REACTIVATION OF THE HIPPOCAMPAL COGNITIVE MAP IN GOAL-DIRECTED SPATIAL TASKS

by

Haibing Xu

August, 2017

A thesis presented to the
Graduate School
of the
Institute of Science and Technology Austria, Klosterneuburg, Austria
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

IST AUSTRIA
Institute of Science and Technology

The dissertation of Haibing Xu, titled *Reactivation of the Hippocampal Cognitive Map in Goal-Directed Spatial Tasks* is approved by:

Supervisor: **Prof. Dr. Jozsef Csicsvari**, IST Austria, Klosterneuburg, Austria

Committee Member: **Prof. Dr. Peter Jonas**, IST Austria, Klosterneuburg, Austria

Committee Member: **Prof. Dr. David M Bannerman**, Department of Experimental Psychology, University of Oxford, Oxford, UK

Exam Chair: **Prof. Dr. Maximilian Jösch**, IST Austria, Klosterneuburg, Austria

I hereby declare that this dissertation is my own work and that it does not contain other people's work without this being so stated; this thesis does not contain my previous work without this being stated, and the bibliography contains all the literature that I used in writing the dissertation.

I declare that this is a true copy of my thesis, including any final revisions, as approved by my thesis committee, and that this thesis has not been submitted for a higher degree to any other university or institution.

I certify that any republication of materials presented in this thesis has been approved by the relevant publishers and co-authors.

Signature: _____

Haibing Xu

August 22, 2017

Abstract

The hippocampus is a key brain region for memory and notably for spatial memory, and is needed for both spatial working and reference memories. Hippocampal place cells selectively discharge in specific locations of the environment to form mnemonic representations of space. Several behavioral protocols have been designed to test spatial memory which requires the experimental subject to utilize working memory and reference memory. However, less is known about how these memory traces are presented in the hippocampus, especially considering tasks that require both spatial working and long-term reference memory demand. The aim of my thesis was to elucidate how spatial working memory, reference memory, and the combination of both are represented in the hippocampus.

In this thesis, using a radial eight-arm maze, I examined how the combined demand on these memories influenced place cell assemblies while reference memories were partially updated by changing some of the reward-arms. This was contrasted with task variants requiring working or reference memories only. Reference memory update led to gradual place field shifts towards the rewards on the switched arms. Cells developed enhanced firing in passes between newly-rewarded arms as compared to those containing an unchanged reward. The working memory task did not show such gradual changes. Place assemblies on occasions replayed trajectories of the maze; at decision points the next arm choice was preferentially replayed in tasks needing reference memory while in the pure working memory task the previously visited arm was replayed. Hence trajectory replay only reflected the decision of the animal in tasks needing reference memory update. At the reward locations, in all three tasks outbound trajectories of the current arm were preferentially replayed, showing the animals' next path to the center. At reward locations trajectories were replayed preferentially in reverse temporal order. Moreover, in the center reverse replay was seen in the working memory task but in the other tasks forward replay was seen. Hence, the direction of reactivation was determined by the goal locations so that part of the trajectory which was closer to the goal was reactivated later in an HSE while places further away from the goal were reactivated earlier.

Altogether my work demonstrated that reference memory update triggers several levels of reorganization of the hippocampal cognitive map which are not seen in simpler working memory demands. Moreover, hippocampus is likely to be involved in spatial decisions through reactivating planned trajectories when reference memory recall is required for such a decision.

Acknowledgments

I am very grateful for the opportunity I have had as a graduate student to explore and incredibly interesting branch of neuroscience, and for the people who made it possible.

Firstly, I would like to offer my thanks to my supervisor Professor Jozsef Csicsvari for his great support, guidance and patience offered over the years. The door to his office was always open whenever I had questions. I have learned a lot from him about carefully designing experiments, asking interesting questions and how to integrate results into a broader picture.

I also express my gratitude to the remarkable post-doc, Dr. Joseph O'Neill. He is a great scientific role model who is always willing to teach, and advice and talk through problems with his full attention.

Many thanks to my wonderful "office mates" over the years and their support and encouragement, Alice Avernhe, Philipp Schönenberger, Desiree Dickerson, Karel Blahna, Charlotte Boccara, Igor Gridchyn, Peter Baracskay, Krisztián Kovács, Dámaris Rangel, Karola Käfer and Federico Stella. They were the ones in the lab for the many useful discussions about science and for making the laboratory such a nice and friendly place to work in. A special thank goes to Michael LoBianco and Jago Wallenschus for wonderful technical support.

I would also like to thank Professor Peter Jonas and Professor David M Bannerman for being my qualifying exam and thesis committee members despite their busy schedule.

I am also very thankful to IST Austria for their support all throughout my PhD.

Finally, I must express my very profound gratitude to my parents and my sister for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching. This accomplishment would not have been possible without them.

Table of Contents

List of Figures

Abbreviations

1D One dimensional

2D Two-dimensional

AP Anterior posterior

CA1 Cornu ammonis 1 area of the hippocampus

CA2 Cornu ammonis 2 area of the hippocampus

CA3 Cornu ammonis 3 area of the hippocampus

CS Complex spike

DG Dentate gyrus

EC Entorhinal cortex

EEG Electroencephalogram

HSE High synchrony event

LED Light-emitting diodes

LTP Long term potentiation

ML Medial lateral

MEC Medial entorhinal cortex

mPFC Medial prefrontal cortex

PCA Principal Component analysis

SD Standard deviation

SEM Standard error of the mean

SWRs Sharp wave/ripple events

VTA Ventral tegmental area

1 Introduction

The ability to remember what we did and where and when events happened has an important evolutionary advantage, enabling us to more efficiently locate previously discovered food resources, avoid predators and find potential mates. Such memory may be stored to be used hours, days or even years later. In addition to using such longer term memories to facilitate successful navigation, a shorter term spatial 'working' memory is continuously updated on a time scale of seconds to minutes. This kind memory allows us to make choices based on where we have just been and, therefore, estimate what might be expected in the immediate future. Both of these memories are dependent on an intact hippocampus which is an evolutionary old brain region in mammals located in the limbic system.

In this dissertation, I look at spatial memory and elucidate circuit processing events necessary for encoding and retrieving memories. In the introduction chapter I briefly describe the main features of the hippocampus. Chapter 1.1 is dedicated to its anatomy. Chapter 1.2 sketches its memory function and introduces the discoveries made from the hippocampal damage and lesion studies. Chapter 1.3 I describe the spatial tuning of cells in hippocampus, in particular I will introduce how such place cells modulate their firing during various spatial memory tasks. In Chapter 1.4 I focus on the experimental work about hippocampal sequence replay. Finally in Chapter 1.5 I give a short overview of the goals of my study.

1.1 Anatomical organization of the hippocampus

The definition of the hippocampal formation used in my dissertation will be the same as that described by Amaral and Lavenex (2007). The hippocampal formation includes brain areas including the hippocampus proper, dentate gyrus (DG), entorhinal cortex (EC), subiculum, presubiculum (which includes the postsubiculum) and the parasubiculum. The hippocampus proper includes the CA3, CA2 and CA1 subregions. The excitatory projections from the DG to CA3, called the mossy fibers, and then from the CA3 to CA1projections, called the Schaffer

collaterals, together form the feed-forward projection system, the “tri-synaptic path” (**Figure 1**). In turn, this circuit forms a loop with the entorhinal cortex (EC), with each sub-region receiving direct input from EC, and the CA1 region sending the projections back to the EC (either directly, or indirectly via the subiculum). Cells in layer 2 of the EC project to the DG and CA3, called the perforant pathway, while layer 3 EC projections to CA1 are called the temporoammonic pathway. Axons of CA3 pyramidal cells make both numerous recurrent connections with other CA3 pyramidal cells (Ishizuka et al., 1990; Li et al., 1994) as well as projecting to the dendritic layers of CA1 via the Schaffer collaterals. The principal cells of the hippocampus proper are pyramidal cells, while granule cells are the primary excitatory cells in the DG. There is a large variety of inhibitory cell types in the hippocampus (Freund and Buzsaki, 1996; Klausberger and Somogyi, 2008).

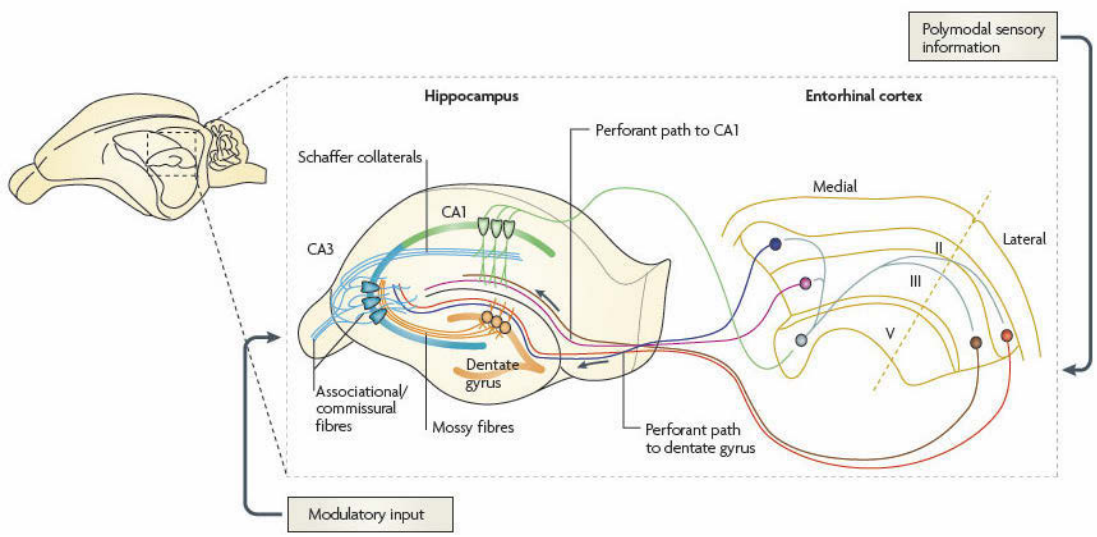

Figure 1 | Anatomy of the hippocampus

The hippocampal formation is a compound structure in the medial temporal lobe of the brain. Polymodal sensory information converges on the entorhinal cortex (EC) from various neocortical regions. Projections originating from the EC form the perforant path that project to the dentate gyrus. More precisely, axons from the layer II of medial and lateral EC innervate proximal and distal dendrites of the dentate granule cells, respectively. Axons of the dentate granule cells form mossy fibers which project to CA3 pyramidal neurons. In turn, CA3 pyramidal neurons project to CA1 via Schaffer collaterals. Finally, pyramidal cells in CA1 and the subiculum project back to the deep layers of the entorhinal cortex. In addition to this circuit, CA3 pyramidal cells also project to other ipsilateral and contralateral CA3 neurons via associational and commissural fibers, respectively. In addition, neurons from layer III of the EC also project directly to CA1 dendrites. Figure adapted from (Neves et al., 2008).

