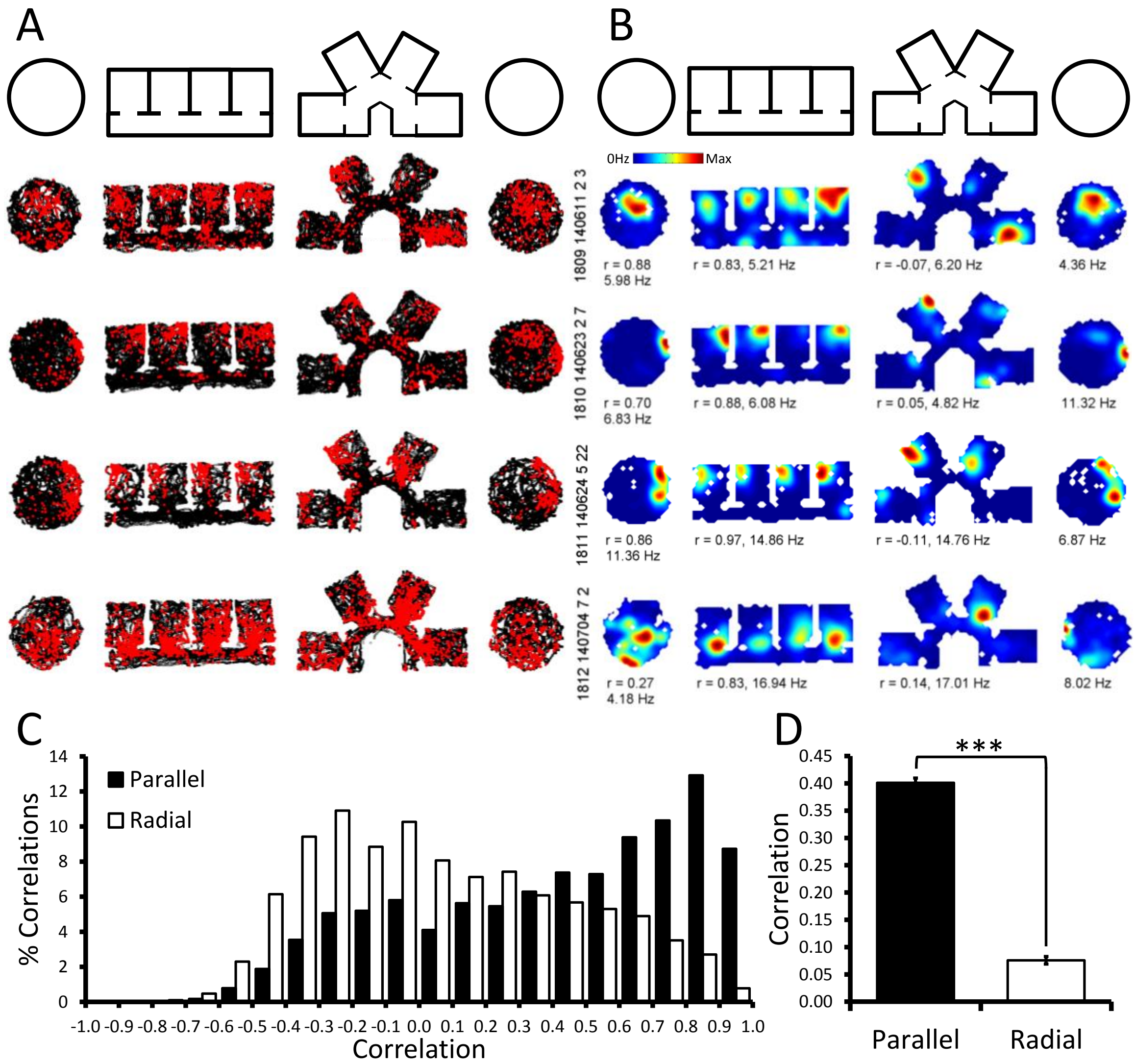
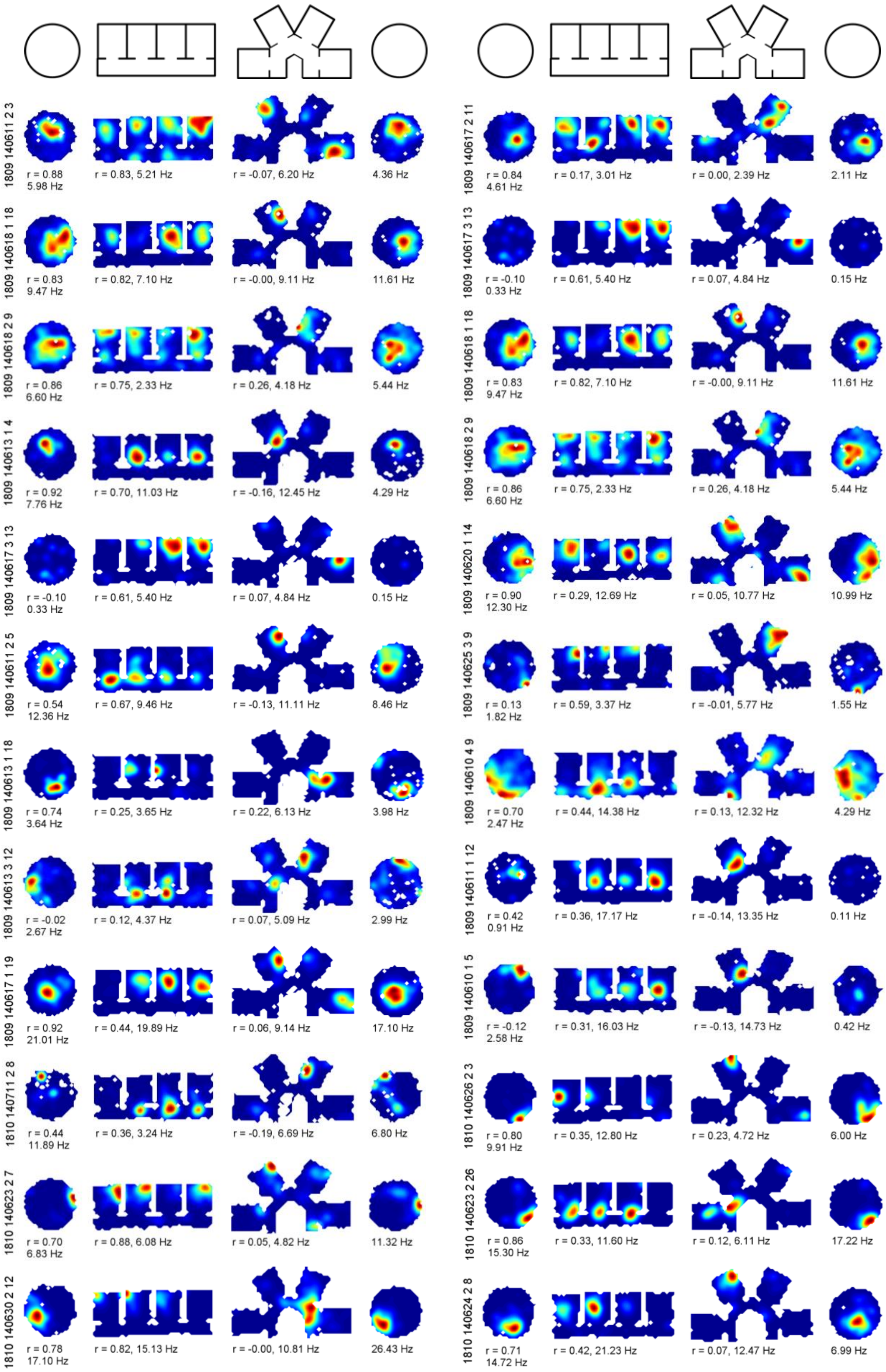


**Figure 6.13:** Place field repetition in the parallel and radial environments. **A** and **B** top row) Schematic of the environments used. Rats were recorded in the cylinder apparatus, the parallel compartment apparatus, the radial compartment apparatus (or vice versa), and again in the cylinder. Below these schematics are shown four example place cells (one per rat and one per row). Cumulative position plots are shown in **A**, here black lines indicate the animal's paths, and red dots indicate the location of individual spikes. Firing rate maps for the same cells are shown in **B**, the rat, date, electrode and cluster are shown to the left of each rate map in vertical text. The mean correlation value between the compartments in each environment and the maximum firing rate are shown below the rate maps. The correlation between cylinder sessions is shown below the leftmost cylinder firing rate map. Additional cell examples can be seen in Figure 6.13. **C**) Distribution of all correlations between radial compartments (filled bars) and parallel compartments (open bars), normalised according to the number of correlations attained from each. **D**) Average correlations (*M* ± *SEM*) from the firing rate maps of the parallel and radial compartments.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r = 0.88
5.98 Hz
r = 0.83, 5.21 Hz
r = -0.07, 6.20 Hz
4.36 Hz
1809 140618 1 18
r = 0.83
9.47 Hz
r = 0.82, 7.10 Hz
r = -0.00, 9.11 Hz
11.61 Hz
1809 140618 2 9
r = 0.86
6.60 Hz
r = 0.75, 2.33 Hz
r = 0.26, 4.18 Hz
5.44 Hz
1809 140613 1 4
r = 0.92
7.76 Hz
r = 0.70, 11.03 Hz
r = -0.16, 12.45 Hz
4.29 Hz
1809 140617 3 13
r = -0.10
0.33 Hz
r = 0.61, 5.40 Hz
r = 0.07, 4.84 Hz
0.15 Hz
1809 140611 2 5
r = 0.54
12.36 Hz
r = 0.67, 9.46 Hz
r = -0.13, 11.11 Hz
8.46 Hz
1809 140613 1 18
r = 0.74
3.64 Hz
r = 0.25, 3.65 Hz
r = 0.22, 6.13 Hz
3.98 Hz
1809 140613 3 12
r = -0.02
2.67 Hz
r = 0.12, 4.37 Hz
r = 0.07, 5.09 Hz
2.99 Hz
1809 140617 1 19
r = 0.92
21.01 Hz
r = 0.44, 19.89 Hz
r = 0.06, 9.14 Hz
17.10 Hz
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r = 0.44
11.89 Hz
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6.80 Hz
1810 140623 2 7
r = 0.70
6.83 Hz
r = 0.88, 6.08 Hz
r = 0.05, 4.82 Hz
11.32 Hz
1810 140630 2 12
r = 0.78
17.10 Hz
r = 0.82, 15.13 Hz
r = -0.00, 10.81 Hz
26.43 Hz
1809 140617 2 11
r = 0.84
4.61 Hz
r = 0.17, 3.01 Hz
r = 0.00, 2.39 Hz
2.11 Hz
1809 140617 3 13
r = -0.10
0.33 Hz
r = 0.61, 5.40 Hz
r = 0.07, 4.84 Hz
0.15 Hz
1809 140618 1 18
r = 0.83
9.47 Hz
r = 0.82, 7.10 Hz
r = -0.00, 9.11 Hz
11.61 Hz
1809 140618 2 9
r = 0.86
6.60 Hz
r = 0.75, 2.33 Hz
r = 0.26, 4.18 Hz
5.44 Hz
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r = 0.90
12.30 Hz
r = 0.29, 12.69 Hz
r = 0.05, 10.77 Hz
10.99 Hz
1809 140625 3 9
r = 0.13
1.82 Hz
r = 0.59, 3.37 Hz
r = -0.01, 5.77 Hz
1.55 Hz
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r = 0.70
2.47 Hz
r = 0.44, 14.38 Hz
r = 0.13, 12.32 Hz
4.29 Hz
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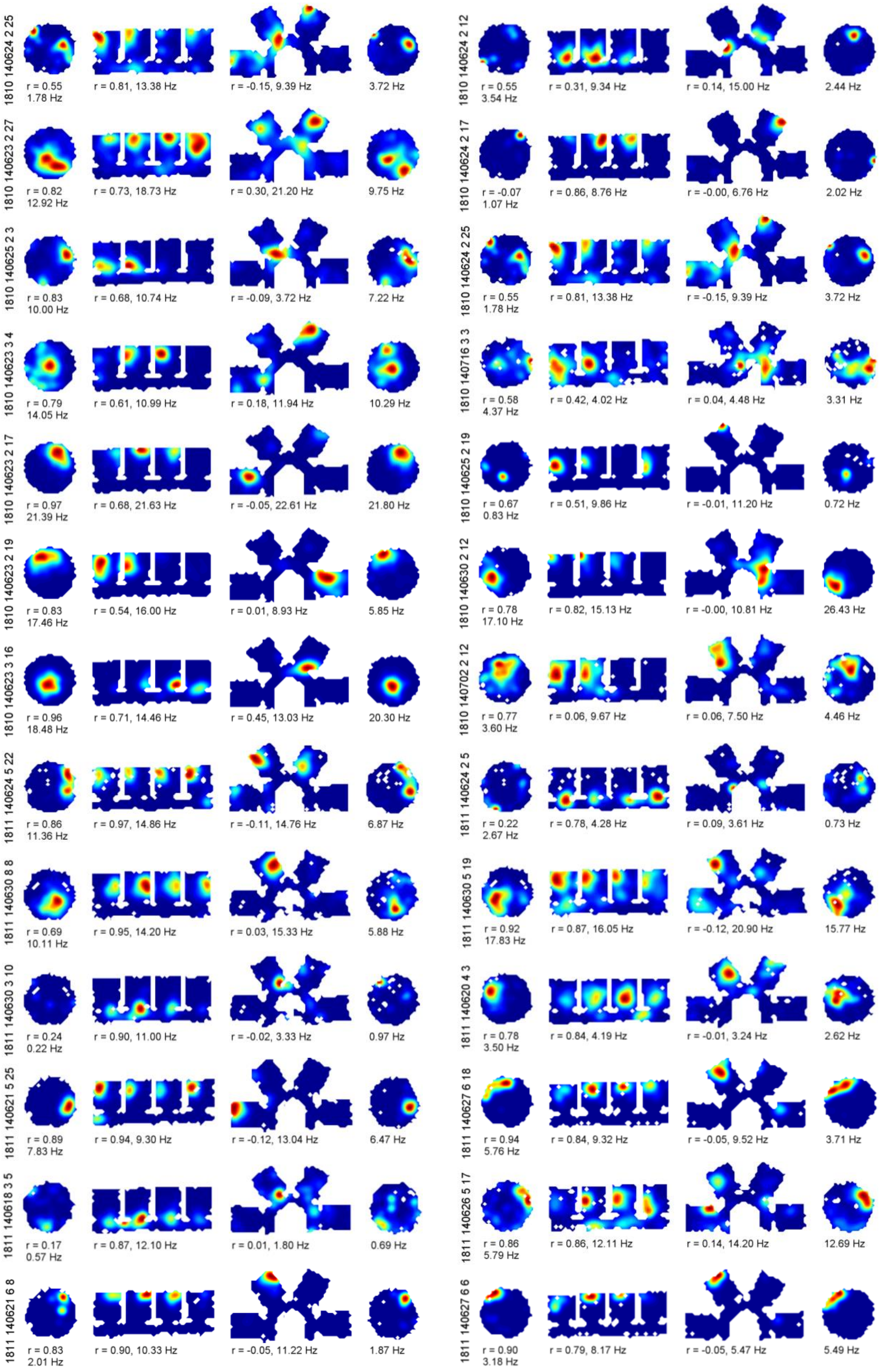
r = 0.42
0.91 Hz
r = 0.36, 17.17 Hz
r = -0.14, 13.35 Hz
0.11 Hz
1809 140610 1 5
r = -0.12
2.58 Hz
r = 0.31, 16.03 Hz
r = -0.13, 14.73 Hz
0.42 Hz
1810 140626 2 3
r = 0.80
9.91 Hz
r = 0.35, 12.80 Hz
r = 0.23, 4.72 Hz
6.00 Hz
1810 140623 2 26
r = 0.86
15.30 Hz
r = 0.33, 11.60 Hz
r = 0.12, 6.11 Hz
17.22 Hz
1810 140624 2 8
r = 0.71
14.72 Hz
r = 0.42, 21.23 Hz
r = 0.07, 12.47 Hz
6.99 Hz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12.92 Hz
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9.75 Hz
1810 140625 2 3
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10.00 Hz
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7.22 Hz
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14.05 Hz
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10.29 Hz
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21.39 Hz
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21.80 Hz
1810 140623 2 19
r = 0.83
17.46 Hz
r = 0.54, 16.00 Hz
r = 0.01, 8.93 Hz
5.85 Hz
1810 140623 3 16
r = 0.96
18.48 Hz
r = 0.71, 14.46 Hz
r = 0.45, 13.03 Hz
20.30 Hz
1811 140624 5 22
r = 0.86
11.36 Hz
r = 0.97, 14.86 Hz
r = -0.11, 14.76 Hz
6.87 Hz
1811 140630 8 8
r = 0.69
10.11 Hz
r = 0.95, 14.20 Hz
r = 0.03, 15.33 Hz
5.88 Hz
1811 140630 3 10
r = 0.24
0.22 Hz
r = 0.90, 11.00 Hz
r = -0.02, 3.33 Hz
0.97 Hz
1811 140621 5 25
r = 0.89
7.83 Hz
r = 0.94, 9.30 Hz
r = -0.12, 13.04 Hz
6.47 Hz
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0.57 Hz
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0.69 Hz
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r = 0.83
2.01 Hz
r = 0.90, 10.33 Hz
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1.87 Hz
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3.54 Hz
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2.44 Hz
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r = -0.07
1.07 Hz
r = 0.86, 8.76 Hz
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2.02 Hz
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1.78 Hz
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3.72 Hz
1810 140716 3 3
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4.37 Hz
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3.31 Hz
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r = 0.67
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r = -0.01, 11.20 Hz
0.72 Hz
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26.43 Hz
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3.60 Hz
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4.46 Hz
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2.67 Hz
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0.73 Hz
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r = 0.92
17.83 Hz
r = 0.87, 16.05 Hz
r = -0.12, 20.90 Hz
15.77 Hz
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r = 0.78
3.50 Hz
r = 0.84, 4.19 Hz
r = -0.01, 3.24 Hz
2.62 Hz
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5.76 Hz
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3.71 Hz
1811 140626 5 17
r = 0.86
5.79 Hz
r = 0.86, 12.11 Hz
r = 0.14, 14.20 Hz
12.69 Hz
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3.18 Hz
r = 0.79, 8.17 Hz
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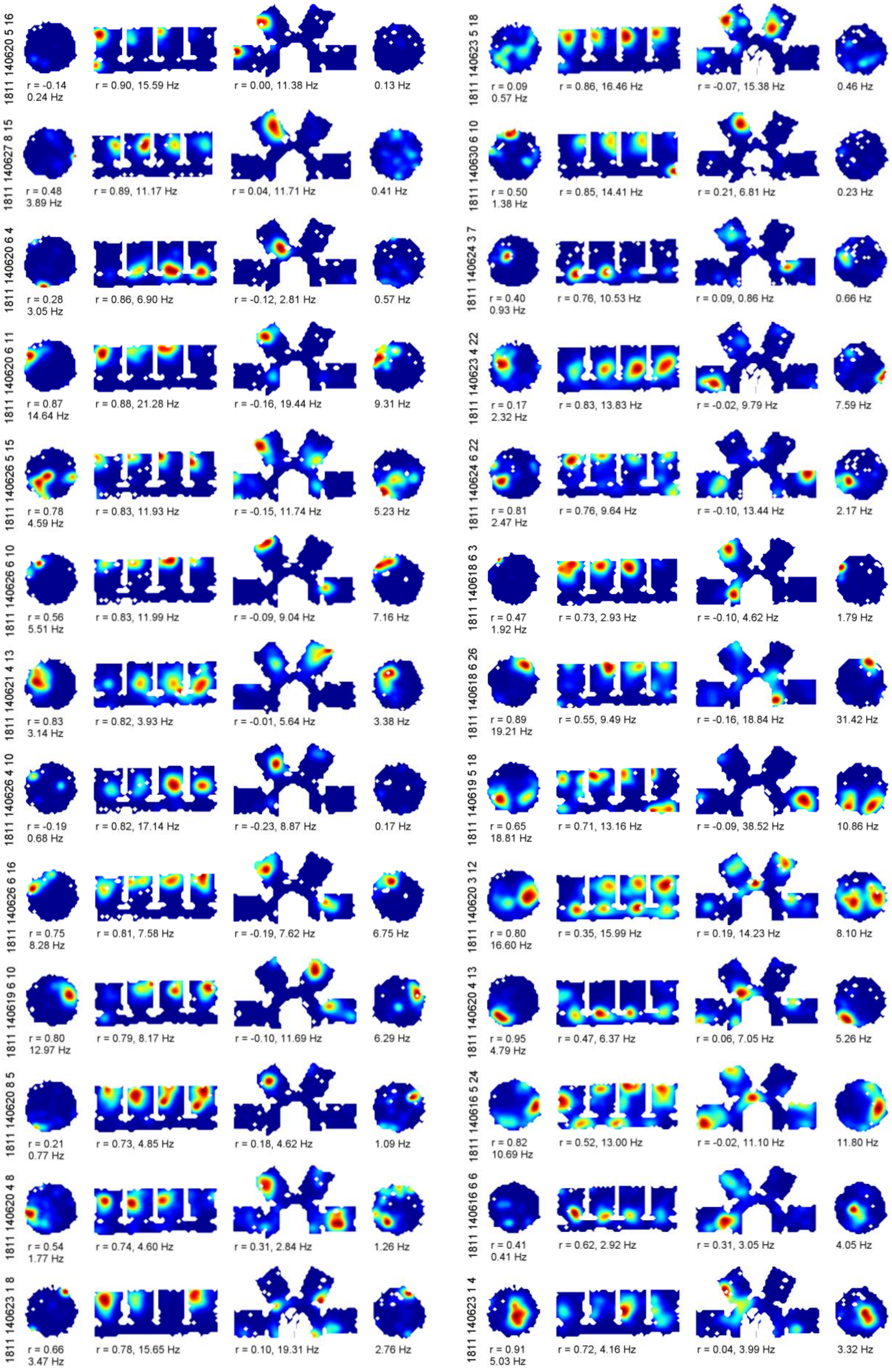
5.49 Hz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0.24 Hz
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0.13 Hz
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r = 0.48
3.89 Hz
r = 0.89, 11.17 Hz
r = 0.04, 11.71 Hz
0.41 Hz
1811 140620 6 4
r = 0.28
3.05 Hz
r = 0.86, 6.90 Hz
r = -0.12, 2.81 Hz
0.57 Hz
1811 140620 6 11
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14.64 Hz
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r = -0.16, 19.44 Hz
9.31 Hz
1811 140626 5 15
r = 0.78
4.59 Hz
r = 0.83, 11.93 Hz
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5.23 Hz
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r = 0.56
5.51 Hz
r = 0.83, 11.99 Hz
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7.16 Hz
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r = 0.83
3.14 Hz
r = 0.82, 3.93 Hz
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3.38 Hz
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r = -0.19
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r = 0.82, 17.14 Hz
r = -0.23, 8.87 Hz
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r = 0.81, 7.58 Hz
r = -0.19, 7.62 Hz
6.75 Hz
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r = 0.80
12.97 Hz
r = 0.79, 8.17 Hz
r = -0.10, 11.69 Hz
6.29 Hz
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r = 0.21
0.77 Hz
r = 0.73, 4.85 Hz
r = 0.18, 4.62 Hz
1.09 Hz
1811 140620 4 8
r = 0.54
1.77 Hz
r = 0.74, 4.60 Hz
r = 0.31, 2.84 Hz
1.26 Hz
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3.47 Hz
r = 0.78, 15.65 Hz
r = 0.10, 19.31 Hz
2.76 Hz
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r = 0.09
0.57 Hz
r = 0.86, 16.46 Hz
r = -0.07, 15.38 Hz
0.46 Hz
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r = 0.50
1.38 Hz
r = 0.85, 14.41 Hz
r = 0.21, 6.81 Hz
0.23 Hz
1811 140624 3 7
r = 0.40
0.93 Hz
r = 0.76, 10.53 Hz
r = 0.09, 0.86 Hz
0.66 Hz
1811 140623 4 22
r = 0.17
2.32 Hz
r = 0.83, 13.83 Hz
r = -0.02, 9.79 Hz
7.59 Hz
1811 140624 6 22
r = 0.81
2.47 Hz
r = 0.76, 9.64 Hz
r = -0.10, 13.44 Hz
2.17 Hz
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1.92 Hz
r = 0.73, 2.93 Hz
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1.79 Hz
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r = 0.89
19.21 Hz
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16.60 Hz
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8.10 Hz
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4.79 Hz
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5.26 Hz
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r = 0.82
10.69 Hz
r = 0.52, 13.00 Hz
r = -0.02, 11.10 Hz
11.80 Hz
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r = 0.41
0.41 Hz
r = 0.62, 2.92 Hz
r = 0.31, 3.05 Hz
4.05 Hz
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r = 0.91
5.03 Hz
r = 0.72, 4.16 Hz
r = 0.04, 3.99 Hz
3.32 Hz

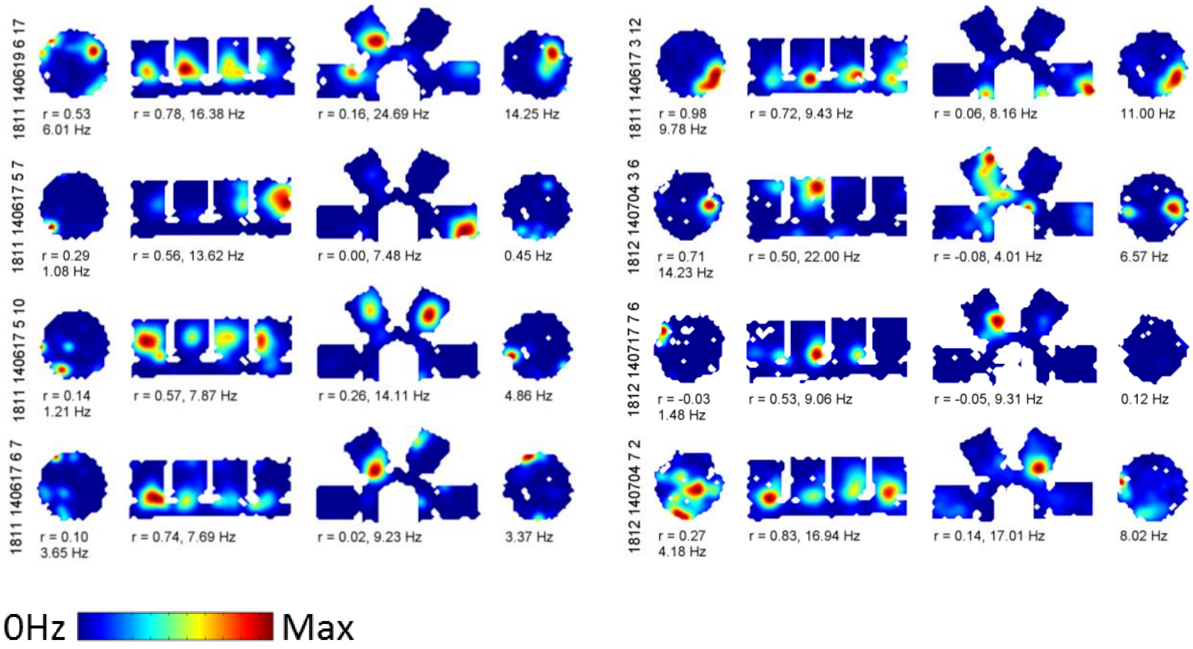

**Figure 6.14:** Additional cell examples which show a high degree of correlation between compartments in the parallel maze. Each cell included here contributed correlation values to one or both of the maze correlation analyses but may not have contributed towards the cylinder analyses. Shown are schematic diagrams of the maze and cylinder environments, below these are the example cells, two per row. To the left of each example, in vertical text, is shown the rat number, date of recording, electrode and cluster. Each firing rate map displays the cell's firing pattern in one of the recording environments, below each of these is given the maximum firing rate value displayed in the firing rate map (unless the maximum was less than 1Hz in which case the maximum was locked to 1Hz) and the mean correlation value for that maze, the cylinder correlation value is shown below the first cylinder firing rate map. For simplicity, mean correlation values are shown here for the maze environments, however, all individual compartment pair correlation values were included in the correlation analyses; the mean correlation values shown here are likely to be lower than specific individual correlations. Additional example cells, recorded in mice, can be seen in Supplementary Figure 2.

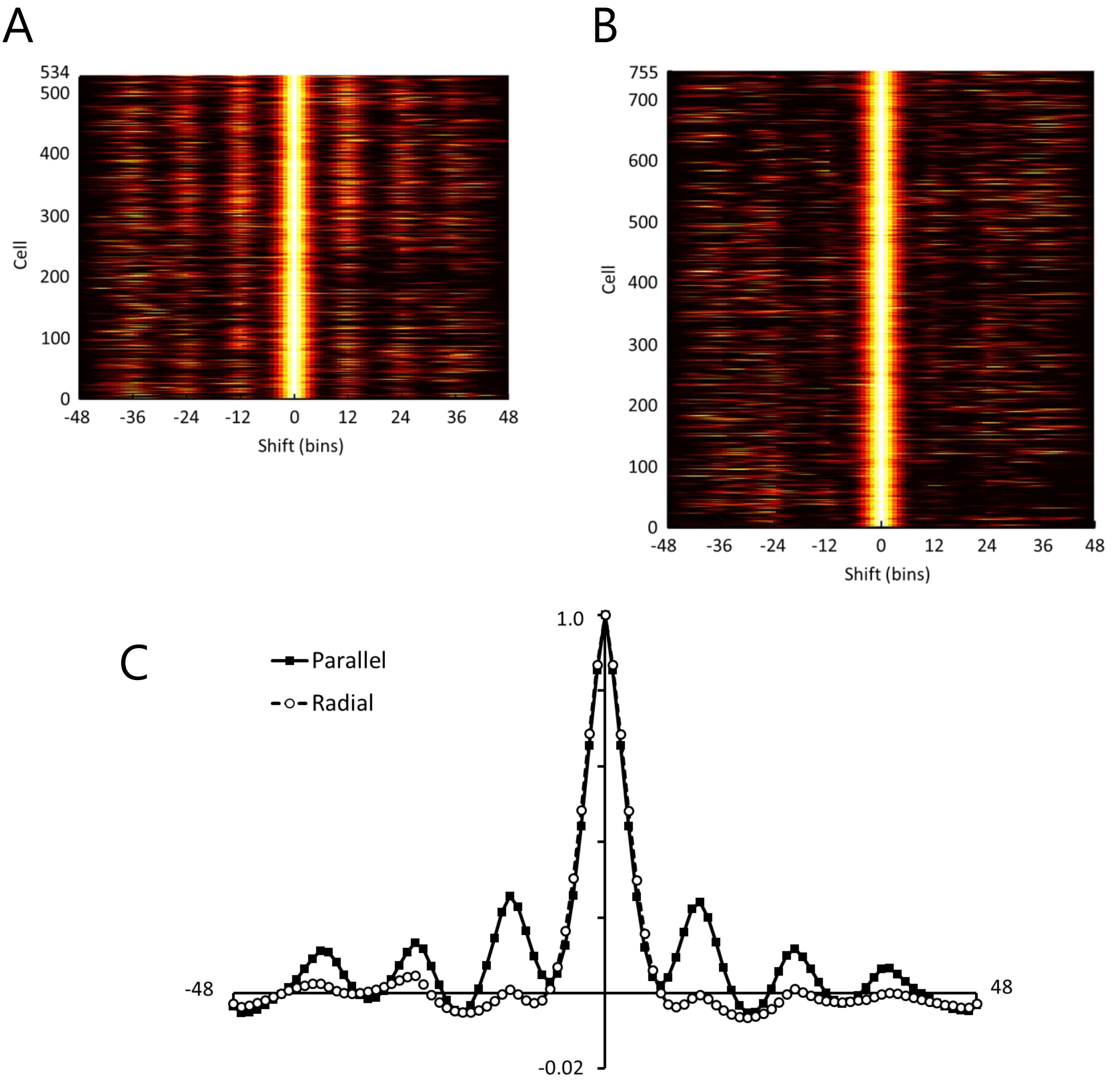

**Figure 6.15:** Autocorrelogram plots for the parallel and radial compartments. Compartment firing rate maps are concatenated and used to generate a self-normalised spatial autocorrelogram. The combined rate map is correlated with itself before being shifted laterally by a distance of 1 bin (3cm), the correlation is recalculated and the process repeated until the maps no longer overlap. **A**) The results of spatial autocorrelograms calculated for every cell included in the parallel analyses (*N* = 534), each row represents one cell. The horizontal axis represents the 96 bin range of shift (each compartment was divided into 12 x 14 bins, width x height), the bright central band represents a correlation value of 1; where the rate maps completely overlapped. A series of six, weaker, periodic bands can be observed, at the +/-12, +/-24 and +/-36 bin points, at these points the maze compartments overlap and repetitive firing causes a significant correlation. **B**) The same as **A** but showing the data for every cell included in the radial analyses (*N* = 755). A series of weaker bands is not nearly as visible. **C**) The mean and *SEM* autocorrelation values for all of the parallel data shown in **A** and radial data shown in **B**. The vertical axis represents the self-normalised autocorrelation score; the horizontal axis again represents the 96 bin range of shift. The central peak of 1.0 at a shift of zero is again obvious, as are the series of weaker peaks in the parallel data where the compartments overlapped. The same periodicity cannot clearly be distinguished in the radial data.

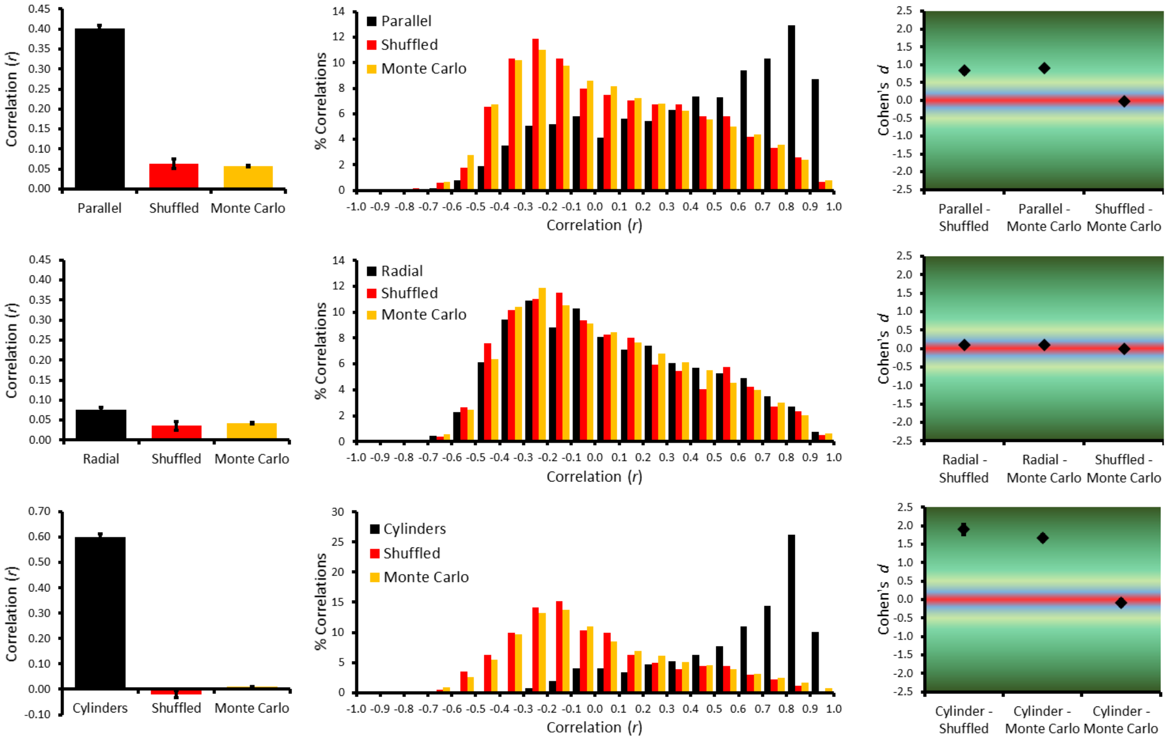

**Figure 6.16:** Distributions of correlations between compartments in the parallel and radial mazes, and between two sessions in the cylinder. The results of shuffling rate maps in the parallel (top row), radial (middle row) and cylinder (bottom row) environments. Left) The mean and *SEM* correlation value observed in each environment without shuffling, when the correlations are performed on data shuffled as in Spiers et al. (2013) and when compartment compartments are shuffled according to a Monte Carlo procedure (100,000 repetitions). Middle) The entire distribution of each correlation procedure. Right) Cohen's *d* effect sizes observed between each of the groups, the colours outline the boundaries for low (red and blue), moderate (yellow) and large (green) effect size ranges, according to Cohen (1988).

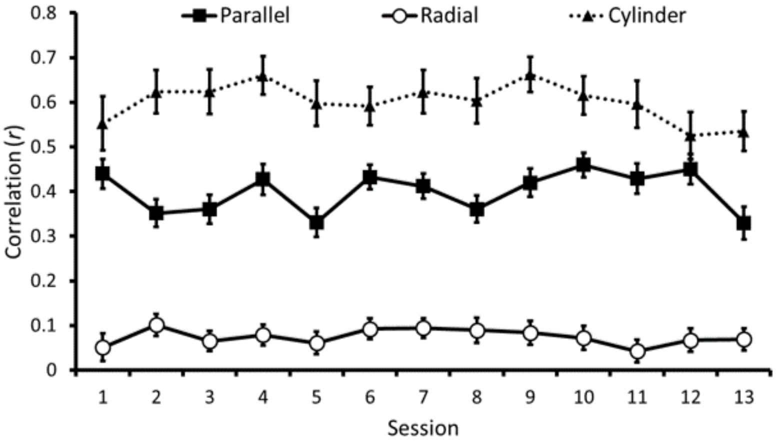

**Figure 6.17:** Correlation between rooms in the parallel and radial environments, and between two sessions in the cylinder, across days.The mean and SEM correlation value observed in the parallel, radial and cylinder environments in each session of the maze for the rats as a group.

*Correlation values in each environment did not change with greater exposure*

Over the course of repeated recordings, the average correlation value obtained in the parallel configuration remained consistently higher than in the radial. The average correlation value obtained in the cylinder sessions also remained consistently high. A between groups repeated measures ANOVA confirms that the mean parallel correlation values are consistently higher than the radial values [$F(1,4) = 16.67$, $p < .05$, $\eta_p^2 = .90$]. This effect can be seen in Figure 6.17.

### 6.4.4 Between Compartment Correlations

*Firing in the 2 middle compartments was more similar than the other compartment pairs*

We looked to see if there was a further relationship in the compartment correlation values, between compartment pair in each maze. We found that in the parallel maze the average correlation value between the different pairs was not randomly distributed [$F(5,2290) = 48.10$, $p < .001$, $\eta_p^2 = .10$], post hoc tests (Tukey's HSD) do not confirm a clear relationship; the correlation between compartments 2&3 is highest and it is significantly different to all other pairs [$p < .001$ all tests] except 1&2 [$p > .60$], however, given our large sample size a number of groups differ at a statistically significant level. To summarise, these tests find that compartment pairs 2&3 and 1&2 form a distinct subgroup, as do pairs 2&4, 1&3 and 3&4 with pair 1&4 in a subgroup of its own. These effects can be seen in Figure 6.18.