1.2 Discoveries made from the hippocampal damage and lesion studies

1.2.1 The case of Henry Molaison (H.M.)

A key way to understand the role of a particular brain region is by examining behavioral impairment caused by its lesion or damage. Although accidentally, that is exactly how the role of the hippocampus and medial temporal lobe regions in memory was first discovered. H.M. is probably the most famous patient in the history of neuroscience. He had a bicycle accident when he was at age nine. Soon afterwards, he began suffering from minor seizures from the age of ten, and had his first major seizure after age 16. At the time, he was suffering from drug-resistant epilepsy: even when given the maximum dosage, his condition of intractable severe epilepsy remained. This led neurosurgeon William Beecher Scoville to surgically remove a large portion of his bilateral medial temporal lobe, covering the two-thirds of the hippocampus and a portion of the entorhinal and perirhinal cortices, the uncus as well as the amygdala.

After surgery, he was impaired in forming new memories about events occurring in his personal life (anterograde amnesia) and in remembering events that happened shortly before the damage (transient retrograde amnesia). This association was first reported by Scoville and Milner (1957), followed by reports by hundreds of neuroscientists throughout H.M.'s life. These studies suggest that the lesion caused a deficit in the ability to from new memories of lifetime events (i.e. episodic memory), regardless of stimulus material, sensory modality (global anterograde amnesia). In addition it suffered from moderate graded retrograde amnesia involving the loss of memory of events prior to the surgery, especially in the two years preceding the ablation (Corkin, 2002). In spite of this memory deficit, his procedural memory (abilities to learn motor tasks such as drawing with the help of a mirror) was mostly preserved as well as his working memory and language abilities (Scoville and Milner, 1957; Corkin, 2002; Smith and Kosslyn, 2007).

HM's case was the first of its kind and, therefore, provided the first evidence for the existence of multiple memory system and the role of the hippocampal region in episodic memory (Squire, 1992; Eichenbaum and Cohen, 2001). This role has since been further

confirmed by many investigations, notably of patients affected by Alzheimer's disease. Alzheimer's is a neurodegenerative disorder that leads to memory loss and ultimately to dementia. The neurodegeneration consists of loss of neurons and synapses in the cerebral cortex and certain subcortical regions, especially in the region of the hippocampal region (Braak and Braak 1991).

1.2.2 Spatial learning and the rodent hippocampus

Soon after the publication of Scoville and Milner (1957), several neuroscientists started to develop animal experimental paradigms to test the effects of hippocampal damage on learning and memory in animals. The study of spatial memory is at the heart of my thesis. Lesion of the rodent hippocampal formation have also been found to cause severe deficits in learning and memory across a range of spatial behavioral tasks, including tasks performed in the T-maze, radial eight-arm maze and Morris water maze. (Rawlins and Olton, 1982; Sutherland et al., 1983; Morris et al., 1982)

1.2.2.1 Spatial working memory on a T-maze alternation task

The T-maze spatial alternation task consists of a start arm (central segment) and two identical goal arms on the sides (Rawlins and Olton, 1982). When the animal performs a number of trails on the maze, they tend to innately alternate between the side arms on each successive trial and such alternation requires the hippocampus. This task can be performed on continuous T-mazes as well in which the side arms are connected with start location of the central arm enabling the uninterrupted movement of the animal (Wood et al., 2000). In the normal T-maze where animals have to be placed back manually to the start location, performing the alternation task requires the hippocampus. By contrast, on the continuous T-mazes animals are able to alternate between arms even without the hippocampus (Ainge et al., 2007a). However, when a delay is introduced between trials on the continuous T-maze the hippocampus was required. Another commonly used version on a T-maze is the delayed non-match to sample task in which trials are divided into two

phases: a sample run and a choice run (Deacon and Rawlins, 2006). On the sample phase, the animal is forced to visit either the left or the right side arm since the other goal arm is blocked. On the choice phase both side arms are open and the animals need to choose the opposite arm. This type of task requires working memory because the animal has to remember the arm it visited before in order to choose accurately the correct arm during the choice run. Rodents with intact hippocampus tend to alternate with minimal error in this task, while animals with complete lesions of the hippocampus usually perform at chance level errors (Deacon and Rawlins, 2006).

1.2.2.2 Spatial reference memory on the Morris water maze

The original place learning task on the Morris water maze was developed by Richard Morris et al. (1982). This maze consists of a large circular tank in which animal has to escape from the water by finding the hidden escape platform hidden below the water surface level. During the spatial acquisition phase, the animal is placed facing the maze wall from where it has to swim to find the platform to escape from the water. The animal is allowed to remain on the platform for a short time before commencing to the next acquisition trial. During the spatial test phase, the escaped platform is removed and the animal has to swim freely for one minute, in order to test the extent to which the animal learned the location of the platform. The swimming paths taken by the animals are monitored by a video camera mounted on the ceiling. Control animals usually spend most of their time swimming around the location in which the platform was previously placed. In contrast, the group with hippocampal lesions tended to swim in a circle and did not show a marked preference for the area close to the platform location (**Figure 2A**). This task, and variants of it, has been widely used to test the memory ability of the animals in a hippocampus-dependent spatial task (Morris et al., 1990; Moser et al., 1993; Bannerman et al., 1999). Others developed similar place learning paradigms in dry conditions where animals have to learn reward locations (Barnes, 1979; Kesner et al., 1991; Gilbert et al., 1998) or avoid a noxious stimulus (Kentros et al., 2004; Lenck-Santini et al., 2008).

1.2.2.3 Radial eight-arm maze task

The radial eight-arm maze can be used for learning tasks to probe both long-term reference and short-term working memory, in rats (Olton and Samuelson, 1976) and mice (Crusio et al., 1987). In rodents, spatial working memory requires the ability to keep trial-specific information active over a limited period of time. Spatial reference memory is a form of long-term memory representing the spatial, contextual, and factual aspects of a task that remains constant between trials. This maze consists of a central platform with eight arms surrounding it (note that six-arm mazes are also used, e.g. in mouse experiments). Doors are usually located at the entrance to each arm to confine the animal in the central platform. At the end of each arm food can be hidden in wells, so that the food could not be seen from the central platform by the animal. The maze is normally surrounded by room objects and numerous visual cues that are visible from different arms.

In the simplest task configuration only spatial working memory is tested (Jarrard, 1993; Schmitt et al., 2003; Niewoehner et al., 2007). In this task, each trial begins by putting food reward at the end of all eight arms and placing the animal on the central platform. The animal is free to traverse the maze and consume the food rewards. During early trials, the animal has no knowledge of the maze layout or rules and, as such, it wanders on the maze, randomly visiting the same arms multiple times. Nevertheless, over subsequent trials, the animal forms an internal representation of the spatial layout of the maze and uses this knowledge to navigate the maze efficiently in order to minimize the number of repeat visits. To succeed on this task, the animal must rely on spatial working memory to keep track of which arms it has visited within a given trial.

A second variant of radial maze tasks involves not only a working memory demand but also reference memory demand as well. In such cases, typically only four out of eight arms are baited with food rewards and these baited arms remain the same across the learning trials. In each trial it is possible to differentiate working and reference memory errors. Both the number of working and reference memory errors increase in rats with hippocampal lesions as compared to control lesion animals demonstrating the involvement of the hippocampus in both memory systems (Schmitt et al., 2003; Jarrard et al., 2004; Niewoehner et al., 2007) (**Figure 2B**).

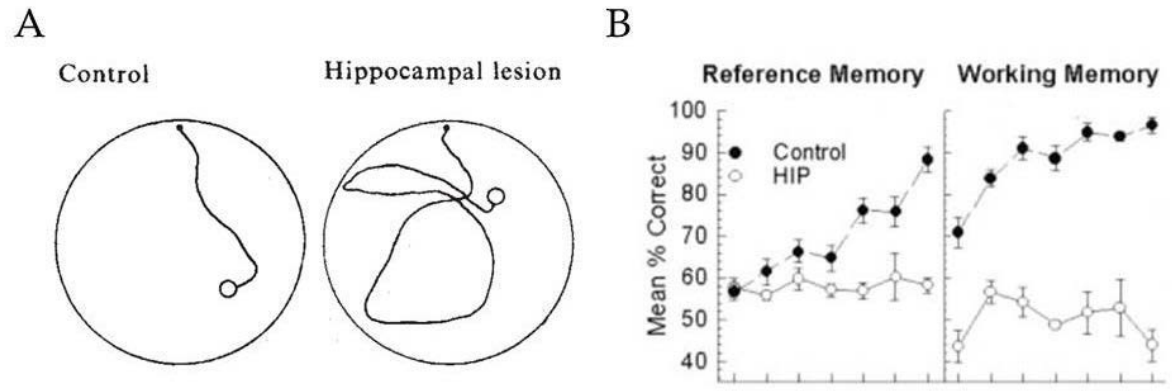

Figure 2 | Hippocampal lesion studies

(A) Representative paths during a probe trial of a rat with hippocampal lesions and a control rat on to reach the escape platform in Morris water maze. The hippocampal-lesion animals took longer and more circuitous routes to find the hidden platform (adapted from Morris et al., 1982).
(B) Performance of rats with excitotoxicity lesion of the hippocampus and control on a version of the radial arm maze task in which the same four arms are baited at the beginning of each trial. The performance in the reference memory and working memory aspects of the task is shown separately (adapted from Jarrard et al., 2004).

1.2.2.4 Task testing the involvement of the dorsal and ventral hippocampi

Lesions along the longitudinal axis of the hippocampus have also revealed that dorsal and ventral portions of the hippocampus encode different information. Ventral lesions impaired fear-related behavior in an elevated plus-maze task in which two arms have side walls while the other two are completely open (Steffenach et al., 2005). Indeed, the ventral hippocampus is connected with a number of brain regions implicated in motivation, emotion, and executive functions (Witter et al., 2013). These connections suggest that the ventral hippocampus is more involved in innate behaviors, such as fear-related behavior and anxiety (Kjelstrup et al., 2002) or the utilization of internal cues (Hock and Bunsey, 1998). By contrast, dorsal lesions have a greater effect on spatial learning than lesions of the ventral region (Moser et al., 1993; Potvin et al, 2006). For this reason dorsal hippocampus recording has been the main focus of my thesis work examining spatial memory representation of neurons.

1.3 Place coding in the hippocampus

1.3.1 Place cell and the cognitive map

The first and most influential observation that the hippocampus is involved in spatial representations was revealed by the discovery of place cells (O'Keefe and Dostrovsky, 1971). In this study, they implanted rats with 8 glass-insulated platinum-plated tungsten microelectrodes, one electrode was moved into the cortical white matter to serve as a reference electrode while the other electrodes were moved down to the dorsal hippocampus in search of units. While rats were running in a counter-clockwise direction around the test platform they monitored the neuronal activity in the dorsal hippocampus. They reported that 8 of the 76 units responded "solely or maximally when the rat was situated in a particular part of the testing platform facing in a particular direction". They suggested that hippocampal neurons fired in response to the visual or tactile sensory inputs and to orientation position.

Next, John O'Keefe performed another study in which hippocampal neurons were recorded when rats were running on a spatial discrimination task on a T-maze (O'Keefe and Conway, 1978). The maze was surrounded by curtains with visual cues in each direction and a light-emitting diode (LED) was mounted on the rats' head to monitor their position. From this study, they clearly demonstrated that many hippocampal cells fire only in one small area of their exploration environment. Those cells coding for the location can function as so-called "place cells" and the region of high firing was referred to as a "place field". They found as well that there was no systematic relationship between the place fields of units in different environments. Based on these findings O'Keefe and Nadel (1978) proposed that such hippocampal place cells form an allocentric cognitive map of their surrounding environment.

When animals are exploring two-dimensional (2D) environments the firing of place fields is largely independent of the heading direction of the animal. By contrast, when animals run on narrow tracks place cells may only fire either in forward or backward directional runs only (McNaughton et al., 1983; O'Keefe and Recce, 1993). It was also shown that the

proportion of such directionally firing place cells increases with the familiarity of the environment (Markus et al., 1995). More recent work also demonstrated that place cell firing in 2D environments is also modulated by the direction at which a place cell approaches its place field. Place cells tend to fire stronger when the direction of the animal will cross the center of the place field (Huxter et al., 2008). Moreover, some cells may modulate their firing according to allocentric head direction of the animal (Acharya et al., 2016).

Place cells were originally discovered in the CA1 region (O'Keefe and Dostrovsky, 1971). Shortly after, Ranck (1973) described two types of neurons in the hippocampal formation: the complex spike (CS) cells and the theta cells. The CS cells were shown to present some spatial modulation; notably linked to rewards and was classified in two categories: approach-consummate and approach-consummate mismatch. These cells were recorded from both CA1 and CA2/CA3 regions. Later, it was suggested that the CS are principal cells and the theta cells are interneurons (Fox and Ranck, 1975). Finally, in 1978, place modulation was clearly reported in the DG (Olton et al., 1978).

1.3.2 Single neuron spatial code in other hippocampal region

Approximately a decade after the discovery of place cells, James Ranck, while investigating the rat parahippocampal region, described neural correlates of directional signals: the head direction cells (Ranck, 1984). And later Ranck lab published a complete account of head direction cells properties (Ranck, 1984; Taube and Muller, 1990). A given head direction cell is active whenever the animal faces a particular direction in the environment, irrespective of where it is or what it is doing. They were first observed in the rats' dorsal presubiculum (also known as postsubiculum), a region that gives strong indirect inputs to the hippocampus.The entorhinal cortex is the hub of the hippocampal region. This quite large parahippocampic area connects sensory, association and directional inputs with the hippocampus proper (Lavenex and Amaral, 2000). Indeed the dorsal part of the hippocampus shows the clearest spatial selectivity (Jung and Wiener, 1994) and receives projections specifically from the dorsolateral band of the medial EC (MEC) (Dolorfo and Amaral, 1998). Therefore, specific

recordings targeted at the dorsal MEC showed a high amount of spatial modulation (Quirk et al., 1992; Fyhn et al., 2004). These spatially modulated neurons are different from place cells. They present multiple firing fields organized in a regular hexagonal grid pattern so that they tessellate the whole environment: hence their name: grid cells (Hafting et al., 2005). In addition, the collective activity of a small number of simultaneously recorded grid cells is sufficient to reconstruct accurately the trajectory of a rat (Fyhn et al., 2004). A large portion of the grid cells code for head direction in addition to their spatial modulation (Sargolini et al., 2006).

1.3.3 Place cells and Remapping

It was found early that the spatial firing activity of place cells can be modified by manipulation of the environment. This modification of firing activity is commonly referred to as remapping, describing the formation of a new place field, the disappearance of current place fields, the change of the locations of place fields or firing rate change of place cells.

Muller and Kubie (1987) first introduced how changing the shape of the arena affected hippocampal place cells activity. They recorded from two familiar environments, one was cylindrical and another was a square. They found that populations of place cells were active in both environments, but the place fields were different. Changes to the environmental cues led to the movement of the place fields or to their remapping. When the cue card attached to the wall of the arena was rotated by 90 degrees, place fields rotated by the same amount. However, changing the cue card, the shape, or size of the environment all resulted in the remapping of place fields. Note however that moderate changes of the size of rectangular enclosures may not lead to remapping but a rescaling of the place fields (Burgess and O'Keefe, 1996). When first described, remapping was referred to as a change in firing or location. This type of remapping was later termed "global remapping", showing that place fields randomly rearrange when a new environment is encountered. In some other situations when the two environments presented have just minor differences, for example, when place fields were recorded in the same enclosure but in different recording rooms, place cells retained the same firing field locations in both environments but firing

rates were different. Such a situation was called “rate remapping” (Fyhn et al., 2004; Leutgeb et al., 2005).

1.3.4 Place cells and multiple behavioral goals

While in the last part I discussed the behavior of hippocampal neurons when the animal performed a simple task, involving random foraging or running back and forth for food on a linear track, this part covers hippocampal cell activity responses during spatial memory tasks. In general, hippocampal neurons respond to the animal’s place and to a variable associated with the memory task. Although more recent work examines these responses in relation to place cells, earlier work measured behavior-related cell firing responses without the strict control of place.

1.3.4.1 Non-match-to-sample task

To answer the question as to whether hippocampal neurons encode information about external, non-spatial stimuli, Wood et al. (1999) trained rats to perform an odor-guided non-match-to-sample task. On each trial, a cup containing sand scented with one of nine spices was placed on a platform. On half of the trials (a ‘non-match’) the scent was different from that of the previous trial and a food reward was buried at the bottom of the cup. On the other half of the trials (a ‘match’), the odor was the same as that the previous trial and the cup was not baited. The rat had to approach and sniff the cup and subsequently dig in it or turn away. Therefore, the rat had to keep track of the odor presented on the previous trial and decide to dig or turn away from the cup based on the comparison of the current and previous odors. The location of the cup changed on each trial. The firing responses of many recorded cells were associated with a variety of task-associated variables: positon of the cup, odor, matching or non-matching trials. The authors recorded a few cells that showed differential firing with different odor stimuli, independently from the location of the cup. It was suggested that cells show correlations with many aspects of the task: the position, the rat’s approach to the odor cup, the odor being sniffed and the trial type (match or non-match observed). Subsequent studies have refined this experimental design and used few,

systematically arranged fixed cup locations and different shape cups in different environments (McKenzie et al., 2013; McKenzie et al., 2014). Overall place cell assemblies were most separated when different environments were considered followed by differences in the location of cups. However differences were found in relation to object valence (i.e. whether a cup contained food) and the least amount of differences were seen in relation to object type (i.e. different cup type). By now it is widely accepted that place cell activity can be modulated by a variety of task parameters. Whether hippocampal cells in the rodent hippocampus can encode task parameters independent to place remains controversial however and this aspect of the Wood et al. (1999) study has never been replicated.

1.3.4.2 Spatial tasks on T-maze and W-shaped track

As outlined above it has been shown that place cells can exhibit task-related information. In many memory tasks sensitive to hippocampal damage, the animal must not only keep track of its current position but also its previous position in order to decide about future choices. This was first examined by Wood et al., (2000) where the influence of task-dependent variables were examined on the activity of hippocampal place cells in a spatial working memory task (Wood et al., 2000). In this work, rats were trained to navigate through a continuous T-maze in an alternating manner by always choosing the opposite side arm than that it took before. Note that this version of the task was later proven not to be hippocampus dependent as I discussed before (Ainge et al., 2007a). The place cell activity was analyzed in the central stem of the T-maze, and it was found that the firing fields of the same cell in the central stem can be different depending on whether the animal turned right or left at the end of the stem (**Figure 3A**). Moreover such differences in the place fields could not be explained by variation in behavior (head direction, speed, etc.).

In the continuous alternation task it was not clear whether the firing represents the future choice or the previous location of the animal. Numerous studies have attempted to differentiate place field variations related to the past locations (retrospective coding) or future choices (prospective coding) by using complex maze tasks (Ferbinteanu and Shapiro, 2003; Shapiro and Ferbinteanu, 2006). For example, to find out whether the influence on the place fields is retrospective or prospective Frank et al. (2000) trained rats on a W-shaped maze to alternate responses to the left and right arms. The rats were rewards at the end of

the left and right arms but also at the end of the central arm, which they were required to visit between each outside arm visit. Place fields in the center arm were analyzed and it was found that in inbound runs place cells coded retrospectively the previous arms visit while in outbound trials the next arm visit is coded prospectively (Frank et al., 2000). Note however that prospective and retrospective coding could not be properly separated here either because the animal was still alternating between the arms in the center. Because of this, once approaching from one arm it always continued to the opposite arm; therefore, prospective and retrospective coding of cells could not be truly differentiated (**Figure 3B**). Other studies of this kind had similar caveats related to prospective coding given that in such studies always two choices were used in even more complex mazes and some previous location determined the next choice of the animal.

In order to make past visits independent of future choices, Allen et al. (2012), examined the activity of hippocampal neurons during a conditional discrimination task in which the identity of a food reward guided the spatial behavior of the animal. The rat received one of two food types on the central arms of a T-maze and had to enter the right or left arm of the maze to get more of the same food. This study found that the activity of a subgroup of pyramidal cells showed changes in their firing rate on the central arm of the maze depending on the identity of the conditional cue (i.e. next arm choice) or by the previous arm visit. Moreover, the firing of some pyramidal cells was influenced both by the conditional cue and by retrospective position (conjunctive coding cells). Importantly, they found that firing rate was an excellent predictor of the animal's choice on correct trials, but not on error trials. They suggest a dual role of the hippocampus on this task, providing both allocentric spatial information and task contingent information supporting the rat's behavior.

The Allen et al. (2012) study also revealed that conditionally firing place cells do not form new place fields to encode task-contingent information. Instead, the same place field is used and the in-field rate of the place cells is modulated; i.e., place cells use rate remapping. This was shown both in relation to food-guided task and in the continuous alternation task (Allen et al., 2012). A more recent work (O'Neill et al., 2017) shows similar rate remapping during the delayed non-matched to sample task as well, and showed that not only hippocampal place cells but medial entorhinal grid cells exhibit such rate remapping-associated coding.