We found that in the radial maze the average correlation value between the different pairs was also not randomly distributed [*F*(5,2961) = 17.75, $p < .001$, $\eta_p^2 = .03$]. Again, post hoc tests (Tukey's HSD) do not confirm a clear relationship, however the data seem to follow the same pattern as in the parallel maze; the correlation between compartments 2&3 is highest and it is significantly different to all other pairs [$p < .05$ all tests] except 1&2 [$p > .10$]. To summarise, these tests find that compartment pairs 2&3 and 1&2 form a subgroup, 1&2 is also grouped with 3&4, 1&4, 2&4 and 1&3 form a subgroup of their own. These effects can be seen in Figure 6.18.

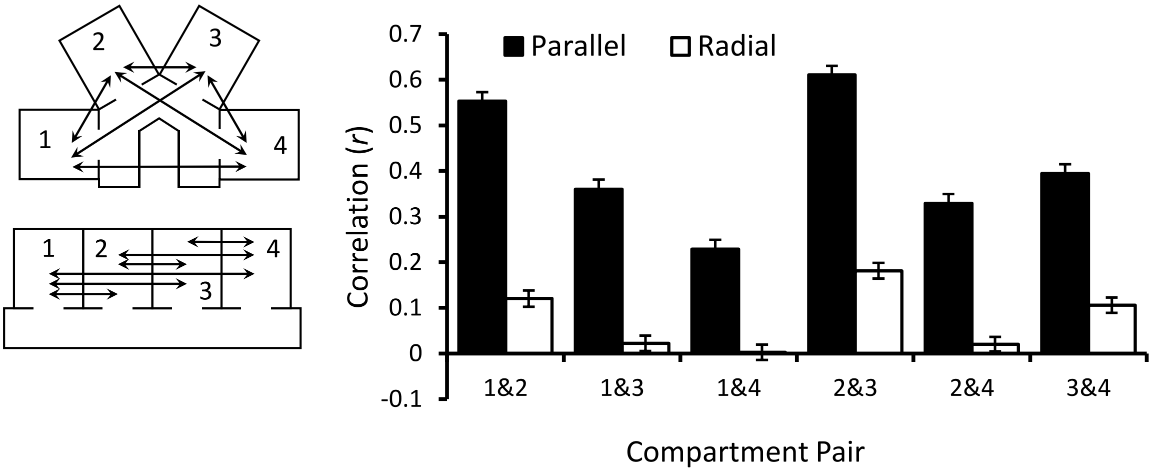

**Figure 6.18:** Compartment pair correlation values. Left) Diagram showing correlation pairs in each maze configuration. Right) Figure showing the correlation values in the parallel and radial maze configurations with each compartment pair shown separately. In both maze compartments 2&3 are the most similarly represented, compartments 1&2 also seem to be highly similar. Compartments 1&4 are the least similar in both environments.

### 6.4.5 Between Maze Correlations

*Compartments 2 and 3 were the most similarly represented between mazes*

We tested the level of correlation between the compartments in our two maze configurations to assess whether firing in one maze was similar at all to the firing observed in the other. We did this by comparing each compartment with its equivalent in the other maze configuration (i.e. compartments 1-1, 2-2, 3-3 and 4-4). We found that the distribution of correlation values was not randomly distributed [*F*(3,1871) = 107.73, $p < .001$, $\eta_p^2 = .15$], post hoc tests (Tukey's HSD) find that each of the compartments has a significantly different overall correlation value [$p < .05$ all tests] except compartments 1 and 4 which have similarly low overall correlation values [$p < .90$ both tests]. These effects can be seen in Figure 6.19.

### 6.4.6 Neighbourhood Analysis

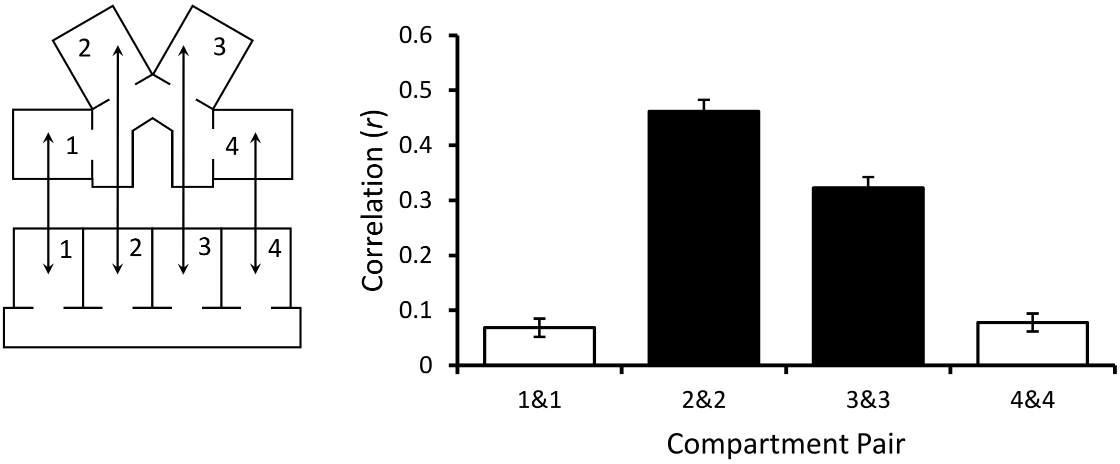

**Figure 6.19:** Between maze compartment pair correlation values. Left) Diagram showing correlation pairs between maze configurations. Right) Figure showing the correlation values for each compartment between the maze configurations. Compartments 2 and 3 are the most similarly represented in each maze, compartments 1 and 4 are not similarly represented.

We assessed rate remapping between the compartments in both of our maze configurations and possible changes in this remapping over time. We ranked compartments according to firing rate, and distance from the compartment with the highest firing rate. The compartment with the highest firing rate was labelled as 0, compartments neighbouring this were labelled 1, the compartment which was next furthest away was labelled 2 and the compartment which the furthest away was labelled 3. We then looked at whether the distance from the compartment with the highest firing rate modulated the firing rate of place cells in other compartments.

For the parallel data, a 2-factor univariate ANOVA (compartment distance and session) highlighted a significant effect of session [$F(14,1994) = 2.42$, $p < .003$, $\eta_p^2 = .02$] and for compartment distance [$F(3,1994) = 103.17$, $p < .001$, $\eta_p^2 = .14$] but not an interaction [$F(42,1994) = 1.04$, $p > .40$, $\eta_p^2 = .02$] although the firing rate of compartment 0 does decrease linearly with session [$r(547) = -0.20$, $p < .001$, Pearson correlation] whereas the others remain stable [$r(547) = -0.06$, $p > .15$, $r(547) = -0.03$, $p > .50$, $r(346) = 0.01$, $p > .85$, respective Pearson correlations]. Post hoc tests (multiple comparisons with a sidak correction) confirm that the firing rate of compartment 0 differs significantly from all the other compartment distances [$p < .001$ all tests], compartment 1 also differs significantly from all the other distances [$p < .001$ all tests], compartments 2 and 3 do not differ from each other [$p > .70$] but also differ together from the other distances [$p < .001$ all tests]. Thus, firing rates in the parallel maze do differ according to the distance from the maximum firing rate compartment, these effects can be seen in Figure 6.20, panel A left.

For the radial data, a 2-factor univariate ANOVA (compartment and session) highlighted a significant effect of session [$F(14,2677) = 2.60$, $p < .001$, $\eta_p^2 = .01$] and for compartment distance [$F(3,2677) = 167.78$, $p < .001$, $\eta_p^2 = .16$] but not an interaction [$F(41,2677) = 0.91$, $p > .60$, $\eta_p^2 = .01$] although compartment at distance 0 and 3 decrease linearly with session [$r(771) = -0.14$, $p < .001$, $r(771) = -0.08$, $p < .05$, respective Pearson correlations] and compartments 2 and 4 do not [$r(771) = -0.06$, $p > .10$, $r(357) = -0.10$, $p > .05$, respective Pearson correlations]. Post hoc tests (multiple comparisons with a sidak correction) confirm that the firing rate in compartment 0 differs significantly from the others [$p < .001$ all tests] but the firing rate at the other distances does not differ [$p > .90$ all tests]. Here, firing rates do not differ according to distance from the compartment with the highest firing rate. These effects can be seen in Figure 6.20, panel B, left.

We also looked at whether an effect would be seen when comparing the first and last recording sessions. In the parallel maze data, a 2-factor (day and compartment distance) repeated-measures ANOVA revealed a main effect of compartment distance [$F(3,101) = 35.26$, $p < .001$, $\eta_p^2 = .51$] a main effect of session [$F(1,101) = 5.86$, $p < .05$, $\eta_p^2 = .06$] and a significant interaction between the two [$F(3,101) = 3.42$, $p < .05$, $\eta_p^2 = .09$]. Post hoc *t*-tests comparing the firing rates at each compartment distance between the two sessions confirm that the firing rate at a compartment distance of 0 differs significantly [$t(63) = 3.26$, $p < .01$], but no other distances differ between the two sessions [$p > .20$, all tests are independent samples $t$-tests]. In the radial maze data, a 2-factor (day and compartment distance) repeated-measures ANOVA revealed a main effect of compartment distance [$F$(3,133) = 71.63, $p < .001$, $\eta_p^2 = .62$] a main effect of session [$F$(1,133) = 6.02, $p < .05$, $\eta_p^2 = .04$] but no significant interaction between the two [$F$(3,133) = 1.34, $p > .20$, $\eta_p^2 = .03$], thus no post hoc tests were performed. These effects can be seen in Figure 6.20.

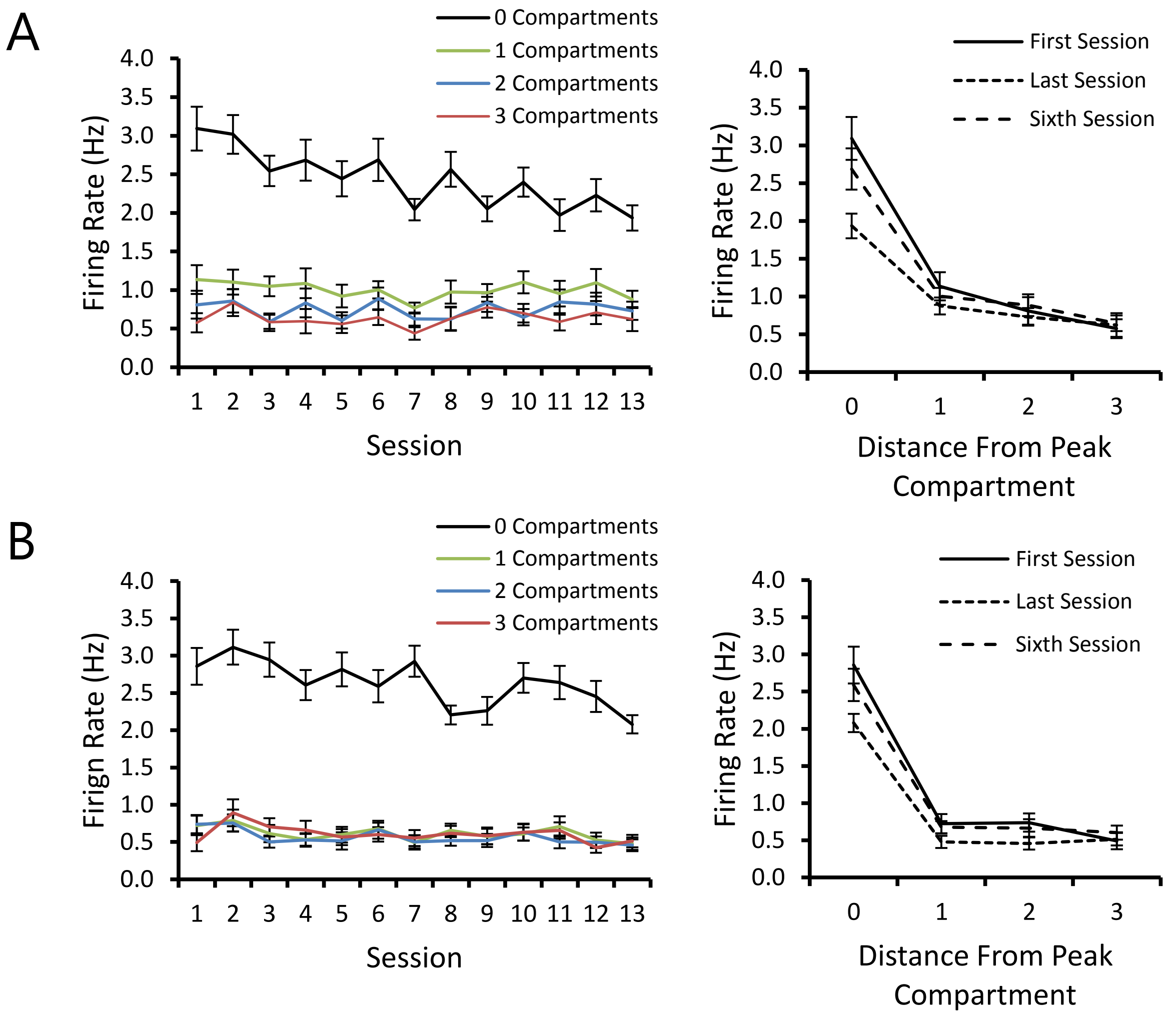

**Figure 6.20:** The neighbourhood firing rate analysis results for the parallel (**A**) and radial (**B**) maze. Left) Showing the mean and *SEM* firing rates in the maze compartments, according to their distance from the compartment with the highest firing rate (0 = the compartment with the highest firing rate, 1 = the compartment or the average of the compartments which are direct neighbours to the one with the highest firing rate). Right) The firing rate in the compartments, ranked according to their distance from the compartment with the highest firing rate, extracted for the first, sixth and last (13th) sessions. The first and last sessions were compared, the sixth session is shown as it was the last session which all 4 rats completed.

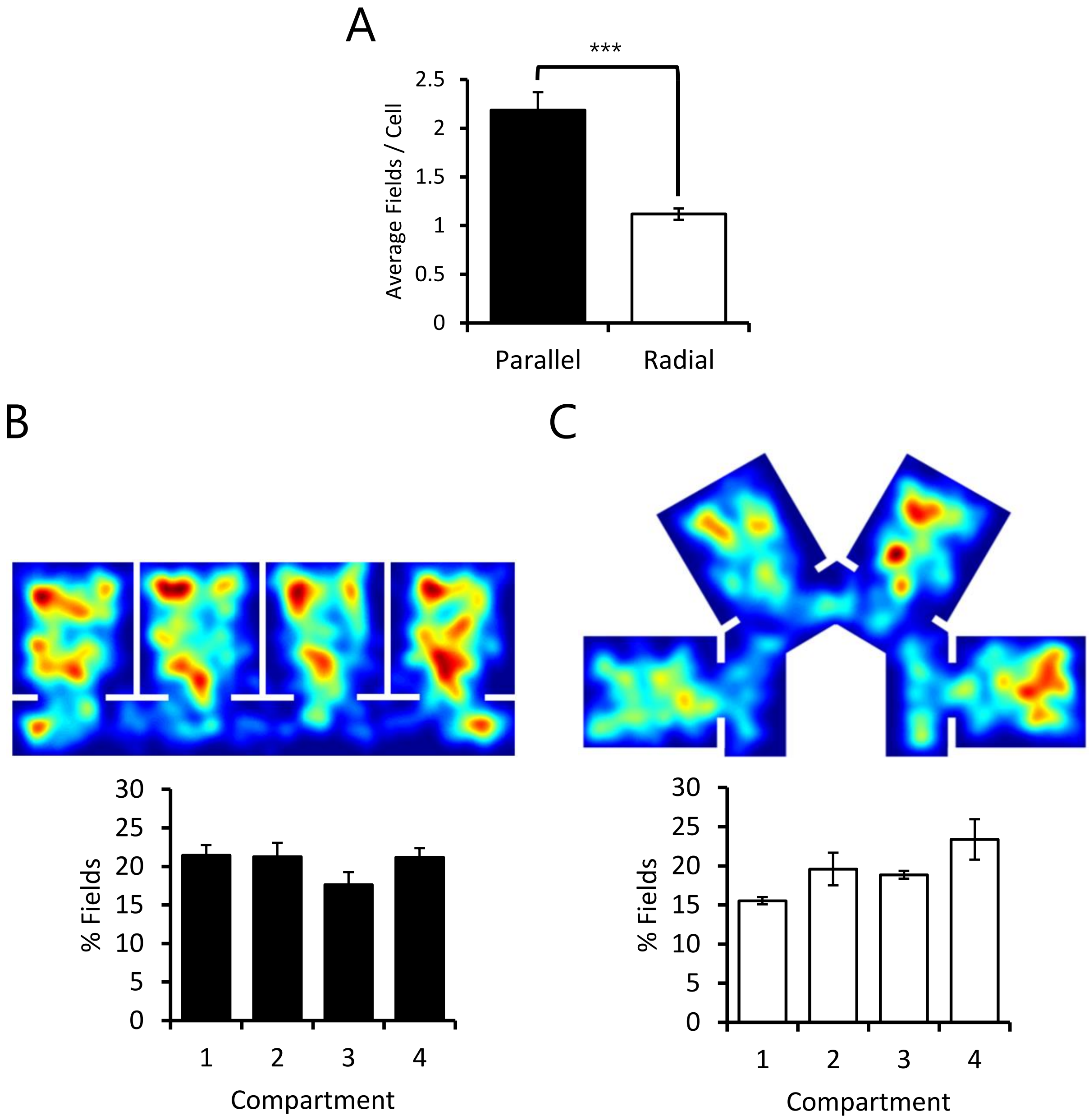

**Figure 6.21:** Distribution of place fields in both maze configurations. **A**) The average number of place fields / cell observed in our parallel and radial maze configuration (error bars represent variability between rats). **B**) A heatmap showing the distribution of place fields in the parallel maze, below this the average number of fields observed in each maze compartment expressed as a percentage of all place fields (error bars represent variability between rats). **C**) The same as B, but showing data for the radial configuration.

### 6.4.7 Place Fields

*Place cells included in our parallel analyses had, on average, a greater number of place fields than those in our radial analyses*

Looking at the place cells included in our correlation analyses, we observed a significantly higher number of place fields per place cell in the parallel maze compartments

(534 place cells, $M = 2.18$ fields/cell, $SEM = 0.18$) than in the radial maze compartments (755 place cells, $M = 1.12$ fields/cell, $SEM = 0.06$), excluding fields in the alleyways. This effect is statistically significant [$t(6) = 5.51$, $p < .002$, $d = 3.89$]. In the parallel maze a similar number of place fields were observed in each compartment [$F(3,15) = 1.49$, $p > .20$], in the radial maze there was a small difference in the distribution of place fields [$F(3,15) = 3.62$, $p < .05$, One-way ANOVA], post-hoc tests (with a sidak correction) confirm a difference between the number of fields observed in boxes 1 and 4 [$p < .05$] no other comparisons reached statistical significance. These effects can be seen in Figure 6.21, a map of all place fields observed in each maze can also be found there.

### 6.4.8 Compartment Morphing

*Morphing the Radial compartments instead of rotating them does not change the observed correlation results*

The correlations observed in the rotated radial maze ($N = 2962$) differ significantly from the same data morphed [$N = 2603$, $t(5563) = -3.56$, $p < .001$, $d = -0.09$] but this is accompanied by a small effect size. The morphed data also differs significantly from its shuffled [$N = 951$, $t(3552) = 4.12$, $p < .001$, $d = 0.16$] and Monte Carlo distributions [$N = 31404$, $t(34005) = 8.39$, $p < .001$, $d = -0.17$] but these are also accompanied by small effect

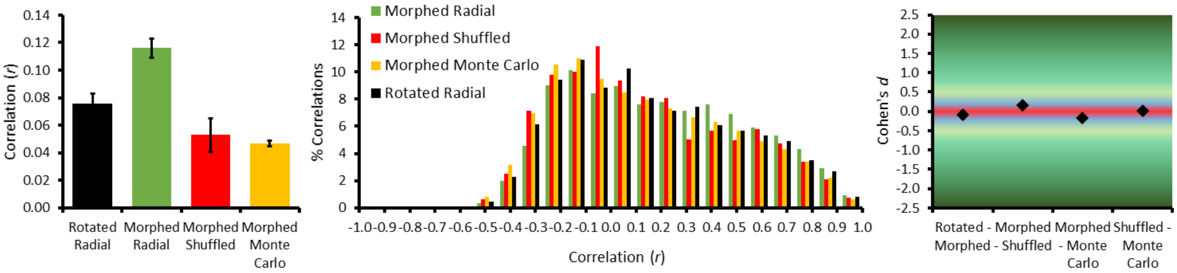

**Figure 6.22:** Distributions of correlations between compartments in the radial configuration when the compartments are morphed instead of rotated. Left) The mean and *SEM* correlation value observed in the rotated data, in the morphed data without shuffling, when the correlations are performed on morphed data shuffled as in Spiers et al. (2013) and when morphed compartments are shuffled according to a Monte Carlo procedure (50,000 repetitions). Middle) The entire distribution of each correlation procedure. Right) Cohen's *d* effect sizes observed between each of the groups, the colours outline the boundaries for low (red and blue), moderate (yellow) and large (green) effect size ranges, according to Cohen (1988).

sizes. As before, the two shuffled distributions do not differ [*t*(32353) = 0.48, *p* > .60, *d* = 0.02]. All tests are independent samples t-tests. These data can be seen in Figure 6.22.

### 6.4.9 Cluster Quality

*Observed correlation values were not influenced by any measure of recording quality*

We assessed the relationship between three measures of recording quality and our correlation values. These analyses include data only from those cells which contributed correlation values to the repetitive firing analyses above. Signal to noise ratio was not found to effect correlation outcome in either the parallel [*r*(532) = -0.01, *p* > .90] or radial [*r*(753) = -0.04, *p* > .30] mazes, nor did Isolation distance [*r*(532) = 0.01, *p* > .80 and *r*(753) = 0.01, *p* > .90 respectively] or $L_{ratio}$ [*r*(532) = -0.02, *p* > .70 and *r*(753) = 0.01, *p* > .80 respectively]. These quality measures cannot account for the firing patterns observed in either maze environment. All tests are independent, pairwise, Pearson's correlations. These relationships can be seen in Figure 6.23.

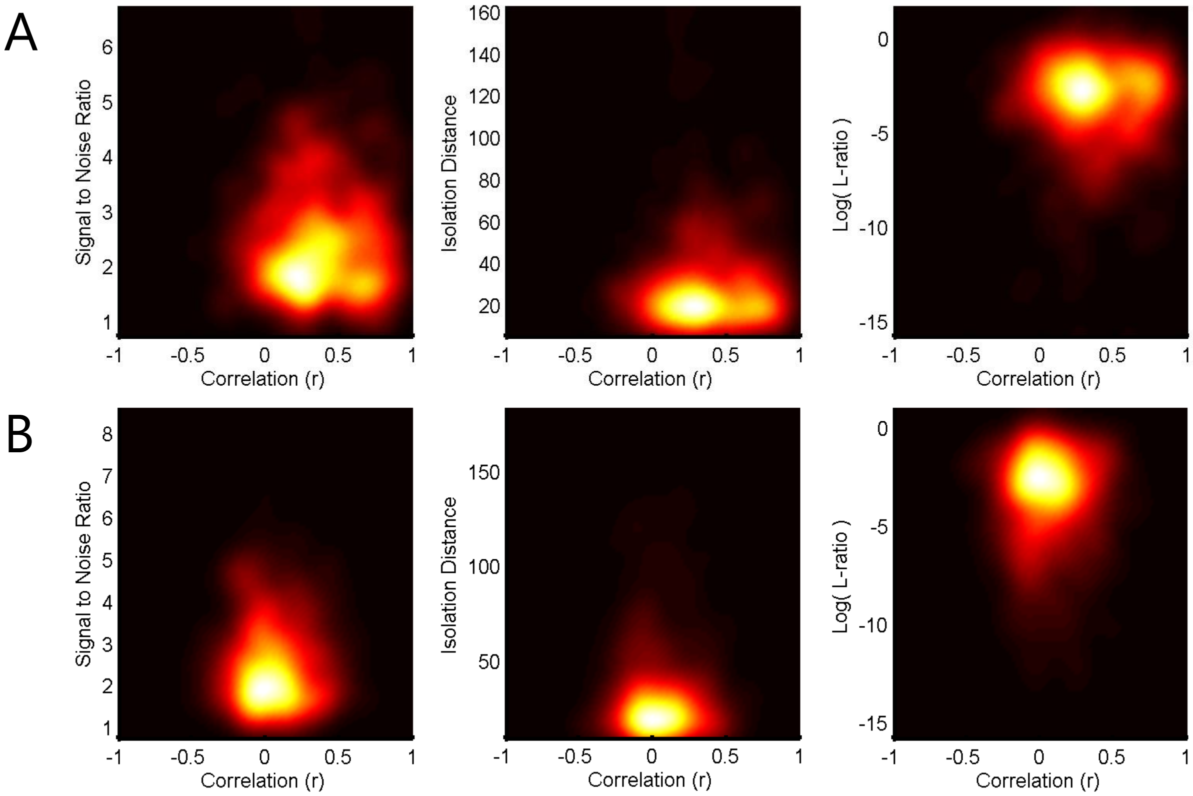

**Figure 6.23:** Recording quality assessment. Histogram 'heat maps' showing the effect of quality measures; signal to noise ratio, isolation distance and $L_{ratio}$ on mean correlation outcome (r) in the parallel (**A**) and radial (**B**) mazes. The round clusters indicate a lack of any significant correlation.

### 6.4.10 BVC Simulation

*A boundary vector cell model of place cell firing predicts our observed repetitive firing results*

For each of our maze configurations we created 2000 BVC firing rate profiles, using these, 500 place cells were simulated in each configuration. In the parallel maze simulation ($\text{parallel}_{\text{sim}}$) 174 (34.80%) of these were active in at least one compartment and thus included in our correlation analyses, yielding 1002 correlation values (5.76 per cell). In the radial maze simulation ($\text{radial}_{\text{sim}}$) a total of 249 (49.80%) cells were included in our correlation analyses, yielding 475 correlation values (1.91 per cell).

The average correlation value observed in the $\text{parallel}_{\text{sim}}$ compartments was significantly higher than that of the $\text{radial}_{\text{sim}}$ compartments [$t(1475) = 86.10$, $p < .001$, $d = 4.80$] assessed using an independent samples t-test. This result is accompanied by a very strong effect size. This effect can be seen in Figure 6.24.

The correlations observed in the $\text{parallel}_{\text{sim}}$ maze (n = 1002) differ significantly from shuffled [$N = 212$, $t(1212) = 61.09$, $p < .001$, $d = 4.62$] and Monte Carlo distributions [$N = 10881$, $t(11881) = 129.72$, $p < .001$, $d = 4.28$] as confirmed by large effect sizes. However, the two shuffled distributions do not differ [$t(11091) = 0.33$, $p > .70$, $d = 0.02$]. The correlations observed in the $\text{radial}_{\text{sim}}$ maze ($N = 475$) differ significantly from the shuffled [$N = 170$, $t(643) = -2.27$, $p < .05$, $d = -0.203$] and Monte Carlo distributions [$N = 7815$, $t(8288) = -3.40$, $p < .001$, $d = -0.16$] but each of these tests is accompanied by a low effect size. The two shuffled distributions did not differ significantly [$t(7983) = 0.42$, $p > .60$, $d = 0.03$]. All tests are independent samples t-tests. These effects can also be seen in Figure 6.24.

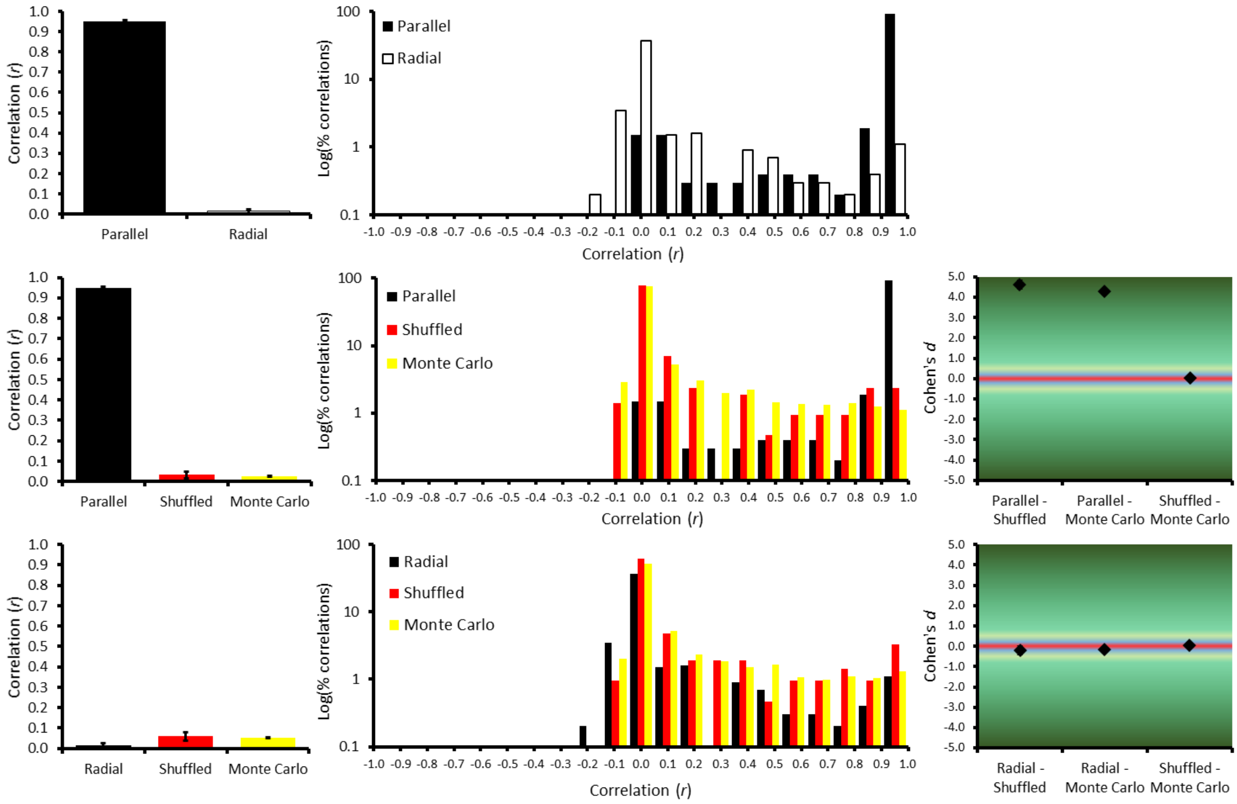

**Figure 6.24:** Distributions of correlations between compartments in the parallel$_{sim}$ and radial$_{sim}$ mazes, using BVC simulated place cell data. Correlation values in the simulated parallel$_{sim}$ and radial$_{sim}$ configurations (top row), in the parallel$_{sim}$ configuration after shuffling procedures (middle row) and in the radial$_{sim}$ configuration after shuffling procedures (bottom row). Left) The mean and *SEM* correlation value observed in each environment without shuffling, when the correlations are performed on data shuffled as in Spiers et al. (2013) and when compartment compartments are shuffled according to a Monte Carlo procedure (100,000 repetitions). Middle) The entire distribution of each correlation procedure. Right) Cohen's *d* effect sizes observed between each of the groups, the colours outline the boundaries for low (red and blue), moderate (yellow) and large (green) effect size ranges, according to Cohen (1988).

## 6.5 Discussion

This study sought to replicate the findings of Spiers et al. (2013) that in an environment composed of multiple, parallel compartments place cells often have repeating place fields and fire similarly in multiple compartments. Our results confirm these findings, we observed a high proportion of repeating place fields in our parallel environment; the frequency of this phenomenon was also shown to be much greater than would be expected by chance. However, we have also expanded on these findings; after introducing a 60° angle between each of our compartments we observed that the frequency of repeating place fields was much lower and matched a level which would be expected by chance. We also observed similar firing patterns in mice (see Supplementary Figure 2) suggesting that this effect may be found in different species. The same cells were recorded in both environments each day, so it is not possible that we happened to record two different populations of place cell. Similarly, we also recorded these cells in a cylindrical environment before and after our maze sessions, the stability of cells in these two sessions was also very high, so it is unlikely the repeating fields we observed are the result of recording instability. Furthermore, we found no relationship between three measures of recording and cluster quality and the frequency of observed place field repetition, so it is not the case that this phenomenon is due to poor recording quality. Together, these results suggest that angular head direction information plays a large role in place field repetition; or rather, it is similar head direction information coupled with identical environments which facilitates place field repetition. We have also reported the results of a Boundary Vector Cell (BVC) model of place cell firing which clearly predicts this pattern of results. This suggests that BVC inputs (and thus indirectly head direction inputs) to either the mEC, HPC or both, are probably the source of repeating place fields.

### 6.5.1 Spiers et al. (2013)

The results reported here agree largely with those of Spiers et al. (2013), we observed the same repeating place field effect in our parallel maze, we also performed the same shuffling and correlation procedures and these yielded very similar results to those reported there. However, we did maintain some variations on their procedures which should be highlighted before continuing to compare our results. We smoothed our compartment rate maps with a Gaussian kernel rather than a mean box filter, we found that the latter produced less realistic maps with lower spatial coherence. Why this should be this case is unclear, our boxes were slightly larger and our bins slightly smaller, which could have attributed to this difference. When calculating inter-compartment correlation values, Spiers et al. (2013) included six correlation values (all possible compartment pairs) for each cell, we found this method was unsuitable as many compartments in our radial maze would often contain few, if any, action potentials. We decided to calculate correlations only when the firing in one or both of the compartments concerned was greater than 1Hz, a cut-off which has been utilised in previous experiments (Skaggs & McNaughton, 1998), we also only included cells which met our criteria for a place cell in that particular environment. With these variations in mind, the distribution of correlation values observed in our parallel environment match very closely to those reported by Spiers et al. (2013), however, we see a slightly higher proportion of low correlation values, this could reflect our larger sample size, or some form of generalisation between our mazes as all rats experienced both the radial and parallel every day. Our shuffled distributions all follow a similar pattern, their means are centred on zero and the distribution follows a shallow slope, decreasing as the correlation value increases. The fact that all of our shuffled distributions (both shuffled distributions in the parallel, radial, cylinder and modelled data and our actual radial data) follow this same pattern suggests that this is some form of underlying distribution. Looking at the distribution of place fields in our mazes, it is clear that certain areas, such as doorways or the back wall of each compartment, are overrepresented. This slight clustering of place fields could be responsible for the shallow slope between 0 and 1 in our shuffled data; randomly paired compartments from different place cells would fall under a heightened (but not great) probability of possessing overlapping place fields, due to the effects of overrepresentation. However, highly negatively correlated compartments are unlikely to find themselves paired; not only is the probability of both compartments having a >1Hz firing rate lowered to 33%[38], but the likelihood of two very anti-correlated firing patterns is probably reasonably low, given the relatively small compartments in our maze. The lowest correlation would result from a field

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[38] Is is impossible to know the exact probability, however, we can assume that there is an equal chance, in shuffled data, of both boxes containing >1Hz firing rate, both boxes being <1Hz and only one box having >1Hz firing rate. This assumption is reasonable; in our parallel analysis 534 place cells fired at >1Hz in at least one box, this yields a possible 3204 correlations (6 correlations per cell), however, 913 (28.50%) correlations were skipped because both boxes were <1Hz, very nearly 1/3. In our radial data the same breakdown is present with 34.61% of correlations skipped, again very nearly 1/3.

at the back of a compartment vs a field at the front, however, the size of the compartment would probably mean that the fields would overlap slightly in the middle, removing the possibility of a truly negative correlation, unless the fields were very small. Regardless of the origins of this shuffled distribution, we do not see the same shape in Spiers et al's., (2013) shuffled data. Why this is the case, remains unclear, especially as it is recognisable also in the shuffled distributions reported by Skaggs and McNaughton (2005). The three shuffled distributions can be seen in Figure 6.25.

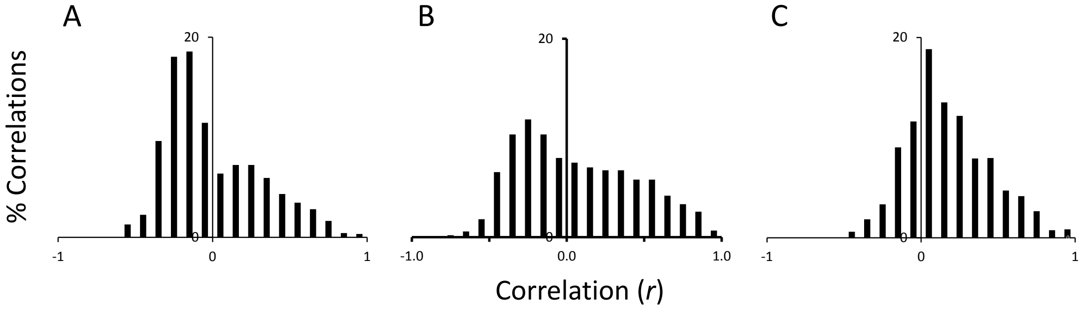

**Figure 6.25:** Comparison of shuffled distributions in the literature. **A**) A shuffled distribution from one of Skaggs and McNaughton's (2005) rats. **B**) The shuffled distribution from our parallel maze data. **C**) The shuffled distribution from Spiers et al's., (2013) multicompartment environment. Our shuffled distribution and that from Skaggs and McNaughton (2005) both peak just below zero and have a mean centred almost perfectly on zero, with a slow slope between zero and one. The distribution reported by Spiers et al. (2013) is more normally distributed around zero.

### 6.5.2 Boundary Vector Cells

We have reported the results of a BVC model of place cell firing which accurately predicts the pattern of results observed in our real data – simulated place cells, created using the input of 15 BVC's, fire repetitively in a simulated parallel maze but do not show this place field repetition in a simulated radial maze. As discussed previously, boundary vector cells or border cells are thought to reside in the subiculum (Barry et al., 2006; Lever et al., 2009) and mEC (Savelli, Yoganarasimha, & Knierim, 2008; Solstad et al., 2008). Each cell has a preferred firing direction and distance, when an animal encounters an environmental boundary where these two intersect the BVC fires. Presumably, BVCs maintain their preferred firing direction using inputs from the head direction system – their firing fields rotate with visual cues and in synchrony with the firing of head direction cells throughout the brain (Barry et al., 2006) – so it is clear that the introduction of additional head direction information, as in our radial maze, will influence the firing of these cells at least as profoundly as head direction cells. With this in mind it becomes clear why we should observe repeating place fields in our parallel but not radial environment; in our parallel maze the compartments are all the same size and shape and they are oriented in the same direction, thus, in this environment BVCs should fire similarly in each compartment. Place cells receiving input from multiple BVCs each firing similarly in each compartment are also going to have repeating place fields. In the radial configuration, the compartments are the same size and shape but they are oriented differently, this results in a different BVC firing pattern in each compartment and thus place cells will fire differently. When we analysed our radial maze data by morphing the individual compartments instead of rotating them, we did not see any change in the resulting correlation distribution. However, it is not clear that we would expect this to be the case. This morphing procedure, carried out on the firing of an individual BVC, would be expected to result in a higher correlation than rotating the compartments, as the preferred firing angle of the BVC is fixed to a global reference frame (as in head direction cells). However, an individual place cell is probably receiving input from multiple BVCs (and neighbouring place cells), each with a different preferred firing direction and *distance*. It is likely that the variability in BVC preferred distances results in highly divergent inputs to each place cell in each compartment and may explain why we did not see repeating place fields in this environment, even when we maintain its global reference frame. In reality, if place cells continued to have repeating place fields in the radial maze, but in different areas of each compartment relative to the maze (but consistent with a global reference frame), we would not have observed a significantly higher number of place fields per cell in the parallel maze. This finding suggests that place cells are not only more likely to have repeating place fields in the parallel maze, they are also more likely to have multiple place fields.

The question remains, though, why our animals were seemingly unable to differentiate the different compartments based on PI information. One explanation is that place cell firing is dictated by an attractor network, such a network has gained recent popularity as it can explain a great deal of experimental data. An attractor represents a state of place cell population activity, for example if an animal is placed in a familiar environment the location of place fields will be stable over time (the animal forms an internal representation of the environment and this is reflected in the firing of place cells). This state represents an attractor, and perhaps a cognitive map. As a population, place cells resist moving away from this state and will do so only when the attractor is sufficiently disrupted and falls into a new state, for instance, moving the animal from the familiar environment to a novel one in a new location. It is clear that this system can account for the observed remapping of place cells between different environments. In terms of an attractor network, our data and those of Spiers et al. (2013), suggest that the visual ambiguity in our parallel multicompartment environment leads to a locally relevant attractor state; because the compartments are visually identical there is not a sufficiently large shift in the attractor and place cells fire similarly in each compartment. This suggests that PI information is not sufficient to drive such a change and thus cannot induce remapping in HPC place cells. This proposal explains the results of Spiers et al's. (2013) later manipulations; when they changed the colour or size of only one compartment they provided information which was sufficient to drive a change in attractor state and thus remapping. Our results build on these findings as our data provide evidence that head direction information may also be sufficient to drive such a change, perhaps directly, or perhaps via grid or border cell inputs to the HPC. Future experiments could look to slowly reduce the angle between our radial maze compartments; if our results can be explained by an attractor network model then place field repetition should be an all or nothing event which occurs when the angle between compartments is no longer sufficient to drive remapping. If place field repetition increases linearly as the angle is reduced then an alternative model should be considered.

An alternative explanation for our results may be related to a hypothesis proposed by Knierim and Hamilton (2011). They argue that distal cues mainly provide an orienting cue, to give an animal a sense of direction. They suggest that local cues, boundaries and PI information provide an animal with information on its location within an environment. In this view, visual cues are utilised by the head direction system, which provides the animal with information regarding its current heading. Evidence for this relationship is well established, the control of visual cues over the preferred firing direction of the head direction system (remember that all head direction cells always rotate in synchrony) has been demonstrated numerous times (Blair & Sharp, 1996; Taube & Burton, 1995; Taube et al., 1990a, 1990b; Valerio & Taube, 2012; Yoder, Clark, Brown, et al., 2011; Yoder, Clark, & Taube, 2011). Knierim and Hamilton (2011) suggest that this head direction information represents an external coordinate system, which is then used to align, scale and orient an internal coordinate system which is based on the firing of grid cells in the mEC. They suggest that boundaries in the environment are used to set this internal system, evidence for this relationship has only surfaced more recently (Krupic, Bauza, Burton, Lever, & O'Keefe, 2014). Experimental data suggests that grid cells maintain their grid phase relative to environmental boundaries (Fyhn et al., 2007; Hafting et al., 2005), furthermore, this relationship continues even when changes are made to a familiar environment; Barry et al. (2007) were able to show that manipulating the size of a familiar environment (by extending one or more walls) results in the stretching of grid fields, much like the extrusion of place cells under similar circumstances (O'Keefe & Burgess, 1996). These findings are supported by reports that grid cells develop their grid representations only after border cells and head direction cells have developed (Langston et al., 2010; Wills, Cacucci, Burgess, & O'Keefe, 2010) and that grid cells in rats raised in a spherical environment have under-developed grid representations compared to rats raised in a cube (Kruge, Waaga, Wernle, Moser, & Moser, 2014; Stella, Si, Kropff, & Treves, 2013). Furthermore, environment walls have been shown to exert powerful control over grid fields (Savelli et al., 2008) and some evidence suggests that these boundaries are used to correct navigational errors which accumulate in darkness (Cheung, 2014; Zhang et al., 2014). In this view it is easy to see how our animals may have consistently formed the same representation for multiple compartments in our parallel apparatus. When the compartments are parallel, head direction information (provided by our cue sheet suspended within the curtain enclosure) is the same in each compartment, this, combined with identical compartment dimensions means that the animal's internal coordinate system has no means with which to discriminate the different boxes. In our radial configuration, however, angular head direction is available and this can be used to align and orient the animal's grid fields in each compartment, thus providing a unique representation. This explanation extends to the results of Derdikman et al. (2009), as they found that the direction in which different alleyways faced, and the direction in which the animal was running, both resulted in unique representations of the environment (although each representation had repeating grid or place fields). We found similar results in a similar apparatus (see Supplementary Figure 1). Future research should look to record grid cells in our maze configurations, it is important to know whether grid cells are forming distinct representations in each of our radial maze compartments, or whether they form a global representation of the whole environment. Future experiments could also introduce additional landmarks around the maze environment, if Knierim and Hamilton's (2011) proposal is correct, then additional distal cues should give animals greater accuracy in terms of their external coordinate system, this could provide them with sufficient information to form distinct representations in the parallel environment. We did not record a large population of place cells in mice, however, the examples we have (see Supplementary Figure 2) suggest that repeating place fields may be more prevalent in the radial maze in mice. Future research could seek to explore the differences between rats and mice, it is possible that the mice have a less well refined internal coordinate system, or form a poorer external coordinate system which makes it more difficult for them to discriminate the compartments even when angular head direction information is available. Alternatively, future experiments could look to disrupt the head direction system in rats. If head direction information is driving the realignment of an internal coordinate system then after removal of this information repeating place fields should be observed in our radial configuration. Such a procedure would have to disrupt the head direction system in an upstream structure such as the postsubiculum, so as to avoid damaging mEC grid cells. However, an experiment such as this would inevitably also disrupt BVCs in the subiculum and mEC, which, as we have discussed, also form the basis of an explanation for our results.

### 6.5.3 Rate Remapping

We report here that place cell firing in the parallel maze, although similar in multiple compartments, in fact carries information regarding the identity of different compartments in the form of rate remapping. We found, using an analysis reported by Spiers et al. (2013), that the firing rate of cells in the parallel maze is slightly influenced by the distance from the compartment with the highest firing rate. In other words, place cells in the parallel maze fire maximally in one compartment, and then incrementally less in the others depending on how far away they are. However, this result is mixed. Although there was modulation of this kind, the relative difference in firing rate was small and may not be biologically relevant. Furthermore, we found a form of 'three step' firing rate pattern; one compartment has a maximum firing rate, the compartments directly neighbouring this have a lower firing rate and compartments further away all form a third homogenous group with equally low firing rates, suggesting that the information derived from this rate remapping may only be enough to discriminate distance from the maximal compartment, not directionality[39]. We observed these effects only when assessing changes in firing rate over time – a single day's data does not carry a level of discrimination that is statistically significant, which is why such an effect was not found in Spiers et al.'s (2013) analyses. When we compared the data accumulated during the first session to those from the last session, as was reported previously (Spiers et

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[39] Although, admittedly, the analysis involved averaging the values for compartments which occupied the same distance from the maximal compartment. This is only likely to happen for those compartments directly neighbouring the maximal one, thus we may have obscured a directional effect in the data. However, it is difficult to see how such information could be incorporated into compartment firing rates.

al., 2013) we did not find any significant change of firing rate according to compartment distance, with the exception that the maximal firing rate dropped significantly. Any changes in firing rate were strangely absent in the radial maze, where distant compartments actually had much more similar firing rates than they did in the parallel maze. In the radial maze we also did not see any change in firing rates when comparing the first and last sessions. Future research could look to record from animals as they are trained to complete a task in these environments. One might expect that as animals learn to discriminate the compartments, rate remapping will increase in the strength of its modulation to the point where the different compartment distances can each be recognised, although preliminary results utilising a few animals and a small population of cells suggests that this may not be the case (see Supplementary Figure 4).

In our longitudinal analysis of both mazes, we did find a significant drop in the maximal compartment firing rate. It is unclear why the maximal firing rate should drop with experience in the mazes, as this would suggest that the compartments are becoming more similarly represented rather than becoming more greatly discriminated. It is possible that without any need to discriminate the environments our recording animals were less inclined to try and discriminate them. Although it might be expected that as the animals explore the environment they should be building a cognitive map of the environment and over time their discrimination would improve (Nadel, 1992; O'Keefe & Nadel, 1978). Future experiments could explore the effects of this free exploration on spatial learning. Would rats given free exploration in our mazes find our odour task easier or more difficult to learn? Previous findings would suggest that with access to a more global representation, and previous experience of the environment as a whole, rats would find it easier to subsequently learn a task (Blodgett, 1929; O'Keefe & Nadel, 1978; Tolman, 1948). However, our results would suggest that the animals instead form a more homogenous representation with exploration and would thus find the odour task more difficult, at least initially. Earlier associative learning theories may provide a possible attentional mechanism for this effect;

during preexposure to an environment or set of stimuli, animals may learn to ignore cues which are poor predictors of reinforcement and instead learn to attend more to good reinforcement predictors (Mackintosh, 1975; Sutherland & Mackintosh, 1971). Our recording animals did not have to discriminate the compartments, they were almost always rewarded and the only behavioural pattern which was consistent was that once the food rewards were collected in a compartment the animal had to move to a new one, a strategy which would not require discrimination of the different areas. It is possible that under these conditions our recording animals did not have to form a global representation of the environment and did not expend the resources in doing so. This might also explain why we did not see any generalisation between the maze environments – the compartments in our parallel environment remained highly correlated throughout the experiment, regardless of experience. Future experiments are likely to record from animals as they are trained on our odour discrimination task described below, however, it may also be interesting to explore simpler tasks which merely require the animals to move between compartments in a set sequence, similar to Singer et al.'s (2010) W-maze tasks. It would be interesting to see if animals are more likely to form a global representation, or stronger rate remapping if compartment identity is an important cue.

# Experiment 4

## Place Field Repetition and Spatial Learning

### 7.1 Abstract

Hippocampal place cells fire when an animal is in a particular area of an environment and are generally thought to support spatial cognition. Recently, Derdikman et al. (2009) showed that in a hairpin maze composed of a series of parallel alleyways, place cells (and grid cells) tend to fire in multiple alleyways and at approximately the same spatial location relative to the boundaries of each alleyway. Spiers et al. (2001) found similar “place field repetition” as rats explored a multi-compartment environment composed of 4 identical parallel boxes connected by a corridor. This raises the question as to whether, under conditions in which place field repetition between compartments is observed, animals can discriminate between the compartments, or be trained to do so. We tested whether rats (*N* = 6) could learn a spatially-guided odour discrimination task in an environment similar to that used by Spiers et al. (2013) with 4 boxes arranged parallel to each other. A second group of rats (*N* = 6) was trained in the same environment with the 4 boxes arranged in a semi-circular formation to provide directional information; in this environment we would not predict place field repetition. In each box, 4 bowls of sand, each scented with a different spice were available. One of the 4 bowls of sand in each box was baited with a reward, and a different bowl was rewarded in each of the 4 boxes.

Training was carried out in 3 stages. In the first stage, 2 boxes and 2 scents were used, and the rats were trained for 12 trials a day (6 in each box) until they chose correctly on 5/6 trials in both boxes (83%) on 2 consecutive days. The second stage involved 3 boxes and 3 odours, and the final stage involved discriminating between all 4 boxes and all 4 odours. All rats trained in the semi-circular configuration learned the task readily, taking 27 ± 4.9 (*M* ± *SD*) sessions to complete all 3 stages. In contrast, the rats in the parallel

configuration were significantly impaired; after 50 days of training, only 1 rat had reached criterion at all 3 stages (taking 50 days to do so). A further 2 rats had reached criterion at the 2 and 3 box stages, and the remaining 3 rats had reached criterion only at the 2 box stage. These results suggest that rats have difficulty discriminating environments in which place field repetition occurs and is in agreement with a cognitive mapping theory (Tolman, 1948) of place cell activity (O'Keefe & Nadel, 1978). This difficulty increases with the number of compartments; however, with extended training some discrimination is observed. In contrast, spatial learning occurs rapidly in compartments that are oriented in different directions. These results are discussed in light of electrophysiological data collected in previous environments.

## 7.2 Introduction

Our data show that in an environment composed of parallel, visually identical compartments place cells have repeating place fields – they fire similarly in multiple compartments. This effect is not observed in the same environment but with the compartments arranged in a radial configuration. Place cells are thought to form the neural basis of a cognitive map (O'Keefe & Nadel, 1978), an animal's internal representation of its surrounding environment and the task demands associated with it (Tolman, 1948). This hypothesis leads to an obvious prediction then; if place fields reflect an animal's internal representation of its environment and these fields repeat in a parallel environment then we might expect spatial navigation or spatial learning to be more difficult in such an environment. Here it is difficult to discriminate the different compartments based on the firing of place cells. However, in an environment where we do not observe place field repetition, such as our radial maze, we may expect spatial learning to be less impaired, if indeed it is even impaired at all.

There has not been a great deal of research exploring the effects of repeating place fields on spatial learning. Spiers et al. (2013) did not train animals on a task, although they suggest this avenue of research for future experiments. Singer et al. (2010) performed a huge analysis on an accumulation of data from several previous experiments, these experiments were all based on a similar maze design which consists of 3-6 parallel alleyways (Karlsson & Frank, 2008; Karlsson & Frank, 2009; Singer et al., 2010), a design which has been associated with an intact hippocampus (Kim & Frank, 2009). In these tasks rats are rewarded for following specific trajectories or response sequences in apparatus composed of multiple parallel alleyways. Early experiments identified that place cells often fire in similar locations in multiple alleyways (Frank et al., 2000a; Singer & Frank, 2009), this phenomenon was termed 'path equivalence' as the place cells appeared to be representing the animal's different trajectories equivalently. These experiments yielded a number of interesting and relevant results. The task requires the rat to remember on a trial by trial basis, where it has been and where it must go next, learning of this task is impaired following hippocampal damage (Kim & Frank, 2009), furthermore, by introducing a sequence switching procedure to their task Singer and Frank (2009) were able to analyse the errors made by rats when reward sequences were switched. From these errors it was clear that the animals were using a place navigation strategy – they were utilising extra maze cues and an allocentric navigation strategy, rather than merely carrying out a sequence of responses. The authors conclude that although they observe repeating place fields, the animals are able to distinguish the different arms of the maze. Furthermore, they found that the frequency of place field repetition increased with training and was unrelated to whether the animals had learned the task successfully or not at that point. It is unclear if the learning Singer and Frank (2010) report is impaired or not, they mention that *"the multiple-U task is quite difficult for animals to learn quickly"*. Their animals appear to take approximately 200 trials to learn a response sequence and this performance drops to chance level when the same sequence is revisited later in the experiment, although it does seem that these sequences are re-learned more rapidly. It would be interesting to see how quickly animals learn the same task in an environment with additional head direction information, the same task could be carried out on a radial arm maze for instance. Singer and Frank (2010) did find that cells in their task showed significant rate remapping (Leutgeb, Leutgeb, Barnes, et al., 2005), including those cells which had repeating place fields. This was supported by the finding that at the ensemble level, the firing of these cells could be used to distinguish the different alleyways, suggesting that as a population place cells may be able to simultaneously generalise and separate. Similar to Spiers et al. (2013), Singer and Frank (2010) also explored the effects of adding distinct visual and olfactory cues to each of the alleyways in their multiple-U task. Interestingly, unlike Spiers et al. (2013) they did not see a reduction or change in the frequency of place field repetition or rate remapping, in either the maze as a whole or in individual alleyways. Together these results suggest that place field repetition or path equivalence may not impede spatial learning, although it is still unclear whether spatial learning is impaired relative to an environment where repeating place fields are not observed.

If the hippocampus provides a neural substrate for spatial and episodic memory (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Morris & Frey, 1997; O'Keefe & Nadel, 1978; Poucet, 1993), then learning to do different things in different locations should be more difficult in environments which induce repeating place fields. To test this, we trained two groups of Lister hooded rats (*N* = 6/group) on a novel odour-location association task in either the parallel or the radial configuration of the compartments used in the single unit recording experiment described above. The task required rats to dig in pots of scented sand for a food reward. Four pots were situated along the far wall of each compartment. These pots were scented with household spices and a different scented pot was baited in each compartment. This unique association between the reinforced scent and a given compartment was maintained for all sessions. Thus, to identify which pot was baited, the rats had to be able to distinguish between the four different compartments and recall which odour was rewarded in each one. Such biconditional (requiring the consideration of two cues such as location and odour) tasks are thought to be dependent on an intact HPC

(Albasser et al., 2013) although two choice odour discrimination tasks have been found to depend on an intact dorsal striatum (Broadbent, Squire, & Clark, 2007) although the contextual and spatial components of our task are generally heavily dependent on an intact HPC (Jarrard, 1993). Our results show that rats trained in the parallel configuration of the maze are significantly impaired when compared to animals trained in the radial configuration. They took significantly longer to learn the task, made significantly more errors and not all of the animals in this group successfully learned all four odours in all four boxes. In contrast, the radial group did not appear to have any problems learning the task, even at the most difficult stage. The assignment of animals to conditions was then reversed. The animals formerly trained with radially arranged compartments were trained on a new discrimination with the compartments arranged in parallel. The parallel group, was trained on a new discrimination with the compartments arranged radially. The group originally trained with parallel compartments readily learned a new discrimination when it was presented in radially arranged compartments. Overall, odour-location learning in the radial compartments was significantly faster than that of the same animals tested in the parallel compartments. The group trained originally in the radial compartments was not significantly impaired when they were trained in the parallel configuration of the maze. The results of this crossover phase are discussed in terms of Tolman’s (1948) hypotheses and cognitive map theory. The current results support the hypothesis that place cell representations underlie the disambiguation of similar local regions within an environment. Our results show that when different local compartments are oriented in the same direction, significantly more place field repetition is observed than when the local compartments are arranged at an angle to one another. Moreover, in these same compartments, rats have a great deal of difficulty establishing unique odour-environment associations when these are arranged in parallel, whereas such associations are readily acquired when similar compartments are arranged in different directions.

## 7.3 Methods

### 7.3.1 Subjects

For the training portion of the experiment 12 male Lister hooded rats, with an average weight of 300g were used as subjects, a subset of 2 of these animals were implanted when training was completed, at which point they weighed approximately 400-450g, data from these animals are shown only in Supplementary Figure 4. For the free exploration, dwell time portion of the experiment 8, naïve male Lister hooded rats, with a weight between 250-300g were used as subjects. The animals were housed in groups of four in standard cages and maintained under a constant 12 h light/dark cycle. Any testing was performed during the light phase of this cycle. Throughout testing, rats were food deprived such that they maintained approximately 90% (and not less than 80%) of their free-feeding weight or the weight which would be achieved when granted ad lib feeding. Animals were given free access to water at all times when in their home cages. Testing was usually performed 5 days a week during the usual working weekdays. Compliance was ensured with national [Animals (Scientific Procedures) Act, 1986] and international [European Communities Council Directive of November 24, 1986 (86/609/EEC)] legislation governing the maintenance of laboratory animals and their use in scientific experiments. Experiments underwent further ethical and procedural approval by the Named Veterinary Surgeon and Named Animal Care and Welfare Officer responsible for overseeing experiments in the host laboratory.

### 7.3.2 Apparatus

We used the same two configurations of the multicompartment maze used in the recording experiment described above. As in the recording experiment, the maze was situated in a large curtained enclosure with an opaque white curtain ceiling. A white directional cue sheet was placed on the curtain wall opposite the maze compartments. We used transparent cylindrical pots (6.5 cm x 7.6 cm, diameter x height, Nalgene, NY) as sand wells throughout the experiment.

### 7.3.3 Procedure

Before starting the odour discrimination task rats were trained to dig for food rewards (Chocolate cereal loops, 'Weetos', Weetabix, UK) in pots of odourless sand. Once rats could reliably retrieve rewards which were fully buried below the sand surface they were assessed in a short digging task, this consisted of a simple odour discrimination combined with digging. This shaping and pretraining was carried out in a distinct piece of apparatus which consisted of a 1m x 1m square environment with 20 cm high walls. This apparatus was placed outside of the curtain enclosure described above and was not used again during the experiment. Rats were presented with two pots, each filled with fennel or coffee odourised sand. Each odour was rewarded, with a buried food reward as before, for half of the rats but the position of these odours was alternated randomly. Rats were given 10 such trials a day until they reached a criterion of 9 out of 10 first choices correct for two days in a row. Rats were then ranked based on the number of days they took to reach criterion, the number of digs they made which were correct first time in the two criterion days and the number of excessive digs they made before successfully excavating the reward on these days (a rat could dig in the correct well first time but subsequently require more digs before retrieving the food or dig any number of times in the incorrect pot, thus they were penalised for this). Using these ranks the rats were divided into two performance matched groups such that the best and worst rat belonged to the same group. One of these groups were assigned to the parallel maze configuration, the other to the radial configuration.

The task demands were identical for each maze configuration; four pots of sand were placed in each box, these pots were odourised with four odours and arranged in the same order in each box (from left to right: basil, coriander, cumin and rosemary)[40]. Only one of these odours were rewarded in each box and each odour was rewarded only in one box. A trial consisted of removing the door to a box, once the rat had entered and made a choice of sand well he was removed to the alley and the door was replaced. Rats were given six such trials to each box, per day, in pseudorandom order[41], but only one opportunity to dig per trial. Thus, to retrieve the food rewards a rat had to distinguish and dig in the sandwell with the correct odour or spatial location in each box.

To avoid irrevocably frustrating the rats, we trained the task in three stages. The task started with only two boxes, the odours assigned to these boxes were present in each but the unused odours were replaced with plain, unodourised sand wells so that rats did not learn to ignore odours used later in the experiment. When rats were able to distinguish the boxes (5/6 of their choices were correct in each box) a previously unused box was made available to the rat and the odour associated with that box replaced one of the plain sand wells in the original two boxes. This process was repeated before rats continued to the final, four box stage. A representative progression through the stages can be seen in Figure 7.1. A cut-off limit on the number of days spent training at each stage was imposed, these were 40 days at the two box stage, 30 days at the three box stage and 15 at the four box stage. If a rat did not meet the established criterion before these limits they were unable to progress to the next stage and their training on this maze configuration stopped.

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[40] Odours were mixed accordingly: 0.5g of powdered odour substrate per 100g baked children's play sand. 2g of chocolate cereal dust was also mixed per 100g of sand to control for the reward's odour. Each sand well was filled with 200g of this odourised sand mix to give a maximum depth of 4cm - rewards were typically buried between 1 and 2cm below the surface of this medium.

[41] The order was randomised each day but in such a way that rats visited a box no more than 2 times in a row (but visited each box 2 times in a row at least once).

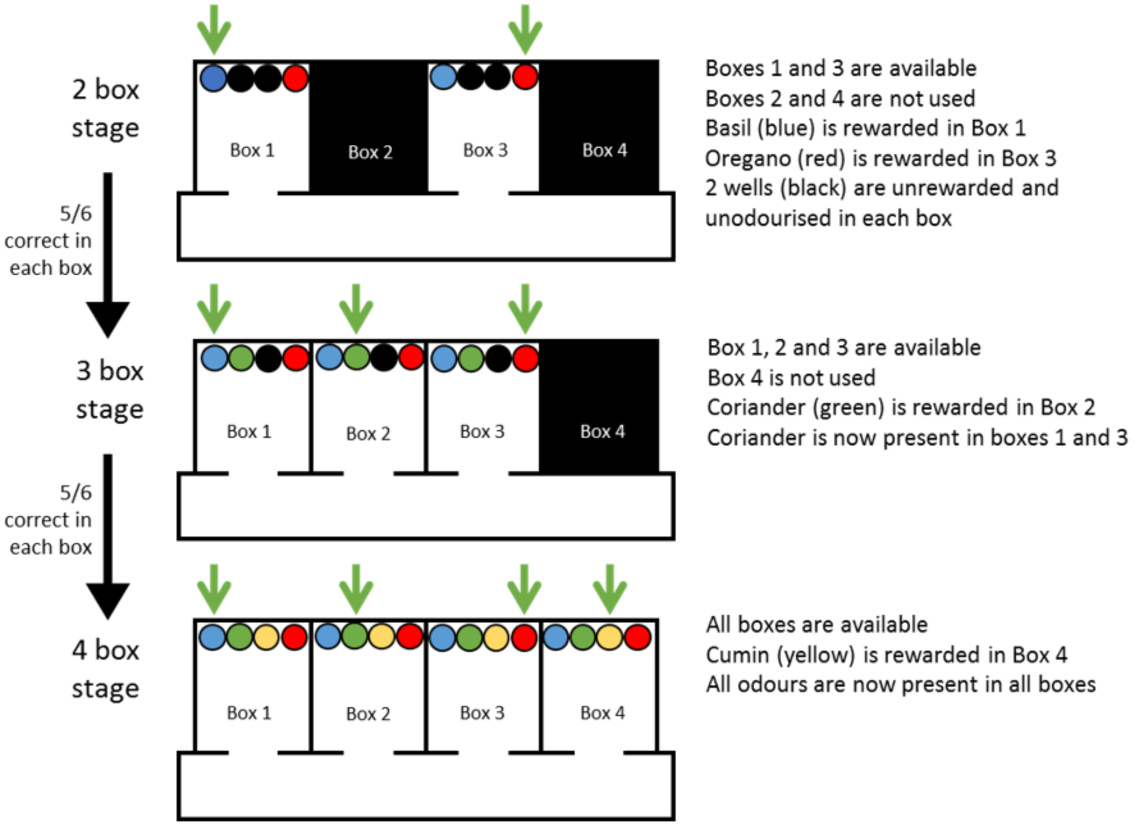

**Figure 7.1:** Figure showing a representative progression through the different training stages for a rat in the parallel group. In each group half of the rats started with boxes 1 and 3 open, box 2 was opened next and finally box 4. The other half started with boxes 2 and 4 open, box 3 was opened next and finally box 1 (the mirror opposite of the other rats). This was performance matched between groups. The procedure outlined here was identical for rats in the radial configuration. A cut-off limit on the number of days spent training at each stage was imposed, these were 40 days at the two box stage, 30 days at the three box stage and 15 at the four box stage.

A number of features were controlled through counterbalancing, design or procedure. Within each group, half of the rats started with boxes 1 and 3 available, the other half with 2 and 4. For all rats the third box opened was the one between these two and the fourth was the box that was left. Within a group the odours rewarded in each box were different for each rat, such that two rats may both be rewarded for the same odour in the same box but never for the same odours in multiple boxes. These controls were both performance matched between groups such that in each group, rats of the same rank were rewarded for the same odours in the same boxes in the same order. The mazes were cleaned daily with scented detergent and boxes randomly swapped positions twice a day as did the sand wells and doors. Sand wells were kept filled to the same level with sand and odours were replenished at least once a week, every couple of days odourised sand was returned to a corresponding container of odourised stock sand and then redistributed to the sand wells. When baiting a sand well the experimenter also smoothed the surface of every sand well in that box, this eliminated distinguishable features in the surface of the sand and also maintained the same level of 'human odour' in each of the wells.

Once rats had completed all stages in their original assigned configuration, or failed to meet criterion performance before the cut-off training limit, they were given a brief rest period of 2 days, they then repeated training as described above on the alternative maze configuration. The four sand well odours were replaced with four novel ones (left to right: tarragon, marjoram, cinnamon and oregano), rats were rewarded for sand wells in different locations to those used previously in at least 3 of the 4 boxes. Upon completion of training on each maze, whether rats failed to meet criterion before the cut-off training limit or not, their use of reward odours was assessed through probe trials. For these, animals completed two additional days of training as before, however, on 2 of the 6 trials to each box a reward was not buried in the rewarded sand well, instead the rats had to dig in the correct location before the reward was presented to them. In this way we were able to assess their reliance on the odour of buried food rewards under normal training conditions.

#### 7.3.3.1 Compartment Dwell Time

We assessed the box preferences of 8 naïve rats in our maze environments, these rats were not food deprived and had not experienced any previous maze environment. Rats explored the maze in both the parallel and radial configurations, these sessions were separated by 24 hours and the order was counterbalanced between rats. The maze was cleaned with scented detergent between animals. In both mazes the rats were placed in the middle of the alleyway facing away from the experimenter. They then freely explored the maze for 20 minutes during which time the experimenter remained outside the curtain enclosure and observed the animal's behaviour via a ceiling mounted CCTV camera. The number of entries to each box were scored; an entry was defined as the point at which the rat's entire body passed from one side of a doorway to the other, not including the tail. The rat's position was tracked using the Axona USB system (Axona Ltd., St. Albans, UK) described previously, this was done by tracking the rat's black head patterning against the relatively light maze surface. The amount of time spent in each maze box was then calculated from this data using custom Matlab scripts.

## 7.4 Results

### *The performance of rats trained initially on the parallel maze was significantly impaired*

All of the rats were trained on each configuration of the maze. Concentrating, however, on the first maze rats were trained on we saw a clear and significant deficit in the performance of the rats trained on the parallel maze. At the two and three box stages, rats on the parallel maze took significantly longer to reach criterion ($M$ = 22.00, $SD$ = 4.98 and $M$ = 24.17, $SD$ = 5.60, respectively) than rats on the radial maze ($M$ = 9.33, $SD$ = 2.25 and $M$ = 10.67, $SD$ = 4.55, respectively), independent sample t-tests show this deficit to be statistically significant [$t(10) = 5.68$, $p < .001$ and $t(10) = 4.58$, $p < .001$ respectively] as does a repeated measures ANOVA testing both stages [$F(1,10) = 36.11$, $p < .001$].

At the four box stage, rats on the parallel maze took a longer length of time to reach criterion ($M$ = 10.00, $SD$ = 5.77) than rats on the radial maze at this stage ($M$ = 4.83, $SD$ = 1.17) but this effect is not statistically significant [$t(3.2) = 1.77$, $p > .05$]. However, two rats in the parallel group failed to meet criterion at the 3 box stage, a further two animals failed to meet criterion at the four box stage, leaving only two rats in the parallel configuration who fully met criterion here. These effects can be seen in Figure 7.2 and Figure 7.4.

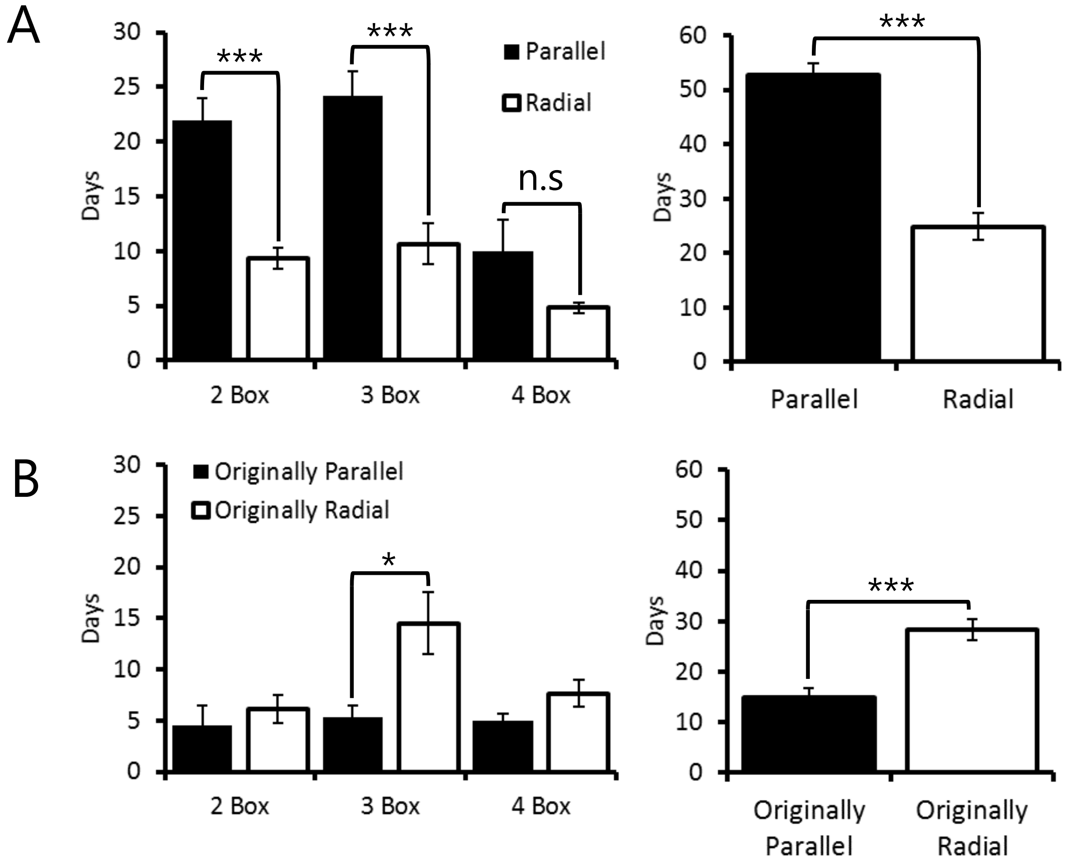

**Figure 7.2:** Performance in the discrimination task. Showing the mean and *SEM* number of days taken for each group to complete each stage of training in their first experience of the maze (**A**) and in their crossed over version of the maze (**B**). i.e., the rats first trained in the parallel maze are the 'parallel' group in A, this group was crossed over to the radial maze after training and is shown as 'originally parallel' in B. The mean and *SEM* total number of days spent training on each maze are also shown in the right column.

### *The performance of rats in the crossover phase of the experiment was unimpaired and in some cases actually better*

Rats trained initially on the parallel maze were subsequently trained on the radial maze and vice versa. Concentrating now, on the second maze each group was trained on, we did not see a deficit in the performance of the rats originally trained on the radial maze and crossed over to the parallel maze. Their performance was significantly better than the original parallel group at every stage except the 3 box stage [$t(10) = 6.49$, $p < .001$, $t(10) = 2.55$, $p < .05$ and $t(4.35) = 0.73$, $p > .50$ respectively] and they completed the training in an overall faster time [$t(10) = -4.73$, $p < .001$]. They also performed significantly better than they did in their previous training on the radial maze in the 2 and 4 box stages but not the 3 box stage [$t(5) = 2.78$, $p < .05$, $t(5) = -0.86$, $p > .40$ and $t(5) = -3.11$, $p < .05$ respectively] but they did not complete the training in a significantly faster overall time [*t*(5) = -0.85, *p* > .40]. All tests are paired samples t-tests.

The performance of the rats originally trained on the parallel maze and crossed over to the radial maze was significantly improved and in some ways better than the original radial group. Their performance was significantly better than the original radial group at every stage except the 4 box stage [*t*(10) = -2.26, *p* < .05, *t*(10) = -2.48, *p* < .05 and *t*(10) = 0.20, *p* > .80 respectively] and they completed the training in an overall faster time [*t*(10) = -3.21, *p* < .001]. They also performed significantly better than they did in their previous training on the parallel maze in the 2 and 3 box stages but not the 4 box stage [*t*(5) = 6.27, *p* < .002, *t*(5) = 7.94, *p* < .001 and *t*(3) = 1.66, *p* > .10 respectively] and they completed the training in a significantly faster overall time [*t*(5) = 12.02, *p* < .001]. All tests are paired samples t-tests. It should also be noted that all rats in both groups completed all of the stages in the crossover phase of the experiment. These multiple interactions can be visualised in Figure 7.3.

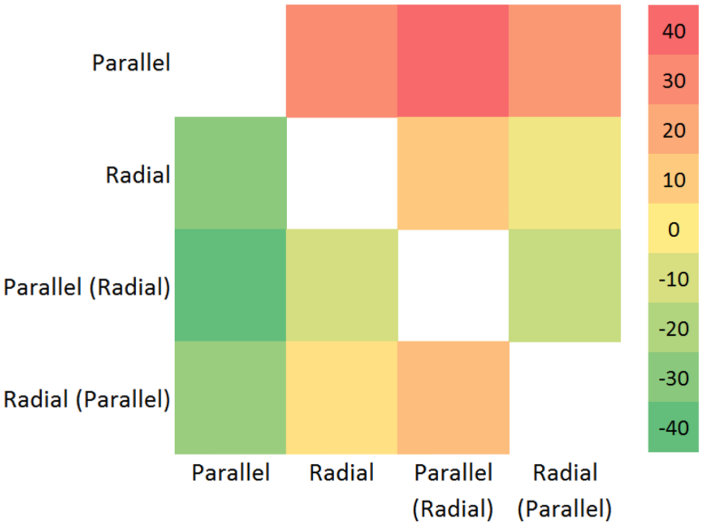

**Figure 7.3:** Showing the relative difference between each possible combination of maze training. The total number of days the groups along the Y axis took to complete training are subtracted from the groups along the X axis. Green colours show that the Y group performed better than the X group, red colours represent the opposite. Brackets highlight when a group was crossed over to the opposite configuration of the maze (i.e., Parallel [Radial] is the performance of the group originally trained on the parallel maze when they were trained on the radial maze). For instance, parallel vs parallel (radial) is dark red, showing that the rats trained on the parallel maze performed much worse on this maze than they did when they were subsequently trained on the radial maze.