In all these experiments, it has been demonstrated that a portion of the place cells carry information about the temporal context since past or future events could be predicted by analyzing the firing patterns and that rate remapping underlines such task-related coding

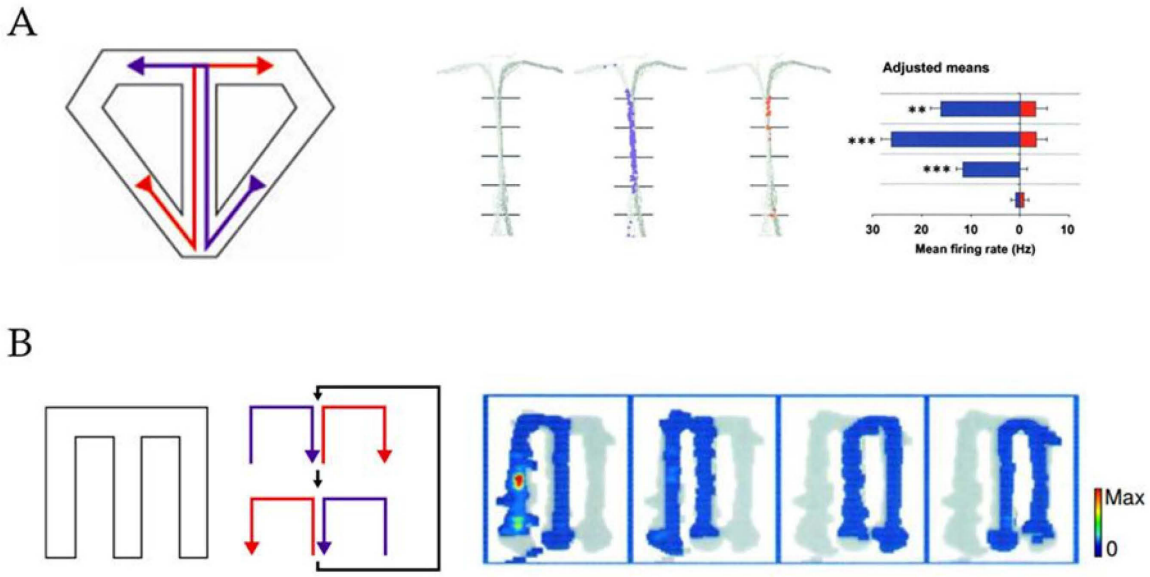

Figure 3 | Schematic illustration of the arenas and hippocampal conditional firing during the continuous rewarded alternation tasks

(A) Left panel: Modified T-maze used by Wood et al. (2000) to test rats on a continuous rewarded alternation task. Right panel: One pyramidal cell showing conditional firing on the central arm of the T-maze depending on the trial types (left-turn or right-turn). (Adapted from Wood et al., 2000)
(B) Left panel: The W track environment used by Frank et al. (2000). The animal ran in the following pattern: left, center, right, center, left, center and so on. Right panel: a CA1 cell showing the trajectory represented in each column. (Adapted from Frank et al., 2000)

1.3.4.3 Goal-directed learning task in two-dimensional environments

Place fields are found throughout the rat's environment. However, previous studies have shown that locations of place fields are not distributed homogeneously when animals engage in memory tasks. In a reference memory version of an annular water maze task where a rat had to find a hidden platform, it was shown that place fields accumulate around the hidden platform (Hollup et al., 2001). In another study, using a conditioned place preference task it was found that place cells exhibit a distinct secondary place field at the goal location, which triggers the release of a reward (Hok et al., 2007). Since those cells just fire near the goal location where the animals were waiting for a food pellet to be dropped in

the arena, there is a concern that the secondary place field may reflect network activity patterns during immobility such as sharp wave ripples (see below) that increase cell firing and may cause increased firing at the goal zone.

The spatial distribution of place field can be affected not only by goals per se but by the change of such goal locations. Dupret et al., (2010) trained rats to collect three food rewards from the cheeseboard arena. In this task the location of the food changed daily and every day the rats had to learn the new location of the food rewards. Mirroring the behavioral demand, the place fields of cells remapped daily many of them firing near the newly-baited reward locations. In this experiment, most of the place cells shifted their place fields towards one of the three daily changing reward locations. Importantly, such place field shift was observed in the CA1 region only, not in CA3. Moreover, goal-oriented place field shift occurred when animals had to use allocentric navigation to locate the food: when local guide posts marked the location of the food, no goal-remapping took place.

1.4 Hippocampal replay sequences

1.4.1 Sharp Wave/Ripple patterns

Electrical activity patterns of local field potentials in the hippocampus were first categorized according to the stereotyped behavior of the animal. Vanderwolf (1969) implanted an electrode into the hippocampus of freely moving rats and recorded local field potentials during different behavioral patterns and identified three behavioral states: a rhythmical theta state, a large irregular amplitude activity (LIA) state, and a small amplitude irregular activity (SIA) state (Vanderwolf, 1969)(**Figure 4A**). Theta oscillations ranges from 6 to 12 Hz in behaving rodents but has been reported slower in others species, e.g. 4 Hz in the rabbit (Green and Arduini, 1954). Theta rhythm is found when rats are moving or exploring. The LIA state is thought to represent a more irregular state of the network; a state in which memories previously encoded in the hippocampus are thought to be strengthened or transferred to other brain regions (Buzsaki, 1983; Buzsaki, 1989). This LIA state is characterized by irregularly occurring sharp waves of ~50-100ms duration, and associated high frequency (150-250Hz) ripple oscillations (Buzsaki et al., 1992) (**Figure 4B**). Sharp

wave/ripple patterns (SWR) occur mainly during slow wave sleep, waking immobility, brief interruptions of exploratory behavior and consummatory behaviors. During the initiation of SWR, neurons in the entorhinal cortex are relatively silent, therefore, SWR are usually considered to be generated within the hippocampus from the interactions of neurons in the CA3 region (Mizuseki et al., 2009). During SWRs both firing rate and the synchronization of neurons in the CA3 and CA1 regions increase. The degree of increase in firing rate and synchrony is higher in the CA1 region as compared to CA3 region but firing emerges earlier in CA3 than in CA1 (Csicsvari et al., 2000). Therefore, SWRs are thought to originate in the CA3 and drive CA1 neurons. It has been suggested that the high frequency neuronal activity during SWRs is well suited for the long-term potentiation of synapses (Buzsaki, 1989; King et al., 1999; Brzosko et al., 2015). This activity occurring while animals are in the inattentive awake states and during sleep may reflect a consolidation process involving the transfer of information from hippocampus to extrahippocampal regions (Olafsdottir et al., 2016).

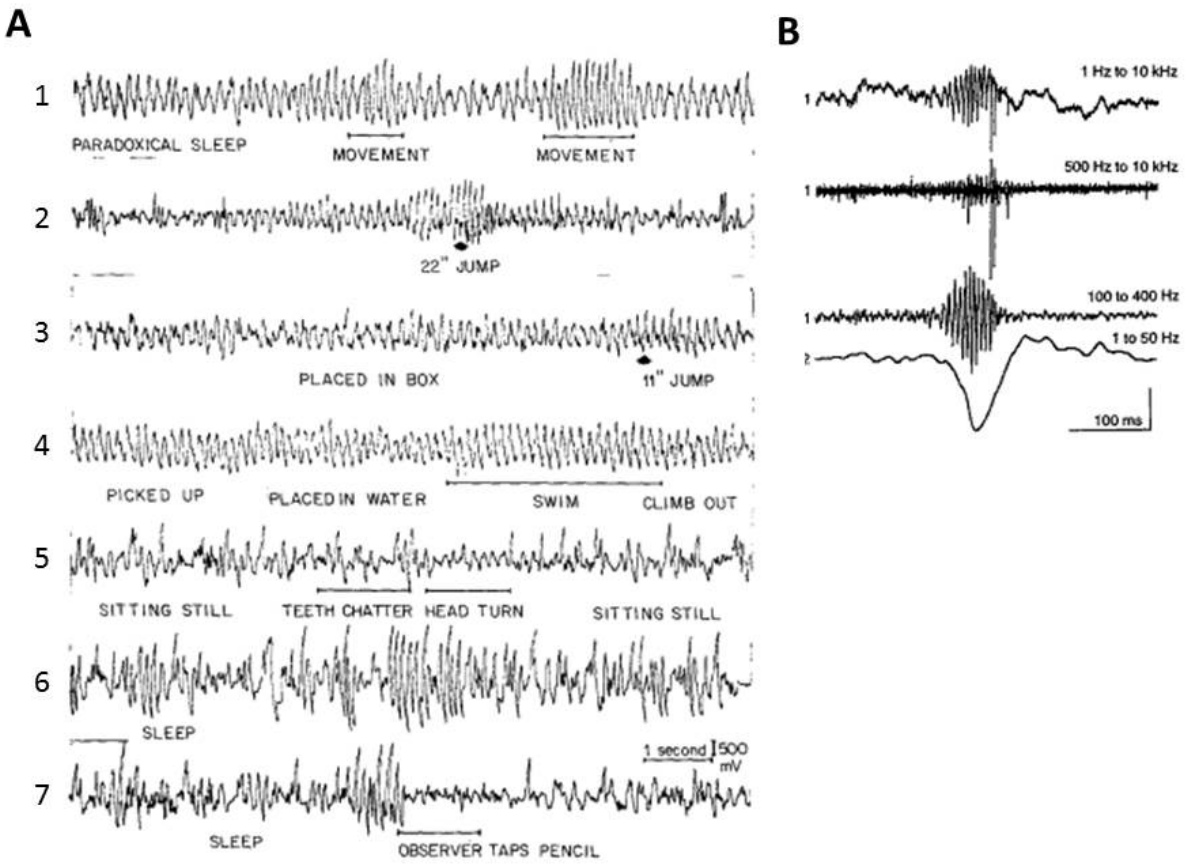

Figure 4 | Oscillatory wave patterns in the hippocampus

(A) The different electrical patterns of activity in the hippocampus and their correlated behaviors. Theta is observed throughout different behavioral states; (1) rapid-eye movement (REM) sleep, (2, 3) jumping, and swimming (4). During quiet sitting (5) and slow wave sleep (6) is when large irregular amplitude activity takes place and large amplitude sharp waves occur. (Adapted from Vanderwolf et al., 1969)
(B) LIA ripples and sharp waves in broad-band recordings (the very top) and filtered at different frequency bands. Recordings from electrode 1 are from CA1 pyramidal layer. Electrode 2 (bottom) was placed in the stratum radiatum of the CA1. (Adapted from Buzsaki et al., 1992)

1.4.2 SWR-associated place-cell sequences

If neuronal activity during rest plays a role in the transfer or consolidation of memories, the activity patterns of neurons during sleep would likely represent information from the animal's recent waking experiences. This was first experimentally demonstrated by Wilson and McNaughton (1994); they showed that in sleep the previous waking activity patterns of place cells are reactivated. They calculated the cross-correlations of the spike trains for pairs of place cells during a run session and during sleep sessions before (pre) and after (post) the run session. Correlation between cells with overlapping place fields was high during the run session, and this strong correlation persisted in the post-sleep as well. However, their correlations during run were not (or weakly) related to that in pre-sleep.