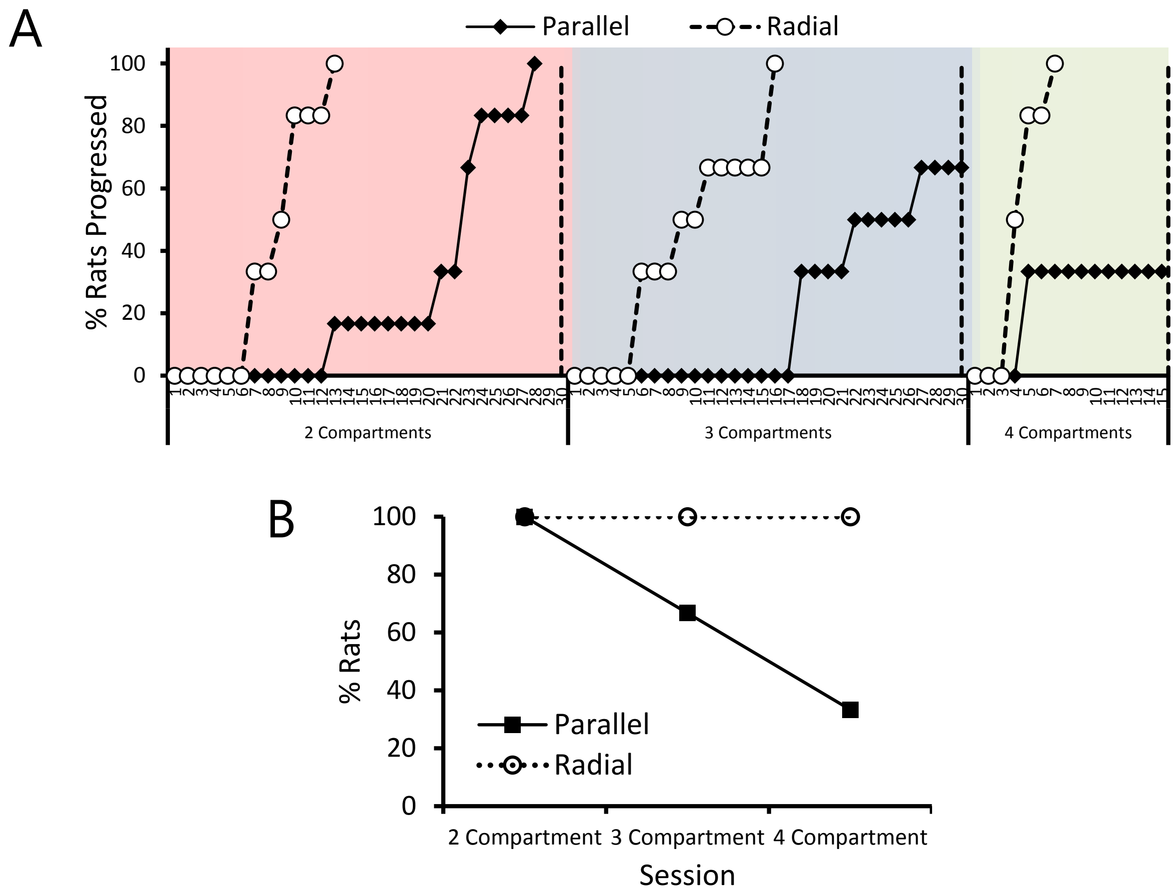

**Figure 7.4:** Showing alternative measures of performance in the behavioural task. **A**) Cumulative frequency plots showing the % of rats who were training in each stage for every experiment day. These graphs are normalised such that session 1 of each stage represents every rat's first day in that stage. The different colour backdrops represent the start and end of each stage. **B**) Showing the % of rats who successfully learned all the odours in all of the compartments at each stage. From these measures it is clear that animals trained in radial compartments reached criterion in fewer sessions than those trained in parallel compartments. This was evident at each stage of training (2-compartment, 3-compartment, and 4-compartment). Furthermore, two of the six animals trained in parallel compartments group failed to reach criterion in the 3-compartment stage, and only two animals in this group eventually reached criterion in the 4-compartment stage.

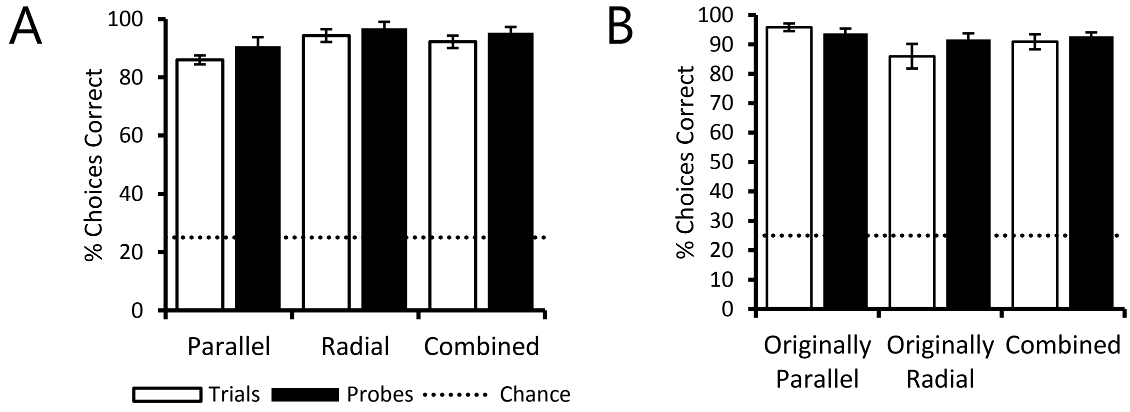

**Figure 7.5:** Showing unrewarded, odour probe trial results. Bars show the performance of rats during unrewarded probe trials (Probes) and rewarded probe trials (Trials) in the parallel and radial mazes and when both groups are combined. This is shown for the rats' first experience of the maze (**A**) and for when they were crossed over to the alternative configuration (**B**).

*Neither group of rats relied upon the odour of the food reward to perform the task*

Non-baited probe sessions confirmed that the animals used the scent of the sand, and not that of the reward, to guide behaviour. This was shown by equal task performance even when the food rewards were not present when the rats were choosing a sand well. In their first experience of the maze the rats performed similarly in the unrewarded probe trials as they did in ordinarily baited trials carried out in the same session [$t(14) = 1.08$, $p > .30$], there was similarly no difference between probe trials and baited trials assessed at the end of the crossover half of the experiment [$t(22) = 0.63$, $p > .50$]. All tests are independent samples t-tests carried out on data from both groups combined. See Figure 7.5 for these results.

*Rats made significantly more errors in the parallel configuration - in the middle two boxes*

When rats were initially trained on the maze, animals training in the parallel version of the task made significantly more errors than those in the radial configuration (this performance deficit is described above). Looking more closely at total number of errors rats made in each box, it is also clear that the rats in the parallel configuration made a significant portion of these errors in the inner boxes, 2 and 3 when compared to the outer boxes, 1 and

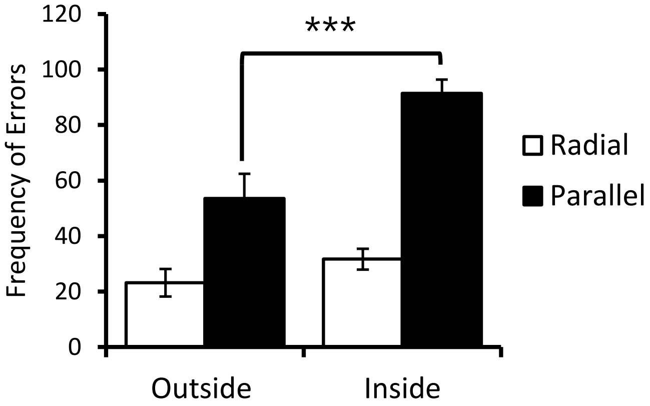

**Figure 7.6:** Distribution of errors in the parallel and radial mazes. Showing the mean and *SEM* total number of errors made by each rat in the parallel and radial mazes (first experience only) in the 'inside' boxes, 2 and 3 and the 'outside' boxes, 1 and 4. In the parallel maze the rats make significantly more errors and they are significantly more likely to make these errors in the inner two boxes.

4 [*t*(20) = -3.90, *p* < .001]. This effect was not observed in the errors made by the rats in the radial configuration, where the number of errors made in the inner and outer boxes did not differ significantly [*t*(22) = -1.36, *p* > .10]. This effect can be seen in Figure 7.6.

### 7.4.1 Dwell Time Behaviour

*Rats visited outer boxes more than inner ones in the parallel configuration but not in the radial*

A one-way ANOVA found no significant difference between the number of visits to boxes 1 and 4 in either maze [*p* > .90], the data for these two boxes were combined. The same was found for the number of visits to boxes 2 and 3 [*p* > .90], the data for these two boxes were also combined. However, when exploring the parallel configuration of the maze, rats visited the outer boxes (*M* = 8.63, *SD* = 2.13) more frequently than the inner boxes (*M* = 3.75, *SD* = 1.61) [*F*(3,28) = 16.93, *p* < .0001, one-way ANOVA]. This effect was not observed in the radial configuration of the maze where rats visited the outer boxes (*M* = 8.06, *SD* = 2.02) with a similar frequency to the inner boxes (*M* = 8.25, *SD* = 2.52) [*F*(3,28) = .20, *p* > .80, one-way ANOVA]. This effect can be seen in Figure 7.7.

*Rats spent more time in the outer boxes than inner ones in the parallel configuration but not in the radial*

A one-way ANOVA found no significant difference between the length of time spent in boxes 1 and 4 in either maze [*p* > .90], the data for these two boxes were combined. The same was found for the time spent in boxes 2 and 3 [*p* > .40], the data for these two boxes were also combined. However, similar to the frequency of visits, when exploring the parallel configuration of the maze rats spent more time investigating the outer boxes (*M* = 14.69, *SD* = 3.27) than the inner ones (*M* = 7.78, *SD* = 3.60) [*F*(3,28) = 12.40, *p* < .0001, one-way ANOVA]. Again, this effect was not observed in the radial configuration of the maze, here rats spent a similar length of time in the outer boxes (*M* = 14.30, *SD* = 5.83) and the inner ones (*M* = 11.60, *SD* = 2.69) [*F*(3,28) = .98, *p* > .40, one-way ANOVA]. This effect can also be seen in Figure 7.7.

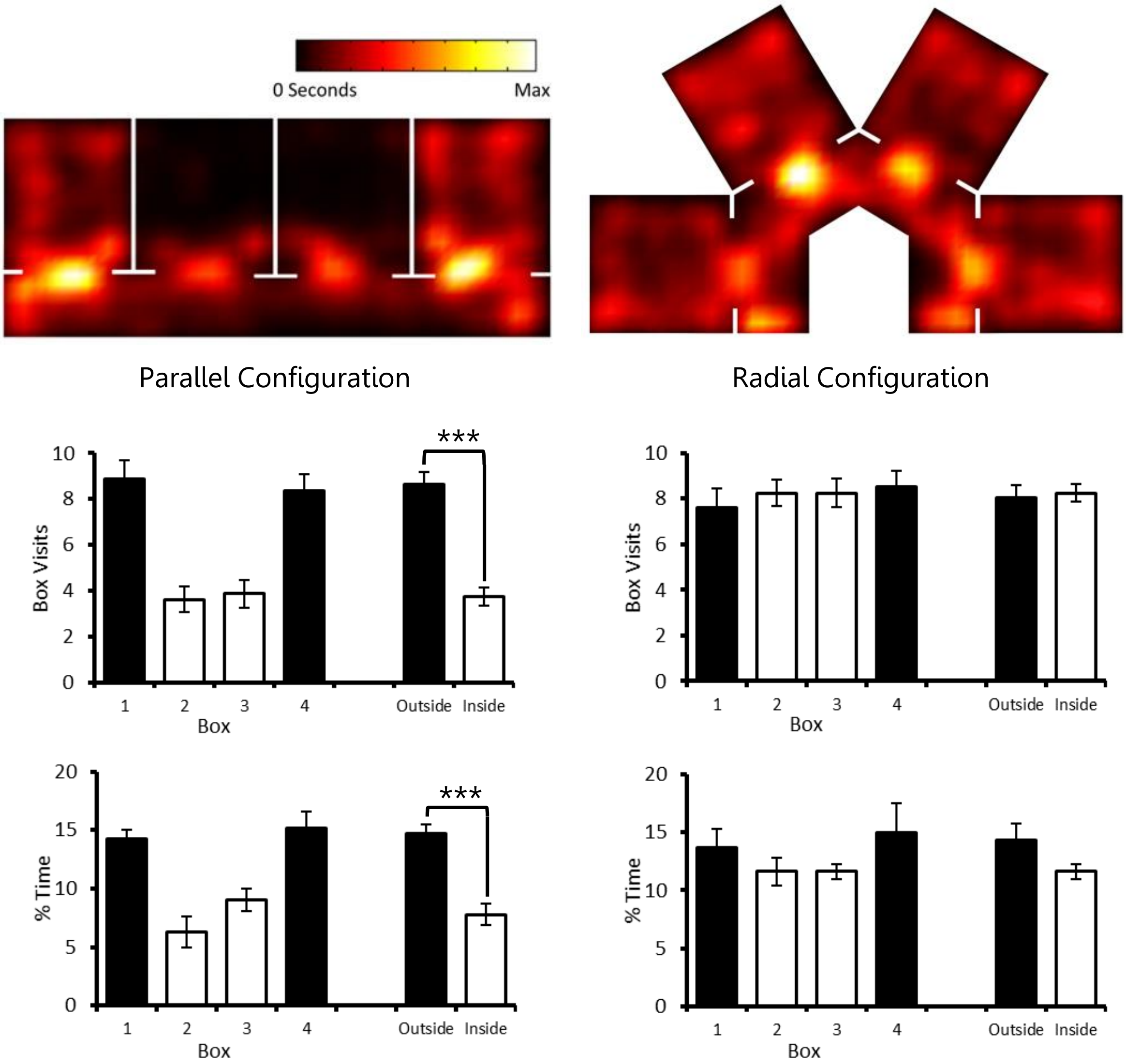

**Figure 7.7:** Dwell time data for the parallel and radial mazes. Showing data for the parallel maze in the left column and for the radial maze in the right column. Top row contains dwell time heat maps for the two maze configurations, these maps show the average time spent by the rats in each area of the maze, hot colours denote areas where the rats spent a lot of time, dark colours or black denotes areas where the rats spent very little or no time. The middle row shows the mean and *SEM* number of visits to each maze box, as well as the combined mean and *SEM* for the outside boxes (1 and 4) and inside boxes (2 and 3), the bottom row shows the same information for dwell time. Dwell time is expressed as a percentage of the total session time which was always 20 minutes.

## 7.5 Discussion

We trained two groups of animals on an odour discrimination task in two different environments. The first environment consisted of four parallel compartments joined by a corridor, the second environment consisted of the same four compartments arranged in a radial configuration with a 60° angle between each of them, and these were joined by a different shaped corridor. We found that animals trained in the first, parallel configuration were significantly impaired in learning an odour discrimination task relative to the animals trained in the radial configuration. They took significantly longer to learn the task at almost every stage and overall took approximately twice as long. Furthermore, only two of the animals in this group successfully learned the whole task (all four odours in all four compartments) whereas all six animals in the radial group learned everything. After this period of training rats were swapped between mazes, rats previously trained in the parallel environment were trained in the radial configuration and vice versa. In this phase of the experiment both groups successfully learned the task fully. The rats previously trained in the parallel environment did significantly better in the radial configuration than their parallel performance and moderately better than the original radial group. The radial group were not impaired when trained in the parallel maze, they were moderately faster than their own performance in the radial maze and significantly faster than the original parallel group. In an earlier experiment it was reported that rats spent more time in the outer compartments of maze identical to our parallel configuration (Spiers et al., 2013). We did not see this same effect in our recording data, however, we encouraged rats to explore the maze fully using food rewards and this may have occluded any effect. To investigate it further, we recorded the behaviour of 8 naïve, satiated rats as they freely explored both mazes, separated by a period of 24 hours. We found an extremely strong effect in this group; the animals spent significantly longer in the outer boxes of our parallel maze and visited them significantly more often, thus replicating the results of Spiers et al. (2013). This effect was not observed in the radial configuration. Together our results support the hypothesis that place cell representations underlie the disambiguation of similar local regions within an environment. When different local compartments are oriented in the same direction, significantly more place field repetition is observed than when the local compartments are arranged at an angle to one another. Now we have also shown that rats have a great deal of difficulty establishing unique odour-environment associations when compartments are arranged in parallel. In contrast, such associations are readily acquired when similar compartments are arranged in different directions. The observed sensitivity to angular orientation of both place cells and spatial learning suggests that directional information underlies the disambiguation of radially arranged environments and, presumably, the global representation of location.

A discussion of the neurophysiological mechanisms underpinning the spatial learning effect we see here has been made in the previous chapter. Chiefly, the increased head direction information afforded by the radial configuration of our maze may lead to more distinct Boundary Vector Cell (BVC) representations for each compartment, the firing of place cells may then be largely effected by inputs from these neurons, thus leading to greater place cell discrimination in the radial maze. Regardless of the neurophysiological explanation, our results suggest that place cells do indeed underlie spatial navigation and spatial learning, as suggested by O'Keefe and Nadel (1978). Here, though, we have shown that repeating place fields may be linked to an impairment in spatial learning, a finding which has not been demonstrated previously. Spiers et al. (2013) reported place field repetition in a maze identical to our parallel configuration, however, they did not investigate the contribution of head direction information. They also did not attempt to train animals in their environments, although it was suggested as an avenue of future research. Derdikman et al. (2009) reported both grid field fragmentation and place field repetition in a maze composed of multiple alleyways. However, in this task the rats merely had to navigate through the single track maze, from one end to the other. Thus, it is impossible to determine if the behaviour of these animals was impaired in any way, although the task is not one which is likely to be sensitive to impairment anyway. Derdikman et al.'s (2009) task could be modified to include a spatial discrimination; if animals were required to leave the maze at a particular point or stop at a particular spatial location and wait for a food reward as in Hok et al. (2007). Singer et al. (2010) report frequent 'path equivalence' in their maze, which appears to be the same phenomenon as place field repetition. They see this even while animals successfully complete their task, however, again there is not an environment to compare the observed path equivalence, or spatial learning to. Thus, it remains unclear whether animals trained on Singer et al.'s (2010) task would learn more quickly if their alleyways were not parallel to one another.

### 7.5.1 Path Equivalence

Singer et al. (2010) report that the frequency of path equivalence actually increases as animals learn their task. The rats in their experiment appear to be utilising an allothetic strategy and, according to their performance, are able to discriminate the different alleyways. Why path equivalence increases remains unclear. The authors conclude that in their task, path equivalence may facilitate improved spatial learning, as it helps the animal to associate a similar behaviour to several different locations. During single unit recording, our animals were not required to 'do' anything, they simply had to perform the same behaviour in each compartment, collect scattered food rewards. Singer et al.'s (2010) explanation could account for the repeating place fields we observed during our recordings, place cells may simply have been encoding a specific behaviour (foraging) in multiple environments. However, this explanation cannot account for the lack of repeating fields in our radial configuration where the same behaviour/compartment relationship was maintained. It is likely that although path equivalence increased as rats learned their task, rate coding also increased. Singer et al. (2010) were able to show, quite extensively, that rate coding was sufficient to distinguish the alleyways at a population level. However, they do not report whether this coding becomes more prevalent or more strongly modulated with experience.

Future experiments could record place cells while animals are trained on our odour discrimination task; based on our hypothesis, we would expect place field repetition to decrease (or for rate coding to increase) as animals learn to discriminate compartments in the parallel maze configuration. If this is not the case then this hypothesis would require careful re-examination. However, Singer et al.'s (2010) explanation would not be any more convincing, as the rats in our odour task are required to perform a different response in each compartment. Digging in cumin scented sand in one compartment is not the correct response in another compartment. Thus, if repeating place fields do not decrease as rats learn our task then they cannot represent the application of a specific behaviour to multiple spatial locations. Preliminary evidence (Supplementary Figure 4) suggests that this may be the case.

A different explanation may be that path equivalence and place field repetition are two distinct phenomena. In Singer et al.'s (2010) task, path equivalence occurs during a period of identical behaviour – approaching a food reward or making a left or right turn. Furthermore, as in Derdikman et al.'s (2009) experiment, these cells only fire when the animal is moving through the maze in a particular direction (see Figure 7.8). It could be that these repeating fields are due to some form of goal overrepresentation or reward anticipation, although this is unlikely because path equivalence is observed in parts of the maze where the rewards are not visible to the rat. It is more likely that these fields signify a particular behavioural event or response sequence. Path equivalence observed during periods of highly stereotypical behaviour (Derdikman et al., 2009; Singer et al., 2010) then, may be functionally different to the repetition of place fields observed in more open field environments (Skaggs & McNaughton, 1998; Spiers et al., 2013). The dorsolateral striatum

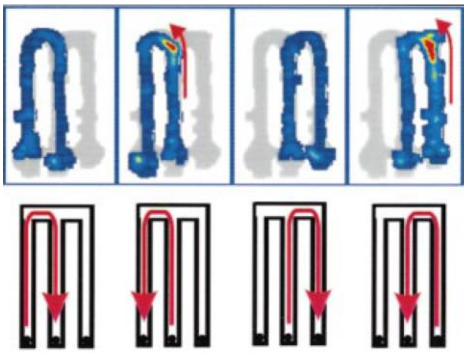

**Figure 7.8:** An example place cell which shows 'path equivalence' in Frank et al.'s (2000a) W-maze. The cell has a place field whenever the animal makes a left turn, but only when it is running through the maze from right to left. Taken from (Frank et al., 2000a), Figure 6.

has been implicated in the formation of habits and automated response sequences (Barnes, Kubota, Hu, Jin, & Graybiel, 2005), as has the neostriatum in humans (Knowlton, Mangels, & Squire, 1996), it appears to do this in communication with the infralimbic cortex (Smith & Graybiel, 2013). Neurons in the striatum often fire as an animal makes a specific behaviour or response (Jin & Costa, 2010; Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; Thorn et al., 2010), for instance a neuron may fire whenever a rat makes a left turn (see Figure 7.9). These firing properties are very similar to those seen in place cells which show path equivalence. It may be the case that path equivalence is the result of a task coming under control of the striatum, this would explain why Singer et al. (2010) saw an increase as rats were trained more, although it does not explain how the animals were still seemingly using an allocentric navigation strategy. In contrast to Singer et al.'s (2010) and Derdikman et al.'s (2009) very repetitive tasks, the behaviour of the animals in our environments was quite varied within individual place fields, as the animals were allowed to explore and behave freely. There may be a distinction between path equivalence, which is the result of task events and behavioural responses, and repeating place fields, which are the result of geometric boundaries. However, future experiments using a multicompartment environment such as ours should look to see if place cell firing is modulated by head direction[42]. If they are not then this would provide evidence that path equivalence and place field repetition are not identical phenomena.

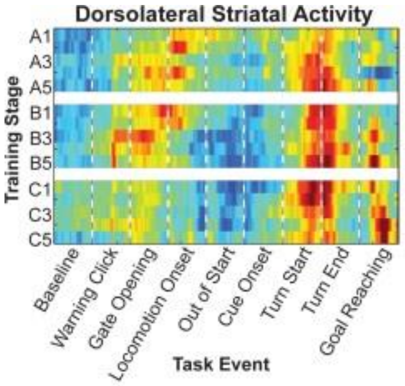

**Figure 7.9:** Ensemble activity in the striatum at different stages of training. Over time these neurons develop event specific responses specific to task action boundaries such as starting, turning or reaching the goal. From (Thorn, Atallah, Howe, & Graybiel, 2010), Figure 2.

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[42] Preliminary analyses (not reported here) suggest that the firing of place cells which have fields in our maze doorways are modulated by HD. However, it is unclear whether this is an effect of velocity. Future experiments should make use of tracking LEDs which are specifically designed for recording HD.

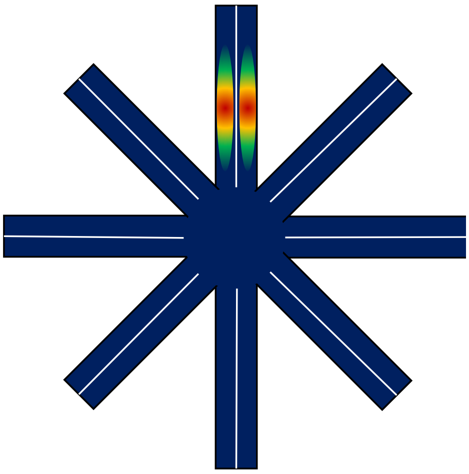

**Figure 7.10:** An alternative design of radial arm maze which incorporates our findings with those of Derdikman et al. (2009) and Singer et al.'s (2010) 'multiple U' task. Shown is an example ratemap of how a place cell may be expected to fire based on our findings.

Singer et al. (2010) report that their rats take a long time to learn their task, approximately 200 trials per sequence. Our odour discrimination task also took animals in our parallel configuration an average of 50 days to complete (by learning it fully or dropping out). To record whilst training our task would be difficult, both in terms of physical complexity and to maintain a sufficient cell ensemble for a long enough period of time. Alternatively, one could incorporate our findings with those of Singer et al.'s (2010) 'multiple-U' task. By dividing the arms of a radial arm maze in two, one may expect to see repeating place fields in parallel arms, but not divergent ones (see Figure 7.10). By using a task similar to Singer et al.'s (2010), where animals are required to visit a particular sequence of arms, rats may confuse parallel arms significantly more than divergent ones. This could be much faster to train than our odour discrimination task or Singer et al.'s (2010) multiple-U task, allowing place cells to be recorded extensively during training. However, this task loses the distinct discrimination response which is unique to our current experiment. Regardless of the task, future research should look to record place cells while animals learn a task in an environment where place field repetition is observed and where the animals are required to make a distinct response in each compartment.

### 7.5.2 Compartments 2 and 3

Spiers et al. (2013) reported that during their recording sessions, rats spent more time in the outer two boxes of their maze than the inner ones. We did not see this effect in our recording data, however, it may have been obscured by our attempts to gain equal coverage over the maze environments during our recording sessions. So, to explore this further, we took 8 naïve rats and allowed them to explore the maze individually, in both of its configurations. These rats were not food deprived and there were no rewards or even experimenters present, so there was no motivation for them to explore. We simply wanted to assess their behaviour under conditions of completely free exploration. In this group of animals we observed a clear effect, even larger than that reported by Spiers et al. (2013). These rats spent significantly less time in the inner two compartments and they visited these significantly less. Related to this, when we look more closely at the errors rats were making during our odour discrimination training we find that in the parallel maze rats made significantly more errors in the two middle compartments, 2 and 3 than the outer ones. Furthermore, in our place cell data we also see that the within-maze compartment pair with the highest average correlation value are 2 and 3, suggesting that place cells represent these two compartments more similarly than any other two. The same effect can be seen in the radial maze data, but here the correlation values are much lower. When we calculated the compartment correlation values between mazes (i.e., compartment 1 in the parallel configuration to compartment 1 in the radial configuration) we also find that between mazes, compartments 2 and 3 are the most similarly represented. Individually these results do not say very much, however, as a collection they tell a very clear story. Of all the compartments, 2 and 3 are represented the most similarly and of all the compartments rats avoid these two significantly more and find them the most difficult to distinguish[43]. These results suggest that the rats may, at least partially, be able to distinguish the outer two compartments from the others in the parallel configuration. This could be because they are found at an end of the alleyway, which is a strong cue for the animal's position. This is supported by reports that repeating place fields are much less frequent in a maze with only two compartments and an alleyway like ours (Skaggs & McNaughton, 1998), that path equivalence is not observed in environments with only two alleyways (Frank et al., 2000a)

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[43] That is to say, the rats find these compartments the hardest to distinguish from the others, not that they find these two compartments the hardest to tell apart.

and that path equivalence is much less frequent in environments composed of 3 alleyways than in environments composed of 6 (Singer et al., 2010). These results confirm the initial reports of Spiers et al. (2013) and support our initial hypothesis, the compartments in which repeating place fields were the most similar were also where the rats' spatial learning was the most impaired. Why the animals avoid these compartments is debatable, one possibility is that the animals were simply showing thigmotactic behaviour – following closely to the environment walls (Lamprea, Cardenas, Setem, & Morato, 2008). Shuttling between compartments 1 and 4 is behaviour indicative of following close to the long, uninterrupted wall of the corridor. If the rats find the repetitive design of the parallel maze more ambiguous they may experience heightened anxiety in this environment and thus thigmotax more (Snihur, Hampson, & Cain, 2008; Treit & Fundytus, 1988). The rats we used were housed in regular, unenriched cage environments and they were not used in any previous experiments or even handled by an experimenter. A test of thigmotaxis effects would be to expose rats to environmental enrichment before conducting the dwell time experiment, as this has been shown to decrease thigmotactic behaviour (Harris, D'Eath, & Healy, 2009). If the rats explore the inner compartments more after early environmental enrichment, it may at least be partially responsible. Future experiments should look to clarify if animals are more anxious in repetitive environments

### 7.5.3 Crossover Performance

After training our animals in the parallel or radial environments, we crossed the groups over, thus training them on opposite configurations. We found, as expected, that the rats trained on the parallel maze performed significantly better when they were trained on the radial maze, we did not expect that they would outperform, in some stages, the original radial group. It was also apparent that the rats trained in the radial maze were unimpaired in the parallel maze and performed significantly better than the original parallel group. This pattern of results appears to be in contradiction to our prediction. However, these results can perhaps be explained in terms of Tolman's (Tolman, 1948) early expectancy and cognitive mapping theories. He proposed that task demands and rules form an important part of a cognitive map, as equally important as spatial information. From our data it would appear that the rats trained in the parallel environment performed poorly, but when they were crossed over to the radial environment they were able to utilise previously learned information about the odour task to perform significantly better once they were able to discriminate the compartments. Tolman (1951b) proposed that, during training, animals form *expectancies* about goals and their corresponding behaviours, he also suggested that given enough experience these expectancies would come to form a *belief*, which animals may apply to other, similar environments or in similar circumstances. Our results would certainly suggest that although learning is impaired in a parallel environment, the little learning which is acquired can easily and quickly be applied in a similar, radial environment, resulting in a much greater rate of acquisition there. Transfer of training rules or information between environments has been shown in simpler spatial tasks (Pearce, Good, Jones, & McGregor, 2004). We also saw that our radial rats, after receiving full and extensive training in the radial maze were unimpaired in the parallel environment. It is more difficult to reconcile this finding. The most obvious explanation is that the animals in this group were able to transfer not only their previous training experience, but also their ability to discriminate the compartments. Future experiments could confirm this by recording cells in rats which have been trained initially in the radial environment. If they transpose their more global representation of the radial environment to the parallel one then the correlation between these two environments should be much higher than would be expected by chance and the frequency of place field repetition should also be much lower, although preliminary evidence suggests that this may not be the case (see Supplementary Figure 4). A slightly different interpretation would be that having learned the odour discrimination task and rules, these rats were able to apply this information to the parallel environment and thus overcome any place field repetition more quickly. Again, recording place cells in rats as they are trained on the task would reveal the nature of this training effect.

# Discussion

## Do animals have a cognitive map?

### 8.1 Review

In Experiment 1 we showed that rats are unable to make a spontaneous spatial inference and take a novel shortcut between two locations. Rats are able, however, to make use of spatial information acquired latently, and prior to training, to utilise shortcuts when they become available. These results suggest that rats are able to acquire, store and utilise spatial knowledge, possibly in the form of a cognitive map, but that they may not be able to use this information to quickly compute novel responses that require map-based navigation. In Experiment 2, we showed that prospective differential firing is dependent on the trajectory the animal is planning to take, rather than the animal's final destination. These results add to a body of evidence which suggests that if the hippocampus maintains a map-based representation of an animal's environment, this information is most often extracted, represented and utilised in the form of trajectories. In Experiment 3, we showed that in an environment with multiple, visually identical compartments, place cells do not form a coherent global representation of the animal's environment, but instead come to represent these surroundings in terms of their individual components. However, we were also able to show that with additional head direction information place cells are more likely to form a global representation of these components. In Experiment 4 we showed that in environments where place cells have a purely local representation, rats are also unable to learn a task which requires knowledge of the whole environment. Again, with additional head direction information this impairment was not observed.

## 8.2 The Cognitive map

A superficial analysis of our results may conclude that rats do not possess a cognitive map of the form suggested by O’Keefe and Nadel (1978) and Tolman (1948). They cannot take improvised shortcuts, an often used test of cognitive mapping ability (Bennett, 1996). The hippocampus, which is thought to represent the neural basis of the cognitive map (O'Keefe & Nadel, 1978) represents future trajectories not future goals, without angular orientation information this representation encodes purely local information such as environment boundaries and this is accompanied by an impairment in spatial learning. However, our results in many ways suggest the alternative.

In Experiment 1 our rats were able to take a shortcut if they had previously explored this route before training. During this exploration period there were no rewards present anywhere on the apparatus and after this exploration the shortcut route was made inaccessible until the probe trials, 11 sessions later. These results suggest that the animals learned the position of the shortcut alleyway and its association with the different maze areas latently (Blodgett, 1929; Meehl & Maccorquodale, 1953; Tolman, 1948). After training they combined this information with the learned goal position to make an informed decision during the shortcut probe. Although the second, non-exposure group was unable to spontaneously infer the properties of the shortcut, the behaviour of the pre-exposure group is almost as remarkable and certainly evidence that these animals accumulated spatial information to form a cognitive map (Tolman, 1948). Previous experiments have demonstrated that detailed geometric or proximal cues can be learned latently and utilised at a later date (Gilroy & Pearce, 2014; Horne, Gilroy, Cuell, & Pearce, 2012) even by zebrafish (Gomez-Laplaza & Gerlai, 2010), in contrast, because our maze was symmetrical in design our animals must have learned the distal cues surrounding the maze, their relation to the goal location and their relation to the shortcut. Indeed, to be successful at the actual task all of the animals had to take the correct route from the central platform and they must have utilised distal cues to achieve this. So why the non-exposed animals could not utilise this same information to take the shortcut is unclear, merely navigating towards a cue near the goal as a beacon would have been a successful strategy. Nor is it clear why they instead chose the alternative ‘novel’ route at an increased level, or why some of the rats chose the familiar, unrewarded route. The shortcut and novel routes were equally novel to both groups, so their increased choice of the novel route could not be due to novelty seeking. The pre-exposed group did not once choose the familiar route; this route was available throughout training but at no point was it rewarded, for all of that time the rats should have formed a negative association with that trajectory.

In Experiment 2 we showed that the prospective differential firing of place cells is dependent on the animal’s next trajectory, not its final destination. These results suggest that place cells may encode trajectory specific information rather than form a global representation of an environment, such as a cognitive map. Since the hippocampus is thought to form the neural basis of such a map (O'Keefe & Nadel, 1978), this casts doubt on the existence of such a representation. However, a number of additional findings indicate that both functions exist in parallel. The first was the observation of many cells which have stable place fields throughout our maze, despite firing in a prospective way in the start box. It is therefore entirely possible for a population of place cells to simultaneously form a representation of an environment and fire in a trajectory specific manner in specific locations. In this way, trajectory dependent firing only adds to the information carried by place cell firing, it does not replace it. On the contrary, it is likely that place cells form a stable spatial representation to which task specific information, such as rewarded trajectories, is added over time and experience. This would be in agreement with Tolman’s (1948) view; he viewed cognitive maps not as purely spatial representations but as also including task and contextual information. The second finding was that our animals had difficulty navigating the two central routes of our maze and they confused these routes more than any other route pair. If our animals were entirely concerned with individual trajectories there is no satisfactory reason why this confusion would occur. The most likely explanation is that the rats were aware that these two trajectories converged at the same spatial location and this ambiguity resulted in greater confusion between the trajectories. Knowledge that these two trajectories lead to the same goal box would require the integration of disconnected spatial information, as the rats never experienced both routes in one continuous episode (as only one entrance to this box was ever open at a time). This integration is something which has been demonstrated in rodents previously (Chapuis et al., 1987) and suggests that these animals formed a contiguous map-like representation of the environment. Coupled with the prospective firing that we have reported here, these findings suggest that rats do possess a cognitive map of the kind proposed by (Tolman, 1948) and that place cells form a suitable neural basis of this spatial representation.

In our third experiment we replicated the findings of Spiers et al. (2013) and showed place field repetition in a series of parallel, visually identical compartments. However, we were also able to show that increased head direction information, afforded by introducing an angle between the compartments, was sufficient to significantly reduce this phenomenon to a level which was no higher than would be expected by chance. The repeating place fields which we observed in our parallel environment appear to reflect only local features of the rat's environment, such as the compartment boundaries. This local encoding could be taken as evidence that place cell firing does not underlie a spatial or cognitive map, or at least not one which provides a globally contiguous representation. However our results highlight a number of important considerations. The first is the most obvious; although we see repeating place fields in our parallel environment, as did Spiers et al. (2013), we did not see this same repetition in our radial configuration. This tells us that rather than being unanimous place cell property, place field repetition represents a distinct and unusual one. An environment composed of multiple, parallel, visually identical compartments is not one which would be found naturally, or often, certainly not in the rat's natural habitat. Even from man-made structures the closest example which could be drawn would have to be an empty office building, hospital ward or prison wing. These structures would have to be empty because people very quickly and prevalently fill them with visual and contextual cues such as furniture and wall decorations. These give a very strong contextual identity to the different environments such that a disoriented person led to a room blindfolded would probably recognise a familiar room within seconds of regaining their vision. The unnatural ambiguity of our parallel environment is perhaps reflected in our naïve group of rats’ reluctance to explore it, possibly a survival instinct designed to prevent small animals getting lost in an environment they may not be able to navigate out of quickly. The second point was raised by Spiers et al. (2013) and demonstrated to a great extent by Singer et al. (2010); even in environments where place fields frequently repeat and their firing does not appear to carry much significant spatial information, their firing rate may be modulated such that as a population the firing of these cells can still be used to determine the animal’s position. We report finding this same phenomenon in our electrophysiological analyses. This suggests that if our hypothesis is true and place field repetition is the result of repeating BVC inputs to the HPC, this firing can still be further modulated by additional, contextual information, perhaps arising from the lEC (Lu et al., 2013). In this way, place cell firing can, again, encode both spatial and contextual information efficiently, suggesting that these cells do form a good neural basis of a cognitive map.

In Experiment 4, however, the finding that repeating place fields are accompanied by an impairment in spatial learning suggests that rate coding in the HPC may be not be sufficient to compensate for this phenomenon. However, these results do support the hypothesis that place cells form the neural basis of a cognitive map if there is one; when the compartments are difficult to discriminate based on the firing of place cells, rat also find these compartments difficult to discriminate as shown by their behaviour. Furthermore, even in the face of these repeating place fields, there is still evidence that the rats may be able to discriminate the compartments. When given the opportunity to explore the environment, naïve animals spend most of their time in the outer compartments, it is likely this is simply the result of thigmotaxis, however, it may indicate that these animals are aware of the environment's overall shape, which would require a map like spatial representation. We also found that during training our main group of animals found the central two compartments the most difficult to learn as they made significantly more errors here. Again, this implies that the animals found the outer compartments easier and more discriminable. We also found that although animals in our parallel group were impaired and most of them failed to learn the task, two of them did learn all four odours in all four compartments, suggesting that they were able to learn the configuration of even this environment. Future research will be required to identify what changes may occur in the place cell map, if any, as animals learn to discriminate compartments in the parallel configuration. Research should also look to see what changes there are, if any, in place cell firing in the outer compartments of such an environment.

## 8.3 The Neural Basis of a Cognitive Map

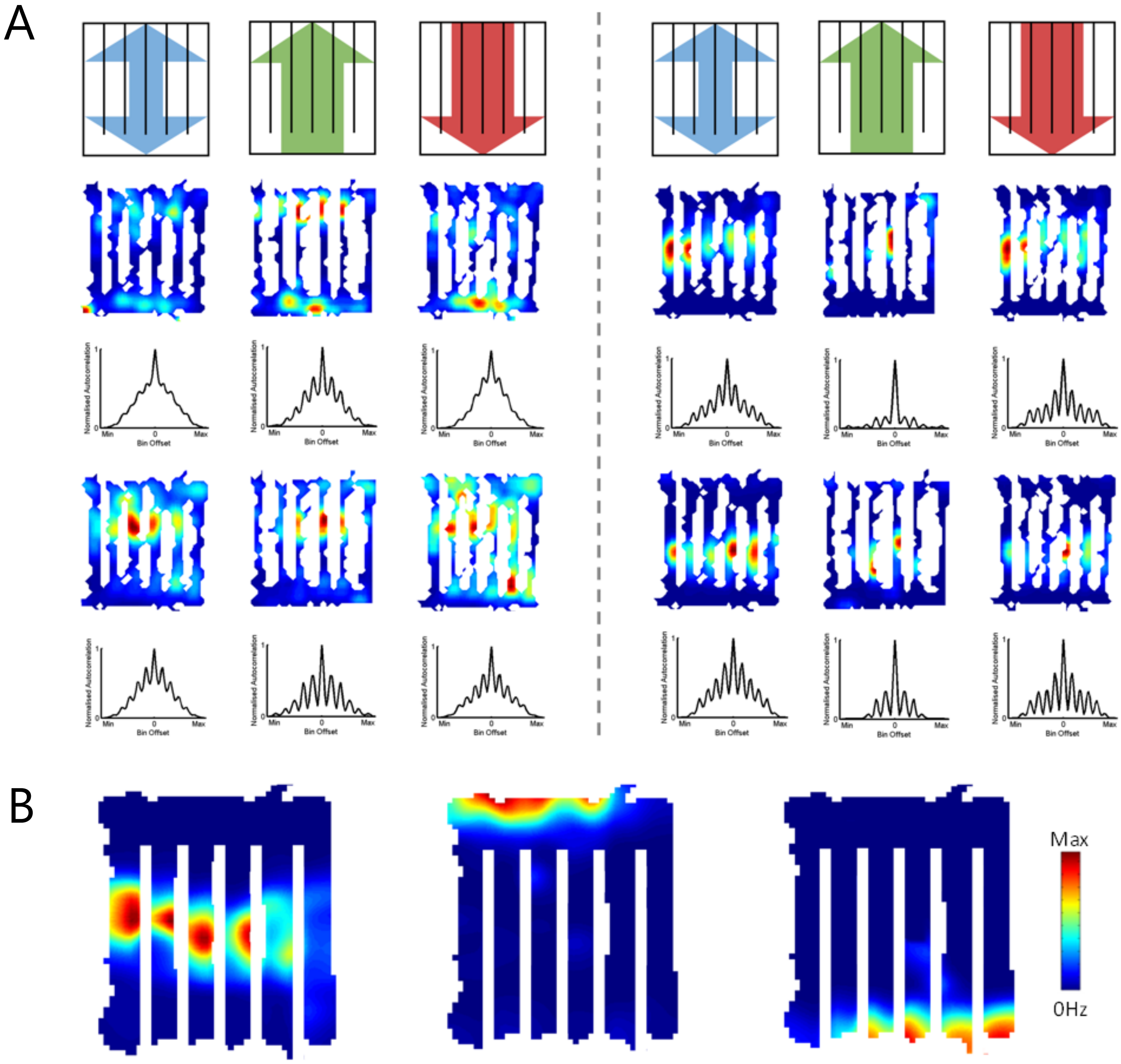
These experiments contribute a number of novel findings to the spatial navigation literature. We have shown that rats are unable to make a spatial inference and take a novel shortcut, unless they have explored this route previously, even if this exploration was unrewarded. These results add to a growing body of evidence which suggests that rats may possess a cognitive map of their environment but that they are not be able to use this information to make sophisticated spatial computations.

We have shown that place cell prospective firing is dependent on the trajectory an animal is planning to take not the destination it is planning to navigate to. These results add to a relatively small body of research which has identified prospective rate remapping as a means by which the HPC can reflect an animal's future behaviour (Ainge, Tamosiunaite, et al., 2007; Wood et al., 2000) and they provide new insight as to what specific behaviour it is encoding.

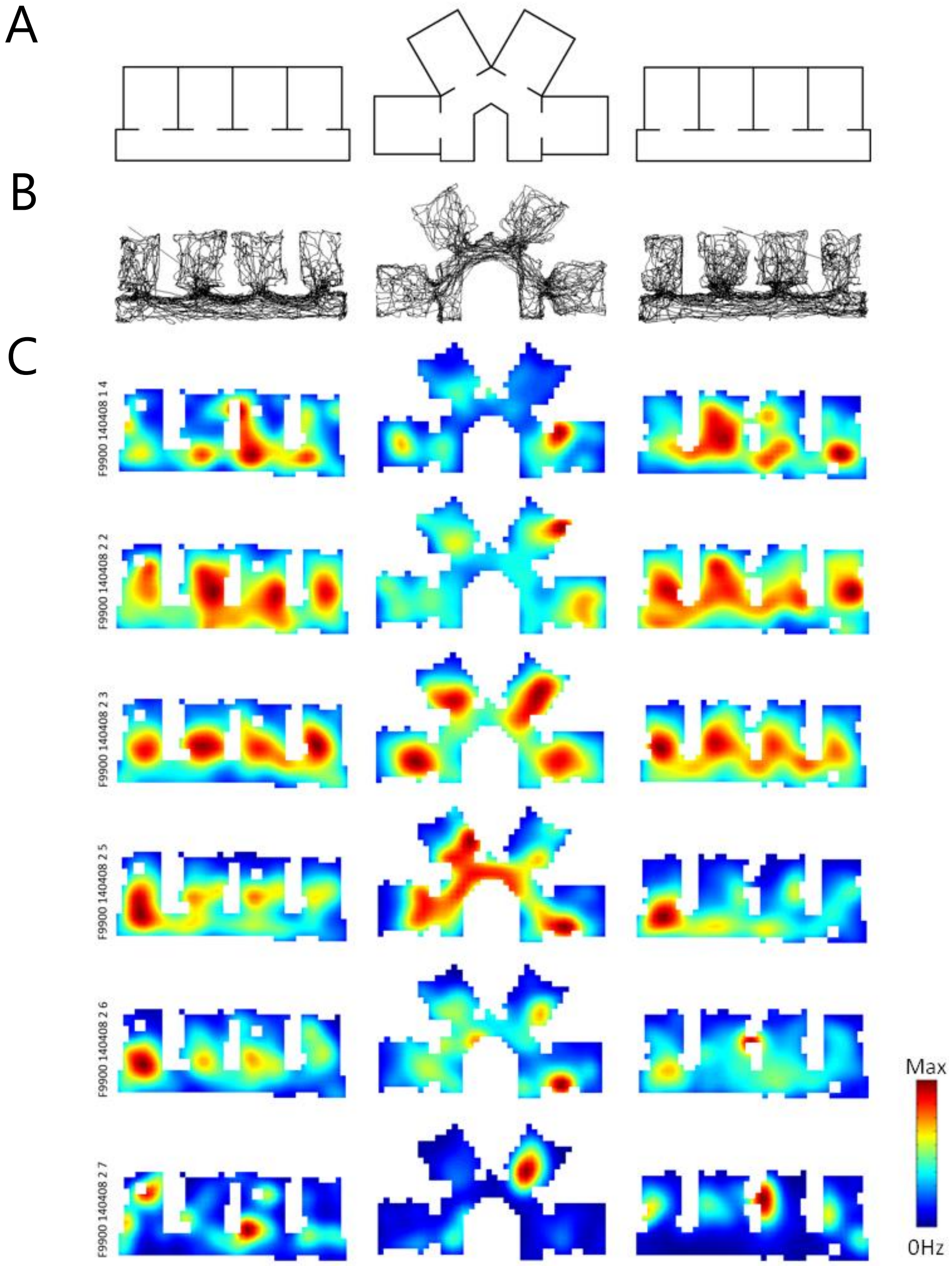
We have replicated the findings of Spiers et al. (2013) by confirming that in an environment composed of multiple parallel compartments place cells have repeating place fields, but we also expanded on these results by showing that additional angular head direction information reduces the frequency of repetitive firing to chance levels. These results further our understanding of place field repetition, how place cell firing represents complex environments and they have provided further evidence that geometric boundaries strongly influence the firing of place cells.

We further expanded on these results by showing that in an environment where place field repetition is frequent, spatial learning is impaired relative to an environment where place field repetition is not more than would be expected by chance. Together these results add to a wealth of studies which have linked place cell activity to active behaviour and navigation, providing demonstrable evidence that place cells, in cooperation with a number of equally complex cell types, form the neural basis of a representation of space and context, forming what Tolman (1948) described as a cognitive map.

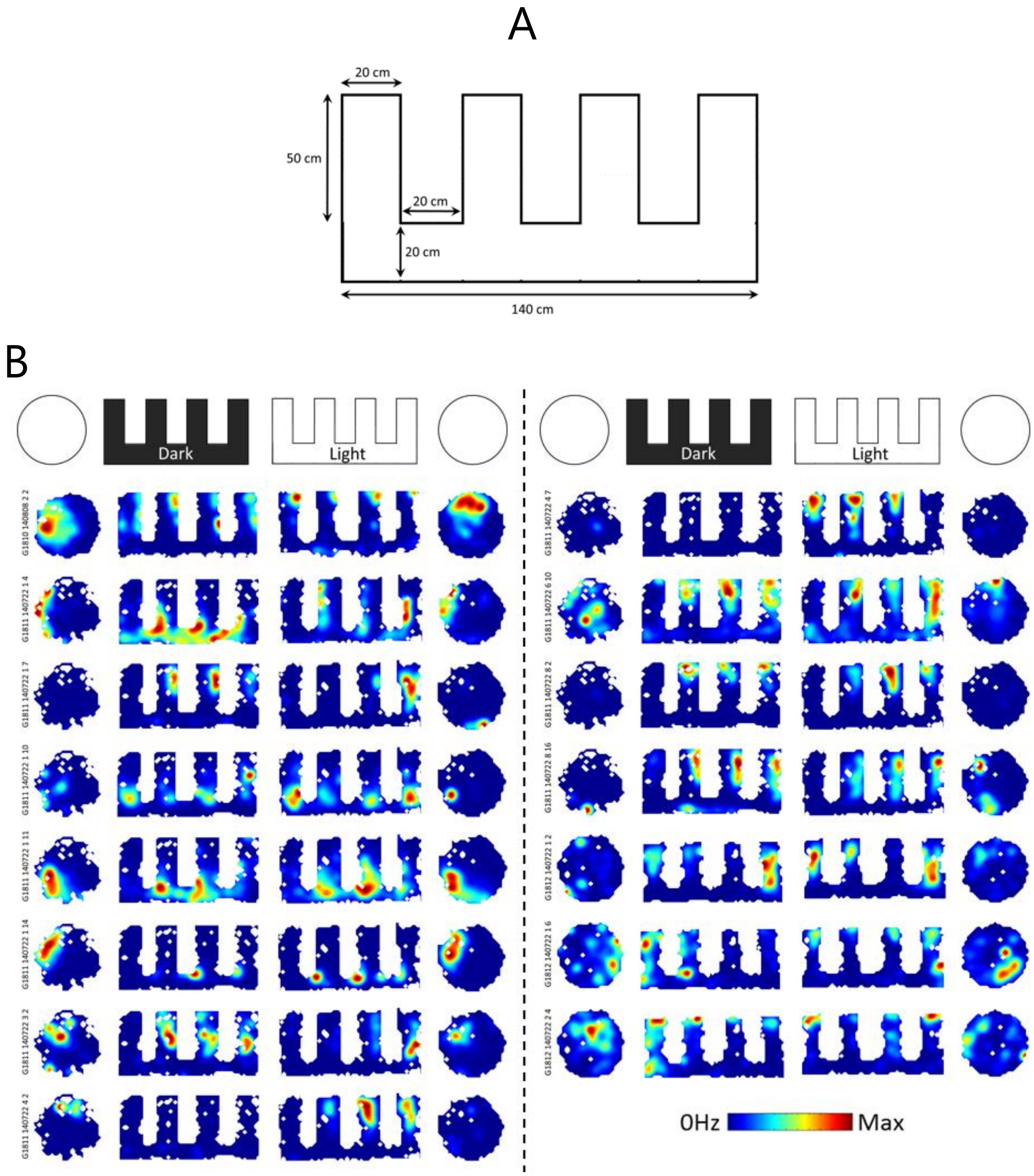
# Supplementary Figures



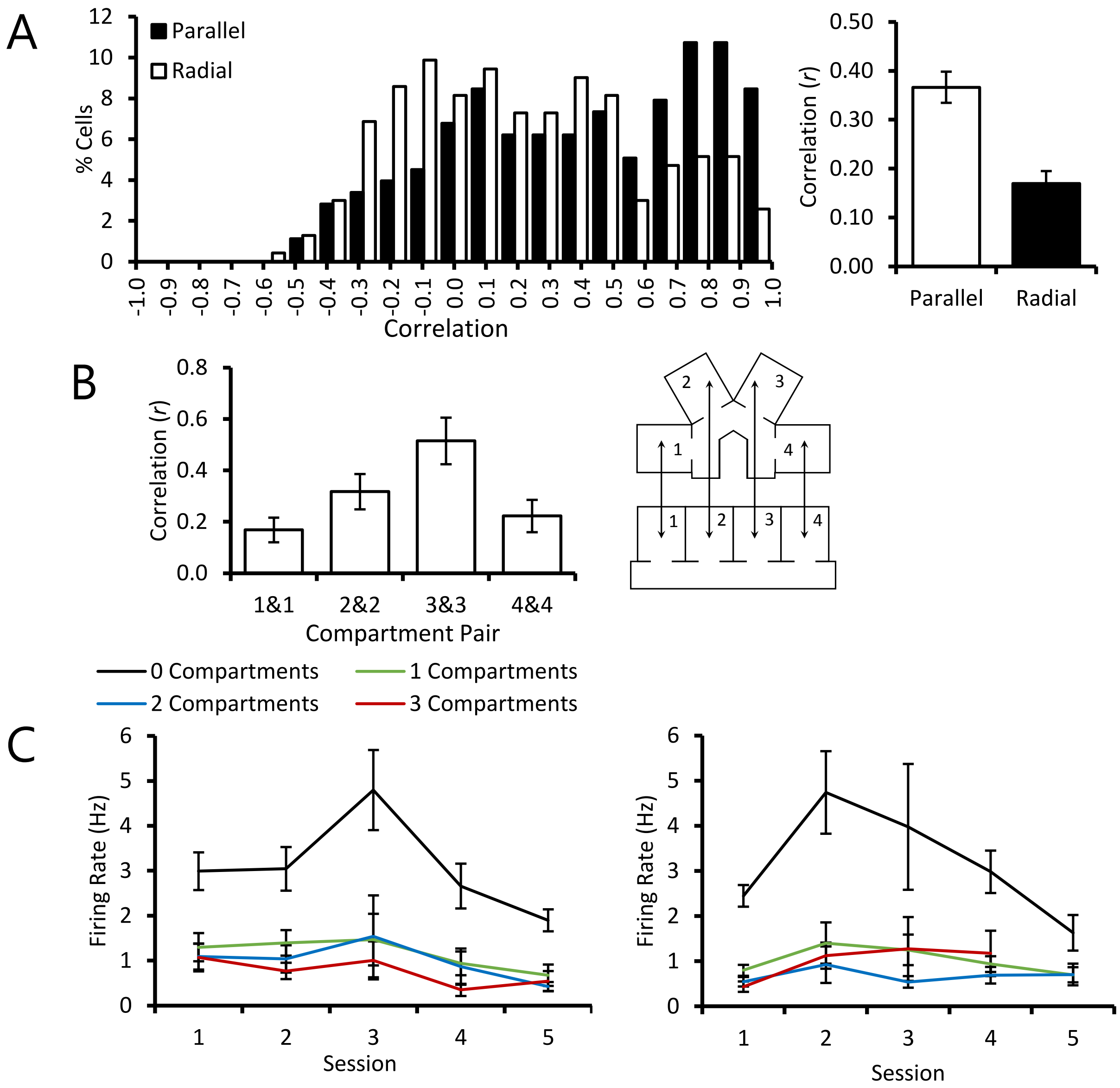
**Supplementary Figure 1:** Showing place cell recording data in a multi-alley maze. **A**) Firing rate maps for place cells (two per row), these are filtered to include only data when the animal was moving in a particular direction – the direction of filtering and a schematic of the maze can be seen in the top row. Directionality was determined by calculating the average direction of movement using a 100ms sliding window, centred on every data point. Below each rate map is shown the result of an autocorrelation procedure (described in section 6.3.7.6) performed on the map, periodic peaks indicate the presence of place field repetition. In each example the periodicity in the autocorrelation plot is higher for one set of filtered data than for the other, suggesting that the firing of place cells is head direction specific. Future experiments should make use of head direction tracking hardware and software for more accurate filtering. **B**) Representative example cells showing repeating place fields in the alleyways, in the joining corridor and in the alley ends, respectively.



**Supplementary Figure 2:** The firing patterns of mouse place cells in our parallel and radial environments. The animal completed 20 minute sessions in the parallel maze, then the radial and finally a second session in the parallel maze. **A**) Schematic showing the layout and order of the mazes used during recording, these environments are described in section 6.3 and were the same as those used in Experiments 3 and 4. **B**) These cells were all recorded in one session, shown here are the tracked positions of the animal in each environment. **C**) Firing rate maps for example place cells (one per row), the animal number, date of recording, electrode and cluster can be found to the left in vertical text. Although this is only a small sample, it appears that repeating place fields are common in both maze environments, more so than in our rats. However, it still seems to be more frequent in the parallel version of the maze. These cells were recorded during the animal's first session on the mazes.



**Supplementary Figure 3:** Parallel platform maze data. **A**) A schematic of the platform maze, with dimensions. **B**) Place cells (maximum of two per row) from 3 animals, recorded as they navigated the environments shown in the first row. Animals explored the cylinder described previously (section 6.3.5) for a minimum of 8 minutes, then the platform environment with no light available for 18 minutes, then the platform environment for a further 18 minutes with light and finally the cylinder environment for another 8 minutes. Between mazes the rats were placed in a holding cylinder. The platforms were swapped and cleaned between rats. The maze had no walls, but every edge was defined by a small wooden ridge, which prevented animals falling from the maze in the dark. Repeating place fields can be observed in both sessions, with generally very little change in firing between the two. These results suggest that physical walls are not necessary to drive place field repetition, environmental boundaries such as vertical drops are sufficient. Boundaries such as these have been shown to influence BVC firing similarly to actual walls (Barry et al., 2006; Lever et al., 2009). Furthermore, these results show that even when the geometric and physical layout of the maze is unobscured to the rats, they are still seemingly unable to distinguish the local areas.



**Supplementary Figure 4:** Results showing the effect of odour discrimination training on place cell firing. Rats (*N* = 2) were fully trained on our odour discrimination task in both maze configurations, they were then implanted and we recorded place cells in both the parallel (*N* = 96, 42 included in correlation analyses, yielding 240 correlation values) and radial (*N* = 95, 50 included in correlation analyses, yielding 312 correlation values) configurations. **A**) The full distribution of correlation values observed in both maze configurations are shown on the left, the mean and SEM values are shown on the right. These values differ significantly [$t(408) = 4.90$, $p < .001$, $d = 0.49$], the parallel value here does not deviate significantly from that observed in untrained animals [$t(2466) = -1.06$, $p > .20$, $d = -0.09$] but the radial value is significantly higher [$t(3193) = 3.63$, $p < .001$, $d = .24$], that data can be seen in section 6.4.2. **B**) The correlation between compartments in the two different configurations, a two-factor univariate ANOVA (compartment pair and correlation values) confirms that this distribution is not what would be expected by chance [$F(3,150) = 4.86$, $p < .005$, $\eta_p^2 = .09$], post hoc tests (Tukey's HSD) identifies pairs 1&1, 2&2 and 4&4 as a distinct subgroup with pairs 2&2 and 3&3 forming a second subgroup. A three-factor univariate ANOVA comparing this data to that from untrained animals confirms a significant difference between the two distributions [$F(1,2014) = 4.56$, $p < .05$, $\eta_p^2 = .01$]. **C**) The neighbourhood firing rate analysis results for the parallel (left) and radial (right) maze, figures show the mean and SEM firing rates in the maze compartments, according to their distance from the compartment with the highest firing rate (0 = the compartment with the highest firing rate, 1 = the compartment or the average of the compartments which are direct neighbours to the one with the highest firing rate). There are insufficient data to perform a 2-factor ANOVA, however, a one-way ANOVA (compartment distance and firing rate) identifies that the firing rates in the parallel maze are modulated by distance from the maximum [$F(3,19) = 15.22$, $p < .001$, $\eta_p^2 = .74$] and post-hoc tests confirm that the maximum compartment firing rate (at a distance of 0) differs from all of the others ($p < .001$ all tests, Sidak correction), which do not differ among themselves. Firing rates in the radial maze are similarly modulated by compartment distance [$F(3,18) = 13.82$, $p < .001$, $\eta_p^2 = .73$] and again the maximum differs from the others ($p < .005$ all tests, Sidak correction) which do not differ.

# Bibliography

Abrahams, S., Morris, R. G., Polkey, C. E., Jarosz, J. M., Cox, T. C., Graves, M., & Pickering, A. (1999). Hippocampal involvement in spatial and working memory: a structural MRI analysis of patients with unilateral mesial temporal lobe sclerosis. *Brain Cogn, 41*(1), 39-65. doi: 10.1006/brcg.1999.1095

Abrahams, S., Pickering, A., Polkey, C. E., & Morris, R. G. (1997). Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. *Neuropsychologia, 35*(1), 11-24.

Adams, C. D., & Dickinson, A. (1981). Instrumental responding following reinforcer devaluation. *The Quarterly Journal of Experimental Psychology Section B, 33*(2), 109-121. doi: 10.1080/14640748108400816

Aggleton, J. P., & Pearce, J. M. (2001). Neural systems underlying episodic memory: insights from animal research. *Philosophical Transactions of the Royal Society of London. Series B, 356*(1413), 1467-1482. doi: 10.1098/rstb.2001.0946

Agnihotri, N. T., Hawkins, R. D., Kandel, E. R., & Kentros, C. (2004). The long-term stability of new hippocampal place fields requires new protein synthesis. *Proc Natl Acad Sci U S A, 101*(10), 3656-3661. doi: 10.1073/pnas.0400385101

Ainge, J. A., Tamosiunaite, M., Woergoetter, F., & Dudchenko, P. A. (2007). Hippocampal CA1 place cells encode intended destination on a maze with multiple choice points. *J Neurosci, 27*(36), 9769-9779. doi: 10.1523/JNEUROSCI.2011-07.2007

Ainge, J. A., van der Meer, M. A., Langston, R. F., & Wood, E. R. (2007). Exploring the role of context-dependent hippocampal activity in spatial alternation behavior. *Hippocampus, 17*(10), 988-1002. doi: 10.1002/hipo.20301

Akesson, S., Morin, J., Muheim, R., & Ottosson, U. (2005). Dramatic orientation shift of white-crowned sparrows displaced across longitudes in the high Arctic. *Curr Biol, 15*(17), 1591-1597. doi: 10.1016/j.cub.2005.07.027

Albasser, M. M., Dumont, J. R., Amin, E., Holmes, J. D., Horne, M. R., Pearce, J. M., & Aggleton, J. P. (2013). Association rules for rat spatial learning: the importance of the hippocampus for binding item identity with item location. *Hippocampus, 23*(12), 1162-1178. doi: 10.1002/hipo.22154

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex. *Annu Rev Neurosci, 9*(1), 357-381. doi: doi:10.1146/annurev.ne.09.030186.002041

Allen, K., Rawlins, J. N., Bannerman, D. M., & Csicsvari, J. (2012). Hippocampal place cells can encode multiple trial-dependent features through rate remapping. *J Neurosci, 32*(42), 14752-14766. doi: 10.1523/jneurosci.6175-11.2012

Alvernhe, A., Van Cauter, T., Save, E., & Poucet, B. (2008). Different CA1 and CA3 representations of novel routes in a shortcut situation. *J Neurosci, 28*(29), 7324-7333. doi: 10.1523/jneurosci.1909-08.2008

Amaral, D. G., & Witter, M. P. (1989). The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience, 31*(3), 571-591.

Andersen, P. (1975). Organization of Hippocampal Neurons and Their Interconnections. In R. Isaacson & K. Pribram (Eds.), *The Hippocampus* (pp. 155-175): Springer US.

Andersen, P. (2007). *The hippocampus book*. Oxford ; New York: Oxford University Press.

Anderson, M. I., & Jeffery, K. J. (2003). Heterogeneous modulation of place cell firing by changes in context. *J Neurosci, 23*(26), 8827-8835.

Angelaki, D. E., & Cullen, K. E. (2008). Vestibular system: the many facets of a multimodal sense. *Annu Rev Neurosci, 31*, 125-150. doi: 10.1146/annurev.neuro.31.060407.125555

Austin, G. A. (1953). Tolman's interpretation of vicarious trial and error. *Psychol Rev, 60*(2), 117-122.

Avargues-Weber, A., Deisig, N., & Giurfa, M. (2011). Visual cognition in social insects. *Annu Rev Entomol, 56*, 423-443. doi: 10.1146/annurev-ento-120709-144855

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends Cogn Sci, 4*(11), 417-423. doi: http://dx.doi.org/10.1016/S1364-6613(00)01538-2

Baddeley, A. D., & Warrington, E. K. (1970). Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behavior, 9*(2), 176-189. doi: http://dx.doi.org/10.1016/S0022-5371(70)80048-2

Balaz, M. A., Capra, S., Hartl, P., & Miller, R. R. (1981). Contextual potentiation of acquired behavior after devaluing direct context-US associations. *Learning and Motivation, 12*(4), 383-397. doi: http://dx.doi.org/10.1016/0023-9690(81)90001-1

Barnes, C. A. (1988). Spatial learning and memory processes: the search for their neurobiological mechanisms in the rat. *Trends Neurosci, 11*(4), 163-169.

Barnes, C. A., McNaughton, B. L., Mizumori, S. J., Leonard, B. W., & Lin, L. H. (1990). Comparison of spatial and temporal characteristics of neuronal activity in sequential stages of hippocampal processing. *Prog Brain Res, 83*, 287-300.

Barnes, C. A., Suster, M. S., Shen, J., & McNaughton, B. L. (1997). Multistability of cognitive maps in the hippocampus of old rats. *Nature, 388*(6639), 272-275. doi: 10.1038/40859

Barnes, T. D., Kubota, Y., Hu, D., Jin, D. Z., & Graybiel, A. M. (2005). Activity of striatal neurons reflects dynamic encoding and recoding of procedural memories. *Nature, 437*(7062), 1158-1161. doi: 10.1038/nature04053

Barry, C., & Burgess, N. (2014). Neural mechanisms of self-location. *Curr Biol, 24*(8), R330-339. doi: 10.1016/j.cub.2014.02.049

Barry, C., Hayman, R., Burgess, N., & Jeffery, K. J. (2007). Experience-dependent rescaling of entorhinal grids. *Nat Neurosci, 10*(6), 682-684. doi: http://www.nature.com/neuro/journal/v10/n6/suppinfo/nn1905_S1.html

Barry, C., Lever, C., Hayman, R., Hartley, T., Burton, S., O'Keefe, J., Jeffery, K., & Burgess, N. (2006). The boundary vector cell model of place cell firing and spatial memory. *Rev Neurosci, 17*(1-2), 71-97.

Bassett, J. P., Tullman, M. L., & Taube, J. S. (2007). Lesions of the tegmentomammillary circuit in the head direction system disrupt the head direction signal in the anterior thalamus. *J Neurosci, 27*(28), 7564-7577. doi: 10.1523/jneurosci.0268-07.2007

Bates, L. A., Sayialel, K. N., Njiraini, N. W., Poole, J. H., Moss, C. J., & Byrne, R. W. (2008). African elephants have expectations about the locations of out-of-sight family members. *Biol Lett, 4*(1), 34-36. doi: 10.1098/rsbl.2007.0529

Bayley, W. S., & Gulliver, F. P. (1908). Section E--Geology and Geography. *Science, 27*(697), 721-733. doi: 27/697/721 [pii] 10.1126/science.27.697.721

Becker, L. (1958). Untersuchungen über das Heimfindevermögen der Bienen. *Zeitschrift für vergleichende Physiologie, 41*(1), 1-25. doi: 10.1007/BF00340239

Benhamou, S. (1996). No evidence for cognitive mapping in rats. *Animal Behaviour, 52*(1), 201-212. doi: http://dx.doi.org/10.1006/anbe.1996.0165

Bennett, A. T. (1996). Do animals have cognitive maps? *J Exp Biol, 199*(Pt 1), 219-224.

Bennett, A. T. D. (1991). *The Ecology of Spatial Memory in European Jays*: University of Oxford.

Benson, A. J., Spencer, M. B., & Stott, J. R. R. (1986). Thresholds for the detection of the direction of whole-body, linear movement in the horizontal plane. *Aviation Space and Environmental Medicine, 57*(11), 1088-1096.

Best, P. J., & Ranck Jr, J. B. (1982). Reliability of the relationship between hippocampal unit activity and sensory-behavioral events in the rat. *Exp Neurol, 75*(3), 652-664. doi: http://dx.doi.org/10.1016/0014-4886(82)90032-2

Best, P. J., & Thomson, L. T. (1984). *Hippocampal place cells show long-term stability of place field activity*. CA: Irvine.

Bett, D., Wood, E. R., & Dudchenko, P. A. (2012). The postsubiculum is necessary for spatial alternation but not for homing by path integration. *Behav Neurosci, 126*(2), 237-248. doi: 10.1037/a0027163

Bigel, M. G., & Ellard, C. G. (2000). The contribution of nonvisual information to simple place navigation and distance estimation: an examination of path integration. *Can J Exp Psychol, 54*(3), 172-185.

Birkhead, T. (Producer). (2009, 11/25/2012). The wisdom of birds – Do Lectures. *Do Lectures – Talks that inspire action.* Retrieved from http://www.dolectures.com/lectures/the-wisdom-of-birds/

Bjerknes, T. L., Moser, E. I., & Moser, M. B. (2014). Representation of geometric borders in the developing rat. *Neuron, 82*(1), 71-78. doi: 10.1016/j.neuron.2014.02.014

Blackstad, T. W. (1956). Commissural connections of the hippocampal region in the rat, with special reference to their mode of termination. *The Journal of Comparative Neurology, 105*(3), 417-537. doi: 10.1002/cne.901050305

Blair, H. T., Cho, J., & Sharp, P. E. (1998). Role of the Lateral Mammillary Nucleus in the Rat Head Direction Circuit: A Combined Single Unit Recording and Lesion Study. *Neuron, 21*(6), 1387-1397. doi: http://dx.doi.org/10.1016/S0896-6273(00)80657-1

Blair, H. T., Cho, J., & Sharp, P. E. (1999). The anterior thalamic head-direction signal is abolished by bilateral but not unilateral lesions of the lateral mammillary nucleus. *J Neurosci, 19*(15), 6673-6683.

Blair, H. T., & Sharp, P. E. (1995). Anticipatory head direction signals in anterior thalamus: evidence for a thalamocortical circuit that integrates angular head motion to compute head direction. *J Neurosci, 15*(9), 6260-6270.

Blair, H. T., & Sharp, P. E. (1996). Visual and vestibular influences on head-direction cells in the anterior thalamus of the rat. *Behav Neurosci, 110*(4), 643-660.

Blanchard, D. C., & Blanchard, R. J. (1972). Innate and conditioned reactions to threat in rats with amygdaloid lesions. *J Comp Physiol Psychol, 81*(2), 281-290.

Blaser, N., Dell'Omo, G., Dell'Ariccia, G., Wolfer, D. P., & Lipp, H.-P. (2013). Testing cognitive navigation in unknown territories: homing pigeons choose different targets. *J Exp Biol, 216*(16), 3123-3131. doi: 10.1242/jeb.083246

Bles, W., de Jong, J. M., & de Wit, G. (1984). Somatosensory compensation for loss of labyrinthine function. *Acta Otolaryngol, 97*(3-4), 213-221.

Blodgett, H. C. (1929). The effect of introduction of reward upon the maze performance of rats. *University of California Publications in Psychology, 4*, 113-134.

Blodgett, H. C. (1946). Reynolds' repetition of Blodgett's experiment on latent learning. *Journal of Experimental Psychology, 36*(2), 184.

Blodgett, H. C., & McCutchan, K. (1947). Place versus response learning in the simple <em>T</em>-maze. *Journal of Experimental Psychology, 37*(5), 412-422. doi: 10.1037/h0059305

Blodgett, H. C., McCutchan, K., & Mathews, R. (1949). Spatial learning in the T-maze: the influence of direction, turn, and food location. *Journal of Experimental Psychology, 39*(6), 800-809. doi: 10.1037/h0058978

Boccara, C. N., Sargolini, F., Thoresen, V. H., Solstad, T., Witter, M. P., Moser, E. I., & Moser, M.-B. (2010). Grid cells in pre- and parasubiculum. *Nat Neurosci, 13*(8), 987-994. doi: http://www.nature.com/neuro/journal/v13/n8/abs/nn.2602.html#supplementary-information

Bodily, K. D., Daniel, T. A., & Sturz, B. R. (2012). The roles of beaconing and dead reckoning in human virtual navigation. *Learning and Motivation, 43*(1–2), 14-23. doi: http://dx.doi.org/10.1016/j.lmot.2012.01.002

Boeddeker, N., Dittmar, L., Stürzl, W., & Egelhaaf, M. (2010). The fine structure of honeybee head and body yaw movements in a homing task. *Proceedings of the Royal Society B: Biological Sciences, 277*(1689), 1899-1906. doi: 10.1098/rspb.2009.2326

Bonnevie, T., Dunn, B., Fyhn, M., Hafting, T., Derdikman, D., Kubie, J. L., Roudi, Y., Moser, E. I., & Moser, M.-B. (2013). Grid cells require excitatory drive from the hippocampus. *Nat Neurosci, 16*(3), 309-317. doi: http://www.nature.com/neuro/journal/v16/n3/abs/nn.3311.html#supplementary-information

Bostock, E., Muller, R. U., & Kubie, J. L. (1991). Experience-dependent modifications of hippocampal place cell firing. *Hippocampus, 1*(2), 193-205. doi: 10.1002/hipo.450010207

Bower, M. R., Euston, D. R., & McNaughton, B. L. (2005). Sequential-context-dependent hippocampal activity is not necessary to learn sequences with repeated elements. *J Neurosci, 25*(6), 1313-1323. doi: 10.1523/jneurosci.2901-04.2005

Breese, C. R., Hampson, R. E., & Deadwyler, S. A. (1989). Hippocampal place cells: stereotypy and plasticity. *J Neurosci, 9*(4), 1097-1111.

Bregy, P., Sommer, S., & Wehner, R. (2008). Nest-mark orientation versus vector navigation in desert ants. *J Exp Biol, 211*(Pt 12), 1868-1873. doi: 10.1242/jeb.018036

Bremmer, F., & Lappe, M. (1999). The use of optical velocities for distance discrimination and reproduction during visually simulated self motion. *Exp Brain Res, 127*(1), 33-42.

Brines, M. L., & Gould, J. L. (1979). Bees have rules. *Science, 206*(4418), 571-573. doi: 10.1126/science.206.4418.571

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2007). Rats depend on habit memory for discrimination learning and retention. *Learning & Memory, 14*(3), 145-151. doi: 10.1101/lm.455607

Brun, V. H., Leutgeb, S., Wu, H.-Q., Schwarcz, R., Witter, M. P., Moser, E. I., & Moser, M.-B. (2007). Impaired Spatial Representation in CA1 after Lesion of Direct Input from Entorhinal Cortex. *Neuron, 57*(2), 290-302. doi: 10.1016/j.neuron.2007.11.034

Bülthoff, H. H., & Edelman, S. (1992). Psychophysical support for a two-dimensional view interpolation theory of object recognition. *Proceedings of the National Academy of Sciences, 89*(1), 60-64. doi: 10.1073/pnas.89.1.60

Bulthoff, H. H., Edelman, S. Y., & Tarr, M. J. (1995). How are three-dimensional objects represented in the brain? *Cereb Cortex, 5*(3), 247-260.

Burak, Y., & Fiete, I. R. (2009). Accurate Path Integration in Continuous Attractor Network Models of Grid Cells. *PLoS Comput Biol, 5*(2), e1000291. doi: 10.1371/journal.pcbi.1000291

Burgess, N., Donnett, J. G., Jeffery, K. J., & O'Keefe, J. (1997). Robotic and neuronal simulation of the hippocampus and rat navigation. *Philos Trans R Soc Lond B Biol Sci, 352*(1360), 1535-1543. doi: 10.1098/rstb.1997.0140

Burgess, N., & O'Keefe, J. (2003). Neural representations in human spatial memory. *Trends Cogn Sci, 7*(12), 517-519.

Burgess, N., Spiers, H. J., & Paleologou, E. (2004). Orientational manoeuvres in the dark: dissociating allocentric and egocentric influences on spatial memory. *Cognition, 94*(2), 149-166. doi: 10.1016/j.cognition.2004.01.001

Burwell, R. D. (2000). The parahippocampal region: corticocortical connectivity. *Ann N Y Acad Sci, 911*, 25-42.

Burwell, R. D., Saddoris, M. P., Bucci, D. J., & Wiig, K. A. (2004). Corticohippocampal contributions to spatial and contextual learning. *J Neurosci, 24*(15), 3826-3836. doi: 10.1523/jneurosci.0410-04.2004

Byrne, R. W. (2000). How monkeys find their way: leadership, coordination, and cognitive maps of African baboons. *On the move: how and why animals travel in groups. University of Chicago Press, Chicago*, 491-518.

Caballero-Bleda, M., & Witter, M. P. (1994). Projections from the presubiculum and the parasubiculum to morphologically characterized entorhinal-hippocampal projection neurons in the rat. *Exp Brain Res, 101*(1), 93-108.

Calton, J. L., Stackman, R. W., Goodridge, J. P., Archey, W. B., Dudchenko, P. A., & Taube, J. S. (2003). Hippocampal place cell instability after lesions of the head direction cell network. *J Neurosci, 23*(30), 9719-9731.

Calvin, W. H. (1998). *The Cerebral Code: Thinking a Thought in the Mosaics of the Mind*: MIT Press.