This discovery that hippocampal neurons with overlapping fields were coactive during post-sleep led to another question, namely whether the temporal order of cell activity was preserved across waking periods and in subsequent sleep (which cell fires first with a sharp wave and which fires later). Lee and Wilson (2002) tested this idea directly by performing a set of experiments in which animals ran on a circular track, and in doing so forced place cells to fire sequentially in the same order on each traversal of the track (Lee and Wilson, 2002). Extending the pair-wise analysis to involve multiple cells at a time, they showed that during subsequence sleep, place cells ensembles are activated in a similar order to that their previous waking sequence order during transient high network synchrony periods, which tend to occur during SWRs. This ordered activity is now commonly referred to as sequential reactivation. Although SWR-associated sequence reactivation was discovered during sleep after a run session, they also occur in awake periods following immobility and even during

exploration-associated behavioral periods (Foster and Wilson, 2006; O'Neill et al., 2006). Most awake replays are local, represent the current environment and tend to begin at the current rewards location (Gupta et al., 2010; Pfeiffer and Foster, 2013; Silva et al., 2015). Together, these experiments show that replay quickly and flexibly represents experiences of an explored environment.

1.4.3 Forward and reverse replay of hippocampal place cells

Since in linear environments place field firing is direction as well as position-dependent, hippocampal replay also has a distinct direction. Foster and Wilson (2006) observed that during SWRs in the awake states, place field sequences replay the trajectories of the animal in the reverse temporal order representing the running trajectory of the animal on a linear track. They observed that reverse replay typically began at the animal's current location and spread backwards when the animal paused after running the length of a linear track. This hippocampal reverse replay may play a role in passing outcome information back through the sequence to update the action of the location along the path. Diba and Buzsaki (2007) replicated the findings of Foster and Wilson (2006) but they also observed replay in the forward direction as well. They observed more reverse replay following a run across the track and more forward replay preceding a run. It suggested that forward replay events, since they traverse the upcoming path, may play a role in planning future behaviors. This finding was not quantified however and subsequent work (Davidson et al., 2009) found that the occurrence of forward or reverse sequences is random. A recent study found however that manipulating the amount of reward can change the propensity of reverse replay but not forward replay (Ambrose et al., 2016). An increase in the expected reward is associated with an increased number of reverse replay events while a decrease is accompanied by fewer reverse replays.

Replay of waking trajectories have not been exclusively observed during SWRs. Some studies have observed them during theta oscillatory cycles (Dragoi and Buzsaki, 2006; Huxter et al., 2008; Foster and Wilson, 2007; Johnson and Redish, 2007). However, place cells tend to fire at progressively earlier theta phases as the animal passes through a place

field, a process called theta phase precession (O'Keefe and Recce, 1993). It has been demonstrated that theta phase precession itself can generate the replay of short trajectory segments; therefore, it is not clear whether trajectory replay reported in some studies represents unique trajectories or simply theta phase precession-related ones. Some of the replay reported during theta oscillations may simply represent replay associated with high network synchronization, many of which are also related to SWRs.

1.4.4 Hippocampal replay in cognitive functions

Hippocampal replay during SWRs may promote spatial learning and the successful recall of spatial memories in multiple ways (Csicsvari and Dupret, 2013; Roumis and Frank, 2015). Replay during sleep may facilitate the successful subsequent recall of spatial memories in two ways. Firstly, it may help the stabilization of spatial memory representations in the hippocampus and, secondly, by transmitting this information to extra-hippocampal locations, it may initiate systems consolidation processes. In contrast, replay that occurred while animals are performing a memory task may be involved in planning and decision making by recalling relevant past memory episodes of performing the task or projecting future actions related to the task. Indeed past work provided support for all such roles.

In relation to replay during sleep it was shown that the more often a reward location was replayed, the better the animal remembered those locations later (Dupret et al., 2010). This work also showed that new goal-related place maps needed to be reinstated in subsequent memory recall sessions for successful recall. Furthermore, it has been demonstrated that disruption of replay through electrical stimulation coincident with detected SWR events during post-behavior sleep leads to impaired spatial learning, suggesting a causal role for SWRs in the consolidation of spatial memories (Girardeau et al, 2009; Ego-Stengel et al., 2010). Moreover, the involvement of hippocampal sleep replay in systems consolidation is suggested by the observation that replayed hippocampal trajectories recruit grid cells in the deep layers (but not the superficial layers) of the medial entorhinal cortex so that only those grid cells are active which encode the currently replayed trajectory segment in the hippocampus (Olafsdottir at al., 2016; O'Neill et al., 2017).

Several studies have tested the role of waking trajectory replay in learning and memory recall. Many examined cell assembly trajectory encoding during spatial memory tasks by detecting replay events in both theta epochs and hippocampal sharp wave ripples (SWR) (Papale et al., 2016). The involvement of SWR-associated replay in spatial working memory task is suggested by the observation that blocking waking SWRs cause working memory deficits. In the study by Jadhav et al. (2012) SWRs were blocked by electrical stimulation while rats were performing a W-shaped maze in a particular order. In this task, within inbound trials, when rats moved from a side arm to the middle arm, spatial reference memory is needed. In contrast, in outbound trials, while rats returned from the central arm to a side arm, they needed to use working memory. Although hippocampal lesion slowed the learning affected both the inbound and outbound trials (Kemere et al., 2013), disrupting of awake SWRs specifically impaired outbound trials but not inbound trials. This suggests the involvement of SWRs in spatial working memory in the W-maze task. The same lab also examined trajectory replay in this task (Singer et al., 2013). While SWR responses of cells predicted whether the animal will make an error, the reactivated trajectories during SWRs did not predict the behavioral choice of the animal per se. Other studies using other spatial paradigms found that theta oscillation-associated replay did not predict which of the alternative goals are selected next; both of them could be replayed (Jackson et al., 2006). At the decision point alternative trajectories can be replayed when the animal stops there to decide where to go next. However, in using a different paradigm in which rewards were placed on a circular track, the length of the replayed trajectories can indicate the animal's choice between near or distant goals albeit the task used did not require spatial working memory demand (Wikenheiser and Redish, 2014). SWR-associated replay has been also examined during goal-related navigation in open field environments. The numbers of SWRs at goal locations predict the future ability of the animal to subsequently recall these learned goals (Dupret et al., 2010). Moreover, another study showed that trajectory replay predicts the direction at which the animal approaches a future fixed goal. When rats performing goal directed navigation in an open field maze, replayed patterns were biased toward the direction of the spatial location where the rat would go next (Pfeiffer and Foster, 2013).

1.5 Aim of the study

So far, the hippocampus has been known to play an important role in spatial navigation to learn and remember behaviorally-relevant places such as the locations of reward. Moreover, the role of the hippocampus has been demonstrated in all memory processing stages, including acquisition, consolidation and recall (Morris, 2006). Many behavioral protocols have been designed to test spatial memory, which require the experimental subject to utilize working memory as well as the formation and recall of a more persistent form of spatial memory. However, it is not fully understood how these memory traces are represented in the hippocampus, especially considering tasks which require both working and longer-term spatial memory demand. Accordingly, the aim of my thesis is to elucidate how spatial working memory, longer-term spatial reference memory, and the combination of both are represented in the hippocampus. To meet the research aim, I used a radial eight-arm maze apparatus to conduct a series of experiments involving three related memory tasks where spatial working and reference memory requirements were controlled. The three tasks either required spatial working or reference memory demand, or the combined used of both of these memory types.

In all these experiments I performed multichannel extracellular recordings in rats to record the parallel activity of many single units in order to investigate the reorganization of the place representations in the hippocampus during spatial learning. An ensemble of place cells can represent an environment such as a maze. Those place cells remap their place fields and many represent goal locations when the animal learns a new set of goals in its environment. The questions I tested in relation to place representations were as follows:

(1). Does place cell remapping only take place in relation with the spatial reference memory tasks or may pure working memory tasks involve similar reorganization?

(2). How do place cells fire near the rewarded location while animals learning tasks requiring spatial working and/or reference memories?

(3). How might place cell firing encode the future or past choices of and animal in different spatial memory tasks?

In my thesis I also examined trajectory replay events that occurred during the task and their functional roles. Investigating the behavioral content represented by the replayed trajectory sequences allowed me to test how replay might contribute to hippocampal navigation when animals were making a decision regarding to which arms to enter next.

2 Methods

2.1 Behavioral paradigm

As mentioned in the introduction, the radial arm maze task is commonly used to test for hippocampal function in memory (Olton and Samuelson, 1976), and has been used to test the effect of disrupting hippocampal circuits in both spatial working memory and more persistent forms of memory. The radial arm maze I used consists of a central platform (15cm diameter) surrounded by eight arms (70cm long and 12cm wide) pointing outward where animals learn to collect food rewards at the ends of the arms. Pneumatically controlled doors can be raised to prevent the entry of the animal to any of the side arms. Efficient collection of rewards requires the animals to learn to avoid visiting an arm twice, i.e., not to make a working memory error. On the other hand, if only a subset of arms (three arms in this thesis) has been baited, the animal has to learn and recall which arms are baited within a single day.

To meet my research goals, I used an eight-arm maze to conduct three experiments where the memory requirement can be separated in each. Most previous findings were also observed in an open-field environment, not in a maze with narrow paths where animal's direction of motion was constrained by the structure of the environment (linear tracks). In the first research experiment, combined memory task, only three arms were baited. In the beginning of the trial, all eight side doors were simultaneously lowered. The trial ended when the animal collected all three food rewards. Once the animal collected the last food reward, all the doors were raised except the one allowing the animal to return to the center. After the animal returned to the central stem, the remaining side door was raised and the next trial started again after a one minute delay. The second research experiment, reference memory task, was designed so that working memory is not required and animals only need to learn the locations of a new set of food rewards on each recording day. Again, only three arms were baited as in the combined task, however, the door of each arm visited was raised once the animal had returned from it, in order to prevent working memory errors. The third experiment, working memory task, only three baited arms open (the remaining arms were blocked by raised doors) and a trial ended once the animal collected the food rewards from all three arms.

For all three of the experiments listed above, each experimental day stared with the pre-probe session in which animals were tested over five trials with the reward arm configuration of the previous day. After the pre-probe session the animals were rested in the center of the maze for 30 mins. After rest, the learning session started in which two of the reward locations were moved to arms that were not rewarded on the previous day (novel–goal arms) while one of the reward arm remained the same (familiar-goal arm). During a learning session 30 trials were performed. There was an additional 30 min rest period after learning session and a subsequent post-probe session when the current baited 3 arms configuration was tested again for an additional 5 trails.