Canto, C. B., Wouterlood, F. G., & Witter, M. P. (2008). What Does the Anatomical Organization of the Entorhinal Cortex Tell Us? *Neural Plasticity, 2008*, 18. doi: 10.1155/2008/381243

Capaldi, E. A., Smith, A. D., Osborne, J. L., Fahrbach, S. E., Farris, S. M., Reynolds, D. R., Edwards, A. S., Martin, A., Robinson, G. E., Poppy, G. M., & Riley, J. R. (2000). Ontogeny of orientation flight in the honeybee revealed by harmonic radar. *Nature, 403*(6769), 537-540. doi: 10.1038/35000564

Carr, M. F., Jadhav, S. P., & Frank, L. M. (2011). Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat Neurosci, 14*(2), 147-153.

Casey, S. M. (1978). Cognitive mapping by the blind. *Journal of Visual Impairment & Blindness, 72*(8), 297-301.

Catanese, J., Viggiano, A., Cerasti, E., Zugaro, M. B., & Wiener, S. I. (2014). Retrospectively and Prospectively Modulated Hippocampal Place Responses Are Differentially Distributed along a Common Path in a Continuous T-Maze. *34*(39), 13163-13169. doi: 10.1523/jneurosci.0819-14.2014

Chapuis, N., Durup, M., & Thinus-Blanc, C. (1987). The role of exploratory experience in a shortcut task by golden hamsters (Mesocricetus auratus). *Animal Learning & Behavior, 15*(2), 174-178. doi: 10.3758/BF03204960

Chapuis, N., & Varlet, C. (1987). Short cuts by dogs in natural surroundings. *The Quarterly Journal of Experimental Psychology Section B, 39*(1), 49-64. doi: 10.1080/14640748708402251

Chen, L., Lin, L.-H., Green, E., Barnes, C., & McNaughton, B. (1994). Head-direction cells in the rat posterior cortex. *Exp Brain Res, 101*(1), 8-23. doi: 10.1007/BF00243212

Chen, L. L., Lin, L. H., Barnes, C. A., & McNaughton, B. L. (1994). Head-direction cells in the rat posterior cortex. II. Contributions of visual and ideothetic information to the directional firing. *Exp Brain Res, 101*(1), 24-34.

Chernetsov, N., Kishkinev, D., & Mouritsen, H. (2008). A long-distance avian migrant compensates for longitudinal displacement during spring migration. *Curr Biol, 18*(3), 188-190. doi: 10.1016/j.cub.2008.01.018

Cheung, A. (2014). Estimating Location without External Cues. *PLoS Comput Biol, 10*(10), e1003927. doi: 10.1371/journal.pcbi.1003927

Chittka, L., & Geiger, K. (1995). Can honey bees count landmarks? *Animal Behaviour, 49*(1), 159-164. doi: http://dx.doi.org/10.1016/0003-3472(95)80163-4

Clark, B. J., Bassett, J. P., Wang, S. S., & Taube, J. S. (2010). Impaired head direction cell representation in the anterodorsal thalamus after lesions of the retrosplenial cortex. *J Neurosci, 30*(15), 5289-5302. doi: 10.1523/jneurosci.3380-09.2010

Clark, B. J., & Taube, J. S. (2011). Intact landmark control and angular path integration by head direction cells in the anterodorsal thalamus after lesions of the medial entorhinal cortex. *Hippocampus, 21*(7), 767-782. doi: 10.1002/hipo.20874

Clark, B. J., & Taube, J. S. (2012). Vestibular and attractor network basis of the head direction cell signal in subcortical circuits. *Front Neural Circuits, 6*, 7. doi: 10.3389/fncir.2012.00007

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, N.J.: L. Erlbaum Associates.

Cohen, N. J., & Eichenbaum, H. (1995). *Memory, Amnesia, and the Hippocampal System*: MIT Press.

Cohen, N. J., & Squire, L. R. (1981). Retrograde amnesia and remote memory impairment. *Neuropsychologia, 19*(3), 337-356.

Colgin, L. L., Moser, E. I., & Moser, M. B. (2008). Understanding memory through hippocampal remapping. *Trends Neurosci, 31*(9), 469-477. doi: 10.1016/j.tins.2008.06.008

Collett, T. S., Cartwright, B. A., & Smith, B. A. (1986). Landmark learning and visuo-spatial memories in gerbils. *Journal of Comparative Physiology A, 158*(6), 835-851. doi: 10.1007/BF01324825

Collett, T. S., & Collett, M. (2002). Memory use in insect visual navigation. *Nat Rev Neurosci, 3*(7), 542-552.

Collett, T. S., Graham, P., Harris, R. A., & Hempel-De-Ibarra, N. (2006). Navigational memories in ants and bees: memory retrieval when selecting and following routes. *Advances in the study of behavior., 36*, 123-172. doi: 10.1016/s0065-3454(06)36003-2

Collett, T. S., & Kelber, A. (1988). The retrieval of visuo-spatial memories by honeybees. *Journal of Comparative Physiology A, 163*(1), 145-150.

Collett, T. S., & Lehrer, M. (1993). Looking and Learning: A Spatial Pattern in the Orientation Flight of the Wasp Vespula vulgaris. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 252*(1334), 129-134. doi: 10.1098/rspb.1993.0056

Collett, T. S., & Rees, J. A. (1997). View-based navigation in Hymenoptera: multiple strategies of landmark guidance in the approach to a feeder. *Journal of Comparative Physiology A, 181*(1), 47-58. doi: 10.1007/s003590050092

Coras, R., Pauli, E., Li, J., Schwarz, M., Rossler, K., Buchfelder, M., Hamer, H., Stefan, H., & Blumcke, I. (2014). Differential influence of hippocampal subfields to memory formation: insights from patients with temporal lobe epilepsy. *Brain, 137*(Pt 7), 1945-1957. doi: 10.1093/brain/awu100

Cordeau, J. P., & Mahut, H. (1964). Some long-term effects of temporal lobe resections on auditory and visual discrimination in monkeys. *Brain, 87*, 177-190.

Corkin, S. (1979). Hidden-figures-test performance: lasting effects of unilateral penetrating head injury and transient effects of bilateral cingulotomy. *Neuropsychologia, 17*(6), 585-605.

Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in case HM. *Seminars in Neurology, 4*, 249-258.

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nat Rev Neurosci, 3*(2), 153-160.

Corkin, S., Amaral, D. G., Gonzalez, R. G., Johnson, K. A., & Hyman, B. T. (1997). H. M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. *J Neurosci, 17*(10), 3964-3979.

Corlett, J. T., Patla, A. E., & Williams, J. G. (1985). Locomotor estimation of distance after visual scanning by children and adults. *Perception, 14*(3), 257-263.

Correll, R. E., & Scoville, W. B. (1967). Significance of delay in the performance of monkeys with medial temporal lobe resections. *Exp Brain Res, 4*(1), 85-96. doi: 10.1007/BF00235220

Cressant, A., Muller, R. U., & Poucet, B. (1997). Failure of centrally placed objects to control the firing fields of hippocampal place cells. *J Neurosci, 17*(7), 2531-2542.

Cruse, H., & Wehner, R. (2011). No Need for a Cognitive Map: Decentralized Memory for Insect Navigation. *PLoS Comput Biol, 7*(3), e1002009. doi: 10.1371/journal.pcbi.1002009

D'Hooge, R., & De Deyn, P. P. (2001). Applications of the Morris water maze in the study of learning and memory. *Brain Res Brain Res Rev, 36*(1), 60-90.

Dacke, M., Baird, E., Byrne, M., Scholtz, Clarke H., & Warrant, Eric J. (2013). Dung Beetles Use the Milky Way for Orientation. *Current Biology, 23*(4), 298-300. doi: 10.1016/j.cub.2012.12.034

Dacke, M., Byrne, M. J., Baird, E., Scholtz, C. H., & Warrant, E. J. (2011). How dim is dim? Precision of the celestial compass in moonlight and sunlight. *Philos Trans R Soc Lond B Biol Sci, 366*(1565), 697-702. doi: 10.1098/rstb.2010.0191

Dacke, M., Nilsson, D.-E., Scholtz, C. H., Byrne, M., & Warrant, E. J. (2003). Animal behaviour: Insect orientation to polarized moonlight. *Nature, 424*(6944), 33-33.

Dacke, M., & Srinivasan, M. (2008). Evidence for counting in insects. *Animal Cognition, 11*(4), 683-689. doi: 10.1007/s10071-008-0159-y

Daw, N. D., Niv, Y., & Dayan, P. (2005). Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. *Nat Neurosci, 8*(12), 1704-1711. doi: http://www.nature.com/neuro/journal/v8/n12/suppinfo/nn1560_S1.html

de Almeida, L., Idiart, M., & Lisman, J. E. (2009). The input-output transformation of the hippocampal granule cells: from grid cells to place fields. *J Neurosci, 29*(23), 7504-7512. doi: 10.1523/jneurosci.6048-08.2009

De Camp, J. E. (1920). Relative distance as a factor in the white rat's selection of a path. *Psychobiology, 2*(3), 245-253. doi: 10.1037/h0075411

de Croissant de Garengeot, R. C. (1742). *Splanchnologie ou L'anatomie des viscères*: Osmont.

de Ibarra, N. H., Philippides, A., Riabinina, O., & Collett, T. S. (2009). Preferred viewing directions of bumblebees (Bombus terrestris L.) when learning and approaching their nest site. *J Exp Biol, 212*(Pt 20), 3193-3204. doi: 10.1242/jeb.029751

Derdikman, D., & Moser, M.-B. (2010). A Dual Role for Hippocampal Replay. *Neuron, 65*(5), 582-584. doi: 10.1016/j.neuron.2010.02.022

Derdikman, D., Whitlock, J. R., Tsao, A., Fyhn, M., Hafting, T., Moser, M. B., & Moser, E. I. (2009). Fragmentation of grid cell maps in a multicompartment environment. *Nat Neurosci, 12*(10), 1325-1332. doi: 10.1038/nn.2396

Deutsch, J. A. (1956). The inadequacy of Hullian derivations of reasoning and latent learning. *Psychol Rev, 63*(6), 389-399.

Deutsch, J. A. (1983). *The Physiological Basis of Memory*: Elsevier Science.

Devan, B. D., & White, N. M. (1999). Parallel Information Processing in the Dorsal Striatum: Relation to Hippocampal Function. *The Journal of Neuroscience, 19*(7), 2789-2798.

Dickson, C. T., Magistretti, J., Shalinsky, M., Hamam, B., & Alonso, A. (2000). Oscillatory activity in entorhinal neurons and circuits. Mechanisms and function. *Ann N Y Acad Sci, 911*, 127-150.

Diwadkar, V. A., & McNamara, T. P. (1997). Viewpoint Dependence in Scene Recognition. *Psychological Science, 8*(4), 302-307. doi: 10.1111/j.1467-9280.1997.tb00442.x

Dolorfo, C. L., & Amaral, D. G. (1998). Entorhinal cortex of the rat: topographic organization of the cells of origin of the perforant path projection to the dentate gyrus. *J Comp Neurol, 398*(1), 25-48.

Drachman, D. A., & Arbit, J. (1966). Memory and the hippocampal complex. II. Is memory a multiple process? *Arch Neurol, 15*(1), 52-61.

Dudchenko, P. A., & Zinyuk, L. E. (2005). The formation of cognitive maps of adjacent environments: evidence from the head direction cell system. *Behav Neurosci, 119*(6), 1511-1523. doi: 10.1037/0735-7044.119.6.1511

Dupret, D., O'Neill, J., Pleydell-Bouverie, B., & Csicsvari, J. (2010). The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nat Neurosci, 13*(8), 995-1002. doi: http://www.nature.com/neuro/journal/v13/n8/abs/nn.2599.html#supplementary-information

Duvernoy, H. M. (2005). *The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI*: Springer.

Dyer, A. G., & Vuong, Q. C. (2008). Insect Brains Use Image Interpolation Mechanisms to Recognise Rotated Objects. *PLoS ONE, 3*(12), e4086. doi: 10.1371/journal.pone.0004086

Dyer, F. C. (1991). Bees acquire route-based memories but not cognitive maps in a familiar landscape. *Animal Behaviour, 41*(2), 239-246. doi: http://dx.doi.org/10.1016/S0003-3472(05)80475-0

Dyer, F. C., & Seeley, T. D. (1989). On the Evolution of the Dance Language. *The American Naturalist, 133*(4), 580-590. doi: 10.2307/2462091

Eichenbaum, H., & Cohen, J. (2001). *From Conditioning to Conscious Recollection : Memory Systems of the Brain: Memory Systems of the Brain*: Oxford University Press, USA.

Eichenbaum, H., & Cohen, N. J. (1988). Representation in the hippocampus: what do hippocampal neurons code? *Trends in Neurosciences, 11*(6), 244-248. doi: http://dx.doi.org/10.1016/0166-2236(88)90100-2

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., & Tanila, H. (1999). The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron, 23*(2), 209-226.

Eichenbaum, H., Kuperstein, M., Fagan, A., & Nagode, J. (1987). Cue-sampling and goal-approach correlates of hippocampal unit activity in rats performing an odor-discrimination task. *J Neurosci, 7*(3), 716-732.

Eichenbaum, H., Stewart, C., & Morris, R. G. (1990). Hippocampal representation in place learning. *J Neurosci, 10*(11), 3531-3542.

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature, 425*(6954), 184-188. doi: http://www.nature.com/nature/journal/v425/n6954/suppinfo/nature01964_S1.html

Elliott, D. (1986). Continuous visual information may be important after all: A failure to replicate Thomson (1983). *Journal of Experimental Psychology: Human Perception and Performance, 12*(3), 388-391. doi: 10.1037/0096-1523.12.3.388

Ennaceur, A. (2010). One-trial object recognition in rats and mice: methodological and theoretical issues. *Behav Brain Res, 215*(2), 244-254. doi: 10.1016/j.bbr.2009.12.036

Esch, H. E., & Burns, J. E. (1995). Honeybees use optic flow to measure the distance of a food source. *Naturwissenschaften, 82*(1), 38-40. doi: 10.1007/bf01167870

Estes, W. K. (1954). *Modern learning theory, a critical analysis of five examples*. New York,: Appleton-Century-Crofts.

Etienne, A., Maurer, R., & Saucy, F. (1988). Limitations in the assessment of path dependent information. *Behaviour, 106*(1/2), 81-111.

Etienne, A. S., & Jeffery, K. J. (2004). Path integration in mammals. *Hippocampus, 14*(2), 180-192. doi: 10.1002/hipo.10173

Etienne, A. S., Maurer, R., Berlie, J., Reverdin, B., Rowe, T., Georgakopoulos, J., & Seguinot, V. (1998). Navigation through vector addition. *Nature, 396*(6707), 161-164. doi: 10.1038/24151

Evans, J. S. (2008). Dual-processing accounts of reasoning, judgment, and social cognition. *Annu Rev Psychol, 59*, 255-278. doi: 10.1146/annurev.psych.59.103006.093629

Fajen, B. R., & Matthis, J. S. (2013). Visual and Non-Visual Contributions to the Perception of Object Motion during Self-Motion. *PLoS ONE, 8*(2), e55446. doi: 10.1371/journal.pone.0055446

Fanselow, M. S. (1986). Associative vs topographical accounts of the immediate shock-freezing deficit in rats: Implications for the response selection rules governing species-specific defensive reactions. *Learning and Motivation, 17*(1), 16-39. doi: http://dx.doi.org/10.1016/0023-9690(86)90018-4

Feigenbaum, J. D., Polkey, C. E., & Morris, R. G. (1996). Deficits in spatial working memory after unilateral temporal lobectomy in man. *Neuropsychologia, 34*(3), 163-176.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex, 1*(1), 1-47.

Fenton, A. A., Csizmadia, G., & Muller, R. U. (2000). Conjoint Control of Hippocampal Place Cell Firing by Two Visual Stimuli: I. the Effects of Moving the Stimuli on Firing Field Positions. *The Journal of General Physiology, 116*(2), 191-210.

Ferbinteanu, J., Holsinger, R. M., & McDonald, R. J. (1999). Lesions of the medial or lateral perforant path have different effects on hippocampal contributions to place learning and on fear conditioning to context. *Behav Brain Res, 101*(1), 65-84.

Ferbinteanu, J., & Shapiro, M. L. (2003). Prospective and retrospective memory coding in the hippocampus. *Neuron, 40*(6), 1227-1239.

Ferbinteanu, J., Shirvalkar, P., & Shapiro, M. L. (2011). Memory modulates journey-dependent coding in the rat hippocampus. *J Neurosci, 31*(25), 9135-9146. doi: 10.1523/jneurosci.1241-11.2011

Ferguson, D. E., Landreth, H. F., & Turnipseed, M. R. (1965). Astronomical orientation of the southern cricket frog, Acris gryllus. *Copeia, 1*(58-66).

Fermin, A., Yoshida, T., Ito, M., Yoshimoto, J., & Doya, K. (2010). Evidence for model-based action planning in a sequential finger movement task. *J Mot Behav, 42*(6), 371-379. doi: 10.1080/00222895.2010.526467

Ferry, A. T., Ongur, D., An, X., & Price, J. L. (2000). Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. *J Comp Neurol, 425*(3), 447-470.

Flynn, J. P., & Wasman, M. (1960). Learning and cortically evoked movement during propagated hippocampal afterdischarges. *Science, 131*, 1607-1608. doi: 10.1126/science.131.3413.1607

Foster, D. J., & Knierim, J. J. (2012). Sequence learning and the role of the hippocampus in rodent navigation. *Curr Opin Neurobiol, 22*(2), 294-300. doi: 10.1016/j.conb.2011.12.005

Foster, D. J., & Wilson, M. A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature, 440*(7084), 680-683. doi: http://www.nature.com/nature/journal/v440/n7084/suppinfo/nature04587_S1.html

Fox, S. E., & Ranck Jr, J. B. (1975). Localization and anatomical identification of theta and complex spike cells in dorsal hippocampal formation of rats. *Exp Neurol, 49*(1), 299-313. doi: http://dx.doi.org/10.1016/0014-4886(75)90213-7

Frank, L. M., Brown, E. N., & Wilson, M. (2000a). Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron, 27*(1), 169-178.

Frank, L. M., Brown, E. N., & Wilson, M. (2000b). Trajectory Encoding in the Hippocampus and Entorhinal Cortex. *Neuron, 27*(1), 169-178. doi: 10.1016/S0896-6273(00)00018-0

Frankland, P. W., Cestari, V., Filipkowski, R. K., McDonald, R. J., & Silva, A. J. (1998). The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. *Behav Neurosci, 112*(4), 863-874.

Freeman, J. H., Jr., Weible, A., Rossi, J., & Gabriel, M. (1997). Lesions of the entorhinal cortex disrupt behavioral and neuronal responses to context change during extinction of discriminative avoidance behavior. *Exp Brain Res, 115*(3), 445-457.

Frisch, K. v. (1950). Die Sonne als Kompaß im Leben der Bienen. *Experientia, 6*(6), 210-221. doi: 10.1007/BF02173654

Frisch, K. v. (1965). *Tanzsprache und Orientierung der Bienen*. Berlin, New York,: Springer-Verlag.

Frisch, K. v. (1967). *The dance language and orientation of bees*. Cambridge, Mass.: Belknap Press of Harvard University Press.

Fuhs, M. C., & Touretzky, D. S. (2006). A spin glass model of path integration in rat medial entorhinal cortex. *J Neurosci, 26*(16), 4266-4276. doi: 10.1523/jneurosci.4353-05.2006

Fuhs, M. C., Vanrhoads, S. R., Casale, A. E., McNaughton, B., & Touretzky, D. S. (2005). Influence of path integration versus environmental orientation on place cell remapping between visually identical environments. *J Neurophysiol, 94*(4), 2603-2616. doi: 10.1152/jn.00132.2005

Fukusima, S. S., Loomis, J. M., & Da Silva, J. A. (1997). Visual perception of egocentric distance as assessed by triangulation. *Journal of Experimental Psychology: Human Perception and Performance, 23*(1), 86-100. doi: 10.1037/0096-1523.23.1.86

Fyhn, M., Hafting, T., Treves, A., Moser, M.-B., & Moser, E. I. (2007). Hippocampal remapping and grid realignment in entorhinal cortex. *Nature, 446*(7132), 190-194. doi: http://www.nature.com/nature/journal/v446/n7132/suppinfo/nature05601_S1.html

Fyhn, M., Hafting, T., Treves, A., Moser, M. B., & Moser, E. I. (2005). Preserved spatial and temporal firing structure in entorhinal grid cells during remapping in the hippocampus. *Soc. Neurosci. Abstr, 198.6*.

Fyhn, M., Molden, S., Witter, M. P., Moser, E. I., & Moser, M.-B. (2004). Spatial Representation in the Entorhinal Cortex. *Science, 305*(5688), 1258-1264. doi: 10.1126/science.1099901

Gabrieli, J. D., Cohen, N. J., & Corkin, S. (1988). The impaired learning of semantic knowledge following bilateral medial temporal-lobe resection. *Brain Cogn, 7*(2), 157-177.

Gaffan, D. (1974). Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *Journal of Comparative and Physiological Psychology, 86*(6), 1100-1109. doi: 10.1037/h0037649

Galani, R., Weiss, I., Cassel, J. C., & Kelche, C. (1998). Spatial memory, habituation, and reactions to spatial and nonspatial changes in rats with selective lesions of the hippocampus, the entorhinal cortex or the subiculum. *Behav Brain Res, 96*(1-2), 1-12.

Galanter, E., & Shaw, W. A. (1954). Cue vs. reactive inhibition in place and response learning. *J Comp Physiol Psychol, 47*(5), 395-398.

Gao, J., Wu, Y., Zhu, Z., Yang, C., Cheng, P., Liu, L., & Sui, J. (2010). Neuronal firing activity of hippocampal pyramidal cells during an auditory discrimination task in conscious guinea pigs. *Behav Brain Res, 212*(1), 35-40. doi: 10.1016/j.bbr.2010.03.031

Garber, P. A. (1988). Foraging decisions during nectar feeding by tamarin monkeys (Saguinus mystax and Saguinus fuscicollis, Callitrichidae, Primates) in Amazonian Peru. *Biotropica, 20*(2), 100-106.

Gaussier, P., Revel, A., Banquet, J. P., & Babeau, V. (2002). From view cells and place cells to cognitive map learning: processing stages of the hippocampal system. *Biol Cybern, 86*(1), 15-28.

Gentry, G., Brown, W. L., & Kaplan, S. J. (1947). An experimental analysis of the spatial location hypothesis in learning. *J Comp Physiol Psychol, 40*(5), 309-322.

Gentry, G., Brown, W. L., & Lee, H. (1948). Spatial Location in the Learning of a Multiple-T Maze. *J Comp Physiol Psychol, 41*(5), 312-318.

Georges-François, P., Rolls, E. T., & Robertson, R. G. (1999). Spatial View Cells in the Primate Hippocampus: Allocentric View not Head Direction or Eye Position or Place. *Cerebral Cortex, 9*(3), 197-212. doi: 10.1093/cercor/9.3.197

Gibson, B., Butler, W. N., & Taube, J. S. (2013). The head-direction signal is critical for navigation requiring a cognitive map but not for learning a spatial habit. *Curr Biol, 23*(16), 1536-1540. doi: 10.1016/j.cub.2013.06.030

Gibson, B. M. (2001). Cognitive maps not used by humans (Homo sapiens) during a dynamic navigational task. *J Comp Psychol, 115*(4), 397-402.

Gilroy, K. E., & Pearce, J. M. (2014). The role of local, distal, and global information in latent spatial learning. *J Exp Psychol Anim Learn Cogn, 40*(2), 212-224. doi: 10.1037/xan0000017

Giocomo, L. M., Stensola, T., Bonnevie, T., Van Cauter, T., Moser, M. B., & Moser, E. I. (2014). Topography of head direction cells in medial entorhinal cortex. *Curr Biol, 24*(3), 252-262. doi: 10.1016/j.cub.2013.12.002

Girardeau, G., Benchenane, K., Wiener, S. I., Buzsaki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. *Nat Neurosci, 12*(10), 1222-1223. doi: 10.1038/nn.2384

Glasauer, S., Amorim, M. A., Vitte, E., & Berthoz, A. (1994). Goal-directed linear locomotion in normal and labyrinthine-defective subjects. *Exp Brain Res, 98*(2), 323-335.

Godden, D. R., & Baddeley, A. D. (1975). Context-dependent memory in two natural environments: on land and underwater. *British Journal of Psychology, 66*(3), 325-331. doi: 10.1111/j.2044-8295.1975.tb01468.x

Golob, E. J., & Taube, J. S. (1999). Head Direction Cells in Rats with Hippocampal or Overlying Neocortical Lesions: Evidence for Impaired Angular Path Integration. *The Journal of Neuroscience, 19*(16), 7198-7211.

Gomez-Laplaza, L. M., & Gerlai, R. (2010). Latent learning in zebrafish (Danio rerio). *Behav Brain Res, 208*(2), 509-515. doi: 10.1016/j.bbr.2009.12.031

Goodridge, J. P., & Taube, J. S. (1995). Preferential Use of the Landmark Navigational System by Head Direction Cells in Rats. *Behavioural Neuroscience, 109*(1), 49-61.

Goodridge, J. P., & Taube, J. S. (1997). Interaction between the postsubiculum and anterior thalamus in the generation of head direction cell activity. *J Neurosci, 17*(23), 9315-9330.

Gothard, K. M., Skaggs, W. E., & McNaughton, B. L. (1996). Dynamics of mismatch correction in the hippocampal ensemble code for space: interaction between path integration and environmental cues. *J Neurosci, 16*(24), 8027-8040.

Gothard, K. M., Skaggs, W. E., Moore, K. M., & McNaughton, B. L. (1996). Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. *J Neurosci, 16*(2), 823-835.

Gould, J. L. (1986a). The Biology of Learning. *Annual Review of Psychology, 37*(1), 163-192. doi: doi:10.1146/annurev.ps.37.020186.001115

Gould, J. L. (1986b). The locale map of honey bees: do insects have cognitive maps? *Science, 232*(4752), 861-863. doi: 10.1126/science.232.4752.861

Gould, J. L. (1990). Honey bee cognition. *Cognition, 37*(1-2), 83-103.

Gould, J. L., & Gould, C. G. (1982). The insect mind: Physics or metaphysics? In D. R. Griffin (Ed.), *Animal Mind -- Human Mind*: Springer-Verlag.

Gould, J. L., & Gould, C. G. (1994). *The Animal Mind*: Scientific American Library.

Gould, J. L., & Gould, C. G. (1995). *The Honey Bee*: Scientific American Library.

Gould, J. L., & Towne, W. F. (1989). On the Evolution of the Dance Language: Response to Dyer and Seeley. *The American Naturalist, 134*(1), 156-159. doi: 10.2307/2462282

Graham, P., & Cheng, K. (2009). Ants use the panoramic skyline as a visual cue during navigation. *Current Biology, 19*(20), R935-R937. doi: http://dx.doi.org/10.1016/j.cub.2009.08.015

Graham, P., Fauria, K., & Collett, T. S. (2003). The influence of beacon-aiming on the routes of wood ants. *J Exp Biol, 206*(Pt 3), 535-541.

Gray, C. M., Maldonado, P. E., Wilson, M., & McNaughton, B. (1995). Tetrodes markedly improve the reliability and yield of multiple single-unit isolation from multi-unit recordings in cat striate cortex. *J Neurosci Methods, 63*(1-2), 43-54.

Grieves, R. M., & Dudchenko, P. A. (2013). Cognitive maps and spatial inference in animals: Rats fail to take a novel shortcut, but can take a previously experienced one. *Learning and Motivation, 44*(2), 81-92. doi: http://dx.doi.org/10.1016/j.lmot.2012.08.001

Griffin, A. L., Eichenbaum, H., & Hasselmo, M. E. (2007). Spatial representations of hippocampal CA1 neurons are modulated by behavioral context in a hippocampus-dependent memory task. *J Neurosci, 27*(9), 2416-2423. doi: 10.1523/jneurosci.4083-06.2007

Griffin, A. L., & Hallock, H. L. (2013). Hippocampal signatures of episodic memory: Evidence from single-unit recording studies. *Front Behav Neurosci, 7*. doi: 10.3389/fnbeh.2013.00054

Guanella, A., & Verschure, P. M. J. (2006). A Model of Grid Cells Based on a Path Integration Mechanism. In S. Kollias, A. Stafylopatis, W. Duch & E. Oja (Eds.), *Artificial Neural Networks – ICANN 2006* (Vol. 4131, pp. 740-749): Springer Berlin Heidelberg.

Gundry, A. J. (1978). Thresholds of perception for periodic linear motion. *Aviation Space and Environmental Medicine, 49*(5), 679-686.

Hafting, T., Fyhn, M., Bonnevie, T., Moser, M.-B., & Moser, E. I. (2008). Hippocampus-independent phase precession in entorhinal grid cells. *Nature, 453*(7199), 1248-1252. doi: http://www.nature.com/nature/journal/v453/n7199/suppinfo/nature06957_S1.html

Hafting, T., Fyhn, M., Molden, S., Moser, M.-B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature, 436*(7052), 801-806. doi: http://www.nature.com/nature/journal/v436/n7052/suppinfo/nature03721_S1.html

Hagan, J. J., Verheijck, E. E., Spigt, M. H., & Ruigt, G. S. (1992). Behavioural and electrophysiological studies of entorhinal cortex lesions in the rat. *Physiol Behav, 51*(2), 255-266.

Haith, A. M., & Krakauer, J. W. (2013). Model-Based and Model-Free Mechanisms of Human Motor Learning. *Advances in experimental medicine and biology, 782*, 1-21. doi: 10.1007/978-1-4614-5465-6_1

Hamilton, D. A., Rosenfelt, C. S., & Whishaw, I. Q. (2004). Sequential control of navigation by locale and taxon cues in the Morris water task. *Behavioural Brain Research, 154*(2), 385-397. doi: http://dx.doi.org/10.1016/j.bbr.2004.03.005

Hampson, R. E., Heyser, C. J., & Deadwyler, S. A. (1993). Hippocampal cell firing correlates of delayed-match-to-sample performance in the rat. *Behav Neurosci, 107*(5), 715-739.

Harris, A. P., D'Eath, R. B., & Healy, S. D. (2009). Environmental enrichment enhances spatial cognition in rats by reducing thigmotaxis (wall hugging) during testing. *Animal Behaviour, 77*(6), 1459-1464. doi: http://dx.doi.org/10.1016/j.anbehav.2009.02.019

Harris, L. R., Jenkin, M., & Zikovitz, D. C. (2000). Visual and non-visual cues in the perception of linear self-motion. *Exp Brain Res, 135*(1), 12-21.

Harrison, D. J. F. A. K. P. G. S. (2004). Martens and Fishers (Martes) in human-altered environments an international perspective. from http://dx.doi.org/10.1007/b99487

Hartley, T., Burgess, N., Lever, C., Cacucci, F., & O'Keefe, J. (2000). Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus, 10*(4), 369-379.

Hartman, H. B. (1979). Receptors signaling gravity orientation in an insect. *Physiologist, 22*(6), S49-50.

Harvey, D. R., Brant, L., & Commins, S. (2009). Differences in cue-dependent spatial navigation may be revealed by in-depth swimming analysis. *Behavioural Processes, 82*(2), 190-197. doi: http://dx.doi.org/10.1016/j.beproc.2009.06.008

Hasselmo, M. E., & Eichenbaum, H. (2005). Hippocampal mechanisms for the context-dependent retrieval of episodes. *Neural Netw, 18*(9), 1172-1190. doi: 10.1016/j.neunet.2005.08.007

Hayman, R. M., Chakraborty, S., Anderson, M. I., & Jeffery, K. J. (2003). Context-specific acquisition of location discrimination by hippocampal place cells. *Eur J Neurosci, 18*(10), 2825-2834.

Hayman, R. M., & Jeffery, K. J. (2008). How heterogeneous place cell responding arises from homogeneous grids--a contextual gating hypothesis. *Hippocampus, 18*(12), 1301-1313. doi: 10.1002/hipo.20513

Hazan, L., Zugaro, M., & Buzsaki, G. (2006). Klusters, NeuroScope, NDManager: a free software suite for neurophysiological data processing and visualization. *J Neurosci Methods, 155*(2), 207-216. doi: 10.1016/j.jneumeth.2006.01.017

Hazen, N. L., Lockman, J. J., & Pick, H. L., Jr. (1978). The Development of Children's Representations of Large-Scale Environments. *Child Development, 49*(3), 623-636. doi: 10.2307/1128229

Henze, D. A., Borhegyi, Z., Csicsvari, J., Mamiya, A., Harris, K. D., & Buzsaki, G. (2000). Intracellular features predicted by extracellular recordings in the hippocampus in vivo. *J Neurophysiol, 84*(1), 390-400.

Heran, H. (1956). Ein Beitrag zur Frage nach der Wahrnehmungsgrundlage der Entfernungsweisung der Bienen (Apis mellifica L.). *Zeitschrift für vergleichende Physiologie, 38*(1-2), 168-218. doi: 10.1007/bf00338625

Hill, A. J. (1978). First occurrence of hippocampal spatial firing in a new environment. *Exp Neurol, 62*(2), 282-297.

Hill, A. J., & Best, P. J. (1981). Effects of deafness and blindness on the spatial correlates of hippocampal unit activity in the rat. *Exp Neurol, 74*(1), 204-217. doi: http://dx.doi.org/10.1016/0014-4886(81)90159-X

Hill, A. J., & Biology, C. I. o. T. D. o. (1979). *Investigations of "spatial" Firing in Dorsal Hippocampus of the Rat*: California Institute of Technology.

Hill, C. W., & Thune, L. E. (1952). Place and response learning in the white rat under simplified and mutually isolated conditions. *Journal of Experimental Psychology, 43*(4), 289-297. doi: 10.1037/h0060647

Hogarth, L., Roberts, W., Roberts, S., & Abroms, B. (2000). Spatial localization of a goal: Beacon homing and landmark piloting by rats on a radial maze. *Animal Learning & Behavior, 28*(1), 43-58. doi: 10.3758/BF03199771

Hok, V., Chah, E., Save, E., & Poucet, B. (2013). Prefrontal cortex focally modulates hippocampal place cell firing patterns. *J Neurosci, 33*(8), 3443-3451. doi: 10.1523/jneurosci.3427-12.2013

Hok, V., Lenck-Santini, P. P., Roux, S., Save, E., Muller, R. U., & Poucet, B. (2007). Goal-related activity in hippocampal place cells. *J Neurosci, 27*(3), 472-482. doi: 10.1523/jneurosci.2864-06.2007

Hok, V., Save, E., Lenck-Santini, P. P., & Poucet, B. (2005). Coding for spatial goals in the prelimbic/infralimbic area of the rat frontal cortex. *Proc Natl Acad Sci U S A, 102*(12), 4602-4607. doi: 10.1073/pnas.0407332102

Holland, R., Thorup, K., Gagliardo, A., Bisson, I. A., Knecht, E., Mizrahi, D., & Wikelski, M. (2009). Testing the role of sensory systems in the migratory heading of a songbird.

Hollup, S. A., Molden, S., Donnett, J. G., Moser, M. B., & Moser, E. I. (2001). Accumulation of hippocampal place fields at the goal location in an annular watermaze task. *J Neurosci, 21*(5), 1635-1644.

Holscher, C., Jacob, W., & Mallot, H. A. (2003). Reward modulates neuronal activity in the hippocampus of the rat. *Behav Brain Res, 142*(1-2), 181-191.

Honzik, C. H. (1936). The sensory basis of maze learning in rats. *Comparative Psychology Monographs, 13*, 113.

Horn, E. (1975). The contribution of different receptors to gravity orientation in insects. *Fortschr Zool, 23*(1), 1-20.

Horne, M. R., Gilroy, K. E., Cuell, S. F., & Pearce, J. M. (2012). Latent spatial learning in an environment with a distinctive shape. *J Exp Psychol Anim Behav Process, 38*(2), 139-147. doi: 10.1037/a0027288

Hoydal, M. A., Wisloff, U., Kemi, O. J., & Ellingsen, O. (2007). Running speed and maximal oxygen uptake in rats and mice: practical implications for exercise training. *Eur J Cardiovasc Prev Rehabil, 14*(6), 753-760. doi: 10.1097/HJR.0b013e3281eacef1

Hu, D., & Amsel, A. (1995). A simple test of the vicarious trial-and-error hypothesis of hippocampal function. *Proc Natl Acad Sci U S A, 92*(12), 5506-5509.

Hu, D., Xu, X., & Gonzalez-Lima, F. (2005). Hippocampal cytochrome oxidase activity of rats in easy and difficult visual discrimination learning. *Int J Neurosci, 115*(5), 595-611. doi: 10.1080/00207450590523440

Hudson, B. B. (1950). One-trial learning in the domestic rat. *Genet Psychol Monogr, 41*(First Half), 99-145.

Hull, C. L. (1950). Behavior postulates and corollaries--1949. *Psychol Rev, 57*(3), 173-180.

Hunsaker, M. R., Mooy, G. G., Swift, J. S., & Kesner, R. P. (2007). Dissociations of the medial and lateral perforant path projections into dorsal DG, CA3, and CA1 for spatial and nonspatial (visual object) information processing. *Behav Neurosci, 121*(4), 742-750. doi: 10.1037/0735-7044.121.4.742

Hunter, W. S. (1920). The temporal maze and kinaesthetic sensory processes in the white rat. *Psychobiology, 2*(1), 1-17. doi: 10.1037/h0073855

Hussein, A. A. W., & George, N. T. (2009). Histological and Morphological Analysis of the Hippocampal Subfields in the Adult Rat. *J Fac Med Baghdad, 51*(3).

Isaacson, R. L. (1972). Hippocampal destruction in man and other animals. *Neuropsychologia, 10*(1), 47-64. doi: http://dx.doi.org/10.1016/0028-3932(72)90042-5

Islam, T., & Fukuzaki, R. (2010). A Model of Path Integration and Navigation Based on Head Direction Cells in Entorhinal Cortex. In K. Wong, B. S. Mendis & A. Bouzerdoum (Eds.), *Neural Information Processing. Theory and Algorithms* (Vol. 6443, pp. 82-90): Springer Berlin Heidelberg.

Israel, I., & Berthoz, A. (1989). Contribution of the otoliths to the calculation of linear displacement. *J Neurophysiol, 62*(1), 247-263.

Israel, I., Chapuis, N., Glasauer, S., Charade, O., & Berthoz, A. (1993). Estimation of passive horizontal linear whole-body displacement in humans. *J Neurophysiol, 70*(3), 1270-1273.

Ivanenko, Y. P., Grasso, R., Israel, I., & Berthoz, A. (1997). The contribution of otoliths and semicircular canals to the perception of two-dimensional passive whole-body motion in humans. *J Physiol, 502 ( Pt 1)*, 223-233.

Jander, R. (1963). Insect Orientation. *Annual Review of Entomology, 8*(1), 95-114. doi: doi:10.1146/annurev.en.08.010163.000523

Janson, C. H., Terborgh, J., & Emmons, L. H. (1981). Non-Flying Mammals as Pollinating Agents in the Amazonian Forest. *Biotropica, 13*(2), 1-6. doi: 10.2307/2388065

Jarrard, L. E. (1983). Selective hippocampal lesions and behavior: effects of kainic acid lesions on performance of place and cue tasks. *Behav Neurosci, 97*(6), 873-889.

Jarrard, L. E. (1993). On the role of the hippocampus in learning and memory in the rat. *Behav Neural Biol, 60*(1), 9-26. doi: http://dx.doi.org/10.1016/0163-1047(93)90664-4

Jeneson, A., & Squire, L. R. (2012). Working memory, long-term memory, and medial temporal lobe function. *Learn Mem, 19*(1), 15-25. doi: 10.1101/lm.024018.111

Jensen, R. (2006). Behaviorism, latent learning, and cognitive maps: needed revisions in introductory psychology textbooks. *Behav Anal, 29*(2), 187-209.

Jin, X., & Costa, R. M. (2010). Start/Stop Signals Emerge in Nigrostriatal Circuits during Sequence Learning. *Nature, 466*(7305), 457-462. doi: 10.1038/nature09263

Jog, M. S., Kubota, Y., Connolly, C. I., Hillegaart, V., & Graybiel, A. M. (1999). Building neural representations of habits. *Science, 286*(5445), 1745-1749.

Johnson, A., & Redish, A. D. (2005). Hippocampal replay contributes to within session learning in a temporal difference reinforcement learning model. *Neural Netw, 18*(9), 1163-1171. doi: 10.1016/j.neunet.2005.08.009

Johnson, A., & Redish, A. D. (2007). Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. *J Neurosci, 27*(45), 12176-12189. doi: 10.1523/jneurosci.3761-07.2007

Jones, S. H., Gray, J. A., & Hemsley, D. R. (1990). The Kamin blocking effect, incidental learning and psychoticism. *Br J Psychol, 81 ( Pt 1)*, 95-109.

Kadir, S. N., Goodman, D. F. M., & Harris, K. D. (2013). High-dimensional cluster analysis with the Masked EM Algorithm. *arXiv:1309.2848 [q-bio.QM]*.

Kalman, R. E. (1960). A New Approach to Linear Filtering and Prediction Problems. *Transactions of the ASME--Journal of Basic Engineering, 82*(D), 35-45.

Karlsson, M. P., & Frank, L. M. (2008). Network dynamics underlying the formation of sparse, informative representations in the hippocampus. *J Neurosci, 28*(52), 14271-14281. doi: 10.1523/jneurosci.4261-08.2008

Karlsson, M. P., & Frank, L. M. (2009). Awake replay of remote experiences in the hippocampus. *Nat Neurosci, 12*(7), 913-918. doi: 10.1038/nn.2344

Kensinger, E. A., Ullman, M. T., & Corkin, S. (2001). Bilateral medial temporal lobe damage does not affect lexical or grammatical processing: evidence from amnesic patient H.M. *Hippocampus, 11*(4), 347-360. doi: 10.1002/hipo.1049

Kentros, C., Hargreaves, E., Hawkins, R. D., Kandel, E. R., Shapiro, M., & Muller, R. V. (1998). Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. *Science, 280*(5372), 2121-2126.

Kerr, K. M., Agster, K. L., Furtak, S. C., & Burwell, R. D. (2007). Functional neuroanatomy of the parahippocampal region: the lateral and medial entorhinal areas. *Hippocampus, 17*(9), 697-708. doi: 10.1002/hipo.20315

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science, 256*(5057), 675-677.

Kim, S., Sapiurka, M., Clark, R. E., & Squire, L. R. (2013). Contrasting effects on path integration after hippocampal damage in humans and rats. *Proc Natl Acad Sci U S A, 110*(12), 4732-4737. doi: 10.1073/pnas.1300869110

Kim, S. M., & Frank, L. M. (2009). Hippocampal Lesions Impair Rapid Learning of a Continuous Spatial Alternation Task. *PLoS ONE, 4*(5), e5494. doi: 10.1371/journal.pone.0005494

Kimble, D. P. (1968). Hippocampus and internal inhibition. *Psychological Bulletin, 70*(5), 285-295.

Klatzky, R. L., Loomis, J. M., Golledge, R. G., Cicinelli, J. G., Doherty, S., & Pellegrino, J. W. (1990). Acquisition of route and survey knowledge in the absence of vision. *J Mot Behav, 22*(1), 19-43.

Knaden, M., & Wehner, R. (2005). Nest mark orientation in desert ants Cataglyphis: what does it do to the path integrator? *Animal Behaviour, 70*(6), 1349-1354. doi: http://dx.doi.org/10.1016/j.anbehav.2005.03.030

Knierim, J. J. (2002). Dynamic interactions between local surface cues, distal landmarks, and intrinsic circuitry in hippocampal place cells. *J Neurosci, 22*(14), 6254-6264. doi: 20026608

Knierim, J. J., & Hamilton, D. A. (2011). Framing spatial cognition: neural representations of proximal and distal frames of reference and their roles in navigation. *Physiol Rev, 91*(4), 1245-1279. doi: 10.1152/physrev.00021.2010

Knierim, J. J., Kudrimoti, H. S., & McNaughton, B. L. (1995). Place cells, head direction cells, and the learning of landmark stability. *J Neurosci, 15*(3 Pt 1), 1648-1659.

Knierim, J. J., & Rao, G. (2003). Distal landmarks and hippocampal place cells: effects of relative translation versus rotation. *Hippocampus, 13*(5), 604-617. doi: 10.1002/hipo.10092

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273*(5280), 1399-1402.

Kobayashi, T., Tran, A. H., Nishijo, H., Ono, T., & Matsumoto, G. (2003). Contribution of hippocampal place cell activity to learning and formation of goal-directed navigation in rats. *Neuroscience, 117*(4), 1025-1035.

Koch, S. (1954). Clark Hull *Modern learning theory: A critical analysis of five examples* (pp. 1-176). East Norwalk, CT, US: Appleton-Century-Crofts.

Krapp, H. G. (2007). Polarization Vision: How Insects Find Their Way by Watching the Sky. *Current Biology, 17*(14), R557-R560. doi: http://dx.doi.org/10.1016/j.cub.2007.05.022

Krechevsky, I. (1932). *The genesis of "hypotheses" in rats*. Berkeley, Calif.: University of California Press.

Kruge, I. U., Waaga, T., Wernle, T., Moser, E. I., & Moser, M. B. (2014). Grid cells require experience with local boundaries during development. *Soc. Neurosci. Abstr, 94.01/SS21*.

Krupic, J., Bauza, M., Burton, S., Lever, C., & O'Keefe, J. (2014). How environment geometry affects grid cell symmetry and what we can learn from it. *Philosophical Transactions* *of the Royal Society B: Biological Sciences, 369*(1635), 20130188. doi: 10.1098/rstb.2013.0188

Kubie, J. L. (1984). A driveable bundle of microwires for collecting single-unit data from freely-moving rats. *Physiol Behav, 32*(1), 115-118.

Kubie, J. L., & Fenton, A. A. (2009). Heading-vector navigation based on head-direction cells and path integration. *Hippocampus, 19*(5), 456-479. doi: 10.1002/hipo.20532

Lackner, J. R., & DiZio, P. (2005). Vestibular, Proprioceptive, and Haptic Contributions to Spatial Orientation. *Annual Review of Psychology, 56*(1), 115-147. doi: doi:10.1146/annurev.psych.55.090902.142023

Lamprea, M. R., Cardenas, F. P., Setem, J., & Morato, S. (2008). Thigmotactic responses in an open-field. *Braz J Med Biol Res, 41*(2), 135-140.

Landgraf, T., Rojas, R., Nguyen, H., Kriegel, F., & Stettin, K. (2011). Analysis of the Waggle Dance Motion of Honeybees for the Design of a Biomimetic Honeybee Robot. *PLoS ONE, 6*(8), e21354. doi: 10.1371/journal.pone.0021354

Langston, R. F., Ainge, J. A., Couey, J. J., Canto, C. B., Bjerknes, T. L., Witter, M. P., Moser, E. I., & Moser, M. B. (2010). Development of the spatial representation system in the rat. *Science, 328*(5985), 1576-1580. doi: 10.1126/science.1188210

Lee, I., Yoganarasimha, D., Rao, G., & Knierim, J. J. (2004). Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. *Nature, 430*(6998), 456-459. doi: 10.1038/nature02739

Leggett, K. E. A. (2011). Home range and seasonal movement of elephants in the Kunene Region, northwestern Namibia. *2011, 41*(1).

Lehrer, M. (1993). Why do bees turn back and look? *Journal of Comparative Physiology A, 172*(5), 549-563. doi: 10.1007/BF00213678

Lehrer, M. (1996). Small-scale navigation in the honeybee: active acquisition of visual information about the goal. *J Exp Biol, 199*(Pt 1), 253-261.

Lehrer, M., & Collett, T. S. (1994). Approaching and departing bees learn different cues to the distance of a landmark. *Journal of Comparative Physiology A, 175*(2), 171-177. doi: 10.1007/BF00215113

Lenck-Santini, P. P., Muller, R. U., Save, E., & Poucet, B. (2002). Relationships between place cell firing fields and navigational decisions by rats. *J Neurosci, 22*(20), 9035-9047.

Lenck-Santini, P. P., Rivard, B., Muller, R. U., & Poucet, B. (2005). Study of CA1 place cell activity and exploratory behavior following spatial and nonspatial changes in the environment. *Hippocampus, 15*(3), 356-369. doi: 10.1002/hipo.20060

Lenck-Santini, P. P., Save, E., & Poucet, B. (2001a). Evidence for a relationship between place-cell spatial firing and spatial memory performance. *Hippocampus, 11*(4), 377-390. doi: 10.1002/hipo.1052

Lenck-Santini, P. P., Save, E., & Poucet, B. (2001b). Place-cell firing does not depend on the direction of turn in a Y-maze alternation task. *Eur J Neurosci, 13*(5), 1055-1058.

Leutgeb, J. K., Leutgeb, S., Moser, M. B., & Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science, 315*(5814), 961-966. doi: 10.1126/science.1135801

Leutgeb, J. K., Leutgeb, S., Treves, A., Meyer, R., Barnes, C. A., McNaughton, B. L., Moser, M. B., & Moser, E. I. (2005). Progressive transformation of hippocampal neuronal representations in "morphed" environments. *Neuron, 48*(2), 345-358. doi: 10.1016/j.neuron.2005.09.007

Leutgeb, S., Leutgeb, J. K., Barnes, C. A., Moser, E. I., McNaughton, B. L., & Moser, M. B. (2005). Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science, 309*(5734), 619-623. doi: 10.1126/science.1114037

Leutgeb, S., Leutgeb, J. K., Treves, A., Moser, M.-B., & Moser, E. I. (2004). Distinct Ensemble Codes in Hippocampal Areas CA3 and CA1. *Science, 305*(5688), 1295-1298. doi: 10.1126/science.1100265

Lever, C., Burton, S., Jeewajee, A., O'Keefe, J., & Burgess, N. (2009). Boundary vector cells in the subiculum of the hippocampal formation. *J Neurosci, 29*(31), 9771-9777. doi: 10.1523/jneurosci.1319-09.2009

Lever, C., Wills, T., Cacucci, F., Burgess, N., & O'Keefe, J. (2002). Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature, 416*(6876), 90-94. doi: 10.1038/416090a

Lewis, F. T. (1923). The significance of the term Hippocampus. *The Journal of Comparative Neurology, 35*(3), 213-230. doi: 10.1002/cne.900350303

Lindberg, E., & Garling, T. (1981). Acquisition of locational information about reference points during blindfolded and sighted locomotion: Effects of a concurrent task and locomotion paths. *Scandinavian Journal of Psychology, 22*(1), 101-108. doi: 10.1111/j.1467-9450.1981.tb00384.x

Liu, X., Muller, R. U., Huang, L. T., Kubie, J. L., Rotenberg, A., Rivard, B., Cilio, M. R., & Holmes, G. L. (2003). Seizure-induced changes in place cell physiology: relationship to spatial memory. *J Neurosci, 23*(37), 11505-11515.

Logothetis, N. K., & Pauls, J. (1995). Psychophysical and physiological evidence for viewer-centered object representations in the primate. *Cereb Cortex, 5*(3), 270-288.

Loomis, J. M., Da Silva, J. A., Fujita, N., & Fukusima, S. S. (1992). Visual space perception and visually directed action. *J Exp Psychol Hum Percept Perform, 18*(4), 906-921.

Loomis, J. M., Klatzky, R. L., Golledge, R. G., Cicinelli, J. G., Pellegrino, J. W., & Fry, P. A. (1993). Nonvisual navigation by blind and sighted: assessment of path integration ability. *J Exp Psychol Gen, 122*(1), 73-91.

Lorente De Nó, R. (1934). Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. *Journal für Psychologie und Neurologie, 46*, 113-177.

Lu, L., Leutgeb, J. K., Tsao, A., Henriksen, E. J., Leutgeb, S., Barnes, C. A., Witter, M. P., Moser, M.-B., & Moser, E. I. (2013). Impaired hippocampal rate coding after lesions of the lateral entorhinal cortex. *Nat Neurosci, 16*(8), 1085-1093. doi: 10.1038/nn.3462

Lyttle, D., Gereke, B., Lin, K. K., & Fellous, J. M. (2013). Spatial scale and place field stability in a grid-to-place cell model of the dorsoventral axis of the hippocampus. *Hippocampus, 23*(8), 729-744. doi: 10.1002/hipo.22132

Maaswinkel, H., Jarrard, L. E., & Whishaw, I. Q. (1999). Hippocampectomized rats are impaired in homing by path integration. *Hippocampus, 9*(5), 553-561. doi: 10.1002/(sici)1098-1063(1999)9:5<553::aid-hipo9>3.0.co;2-g

Maaswinkel, H., & Whishaw, I. Q. (1999). Homing with locale, taxon, and dead reckoning strategies by foraging rats: sensory hierarchy in spatial navigation. *Behav Brain Res, 99*(2), 143-152.

MacCorquodale, K., & Meehl, P. E. (1954). Edward C. Tolman *Modern learning theory: A critical analysis of five examples* (pp. 177-266). East Norwalk, CT, US: Appleton-Century-Crofts.

MacKay, D. G., Burke, D. M., & Stewart, R. (1998). H.M.'s Language Production Deficits: Implications for Relations between Memory, Semantic Binding, and the Hippocampal System. *Journal of Memory and Language, 38*(1), 28-69. doi: http://dx.doi.org/10.1006/jmla.1997.2544

Mackintosh, N. J. (1974). *The Psychology of Animal Learning*: Academic Press.

Mackintosh, N. J. (1975). A theory of attention: Variations in the associability of stimuli with reinforcement. 4. 82

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science, 280*(5365), 921-924.

Maguire, E. A., Frackowiak, R. S., & Frith, C. D. (1997). Recalling routes around london: activation of the right hippocampus in taxi drivers. *J Neurosci, 17*(18), 7103-7110.

Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain, 129*(Pt 11), 2894-2907. doi: 10.1093/brain/awl286

Maher, J. M., Markey, J. C., & Ebert-May, D. (2013). The Other Half of the Story: Effect Size Analysis in Quantitative Research. *CBE Life Sciences Education, 12*(3), 345-351. doi: 10.1187/cbe.13-04-0082

Maier, M. R., & Longhurst, J. U. (1947). Studies of abnormal behavior in the rat; conflict and audiogenic seizures. *J Comp Physiol Psychol, 40*(6), 397-412.

Maier, N. R. F. (1932). The effect of cerebral destruction on reasoning and learning in rats. *The Journal of Comparative Neurology, 54*(1), 45-75. doi: 10.1002/cne.900540105

Maier, N. R. F., & Murphy, G. (1939). *Studies of abnormal behavior in the rat; the neurotic pattern and an analysis of the situation which produces it*. New York, London,: Harper & brothers.

Maren, S., & Holt, W. (2000). The hippocampus and contextual memory retrieval in Pavlovian conditioning. *Behav Brain Res, 110*(1-2), 97-108.

Markus, E. J., Qin, Y. L., Leonard, B., Skaggs, W. E., McNaughton, B. L., & Barnes, C. A. (1995). Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J Neurosci, 15*(11), 7079-7094.

Matthews, B. L., Ryu, J. H., & Bockaneck, C. (1989). Vestibular contribution to spatial orientation. Evidence of vestibular navigation in an animal model. *Acta Otolaryngol Suppl, 468*, 149-154.

Matus-Amat, P., Higgins, E. A., Barrientos, R. M., & Rudy, J. W. (2004). The role of the dorsal hippocampus in the acquisition and retrieval of context memory representations. *J Neurosci, 24*(10), 2431-2439. doi: 10.1523/jneurosci.1598-03.2004

Maurer, A. P., Vanrhoads, S. R., Sutherland, G. R., Lipa, P., & McNaughton, B. L. (2005). Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus, 15*(7), 841-852. doi: 10.1002/hipo.20114

McCulloch, T. L. (1934). Performance preferentials of the white rat in force-resisting and spatial dimensions. *Journal of Comparative Psychology, 18*(1), 85-111. doi: 10.1037/h0074986

McDonald, A. J. (1991). Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neuroscience, 44*(1), 1-14.

McNaughton, B. L., Barnes, C. A., Gerrard, J. L., Gothard, K., Jung, M. W., Knierim, J. J., Kudrimoti, H., Qin, Y., Skaggs, W. E., Suster, M., & Weaver, K. L. (1996). Deciphering the hippocampal polyglot: the hippocampus as a path integration system. *J Exp Biol, 199*(Pt 1), 173-185.

McNaughton, B. L., Barnes, C. A., & O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res, 52*(1), 41-49. doi: 10.1007/BF00237147

McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., & Moser, M.-B. (2006). Path integration and the neural basis of the 'cognitive map'. *Nat Rev Neurosci, 7*(8), 663-678.

McNaughton, B. L., Chen, L. L., & Markus, E. J. (1991). "Dead reckoning," landmark learning, and the sense of direction: a neurophysiological and computational hypothesis. *J Cogn Neurosci, 3*(2), 190-202. doi: 10.1162/jocn.1991.3.2.190

Meehl, P. E., & MacCorquodale, K. (1951). A failure to find the Blodgett effect and some secondary observations on drive conditioning. *Journal of Comparative and Physiological Psychology, 44*(2), 178-183. doi: 10.1037/h0054572

Meehl, P. E., & Maccorquodale, K. (1953). Drive conditioning as a factor in latent learning. *Journal of Experimental Psychology, 45*(1), 20-24. doi: 10.1037/h0057903

Melo, M. A., Cheng, L., Weir, M. D., Hsia, R. C., Rodrigues, L. K., & Xu, H. H. (2013). Novel dental adhesive containing antibacterial agents and calcium phosphate nanoparticles. *J Biomed Mater Res B Appl Biomater, 101*(4), 620-629. doi: 10.1002/jbm.b.32864

Menzel, E. W., Jr., & Juno, C. (1982). Marmosets (Saguinus fuscicollis): Are Learning Sets Learned? *Science, 217*(4561), 750-752. doi: 10.1126/science.217.4561.750

Menzel, R., Geiger, K., Joerges, J., Muller, U., & Chittka, L. (1998). Bees travel novel homeward routes by integrating separately acquired vector memories. *Anim Behav, 55*(1), 139-152.

Milner, B. (1962). Physiologie de l'hippocampe (pp. 257-272): Centre National de la Recherche Scientifique.

Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clin Neurosurg, 19*, 421-446.

Milner, B., Corkin, S., & Teuber, H. L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia, 6*(3), 215-234. doi: http://dx.doi.org/10.1016/0028-3932(68)90021-3

Milton, K. (1981). Distribution Patterns of Tropical Plant Foods as an Evolutionary Stimulus to Primate Mental Development. *American Anthropologist, 83*(3), 534-548. doi: 10.1525/aa.1981.83.3.02a00020

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. *Nature, 273*(5660), 297-298.

Mishkin, M., & Delacour, J. (1975). An analysis of short-term visual memory in the monkey. *J Exp Psychol Anim Behav Process, 1*(4), 326-334.

Mittelstaedt, M. L., & Mittelstaedt, H. (1980). Homing by path integration in a mammal. *Naturwissenschaften, 67*(11), 566-567. doi: 10.1007/BF00450672

Mittelstaedt, M. L., & Mittelstaedt, H. (2001). Idiothetic navigation in humans: estimation of path length. *Exp Brain Res, 139*(3), 318-332.

Mizumori, S. J. (2008). *Hippocampal place fields : relevance to learning and memory*. Oxford; New York: Oxford University Press.

Mizumori, S. J., McNaughton, B. L., Barnes, C. A., & Fox, K. B. (1989). Preserved spatial coding in hippocampal CA1 pyramidal cells during reversible suppression of CA3c output: evidence for pattern completion in hippocampus. *J Neurosci, 9*(11), 3915-3928.

Mizumori, S. J., & Williams, J. D. (1993). Directionally selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. *J Neurosci, 13*(9), 4015-4028.

Moita, M. A., Rosis, S., Zhou, Y., LeDoux, J. E., & Blair, H. T. (2004). Putting fear in its place: remapping of hippocampal place cells during fear conditioning. *J Neurosci, 24*(31), 7015-7023. doi: 10.1523/jneurosci.5492-03.2004

Monaco, J. D., & Abbott, L. F. (2011). Modular realignment of entorhinal grid cell activity as a basis for hippocampal remapping. *J Neurosci, 31*(25), 9414-9425. doi: 10.1523/jneurosci.1433-11.2011

Morgan, C. T., & Morgan, J. D. (1939). Auditory induction of an abnormal pattern of behavior in rats. *Journal of Comparative Psychology, 27*(3), 505-508. doi: 10.1037/h0058757

Morris, R. G. (1999). D.O. Hebb: The Organization of Behavior, Wiley: New York; 1949. *Brain Res Bull, 50*(5-6), 437.

Morris, R. G., & Frey, U. (1997). Hippocampal synaptic plasticity: role in spatial learning or the automatic recording of attended experience? *Philosophical Transactions of the Royal Society B: Biological Sciences, 352*(1360), 1489-1503.

Morris, R. G., Garrud, P., Rawlins, J. N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297*(5868), 681-683.

Morris, R. G. M. (1981). Spatial Localization Does Not Require the Presence of Local Cues. *Learning and Motivation, 12*(2), 239-260. doi: 10.1016/0023-9690(81)90020-5

Moser, E. I., Kropff, E., & Moser, M. B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annu Rev Neurosci, 31*, 69-89. doi: 10.1146/annurev.neuro.31.061307.090723

Moser, E. I., Roudi, Y., Witter, M. P., Kentros, C., Bonhoeffer, T., & Moser, M.-B. (2014). Grid cells and cortical representation. *Nat Rev Neurosci, 15*(7), 466-481. doi: 10.1038/nrn3766

Moser, M. B., & Moser, E. I. (1998). Functional differentiation in the hippocampus. *Hippocampus, 8*(6), 608-619. doi: 10.1002/(SICI)1098-1063(1998)8:6&lt;608::AID-HIPO3&gt;3.0.CO;2-7

Muenzinger, K. F. (1938). Vicarious Trial and Error at a Point of Choice: I. A General Survey of its Relation to Learning Efficiency. *The Pedagogical Seminary and Journal of Genetic Psychology, 53*(1), 75-86. doi: 10.1080/08856559.1938.10533799

Muir, G. M., & Bilkey, D. K. (2001). Instability in the place field location of hippocampal place cells after lesions centered on the perirhinal cortex. *J Neurosci, 21*(11), 4016-4025.

Muller, M., & Wehner, R. (1988). Path integration in desert ants, Cataglyphis fortis. *Proc Natl Acad Sci U S A, 85*(14), 5287-5290.

Müller, M., & Wehner, R. (2010). Path Integration Provides a Scaffold for Landmark Learning in Desert Ants. *Current Biology, 20*(15), 1368-1371. doi: http://dx.doi.org/10.1016/j.cub.2010.06.035

Muller, R. U., Bostock, E., Taube, J. S., & Kubie, J. L. (1994). On the directional firing properties of hippocampal place cells. *J Neurosci, 14*(12), 7235-7251.

Muller, R. U., & Kubie, J. L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J Neurosci, 7*(7), 1951-1968.

Muller, R. U., Kubie, J. L., & Ranck, J. B., Jr. (1987). Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. *J Neurosci, 7*(7), 1935-1950.

Myers, C. E., & Gluck, M. A. (1994). Context, conditioning, and hippocampal rerepresentation in animal learning. *Behav Neurosci, 108*(5), 835-847.

Nadel, L. (1991). The hippocampus and space revisited. *Hippocampus, 1*(3), 221-229. doi: 10.1002/hipo.450010302

Nadel, L. (1992). Multiple memory systems: what and why. *J Cogn Neurosci, 4*(3), 179-188. doi: 10.1162/jocn.1992.4.3.179

Neves, G., Cooke, S. F., & Bliss, T. V. P. (2008). Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nat Rev Neurosci, 9*(1), 65-75.

Nicholson, D. J., Judd, S. P., Cartwright, B. A., & Collett, T. S. (1999). Learning walks and landmark guidance in wood ants (Formica rufa). *J Exp Biol, 202 (Pt 13)*, 1831-1838.

Niimi, M. (1978). Cortical projections of the anterior thalamic nuclei in the cat. *Exp Brain Res, 31*(3), 403-416.

Norgaard, T. (2005). Nocturnal navigation in Leucorchestris arenicola (Araneae, sparassidae). *The Journal of Arachnology, 33*, 533-540.

Nørgaard, T., Gagnon, Y. L., & Warrant, E. J. (2012). Nocturnal Homing: Learning Walks in a Wandering Spider? *PLoS ONE, 7*(11), e49263. doi: 10.1371/journal.pone.0049263

Norgaard, T., Henschel, J. R., & Wehner, R. (2007). Use of local cues in the night-time navigation of the wandering desert spider Leucorchestris arenicola (Araneae, Sparassidae). *J Comp Physiol A Neuroethol Sens Neural Behav Physiol, 193*(2), 217-222. doi: 10.1007/s00359-006-0178-6

Norgaard, T., Nilsson, D. E., Henschel, J. R., Garm, A., & Wehner, R. (2008). Vision in the nocturnal wandering spider Leucorchestris arenicola (Araneae: Sparassidae). *J Exp Biol, 211*(Pt 5), 816-823. doi: 10.1242/jeb.010546

Norman, G., & Eacott, M. J. (2004). Impaired object recognition with increasing levels of feature ambiguity in rats with perirhinal cortex lesions. *Behav Brain Res, 148*(1-2), 79-91.

Nunn, J. A., Graydon, F. J., Polkey, C. E., & Morris, R. G. (1999). Differential spatial memory impairment after right temporal lobectomy demonstrated using temporal titration. *Brain, 122 ( Pt 1)*, 47-59.

Nunn, J. A., Polkey, C. E., & Morris, R. G. (1998). Selective spatial memory impairment after right unilateral temporal lobectomy. *Neuropsychologia, 36*(9), 837-848.

O'Keefe, J. (1976). Place units in the hippocampus of the freely moving rat. *Exp Neurol, 51*(1), 78-109. doi: http://dx.doi.org/10.1016/0014-4886(76)90055-8

O'Keefe, J. (1979). A review of the hippocampal place cells. *Prog Neurobiol, 13*(4), 419-439.

O'Keefe, J., & Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature, 381*(6581), 425-428. doi: 10.1038/381425a0

O'Keefe, J., & Conway, D. H. (1978). Hippocampal place units in the freely moving rat: why they fire where they fire. *Exp Brain Res, 31*(4), 573-590.

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res, 34*(1), 171-175.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford; New York: Clarendon Press ; Oxford University Press.

O'Keefe, J., & Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus, 3*(3), 317-330. doi: 10.1002/hipo.450030307

O'Keefe, J., & Speakman, A. (1987). Single unit activity in the rat hippocampus during a spatial memory task. *Exp Brain Res, 68*(1), 1-27.

O'Reilly, K. C., Alarcon, J. M., & Ferbinteanu, J. (2014). Relative contributions of CA3 and medial entorhinal cortex to memory in rats. *Front Behav Neurosci, 8*, 292. doi: 10.3389/fnbeh.2014.00292

Olton, D. S., Branch, M., & Best, P. J. (1978). Spatial correlates of hippocampal unit activity. *Exp Neurol, 58*(3), 387-409. doi: http://dx.doi.org/10.1016/0014-4886(78)90096-1

Olton, D. S., & Samuelson, R. J. (1976). Remembrance of places passed: Spatial memory in rats. *Journal of Experimental Psychology: Animal Behavior Processes, 2*(2), 97-116. doi: 10.1037/0097-7403.2.2.97

Olton, D. S., Walker, J. A., & Gage, F. H. (1978). Hippocampal connections and spatial discrimination. *Brain Res, 139*(2), 295-308.

Orbach, J., Milner, B., & Rasmussen, T. (1960). Learning and retention in monkeys after amygdala-hippocampus resection. *Arch Neurol, 3*, 230-251.

Parron, C., & Save, E. (2004). Evidence for entorhinal and parietal cortices involvement in path integration in the rat. *Exp Brain Res, 159*(3), 349-359. doi: 10.1007/s00221-004-1960-8

Pavlov, I. P., & Anrep, G. V. (2003). *Conditioned Reflexes*: Dover Publications.

Pearce, J. M., Good, M. A., Jones, P. M., & McGregor, A. (2004). Transfer of spatial behavior between different environments: implications for theories of spatial learning and for the role of the hippocampus in spatial learning. *J Exp Psychol Anim Behav Process, 30*(2), 135-147. doi: 10.1037/0097-7403.30.2.135

Penfield, W., & Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Arch Neurol Psychiatry, 79*(5), 475-497.

Penick, S., & Solomon, P. R. (1991). Hippocampus, context, and conditioning. *Behav Neurosci, 105*(5), 611-617.

Pennartz, C. M. A., Ito, R., Verschure, P. F. M. J., Battaglia, F. P., & Robbins, T. W. (2011). The hippocampal–striatal axis in learning, prediction and goal-directed behavior. *Trends in Neurosciences, 34*(10), 548-559. doi: 10.1016/j.tins.2011.08.001

Perrett, D. I., Oram, M. W., & Ashbridge, E. (1998). Evidence accumulation in cell populations responsive to faces: an account of generalisation of recognition without mental transformations. *Cognition, 67*(1-2), 111-145.

Peters, R. (1978). 5 - Communication, Cognitive Mapping, and Strategy in Wolves and Hominids. In R. L. H. S. Sharp (Ed.), *Wolf and Man* (pp. 95-107): Academic Press.

Pfeiffer, B. E., & Foster, D. J. (2013). Hippocampal place-cell sequences depict future paths to remembered goals. *Nature, 497*(7447), 74-79. doi: 10.1038/nature12112

http://www.nature.com/nature/journal/v497/n7447/abs/nature12112.html#supplementary-information

Pfeiffer, K., & Homberg, U. (2007). Coding of azimuthal directions via time-compensated combination of celestial compass cues. *Curr Biol, 17*(11), 960-965. doi: 10.1016/j.cub.2007.04.059

Phillips, R. G., & LeDoux, J. E. (1992). Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci, 106*(2), 274-285.

Piaget, J. (1952). *La naissance de l'intelligence chez l'enfant*: International Universities Press.

Pittman, S. E., Hart, K. M., Cherkiss, M. S., Snow, R. W., Fujisaki, I., Smith, B. J., Mazzotti, F. J., & Dorcas, M. E. (2014). Homing of invasive Burmese pythons in South Florida: evidence for map and compass senses in snakes. *Biol Lett, 10*(3), 20140040. doi: 10.1098/rsbl.2014.0040

Poucet, B. (1993). Spatial cognitive maps in animals: new hypotheses on their structure and neural mechanisms. *Psychol Rev, 100*(2), 163-182.

Poucet, B., Lenck-Santini, P.-P., Paz-Villagrán, V., & Save, E. (2003). Place cells, neocortex and spatial navigation: a short review. *Journal of Physiology-Paris, 97*(4–6), 537-546. doi: http://dx.doi.org/10.1016/j.jphysparis.2004.01.011

Pouzet, B., Welzl, H., Gubler, M. K., Broersen, L., Veenman, C. L., Feldon, J., Rawlins, J. N., & Yee, B. K. (1999). The effects of NMDA-induced retrohippocampal lesions on performance of four spatial memory tasks known to be sensitive to hippocampal damage in the rat. *Eur J Neurosci, 11*(1), 123-140.

Powell, R. A. (1978). A comparison of fisher and weasel hunting behavior. *Carnivore, 1*, 28-34.

Prados, J., & Redhead, E. S. (2002). Preexposure effects in spatial learning: From gestaltic to associative and attentional cognitive maps. *Psicológica, 23*(1), 59-78.

Puryear, C. B., King, M., & Mizumori, S. J. (2006). Specific changes in hippocampal spatial codes predict spatial working memory performance. *Behav Brain Res, 169*(1), 168-175. doi: 10.1016/j.bbr.2005.12.007

Quirk, G. J., Muller, R. U., & Kubie, J. L. (1990). The firing of hippocampal place cells in the dark depends on the rat's recent experience. *J Neurosci, 10*(6), 2008-2017.

Quirk, G. J., Muller, R. U., Kubie, J. L., & Ranck, J. B., Jr. (1992). The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. *J Neurosci, 12*(5), 1945-1963.

Ragozzino, K. E., Leutgeb, S., & Mizumori, S. J. (2001). Dorsal striatal head direction and hippocampal place representations during spatial navigation. *Exp Brain Res, 139*(3), 372-376.

Ranck, J. B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. *Exp Neurol, 41*(2), 461-531.

Ranck Jr, J. B. (1984). Head direction cells in the deep layer of dorsal presubiculum in freely moving rats. *Soc. Neurosci. Abstr., 10*, 599.

Randolf Menzel, Lars Chittka, Stefan Eichmuller, Karl Geiger, Dagmar eitsch, & Knoll, P. (1990). Dominance of celestial cues over landmarks disproves map-like orientation in honey bees. *Z. Naturforsch, 45c*, 723-726.

Rauch, S. L., Savage, C. R., Brown, H. D., Curran, T., Alpert, N. M., Kendrick, A., Fischman, A. J., & Kosslyn, S. M. (1995). A PET investigation of implicit and explicit sequence learning. *Human Brain Mapping, 3*(4), 271-286. doi: 10.1002/hbm.460030403

Rauch, S. L., Whalen, P. J., Savage, C. R., Curran, T., Kendrick, A., Brown, H. D., Bush, G., Breiter, H. C., & Rosen, B. R. (1997). Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Hum Brain Mapp, 5*(2), 124-132.

Raudies, F., & Hasselmo, M. E. (2012). Modeling Boundary Vector Cell Firing Given Optic Flow as a Cue. *PLoS Comput Biol, 8*(6), e1002553. doi: 10.1371/journal.pcbi.1002553

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., & Acker, J. D. (2005). Regional brain changes in aging healthy adults:

general trends, individual differences and modifiers. *Cereb Cortex, 15*(11), 1676-1689. doi: 10.1093/cercor/bhi044

Redhead, E. S., & Hamilton, D. A. (2007). Interaction between locale and taxon strategies in human spatial learning. *Learning and Motivation, 38*(3), 262-283. doi: http://dx.doi.org/10.1016/j.lmot.2006.11.003

Redhead, E. S., Hamilton, D. A., Parker, M. O., Chan, W., & Allison, C. (2013). Overshadowing of geometric cues by a beacon in a spatial navigation task. *Learn Behav, 41*(2), 179-191. doi: 10.3758/s13420-012-0096-0

Redish, A. D. (1999). *Beyond the Cognitive Map: From Place Cells to Episodic Memory*. MIT Press.

Redish, A. D., Elga, A. N., & Touretzky, D. S. (1996). A coupled attractor model of the rodent head direction system. *Network: Computation in Neural Systems, 7*(4), 671-685. doi: doi:10.1088/0954-898X_7_4_004

Redish, A. D., & Touretzky, D. S. (1997). Cognitive maps beyond the hippocampus. *Hippocampus, 7*(1), 15-35. doi: 10.1002/(SICI)1098-1063(1997)7:1&lt;15::AID-HIPO3&gt;3.0.CO;2-6

Redish, A. D., & Touretzky, D. S. (1998). The role of the hippocampus in solving the Morris water maze. *Neural Comput, 10*(1), 73-111.

Redlick, F. P., Jenkin, M., & Harris, L. R. (2001). Humans can use optic flow to estimate distance of travel. *Vision Research, 41*(2), 213-219. doi: http://dx.doi.org/10.1016/S0042-6989(00)00243-1

Reichardt, W., & Wenking, H. (1969). Optical detection and fixation of objects by fixed flying flies. *Naturwissenschaften, 56*(8), 424-425.

Reinhard, J., Srinivasan, M. V., Guez, D., & Zhang, S. W. (2004). Floral scents induce recall of navigational and visual memories in honeybees. *J Exp Biol, 207*(Pt 25), 4371-4381. doi: 207/25/4371 [pii] 10.1242/jeb.01306

Rescorla, R. A. (1990). Evidence for an association between the discriminative stimulus and the response-outcome association in instrumental learning. *J Exp Psychol Anim Behav Process, 16*(4), 326-334.

Rescorla, R. A., & Wagner, A. W. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Classical Conditioning II: Current Research and Theory* (pp. 64-99): Appleton-Century-Crofts.

Restle, F. (1957). Discrimination of cues in mazes: a resolution of the place-vs.-response question. *Psychol Rev, 64*(4), 217-228.

Reynolds, B. (1945). A repetition of the Blodgett experiment of latent learning. *J Exp Psychol, 35*, 504-516.

Rieser, J. J., Ashmead, D. H., & Pick, H. L. (1988). Perception of walking without vision-uncoupling proprioceptive and visual flow. *Bulletin of the Psychonomic Society, 26*(6), 491-491.

Rieser, J. J., Ashmead, D. H., Talor, C. R., & Youngquist, G. A. (1990). Visual perception and the guidance of locomotion without vision to previously seen targets. *Perception, 19*(5), 675-689.

Rieser, J. J., Guth, D. A., & Hill, E. W. (1986). Sensitivity to perspective structure while walking without vision. *Perception, 15*(2), 173-188.

Rieser, J. J., Hill, E. W., Talor, C. R., Bradfield, A., & Rosen, S. (1992). Visual experience, visual field size, and the development of nonvisual sensitivity to the spatial structure of outdoor neighborhoods explored by walking. *J Exp Psychol Gen, 121*(2), 210-221.

Rieser, J. J., Lockman, J. J., & Pick, H. L., Jr. (1980). The role of visual experience in knowledge of spatial layout. *Percept Psychophys, 28*(3), 185-190.

Ritchie, B. F., Aeschliman, B., & Pierce, P. (1950). Studies in spatial learning. VIII. Place performance and the acquisition of place dispositions. *Journal of Comparative and Physiological Psychology, 43*(2), 73-85. doi: 10.1037/h0055224

Roberts, W. A., Cruz, C., & Tremblay, J. (2007). Rats take correct novel routes and shortcuts in an enclosed maze. *J Exp Psychol Anim Behav Process, 33*(2), 79-91. doi: 10.1037/0097-7403.33.2.79

Robertson, R. G., Rolls, E. T., & Georges-François, P. (1998). Spatial view cells in the primate hippocampus: effects of removal of view details. *J Neurophysiol, 79*(3), 1145-1156.