2.2 Animals, microdrive construction and surgical procedure

Seven adult male rats (Long Evans) were used as subjects for these experiments. They were housed in groups of 3 with ad-lib access to water at all times but they were housed individually after the electrode implantation surgery. A 12-hour light: 12-hour dark cycle was maintained, with all behavioral testing conducted during the light phase. The rats weighted 250-350g at the time of surgery. All procedures involving experimental animals were carried out in accordance with Austrian federal law (1974) under a project license approved by the Austrian Federal Science Ministry.

Microdrives holding sixteen individually moveable tetrodes were used for neural recording. The tetrodes were constructed from 4 individual tungsten wires (H-Formvar insulation with Butyral bond coat, California Fine Wire, Grover Beach CA) 12 µm in diameter, twisted and then heated in order to bind them into a single bundle. Prior to the implantation, the tetrode tips were plated with gold to reduce their impedance to 200-300kΩ. Tetrodes were mounted to individual screws which allowed the tetrodes to be lowered by turning the screws (100 microns per one full rotation of the screw).

All rats were anaesthetized with isoflurane (0.5%–3%), oxygen (1–2 l/min), and an initial dose of buprenorphine (0.1 mg/kg). Then the animal was placed on a stereotaxic frame with the head levelled between bregma and lambda. During surgery, the craniotomy was centered at the dorsal hippocampal region CA1 (3.5 mm anterior-posterior, AP and 2.5mm medial-lateral axis, ML) and the electrodes were then implanted into the deep layer of the neocortex. Two screws positioned above the cerebellum served as ground, and reference

electrodes. Six additional stainless-steel anchor screws were used in order to permanently attach the microdrive assembly to the scull. The electrodes and the microdrive apparatus were paraffin wax coated and daubed with dental acrylic to encase the electrode-microdrive assembly and anchor it to the screws in the skull.

2.3 Tetrode adjusting and recording

Wide-band (0.4 Hz-9 kHz) recordings were taken and the amplified local field potential and multiple-unit activity were continuously digitized at 24 kHz using a 64-channel data acquisition system (Axona Ltd, St. Albans, UK). Two red LEDs mounted on the preamplifier headstage were used to track the location of the animal. In order to simultaneously move 16 tetrodes into the pyramidal layer of CA1, tetrodes were adjusted over two weeks while using local field potential signatures as guidance. Adjusting is complicated by the large number of tetrodes which push the brain tissue and swelling which is present for several days following surgery. During surgery the tetrodes were lowered into the deep layers of the neocortex, which area is characterized by spiking activity that is less dense than in the hippocampal pyramidal cells layer, and shows spindles and delta waves during sleep. After tetrodes pass through the cortex, they enter the corpus callosum where no spiking activity is observed. When tetrodes reach the upper layers of CA1, sharp waves can begin to be seen as upwards deflections in the LFP in the stratum oriens which then reverse near the cell body layer. In addition in the stratum oriens, ripple oscillations appear on the sharp waves as the waves increase in magnitude and then decrease as the ripples reach their maximum amplitude and spikes begin to appear. Experiments start when all, or sufficient number of tetrodes show signs of optimal amplitude unit activty. It is often necessary to perform small adjustments at the end of experiment days due to continued movement of tetrodes.

2.4 Training procedures

Following the recovery period after surgery, the animals were exposed to the maze, over a period of 14 days. Four animals were trained to the combined working and reference memory task (combined memory task) and three additional animals performed the reference memory task (reference memory task) and working memory task (working memory task). Animal were placed on food restriction (>85 % of initial weight with a 10g

gain each week), once they had passed the 7 days recovery period and exceeded their pre-surgery weight.

To train the animals for the combined memory task, initially, for two training days, all eight side-arms contained food and the animals had to collect food on all eight arms before a trial ended and the side arms were rebaited. During this initial training, 10-15 trials were performed. After this, for the next 4-5 training days, animals had to perform the three arm baited task until they performed at least 10 trials successfully without errors (maximum 50 trials per day). During the training both the learning and the probe sessions were performed. In the final training day it was required that the animals were able to perform 10 trials without errors within the first 30 trials otherwise a further training day was added before recording could start.

The same animals were used for both working and reference memory tasks (a separate cohort of animals was used for the combined task). For these animals the training procedure during the first two days was identical to that in the combined memory task, i.e., sessions were used in which all eight arms were baited. After this initial training, only one training day was needed to familiarize the animal with the working memory task after which four recording days were performed. After these days with the working memory task, animals were trained to the reference memory task. Training procedure was like in the combined memory task, only within each trial the visited arms were blocked after the animal returned from them.

2.5 Position tracking system and spike sorting

The motion of the rat on the maze was tracked by following the trajectory of the two LEDs attached to the head stage. A video camera (Handycam, Sony) was mounted on the ceiling above the recording environment and connected to the dacqTrack video tracking system of the Axona recording system (Axona Ltd, St. Albans, UK). The tracking signal was recorded together with the electrophysiological data on the same data file and read offline to timestamp every tracking sample.

The tetrodes were lowered into the CA1 pyramidal cells layer of the hippocampus, which is densely populated with neuronal cell bodies, and action potentials (spikes) of many cells can be recorded simultaneously from a single tetrode location in this layer. Based on their

waveforms, a spike sorting method was developed to separate the action potentials of different neurons. Spikes were extracted offline from the digitally-filtered (0.8-9 kHz) signal. Action potentials with a power of >5 SD from the baseline mean were selected and spike features were then extracted using principal components analyses. Spikes from putative individual neurons were segregated into single units by using automatic clustering software (Harris et al., 2000). These automatically generated clusters were manually refined by a graphical cluster cutting program. Only units with clear cluster boundaries and refractory period in their autocorrelation were used for further analysis. CA1 pyramidal neurons and interneurons were discriminated by their autocorrelation, firing rate and wave form as previously described (Csicsvari et al., 1999). We further confirmed the quality of cluster separation by using the isolation distance based on Mahalanobis distance (Harris et al., 2000) ensuring that calculated spikes clusters did not overlap during the course of recording. In this way we were able to identify the activity of 2420 CA1 pyramidal units.

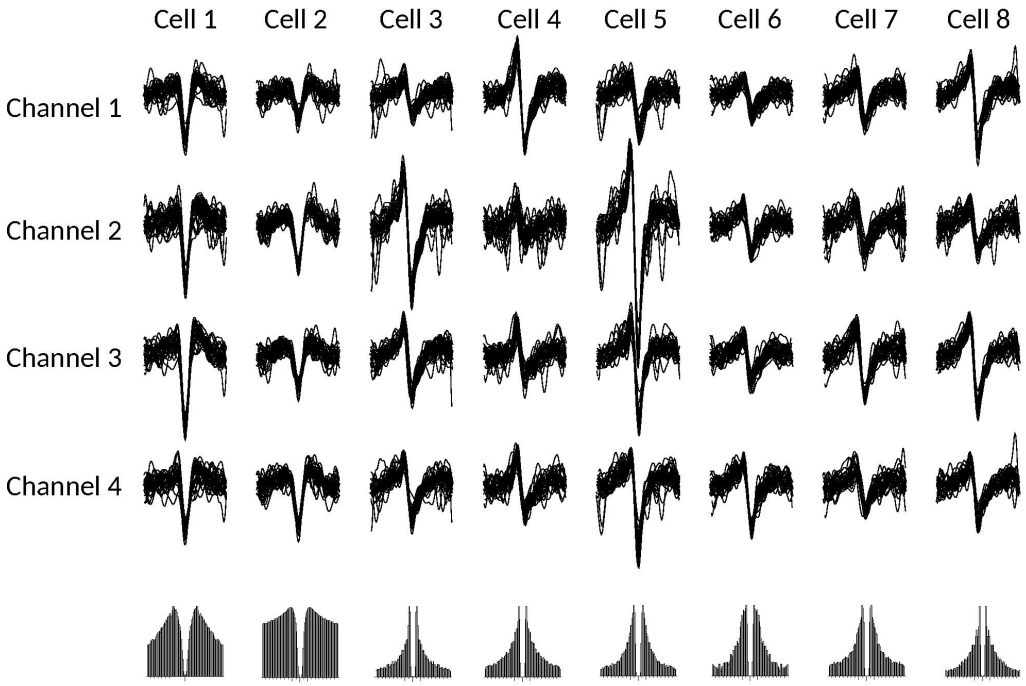

Figure 5 | Waveforms of action potentials and inter-spike interval of recorded cells

(Top) Waveforms of the action potentials recorded from one tetrode. The spikes were grouped into 8 clusters (putative cells) based on principal component analysis on their wave forms. Note that the typical wave form of one cluster varies across the four recording channels.

(Bottom) Autocorrelograms (in a ±50 ms time window) from the same cells as in (Top) recorded from the CA1 region (2 interneurons and 6 pyramidal cells). Each histogram plot has a clear refractory period.

2.6 Calculation of rate maps

Two-dimensional (2D) place-rate maps were calculated by subdividing the environment on a grid containing 2x2 cm bins. A 2x2 cm square was overlaid on this grid, for each spike of a given cell, centered on the position of the animal when the spike was emitted. Each bin was then incremented by the degree to which this square overlapped with it. The same procedure was then performed with the animal position tracking data to produce a map of occupancy. Both the occupancy (time spent in each bin) and spike matrices were then smoothed with a Gaussian kernel function (SD = 6 cm), and divided to produce a place rate map.

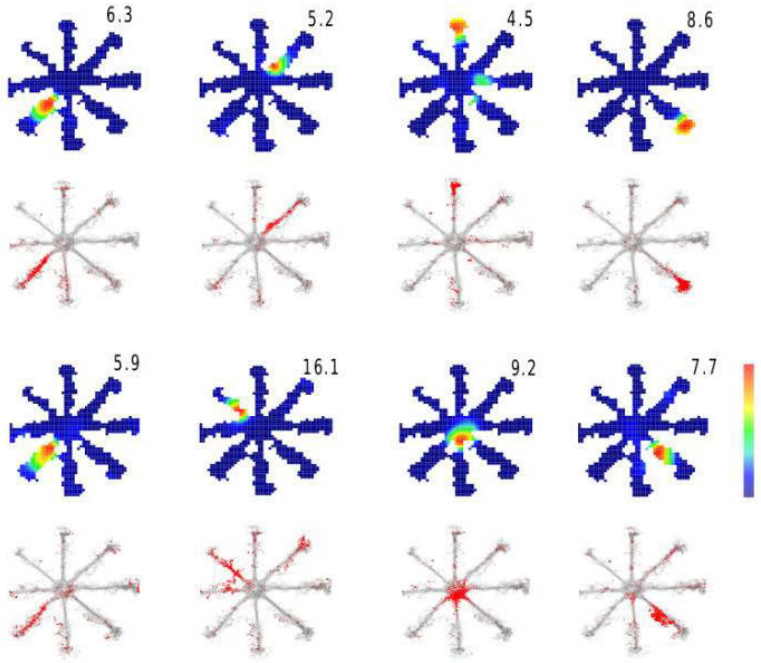

Figure 6 | Different place cells have different firing fields on the eight-arm maze.

The eight density plots represent the firing rate of eight CA1 pyramidal cells on the radial eight-arm maze. The cells fired only when the rat was at a specific location on the maze. Top rows, color-coded place-rate maps; bottom rows, individual spike locations (red dots) superimposed on the rat's path on all trials (grey traces).

To test for the rate modulation of trial type, place field shift and replay using Bayesian encoding, one dimensional (1D) place maps were calculated using a similar procedure as above for each arm of the maze. The distance between the locations where the arm was entered and that of the food reward was 70cm. Moreover, place maps were calculated separately for inbound and outbound passes for the 1D map. In these calculations 70 bins, i.e. 1 cm bins were used for each arm. A linear place field was defined as an area of the environment containing the bin with the highest firing rate and extending both sides until it reached a threshold of 10% of the peak firing rate. If one cell had its 2D place field peak on one or more arms, only the trials in which the rat ran through the place field peak were used in the calculation of its linear place field.

2.7 High synchrony events (HSEs)

High synchrony periods were detected using the multiunit activity (MUA) of clustered spikes, as previously study described (Davidson et al., 2009; O'Neill et al., 2017). We therefore calculated the percentage of pyramidal cells firing together in 200ms windows to estimate the network synchrony of place cells while rats were performing on the maze. A smoothed histogram (1ms bins; Gaussian kernel, SD = 15ms) was constructed of the synchronous spiking rate over time. The time windows with a high level of synchrony (synchrony > 3 SD above the mean) were detected for each rat and the position of the animal at that time was calculated. Events containing fewer than 5 spikes, 4 cells or with less than 10% of the population of neurons active were rejected, as were events shorter than 75ms or greater than 750ms. The beginning of HSE was then adjusted to the time of the first spike. The HSE was then subdivided into 20ms windows until the last window containing a spike was reached. Following this procedure, all HSE events with less than 4 windows were rejected from further analysis.

2.8 Replay during HSE's

Each detected HSE was subdivided into 20ms time windows and population vectors representing the spike counts of different pyramidal cells in a given time window were calculated. Then I used the Bayesian place prediction (Zhang et al., 1998) method to calculate a probability of different positions for each population vector of the event. Probability maps were calculated for each arm both for inbound and outbound trials. The

formula below gave the probability that a given population vector represented a given place:

$$P(x|n) = P(n|x)P(x)/P(n).$$

P(x) represents the probability that the animal is at a given location considering the exploration session was set to a uniform distribution, not to bias our analysis by any place preference of the animal (Zhang et al., 1998). P(n|x) represents the conditional probability that a given spike count occurs at a location. This was estimated using the firing rates of the place-rate maps, assuming that the number of spikes follow a Poisson distribution. P(n), the normalizing constant, was used to ensure that P(x|n) summed up to one.

I then run an optimization procedure to see which arm produced the maximum summed probabilities across the frames of probability maps representing different time windows of the HSE. The procedure allowed a jump of 0-20 bins across probability maps of neighboring time windows (i.e., neighboring frames), assuming that replayed trajectories can jump maximum of 20 bins in each step. I allowed forward or reverse replays to occur. For forward replay jump across consecutive time windows was allowed in the forward direction on the probability maps calculated for the inbound or backward movement using the outbound probability maps while for reverse replay forward movement on maps were allowed on the outbound map and backward movement on the inbound maps. For the replayed trajectory I selected the arm that yielded the maximum summed probabilities across all frames and the positions were extracted from the map positions in the frames that yielded the maximum summed probabilities. However frames with zero probabilities were excluded from the trajectories. I only considered trajectories with minimum 4 frames and only those that exhibited sufficient movement by covering at least 20 bins and had an average speed larger than 2 bins per frame.

To check whether the trajectories I detected can be generated due to the sequential firing of place cells with random spatial representations, I compared the summed probability of our procedure against shuffled data in which place fields of the cells were rotated on each arm for in- and outbound trials separately. For each cell, the place fields constructed were randomly shifted along the arm independently, with bins extending off the end of the arm wrapped to the start. Next, I established maximized summed probabilities using the same

procedure as above using the rotated place fields, over 100 different shuffled events. This method preserved spike timing and firing rate statistics while disrupting the spatial coding of the cells used in the reconstruction. I then established a distribution of replay scores (summed probabilities divided by the number of frames) across 100 shuffles. From this shuffled data I established a further score (replay z-score) showing the distance of the replay score from the mean of the shuffled distribution by subtracting the mean of the shuffled data from the replay score and normalizing by its standard deviation (Grosmark and Buzsaki, 2016; O'Neill et al., 2017).

2.9 Forward and reverse replay

To determine whether the replay was in the forward or reverse direction I tested whether inbound and outbound maps were used for inbound and outbound movement of trajectories, respectively, indicating a forward replay while in reverse replay the map movement direction were the opposite of that of the trajectory movements (see Replay during HSEs section above).

2.10 Detection of SWR events

I detected SWR in the CA1 region of the hippocampus during sleep (Csicsvari et al., 1999) and exploration (O'Neill et al., 2006) as previously described. Briefly, local field potentials were first band pass filtered (150-250 Hz), and a reference signal (from a channel that did not contain ripple oscillations) was subtracted to eliminate common-mode noise (such as muscle artefacts). The power of the differential filtered signal was calculated for each electrode and summed across electrodes designated as being in the CA1 pyramidal cell layer. The power was calculated by summing the squared sample values within a sliding window (16ms) and calculating the square root of this sum (root mean square). The mean and SD of the power signal were calculated to determine the detection threshold. During SWR events, the power substantially increased, enabling the detection of the beginning, peak, and end of individual ripple episodes. The threshold for ripple detection was set to seven standard deviations above the background mean. The beginning and end of oscillatory epochs were marked at points at which the power reduced to <1 SD.

2.11 Statistical analyses

Most statistical analyses were performed using C programs, or R (http://www.r-project.org).

For quantifying the representations of the reactivated HSE trajectories analysis of variance followed by Tukey's post-hoc multiple group comparison was used. For the comparison of distributions of reactivation scores and place filed locations Kolmogorov–Smirnov test was used. Binomial test was used for bias of shifting scores and firing rate scores. .

The ANCOVA analysis was performed using spike firing rates established on tested arm and movement direction. The tested arm was divided into 5 spatial bins along the path, in which rate and speed were calculated on each trial in which the animal visited the arms with the appropriate previous or next arm visits. Only units that had larger than 1 Hz mean rate on the tested arm were included in the analysis. I then used an ANCOVA (using R software package) in order to ask if firing rate varied with trial stage (factors: two alternative arms to visit next or before), given changes in the mean speed.

3 Results

3.1 Assessment of performance on the radial eight-arm maze

I recorded from pyramidal neurons (n=2420) in the dorsal CA1 of hippocampus while rats (n=7; 4 rats for combined memory task and 3 rats for reference and working memory tasks) acquired and performed a spatial memory task on a radial eight-arm maze in which they had to collect hidden food rewards located at the ends of three arms of the maze (**Figure 7A**). Animals had to collect the food from all three arms before a trial ended after which new food rewards were provided at the same arms and a new trial started. In each recording day the location of one rewarded arm remained the same as on the previous day (i.e., familiar-goal arm), while the two other baited arms were selected from those that did not contain rewards the previous experimental day (i.e., novel-goal arms). Therefore, each animal had to partially update their goal-related reference memory representations daily in order to encode and remember which of the eight arms contained food. At the same time they also had to keep track of the visited arms in each trial (**Figure 7B**). In addition to this combined task, I employed two control tasks that only required either the use of spatial working or reference memory. In the spatial reference memory task (**Figure 7C**), the animal was prevented from making working memory errors by blocking each visited arm for the remainder of the trial after a visit from the animal. In the spatial working memory task (**Figure 7D**), arms not containing food were blocked from the beginning of each trial, therefore, the animal did not need to remember which of the arms were baited in order to collect the rewards but it had to keep track of the already visited arms within each trial. These two control tasks kept the same familiar- and novel-goal arm selection protocol as described for the combined task. In all tasks, the animals' memory retention was further tested in probe trials after learning (post-probe) (**Figure 8A**). Moreover, before the learning session a pre-probe session was performed where the animal had to collect food using the goal configuration of the previous learning day. Animals rested for ~30 min between the learning and the probe trials.

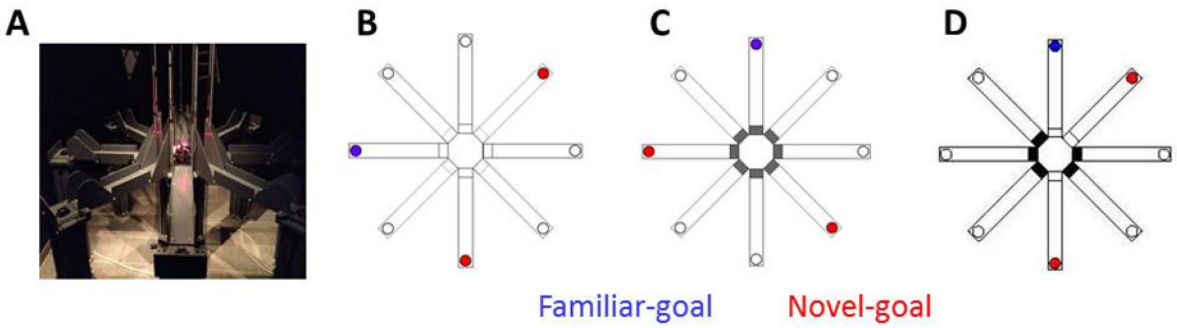

Figure 7 | Experimental set up and three different spatial memory tasks

(A) Experimental set up including the radial eight-arm maze with external cues.
(B-D) Illustration of the behavioral paradigm. In the combined working and reference memory task (Combined) all arms were open with three containing rewards (B). In the reference memory task (Reference) each arm that animal had already visited in a trial were blocked (gray bars in the center) (C). In the working memory task (Working) arms not containing rewards are blocked from the beginning of the trials (black bars in the center) (D).

In each recording day the behavioral performance of animals was recorded and the following behavioral measures were analyzed in the three spatial tasks. Learning performance was estimated by the number of arm entries (animal had to enter with all four paws to the respective arm to qualify for an arm visit) to find all rewards per trial (**Figure 8B-D**). Animals took 10-15 trials to learn the task each day in the combined task (with <4 average arm visits per session), while in the control tasks fewer 5-10 trials were required (**Figure 8B**). Within the first 5 trials animals made far fewer errors in the working memory task than in the other tasks needed reference memories. Spatial reference memory can be assessed by rewarding a certain three arms but always rewarding the same arms. A reference memory error was scored when the animal entered a non-rewarded arm. Animals during the learning phase of the recordings made more reference memory errors in the combined task than in the reference memory task but once the new goal locations were learned (i.e. after 15 trials), the performance was similar between the two tasks (**Figure 8C**). During the spatial working memory task, animals were prevented from making any reference memory errors by closing off the access to the unbaited arms. Working memory errors were measured by the number of instances the animal returned to an arm that was already visited during the same trial. Mean working memory errors were assessed in the combined and working memory tasks. Initially animals made more working memory errors

in the combined task than in the working memory task but once animals learned the combined task (>15 trials) the mean working memory error rates were minimal and similar in both tasks (**Figure 8D**).