Rock, I., & DiVita, J. (1987). A case of viewer-centered object perception. *Cognitive Psychology, 19*(2), 280-293. doi: http://dx.doi.org/10.1016/0010-0285(87)90013-2

Rolls, E. T. (1999). Spatial view cells and the representation of place in the primate hippocampus. *Hippocampus, 9*(4), 467-480. doi: 10.1002/(sici)1098-1063(1999)9:4<467::aid-hipo13>3.0.co;2-f

Rolls, E. T., Stringer, S. M., & Elliot, T. (2006). Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning. *Network, 17*(4), 447-465. doi: 10.1080/09548980601064846

Ronacher, B., Gallizzi, K., Wohlgemuth, S., & Wehner, R. (2000). Lateral optic flow does not influence distance estimation in the desert ant Cataglyphis fortis. *J Exp Biol, 203*(Pt 7), 1113-1121.

Ronacher, B., & Wehner, R. (1995). Desert ants Cataglyphis fortis use self-induced optic flow to measure distances travelled. *Journal of Comparative Physiology A, 177*(1), 21-27. doi: 10.1007/bf00243395

Rosenbaum, R. S., Cassidy, B., & Herdman, K. A. (2015). Patterns of preserved and impaired spatial memory in a case of developmental amnesia. *Frontiers in Human Neuroscience, 9*. doi: 10.3389/fnhum.2015.00196

Rosenbaum, R. S., Priselac, S., Kohler, S., Black, S. E., Gao, F., Nadel, L., & Moscovitch, M. (2000). Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nat Neurosci, 3*(10), 1044-1048. doi: 10.1038/79867

Rosenzweig, E. S., Redish, A. D., McNaughton, B. L., & Barnes, C. A. (2003). Hippocampal map realignment and spatial learning. *Nat Neurosci, 6*(6), 609-615. doi: 10.1038/nn1053

Rossel, S., & Wehner, R. (1984). Celestial orientation in bees: the use of spectral cues. *Journal of Comparative Physiology A, 155*(5), 605-613. doi: 10.1007/BF00610846

Rossel, S., Wehner, R., & Lindauer, M. (1978). E-Vector orientation in bees. *Journal of comparative physiology, 125*(1), 1-12. doi: 10.1007/BF00656826

Rowland, D. C., Yanovich, Y., & Kentros, C. G. (2011). A stable hippocampal representation of a space requires its direct experience. *Proc Natl Acad Sci U S A, 108*(35), 14654-14658. doi: 10.1073/pnas.1105445108

Rumelhart, D. E., McClelland, J. L., & University of California, S. D. P. R. G. (1986). *Parallel Distributed Processing: Foundations*. MIT Press.

Sams, C. F., & Tolman, E. C. (1925). Time discrimination in white rats. *Journal of Comparative Psychology, 5*(3), 255-263. doi: 10.1037/h0074866

Samsonovich, A., & McNaughton, B. L. (1997). Path integration and cognitive mapping in a continuous attractor neural network model. *J Neurosci, 17*(15), 5900-5920.

Samu, D., Eros, P., Ujfalussy, B., & Kiss, T. (2009). Robust path integration in the entorhinal grid cell system with hippocampal feed-back. *Biological Cybernetics, 101*(1), 19-34. doi: 10.1007/s00422-009-0311-z

Sanderson, D. J., Pearce, J. M., Kyd, R. J., & Aggleton, J. P. (2006). The importance of the rat hippocampus for learning the structure of visual arrays. *Eur J Neurosci, 24*(6), 1781-1788. doi: 10.1111/j.1460-9568.2006.05035.x

Sargolini, F., Fyhn, M., Hafting, T., McNaughton, B. L., Witter, M. P., Moser, M. B., & Moser, E. I. (2006). Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science, 312*(5774), 758-762. doi: 10.1126/science.1125572

Save, E., Cressant, A., Thinus-Blanc, C., & Poucet, B. (1998). Spatial firing of hippocampal place cells in blind rats. *J Neurosci, 18*(5), 1818-1826.

Save, E., Guazzelli, A., & Poucet, B. (2001). Dissociation of the effects of bilateral lesions of the dorsal hippocampus and parietal cortex on path integration in the rat. *Behav Neurosci, 115*(6), 1212-1223.

Save, E., Nerad, L., & Poucet, B. (2000). Contribution of multiple sensory information to place field stability in hippocampal place cells. *Hippocampus, 10*(1), 64-76. doi: 10.1002/(sici)1098-1063(2000)10:1<64::aid-hipo7>3.0.co;2-y

Save, E., & Poucet, B. (2000). Involvement of the hippocampus and associative parietal cortex in the use of proximal and distal landmarks for navigation. *Behav Brain Res, 109*(2), 195-206.

Savelli, F., & Knierim, J. J. (2010). Hebbian analysis of the transformation of medial entorhinal grid-cell inputs to hippocampal place fields. *J Neurophysiol, 103*(6), 3167-3183. doi: 10.1152/jn.00932.2009

Savelli, F., Yoganarasimha, D., & Knierim, J. J. (2008). Influence of boundary removal on the spatial representations of the medial entorhinal cortex. *Hippocampus, 18*(12), 1270-1282. doi: 10.1002/hipo.20511

Scharlock, D. P. (1955). The role of extramaze cues in place and response learning. *Journal of Experimental Psychology, 50*(4), 249-254. doi: 10.1037/h0043052

Schmitzer-Torbert, N., Jackson, J., Henze, D., Harris, K., & Redish, A. D. (2005). Quantitative measures of cluster quality for use in extracellular recordings. *Neuroscience, 131*(1), 1-11. doi: 10.1016/j.neuroscience.2004.09.066

Schmitzer-Torbert, N., & Redish, A. D. (2004). Neuronal activity in the rodent dorsal striatum in sequential navigation: separation of spatial and reward responses on the multiple T task. *J Neurophysiol, 91*(5), 2259-2272. doi: 10.1152/jn.00687.2003

Schmolck, H., Kensinger, E. A., Corkin, S., & Squire, L. R. (2002). Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus, 12*(4), 520-533. doi: 10.1002/hipo.10039

Schöne, H. (1996). Orientation flight behavior in honeybees released from open or covered containers — after or without displacement. *Journal of Comparative Physiology A, 179*(4), 593-597. doi: 10.1007/BF00192325

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry, 20*(1), 11-21.

Seeley, T. D. (1995). *The wisdom of the hive : the social physiology of honey bee colonies*. Cambridge, Mass.: Harvard University Press.

Segal, M., & Olds, J. (1973). Activity of units in the hippocampal circuit of the rat during differential classical conditioning. 2. 82

Sewards, T. V., & Sewards, M. A. (2003). Input and output stations of the entorhinal cortex: superficial vs. deep layers or lateral vs. medial divisions? *Brain Res Brain Res Rev, 42*(3), 243-251.

Shapiro, M. L., Kennedy, P. J., & Ferbinteanu, J. (2006). Representing episodes in the mammalian brain. *Curr Opin Neurobiol, 16*(6), 701-709. doi: 10.1016/j.conb.2006.08.017

Shapiro, M. L., Tanila, H., & Eichenbaum, H. (1997). Cues that hippocampal place cells encode: dynamic and hierarchical representation of local and distal stimuli. *Hippocampus, 7*(6), 624-642. doi: 10.1002/(SICI)1098-1063(1997)7:6&lt;624::AID-HIPO5&gt;3.0.CO;2-E

Sharp, P. E. (1997). Subicular cells generate similar spatial firing patterns in two geometrically and visually distinctive environments: comparison with hippocampal place cells. *Behav Brain Res, 85*(1), 71-92.

Sharp, P. E., & Green, C. (1994). Spatial correlates of firing patterns of single cells in the subiculum of the freely moving rat. *J Neurosci, 14*(4), 2339-2356.

Sharp, P. E., Tinkelman, A., & Cho, J. (2001). Angular velocity and head direction signals recorded from the dorsal tegmental nucleus of gudden in the rat: implications for path integration in the head direction cell circuit. *Behav Neurosci, 115*(3), 571-588.

Shettleworth, S. J. (2009). *Cognition, Evolution, and Behavior*: Oxford University Press, USA.

Shettleworth, S. J., & Sutton, J. E. (2005). Multiple systems for spatial learning: dead reckoning and beacon homing in rats. *J Exp Psychol Anim Behav Process, 31*(2), 125-141. doi: 10.1037/0097-7403.31.2.125

Shrager, Y., Kirwan, C. B., & Squire, L. R. (2008). Neural basis of the cognitive map: Path integration does not require hippocampus or entorhinal cortex. *Proceedings of the National Academy of Sciences, 105*(33), 12034-12038. doi: 10.1073/pnas.0805414105

Si, A., Srinivasan, M. V., & Zhang, S. (2003). Honeybee navigation: properties of the visually driven 'odometer'. *J Exp Biol, 206*(Pt 8), 1265-1273.

Si, B., & Treves, A. (2009). The role of competitive learning in the generation of DG fields from EC inputs. *Cogn Neurodyn, 3*(2), 177-187. doi: 10.1007/s11571-009-9079-z

Simons, D. J., & Wang, R. F. (1998). Perceiving Real-World Viewpoint Changes. *Psychological Science, 9*(4), 315-320. doi: 10.1111/1467-9280.00062

Singer, A. C., & Frank, L. M. (2009). Rewarded Outcomes Enhance Reactivation of Experience in the Hippocampus. *Neuron, 64*(6), 910-921. doi: 10.1016/j.neuron.2009.11.016

Singer, A. C., Karlsson, M. P., Nathe, A. R., Carr, M. F., & Frank, L. M. (2010). Experience dependent development of coordinated hippocampal spatial activity representing the similarity of related locations. *J Neurosci, 30*(35), 11586-11604. doi: 10.1523/JNEUROSCI.0926-10.2010

Singer, R. A., Abroms, B. D., & Zentall, T. R. (2006). Formation of a Simple Cognitive Map by Rats. *International Journal of Comparative Psychology, 19*(4).

Skaggs, W. E., Knierim, J. J., Kudrimoti, H. S., & McNaughton, B. L. (1995). A model of the neural basis of the rat's sense of direction. *Adv Neural Inf Process Syst, 7*, 173-180.

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science, 271*(5257), 1870-1873.

Skaggs, W. E., & McNaughton, B. L. (1998). Spatial firing properties of hippocampal CA1 populations in an environment containing two visually identical regions. *J Neurosci, 18*(20), 8455-8466.

Skaggs, W. E., McNaughton, B. L., & Gothard, K. M. (1993). *An Information-Theoretic Approach to Deciphering the Hippocampal Code*. Paper presented at the Advances in Neural Information Processing Systems 5, [NIPS Conference].

Smith, D. M., & Mizumori, S. J. (2006a). Hippocampal place cells, context, and episodic memory. *Hippocampus, 16*(9), 716-729. doi: 10.1002/hipo.20208

Smith, D. M., & Mizumori, S. J. (2006b). Learning-related development of context-specific neuronal responses to places and events: the hippocampal role in context processing. *J Neurosci, 26*(12), 3154-3163. doi: 10.1523/jneurosci.3234-05.2006

Smith, Kyle S., & Graybiel, Ann M. (2013). A Dual Operator View of Habitual Behavior Reflecting Cortical and Striatal Dynamics. *Neuron, 79*(2), 361-374. doi: http://dx.doi.org/10.1016/j.neuron.2013.05.038

Smith, M. L., & Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. *Neuropsychologia, 19*(6), 781-793.

Snihur, A. W., Hampson, E., & Cain, D. P. (2008). Estradiol and corticosterone independently impair spatial navigation in the Morris water maze in adult female rats. *Behav Brain Res, 187*(1), 56-66. doi: 10.1016/j.bbr.2007.08.023

Solstad, T., Boccara, C. N., Kropff, E., Moser, M. B., & Moser, E. I. (2008). Representation of geometric borders in the entorhinal cortex. *Science, 322*(5909), 1865-1868. doi: 10.1126/science.1166466

Solstad, T., Moser, E. I., & Einevoll, G. T. (2006). From grid cells to place cells: a mathematical model. *Hippocampus, 16*(12), 1026-1031. doi: 10.1002/hipo.20244

Speakman, A., & O'Keefe, J. (1990). Hippocampal Complex Spike Cells do not Change Their Place Fields if the Goal is Moved Within a Cue Controlled Environment. *Eur J Neurosci, 2*(6), 544-555.

Spence, K. W., & Lippitt, R. (1946). An experimental test of the sign-gestalt theory of trial and error learning. *Journal of Experimental Psychology, 36*(6), 491.

Spiers, H. J., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2001). Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. *Hippocampus, 11*(6), 715-725. doi: 10.1002/hipo.1087

Spiers, H. J., Hayman, R. M., Jovalekic, A., Marozzi, E., & Jeffery, K. J. (2013). Place Field Repetition and Purely Local Remapping in a Multicompartment Environment. *Cereb Cortex*. doi: 10.1093/cercor/bht198

Squire, L. R. (2009). The Legacy of Patient H.M. for Neuroscience. *Neuron, 61*(1), 6-9. doi: 10.1016/j.neuron.2008.12.023

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Srinivasan, M. V., Zhang, S., Altwein, M., & Tautz, J. (2000). Honeybee navigation: Nature and calibration of the 'odometer'. *Science, 287*(5454), 851-853.

Srinivasan, M. V., Zhang, S. W., & Bidwell, N. J. (1997). Visually mediated odometry in honeybees. *Journal of Experimental Biology, 200*(19), 2513-2522.

Srinivasan, M. V., Zhang, S. W., Lehrer, M., & Collett, T. S. (1996). Honeybee navigation en route to the goal: Visual flight control and odometry. *Journal of Experimental Biology, 199*(1), 237-244.

Stabentheiner, A., & Hagmüller, K. (1991). Sweet food means "Hot Dancing" in honeybees. *Naturwissenschaften, 78*(10), 471-473. doi: 10.1007/bf01134389

Stackman, R. W., & Taube, J. S. (1998). Firing properties of rat lateral mammillary single units: head direction, head pitch, and angular head velocity. *J Neurosci, 18*(21), 9020-9037.

Stavenga, D. (1979). Pseudopupils of Compound Eyes. In H. Autrum (Ed.), *Comparative Physiology and Evolution of Vision in Invertebrates* (Vol. 7 / 6 / 6 A, pp. 357-439): Springer Berlin Heidelberg.

Steenhuis, R. E., & Goodale, M. A. (1988). The effects of time and distance on accuracy of target-directed locomotion: does an accurate short-term memory for spatial location exist? *J Mot Behav, 20*(4), 399-415.

Stella, F., Si, B., Kropff, E., & Treves, A. (2013). Grid cells on the ball. *Journal of Statistical Mechanics: Theory and Experiment, 2013*(03). doi: 10.1088/1742-5468/2013/03/P03013

Sturzl, W., & Zeil, J. (2007). Depth, contrast and view-based homing in outdoor scenes. *Biol Cybern, 96*(5), 519-531. doi: 10.1007/s00422-007-0147-3

Suboski, M., Greenner, R., & Spevack, A. (1967). A failure to obtain "Hudson's effect" following one-trial discriminated avoidance training. *Psychonomic Science, 9*(11), 577-578. doi: 10.3758/bf03327897

Sun, H. J., Campos, J. L., Young, M., Chan, G. S., & Ellard, C. G. (2004). The contributions of static visual cues, nonvisual cues, and optic flow in distance estimation. *Perception, 33*(1), 49-65.

Sutherland, N. S., & Mackintosh, N. J. (1971). *Mechanisms of animal discrimination learning*: Academic Press.

Sutherland, R. J., Kolb, B., & Whishaw, I. Q. (1982). Spatial mapping: definitive disruption by hippocampal or medial frontal cortical damage in the rat. *Neuroscience Letters, 31*(3), 271-276. doi: http://dx.doi.org/10.1016/0304-3940(82)90032-5

Swanson, L. W. (1977). The anatomical organization of septo-hippocampal projections. *Ciba Found Symp*(58), 25-48.

Takei, Y., Grasso, R., Amorim, M. A., & Berthoz, A. (1997). Circular trajectory formation during blind locomotion: a test for path integration and motor memory. *Exp Brain Res, 115*(2), 361-368.

Tanila, H. (1999). Hippocampal place cells can develop distinct representations of two visually identical environments. *Hippocampus, 9*(3), 235-246. doi: 10.1002/(sici)1098-1063(1999)9:3<235::aid-hipo4>3.0.co;2-3

Taube, J. (1995). Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *The Journal of Neuroscience, 15*(1), 70-86.

Taube, J. S. (1998). Head direction cells and the neurophysiological basis for a sense of direction. *Prog Neurobiol, 55*(3), 225-256.

Taube, J. S. (2007). The head direction signal: origins and sensory-motor integration. *Annu Rev Neurosci, 30*, 181-207. doi: 10.1146/annurev.neuro.29.051605.112854

Taube, J. S., & Burton, H. L. (1995). Head direction cell activity monitored in a novel environment and during a cue conflict situation. *J Neurophysiol, 74*(5), 1953-1971.

Taube, J. S., Kesslak, J. P., & Cotman, C. W. (1992). Lesions of the rat postsubiculum impair performance on spatial tasks. *Behav Neural Biol, 57*(2), 131-143.

Taube, J. S., Muller, R. U., & Ranck, J. B., Jr. (1990a). Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *J Neurosci, 10*(2), 420-435.

Taube, J. S., Muller, R. U., & Ranck, J. B., Jr. (1990b). Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *J Neurosci, 10*(2), 436-447.

Taube, J. S., Muller, R. U., & Ranck Jr, J. B. (1987). A quantitative analysis of head-direction cells in the postsubiculum. *Soc. Neurosci. Abstr., 13*, 1332.

Tautz, J., Zhang, S., Spaethe, J., Brockmann, A., Si, A., & Srinivasan, M. (2004). Honeybee Odometry: Performance in Varying Natural Terrain. *PLoS Biol, 2*(7), e211. doi: 10.1371/journal.pbio.0020211

Taylor, J. G., & Reichlin, B. (1951). Vicarious trial and error. *Psychol Rev, 58*(6), 389-402.

Teng, E., & Squire, L. R. (1999). Memory for places learned long ago is intact after hippocampal damage. *Nature, 400*(6745), 675-677. doi: 10.1038/23276

Teuber, H., & Weinstein, S. (1956). ABility to discover hidden figures after cerebral lesions. *A.M.A. Archives of Neurology & Psychiatry, 76*(4), 369-379. doi: 10.1001/archneurpsyc.1956.02330280027003

Thiélin-Bescond, M., & Beugnon, G. (2005). Vision-independent odometry in the ant Cataglyphis cursor. *Naturwissenschaften, 92*(4), 193-197. doi: 10.1007/s00114-005-0609-1

Thistlethwaite, D. (1951). A Critical Review of Latent Learning and Related Experiments. *Psychological Bulletin, 48*(2), 97-129. doi: Doi 10.1037/H0055171

Thom, C., Gilley, D. C., Hooper, J., & Esch, H. E. (2007). The Scent of the Waggle Dance. *PLoS Biol, 5*(9), e228. doi: 10.1371/journal.pbio.0050228

Thompson, L. T., & Best, P. J. (1990). Long-term stability of the place-field activity of single units recorded from the dorsal hippocampus of freely behaving rats. *Brain Res, 509*(2), 299-308.

Thompson, M. E., & Thompson, J. P. (1949). Reactive inhibition as a factor in maze learning; the role of reactive inhibition in studies of place learning versus response learning. *J Exp Psychol, 39*(6), 883-891.

Thomson, J. A. (1983). Is continuous visual monitoring necessary in visually guided locomotion? *J Exp Psychol Hum Percept Perform, 9*(3), 427-443.

Thorn, C. A., Atallah, H., Howe, M., & Graybiel, A. M. (2010). Differential dynamics of activity changes in dorsolateral and dorsomedial striatal loops during learning. *Neuron, 66*(5), 781-795. doi: 10.1016/j.neuron.2010.04.036

Thorup, K., Bisson, I. A., Bowlin, M. S., Holland, R. A., Wingfield, J. C., Ramenofsky, M., & Wikelski, M. (2007). Evidence for a navigational map stretching across the continental U.S. in a migratory songbird. *Proc Natl Acad Sci U S A, 104*(46), 18115-18119. doi: 10.1073/pnas.0704734104

Tolman, E. C. (1938). The determiners of behavior at a choice point. *Psychological Review, 45*(1), 1–41.

Tolman, E. C. (1939). Prediction of vicarious trial and error by means of the schematic sowbug. *Psychological Review, 46*(4), 318-336. doi: 10.1037/h0057054

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychol Rev, 55*(4), 189-208.

Tolman, E. C. (1949). THE PSYCHOLOGY OF SOCIAL LEARNING. *Journal of Social Issues, 5*(S3), 5-18. doi: 10.1111/j.1540-4560.1949.tb02393.x

Tolman, E. C. (1951a). *Collected papers in psychology*. Berkeley,: University of California Press.

Tolman, E. C. (1951b). *Purposive behaviour in animals and men*. Berkeley: Univ. of California Press.

Tolman, E. C., & Gleitman, H. (1949a). Studies in spatial learning: VII. Place and response learning under different degrees of motivation. *Journal of Experimental Psychology, 39*(5), 653-659. doi: 10.1037/h0059317

Tolman, E. C., & Gleitman, H. (1949b). Studies in spatial learning; place and response learning under different degrees of motivation. *J Exp Psychol, 39*(5), 653-659.

Tolman, E. C., & Honzik, C. H. (1930a). Degrees of hunger, reward and non-reward, and maze learning in rats. *University of California Publications in Psychology, 4*, 241-256.

Tolman, E. C., & Honzik, C. H. (1930b). *Introduction and removal of reward and maze performance in rats*. Berkeley, Calif.: University of California Press.

Tolman, E. C., & Krechevsky, I. (1933). Means-end-readiness and hypothesis--A contribution to comparative psychology. *Psychological Review, 40*(1), 60-70.

Tolman, E. C., & Minium, E. (1942). VTE in rats: overlearning and difficulty of discrimination. *Journal of Comparative Psychology, 34*(3), 301-306.

Tolman, E. C., Ritchie, B. F., & Kalish, D. (1946a). Studies in spatial learning: Orientation and the short-cut. *J Exp Psychol, 36*, 13-24.

Tolman, E. C., Ritchie, B. F., & Kalish, D. (1946b). Studies in spatial learning; place learning versus response learning. *J Exp Psychol, 36*, 221-229.

Tolman, E. C., Ritchie, B. F., & Kalish, D. (1947). Studies in spatial learning; response learning vs. place learning by the non-correction method. *J Exp Psychol, 37*(4), 285-292.

Touretzky, D. S., & Redish, A. D. (1996). Theory of rodent navigation based on interacting representations of space. *Hippocampus, 6*(3), 247-270. doi: 10.1002/(SICI)1098-1063(1996)6:3<247::AID-HIPO4>3.0.CO;2-K

Treit, D., & Fundytus, M. (1988). Thigmotaxis as a test for anxiolytic activity in rats. *Pharmacol Biochem Behav, 31*(4), 959-962.

Tsang, Y.-c. (1934). *The functions of the visual areas of the cerebral cortex of the rat in the learning and retention of the maze. I-II*. Baltimore: Johns Hopkins Press.

Tsoar, A., Nathan, R., Bartan, Y., Vyssotski, A., Dell'Omo, G., & Ulanovsky, N. (2011). Large-scale navigational map in a mammal. *Proceedings of the National Academy of Sciences, 108*(37), E718–E724. doi: 10.1073/pnas.1107365108

Tulving, E. (1983). *Elements of Episodic Memory*. Clarendon Press.

Tulving, E., Donaldson, W., Bower, G. H., & Research, U. S. O. o. N. (1972). *Organization of memory*. Academic Press.

Ullman, S. (1989). Aligning pictorial descriptions: an approach to object recognition. *Cognition, 32*(3), 193-254.

Valerio, S., & Taube, J. S. (2012). Path integration: how the head direction signal maintains and corrects spatial orientation. *Nat Neurosci, 15*(10), 1445-1453. doi: 10.1038/nn.3215

Van Cauter, T., Camon, J., Alvernhe, A., Elduayen, C., Sargolini, F., & Save, E. (2013). Distinct roles of medial and lateral entorhinal cortex in spatial cognition. *Cereb Cortex, 23*(2), 451-459. doi: 10.1093/cercor/bhs033

Van Cauter, T., Poucet, B., & Save, E. (2008). Unstable CA1 place cell representation in rats with entorhinal cortex lesions. *Eur J Neurosci, 27*(8), 1933-1946. doi: 10.1111/j.1460-9568.2008.06158.x

van der Meer, M. A., & Redish, A. D. (2010). Expectancies in decision making, reinforcement learning, and ventral striatum. *Front Neurosci, 4*, 6. doi: 10.3389/neuro.01.006.2010 van Groen, T., & Wyss, J. M. (1990). The connections of presubiculum and parasubiculum in the rat. *Brain Res, 518*(1-2), 227-243.

van Haeften, T., Wouterlood, F. G., Jorritsma-Byham, B., & Witter, M. P. (1997). GABAergic presubicular projections to the medial entorhinal cortex of the rat. *J Neurosci, 17*(2), 862-874.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential Effects of Early Hippocampal Pathology on Episodic and Semantic Memory. *Science, 277*(5324), 376-380. doi: 10.1126/science.277.5324.376

Vetter, T., Poggio, T., & Bulthoff, H. H. (1994). The importance of symmetry and virtual views in three-dimensional object recognition. *Curr Biol, 4*(1), 18-23.

Viljoen, P. J. (1989). Spatial distribution and movements of elephants (Loxodonta africana) in the northern Namib Desert region of the Kaokoveld, South West Africa/Namibia. *J. Zoology, London, 219*(1), 1-19.

Vollbehr, J. (1975). *Zur Orientierung junger Honigbienen bei ihrem ersten Orientierungsflug*.

Waddell, D., Gans, S., Kempner, P., & Williams, A. (1955). A comparison of place and response learning in very young rats. *Journal of Comparative and Physiological Psychology, 48*(5), 375-377. doi: 10.1037/h0040086

Wallace, D. G., & Whishaw, I. Q. (2003). NMDA lesions of Ammon's horn and the dentate gyrus disrupt the direct and temporally paced homing displayed by rats exploring a novel environment: evidence for a role of the hippocampus in dead reckoning. *Eur J Neurosci, 18*(3), 513-523.

Walters, D., Stringer, S., & Rolls, E. (2013). Path Integration of Head Direction: Updating a Packet of Neural Activity at the Correct Speed Using Axonal Conduction Delays. *PLoS ONE, 8*(3), e58330. doi: 10.1371/journal.pone.0058330

Warrant, E., & Dacke, M. (2010). Visual orientation and navigation in nocturnal arthropods. *Brain Behav Evol, 75*(3), 156-173. doi: 10.1159/000314277

Watanabe, S. (2001). Van Gogh, Chagall and pigeons: picture discrimination in pigeons and humans. *Animal Cognition, 4*(3-4), 147-151. doi: 10.1007/s100710100112

Watson, J. B. (1919). *Psychology, from the standpoint of a behaviorist*. Philadelphia and London,: J. B. Lippincott company.

Wehner, R. (1981). *Spatial vision in arthropods*: Springer-Verlag.

Wehner, R. (1997). The ant's celestial compass system: spectral and polarization channels. In M. Lehrer (Ed.), *Orientation and Communication in Arthropods* (Vol. 84, pp. 145-185): Birkhäuser Basel.

Wehner, R., Bleuler, S., Nievergelt, C., & Shah, D. (1990). Bees navigate by using vectors and routes rather than maps. *Naturwissenschaften, 77*(10), 479-482. doi: 10.1007/BF01135926

Wehner, R., & Lanfranconi, B. (1981). What do the ants know about the rotation of the sky? *Nature, 293*(5835), 731-733.

Wehner, R., & Menzel, R. (1990). Do insects have cognitive maps? *Annu Rev Neurosci, 13*, 403-414. doi: 10.1146/annurev.ne.13.030190.002155

Wehner, R., & Srinivasan, M. (1981). Searching behaviour of desert ants, genusCataglyphis (Formicidae, Hymenoptera). *Journal of comparative physiology, 142*(3), 315-338. doi: 10.1007/BF00605445

Wehner, R., & Wehner, S. (1990). Insect navigation: use of maps or Ariadne's thread? *Ethology Ecology & Evolution, 2*(1), 27-48. doi: 10.1080/08927014.1990.9525492

Whishaw, I. Q., Hines, D. J., & Wallace, D. G. (2001). Dead reckoning (path integration) requires the hippocampal formation: evidence from spontaneous exploration and spatial learning tasks in light (allothetic) and dark (idiothetic) tests. *Behav Brain Res, 127*(1-2), 49-69.

White, R. K. (1943). The case for the Tolman-Lewin interpretation of learning. *Psychological Review, 50*(2), 157-186. doi: 10.1037/h0057002

Whitlock, J. R., & Derdikman, D. (2012). Head direction maps remain stable despite grid map fragmentation. *Front Neural Circuits, 6*, 9. doi: 10.3389/fncir.2012.00009

Wible, C. G., Findling, R. L., Shapiro, M., Lang, E. J., Crane, S., & Olton, D. S. (1986). Mnemonic correlates of unit activity in the hippocampus. *Brain Res, 399*(1), 97-110.

Wiener, J. M., de Condappa, O., Harris, M. A., & Wolbers, T. (2013). Maladaptive bias for extrahippocampal navigation strategies in aging humans. *J Neurosci, 33*(14), 6012-6017. doi: 10.1523/jneurosci.0717-12.2013

Wiener, S. I. (1993). Spatial and behavioral correlates of striatal neurons in rats performing a self-initiated navigation task. *J Neurosci, 13*(9), 3802-3817.

Wiener, S. I., Paul, C. A., & Eichenbaum, H. (1989). Spatial and behavioral correlates of hippocampal neuronal activity. *J Neurosci, 9*(8), 2737-2763.

Wills, T. J., Barry, C., & Cacucci, F. (2012). The abrupt emergence of adult-like grid cell firing during the development of the medial entorhinal cortex. *Frontiers in Neural Circuits, 6*. doi: 10.3389/fncir.2012.00021

Wills, T. J., Cacucci, F., Burgess, N., & O'Keefe, J. (2010). Development of the Hippocampal Cognitive Map in Preweanling Rats. *Science, 328*(5985), 1573-1576. doi: 10.1126/science.1188224

Wills, T. J., Lever, C., Cacucci, F., Burgess, N., & O'Keefe, J. (2005). Attractor dynamics in the hippocampal representation of the local environment. *Science, 308*(5723), 873-876. doi: 10.1126/science.1108905

Wilson, D. I., Watanabe, S., Milner, H., & Ainge, J. A. (2013). Lateral entorhinal cortex is necessary for associative but not nonassociative recognition memory. *Hippocampus, 23*(12), 1280-1290. doi: 10.1002/hipo.22165

Wilson, D. I. G., Langston, R. F., Schlesiger, M. I., Wagner, M., Watanabe, S., & Ainge, J. A. (2013). Lateral Entorhinal Cortex is Critical for Novel Object-Context Recognition. *Hippocampus, 23*(5), 352-366. doi: 10.1002/hipo.22095

Wilson, I. A., Ikonen, S., Gallagher, M., Eichenbaum, H., & Tanila, H. (2005). Age-associated alterations of hippocampal place cells are subregion specific. *J Neurosci, 25*(29), 6877-6886. doi: 10.1523/jneurosci.1744-05.2005

Wilson, I. A., Ikonen, S., Gureviciene, I., McMahan, R. W., Gallagher, M., Eichenbaum, H., & Tanila, H. (2004). Cognitive aging and the hippocampus: how old rats represent new environments. *J Neurosci, 24*(15), 3870-3878. doi: 10.1523/jneurosci.5205-03.2004

Wilson, M. A., & McNaughton, B. L. (1993). Dynamics of the hippocampal ensemble code for space. *Science, 261*(5124), 1055-1058.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679.

Winograd, T. (1975). {Frame representations and the declarative/procedural controversy}. *Representation and understanding: Studies in cognitive science*. doi: citeulike-article-id:11455023

Winslow, J. B. V. P. L. A. L. A. S. d. m. c. e. p. d. T. B. E. r. d. c. (1767). *Exposition anatomique de la structure du corps humain, par M. Winslow*. A Paris: chez Vincent.

Witter, M. (2010). Connectivity of the Hippocampus. In V. Cutsuridis, B. Graham, S. Cobb & I. Vida (Eds.), *Hippocampal Microcircuits* (Vol. 5, pp. 5-26): Springer New York.

Witter, M. P. (1993). Organization of the entorhinal—hippocampal system: A review of current anatomical data. *Hippocampus, 3*(S1), 33-44. doi: 10.1002/hipo.1993.4500030707

Witter, M. P., & Moser, E. I. (2006). Spatial representation and the architecture of the entorhinal cortex. *Trends in Neurosciences, 29*(12), 671-678. doi: http://dx.doi.org/10.1016/j.tins.2006.10.003

Wittlinger, M., Wehner, R., & Wolf, H. (2006). The Ant Odometer: Stepping on Stilts and Stumps. *Science, 312*(5782), 1965-1967. doi: 10.1126/science.1126912

Wohlgemuth, S., Ronacher, B., & Wehner, R. (2001). Ant odometry in the third dimension. *Nature, 411*(6839), 795-798.

Wolbers, T., & Wiener, J. M. (2014). Challenges for identifying the neural mechanisms that support spatial navigation: the impact of spatial scale. *Frontiers in Human Neuroscience, 8*. doi: 10.3389/fnhum.2014.00571

Wolbers, T., Wiener, J. M., Mallot, H. A., & Buchel, C. (2007). Differential recruitment of the hippocampus, medial prefrontal cortex, and the human motion complex during path integration in humans. *J Neurosci, 27*(35), 9408-9416. doi: 10.1523/jneurosci.2146-07.2007

Wood, E. R., Dudchenko, P. A., Robitsek, R. J., & Eichenbaum, H. (2000). Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron, 27*(3), 623-633.

Worchel, P. (1951). Space perception and orientation in the blind. *Psychological Monographs: General and Applied, 65*(15), i-28. doi: 10.1037/h0093640

Wray, M. K., Klein, B. A., Mattila, H. R., & Seeley, T. D. (2008). Honeybees do not reject dances for 'implausible' locations: reconsidering the evidence for cognitive maps in insects. *Animal Behaviour, 76*(2), 261-269. doi: http://dx.doi.org/10.1016/j.anbehav.2008.04.005

Wright, N. F., Erichsen, J. T., Vann, S. D., O'Mara, S. M., & Aggleton, J. P. (2010). Parallel but separate inputs from limbic cortices to the mammillary bodies and anterior thalamic nuclei in the rat. *J Comp Neurol, 518*(12), 2334-2354. doi: 10.1002/cne.22336

Wystrach, A., Beugnon, G., & Cheng, K. (2011). Landmarks or panoramas: what do navigating ants attend to for guidance? *Frontiers in Zoology, 8*(1), 21.

Yoder, R. M., Clark, B. J., Brown, J. E., Lamia, M. V., Valerio, S., Shinder, M. E., & Taube, J. S. (2011). Both visual and idiothetic cues contribute to head direction cell stability during navigation along complex routes. *J Neurophysiol, 105*(6), 2989-3001.

Yoder, R. M., Clark, B. J., & Taube, J. S. (2011). Origins of landmark encoding in the brain. *Trends Neurosci, 34*(11), 561-571. doi: 10.1016/j.tins.2011.08.004

Yoder, R. M., & Taube, J. S. (2011). Projections to the anterodorsal thalamus and lateral mammillary nuclei arise from different cell populations within the postsubiculum: implications for the control of head direction cells. *Hippocampus, 21*(10), 1062-1073. doi: 10.1002/hipo.20820

Yoganarasimha, D., & Knierim, J. J. (2005). Coupling between place cells and head direction cells during relative translations and rotations of distal landmarks. *Exp Brain Res, 160*(3), 344-359. doi: 10.1007/s00221-004-2016-9

Yoganarasimha, D., Yu, X., & Knierim, J. J. (2006). Head direction cell representations maintain internal coherence during conflicting proximal and distal cue rotations: comparison with hippocampal place cells. *J Neurosci, 26*(2), 622-631. doi: 10.1523/jneurosci.3885-05.2006

Young, B. J., Fox, G. D., & Eichenbaum, H. (1994). Correlates of hippocampal complex-spike cell activity in rats performing a nonspatial radial maze task. *J Neurosci, 14*(11 Pt 1), 6553-6563.

Zaknich, A. (2005). *Principles of adaptive filters and self-learning systems*. London: Springer London.

Zeil, J. (1993a). Orientation flights of solitary wasps (Cerceris, Sphecidae, Hymenoptera): I. Description of flight. *Journal of Comparative Physiology A, 172*(2), 189-205.

Zeil, J. (1993b). Orientation flights of solitary wasps (Cerceris, Sphecidae, Hymenoptera): II. Similarities between orientation and return flights and the use of motion parallax. *Journal of Comparative Physiology A, 172*(2), 207-222.

Zeil, J., Boeddeker, N., & Hemmi, J. M. (2008). Vision and the organization of behaviour. *Current Biology, 18*(8), R320-R323. doi: http://dx.doi.org/10.1016/j.cub.2008.02.017

Zeil, J., Boeddeker, N., & Hemmi, J. M. (2009). Visually Guided Behavior. In L. R. Squire (Ed.), *Encyclopedia of Neuroscience* (pp. 369-380). Oxford: Academic Press.

Zeil, J., Hofmann, M. I., & Chahl, J. S. (2003). Catchment areas of panoramic snapshots in outdoor scenes. *J Opt Soc Am A Opt Image Sci Vis, 20*(3), 450-469.

Zeil, J., Kelber, A., & Voss, R. (1996). Structure and function of learning flights in ground-nesting bees and wasps. *J Exp Biol, 199*(Pt 1), 245-252.

Zhang, S., Schönfeld, F., Wiskott, L., & Manahan-Vaughan, D. (2014). Spatial representations of place cells in darkness are supported by path integration and border information. *Front Behav Neurosci, 8*, 222. doi: 10.3389/fnbeh.2014.00222

Zilli, E. A., & Hasselmo, M. E. (2008). Modeling the role of working memory and episodic memory in behavioral tasks. *Hippocampus, 18*(2), 193-209. doi: 10.1002/hipo.20382

Zipf, G. K. (1949). *Human behavior and the principle of least effort; an introduction to human ecology*. Cambridge, Mass.,: Addison-Wesley Press.

Zipser, D. (1985). A computational model of hippocampal place fields. *Behav Neurosci, 99*(5), 1006-1018.

Zoladek, L., & Roberts, W. (1978). The sensory basis of spatial memory in the rat. *Animal Learning & Behavior, 6*(1), 77-81. doi: 10.3758/bf03212006

Zugaro, M. B., Tabuchi, E., & Wiener, S. I. (2000). Influence of conflicting visual, inertial and substratal cues on head direction cell activity. *Exp Brain Res, 133*(2), 198-208.