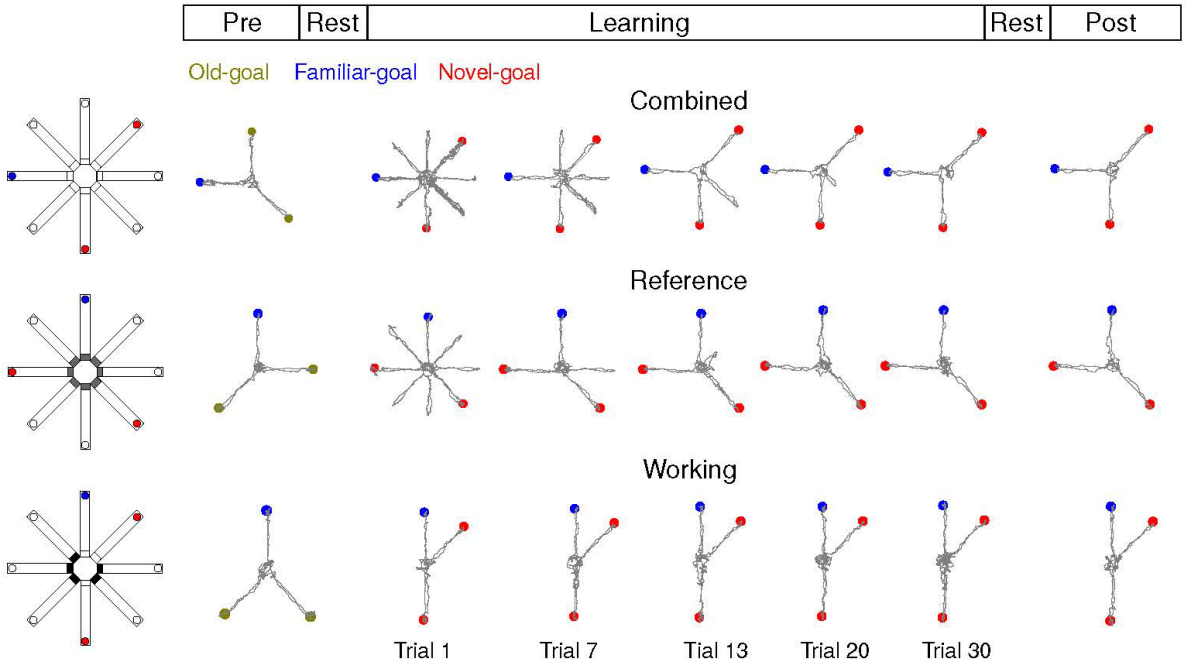

Figure 8 | Behavioral tasks on the radial eight-arm maze requiring reference or working memories or the combination of both

(A) Behavioral tracks of the animals at different learning trials. In the pre-probe trails (pre) the goal-arm configuration from the previous day was tested. During learning trials two new goal arms (red dots) were selected while the third one remains the same (blue dot). In the post-probe trials (post) the memory retention of the animal was tested. Animals were rested for 30 min between the probe and learning trials.
(B) Learning curve of the animals showing the number of arms visits (mean±SEM) before all 3 rewards was collected in a trial.
(C-D) Comparison of reference memory errors (C) and working memory errors (D) during learning. Animals made very few errors once they learned the task (Combined n=16 recording days in 4 rats; Reference n=8 recording days in 3 rats; Working n=8 recording days in 3 rats).

3.2 Goal-related reorganization of hippocampal place fields during learning in the combined task

To investigate how spatial memories for goal locations are represented in the hippocampus during these spatial memory tasks on the eight-arm maze, I first assessed the activity of

place cells. First, I evaluated place cells activity during the combined task that required both working and reference memory demand. Most cells fired on one arm or in the center of the maze, with similar numbers of place fields on each baited arm. Because previous work found that the change of goal configurations leads to the remapping of place cells (Dupret et al., 2010), I examined the goal-related changes to hippocampal spatial maps. I found that during learning, many CA1 place cells exhibited place fields at the novel-goal arms, and maintained the same in subsequent learning trials (**Figure 9A**). I then quantified how similar place fields were during the course of learning to that in the post-probe trial. During the combined task, place field similarity to that observed in the post probe systematically increased across different learning blocks (Regression line, $r=0.6885$, $P<0.0001$). This demonstrates that place maps reorganized gradually during learning (**Figure 9B**). Next I tested whether such changes involved the novel-goal arms, or place fields in the familiar-goal arms changed as well as the results of the partial update of the reference memory representations. When examining the place field similarity of firing fields on familiar-goal and the novel-goal arms separately, the novel-goal arm place fields showed gradual reorganization (Regression line, $r=0.5293$, $P<0.0001$) while the familiar-goal arm did not show significant changes (Regression line, $r=0.1660$, $P=0.1412$) for the combined memory tasks (**Figure 9C**).

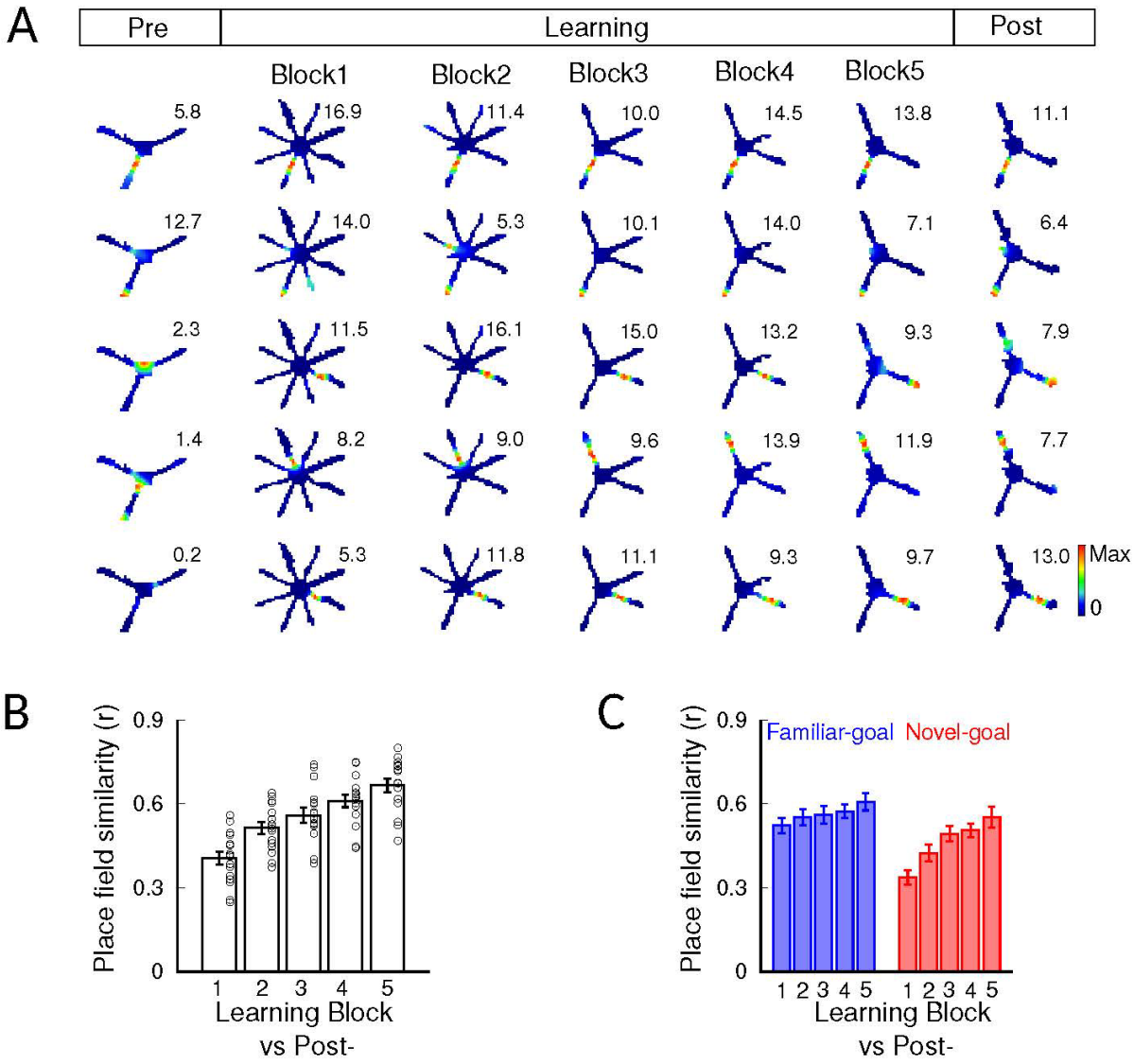

Figure 9 | Gradual reorganization of place fields during learning in the combined task

(A) Firing fields of representative place cells at different trial blocks during learning and in probe sessions (Pre and Post). The color code in the rate maps is from blue (low firing rate) to red (peak firing rate), with the maximum firing rate (Hz) of the color scale indicated on the top right corner of each map.
(B-C) Place field similarity between trial blocks during learning and that in the post-probe session. The entire field (B) or fields on the novel- and familiar-goal arms were compared for all recordings (C). Regression line between block and place field similarity, all: n=80 learning blocks from 4 recording days in 4 rats, r=0.6885, P<0.0001; familiar: n=80 learning blocks from 4 recording days in 4 rats, r=0.1660, P=0.1412; novel-goal: n=80 learning blocks from 4 recording days in 4 rats, r=0.5293, P<0.0001.

3.3 Remapping occurred in the reference memory task, not in the working memory task

From the above results it is unclear whether the gradual changes in place maps were related to spatial working or reference memory demand. Therefore, I also examined the remapping of place fields in the spatial working and reference memory tasks during learning. Similar to the combined task, remapping of place fields was seen in the reference memory task ($r= 0.6994$, $P<0.0001$; **Figure 10A-B**), but not in the working memory task ($r=0.1671$, $P=0.3028$; **Figure 10D,E**). Moreover, in the spatial reference memory task I found that the place field similarity of the familiar-goal arm showing minimal reorganization while the novel-goal arms showed gradual changes for the reference memory task (familiar goal $r=0.1420$, $P=0.9256$; novel goal: $r=0.5630$, $P<0.0001$; **Figure 10C**). This remapping of newly-baited place fields did not occur in the working memory task (familiar goal: $r=0.1834$, $P=0.1438$; novel goal: $r=0.1238$, $P=0.8625$; **Figure 10F**).

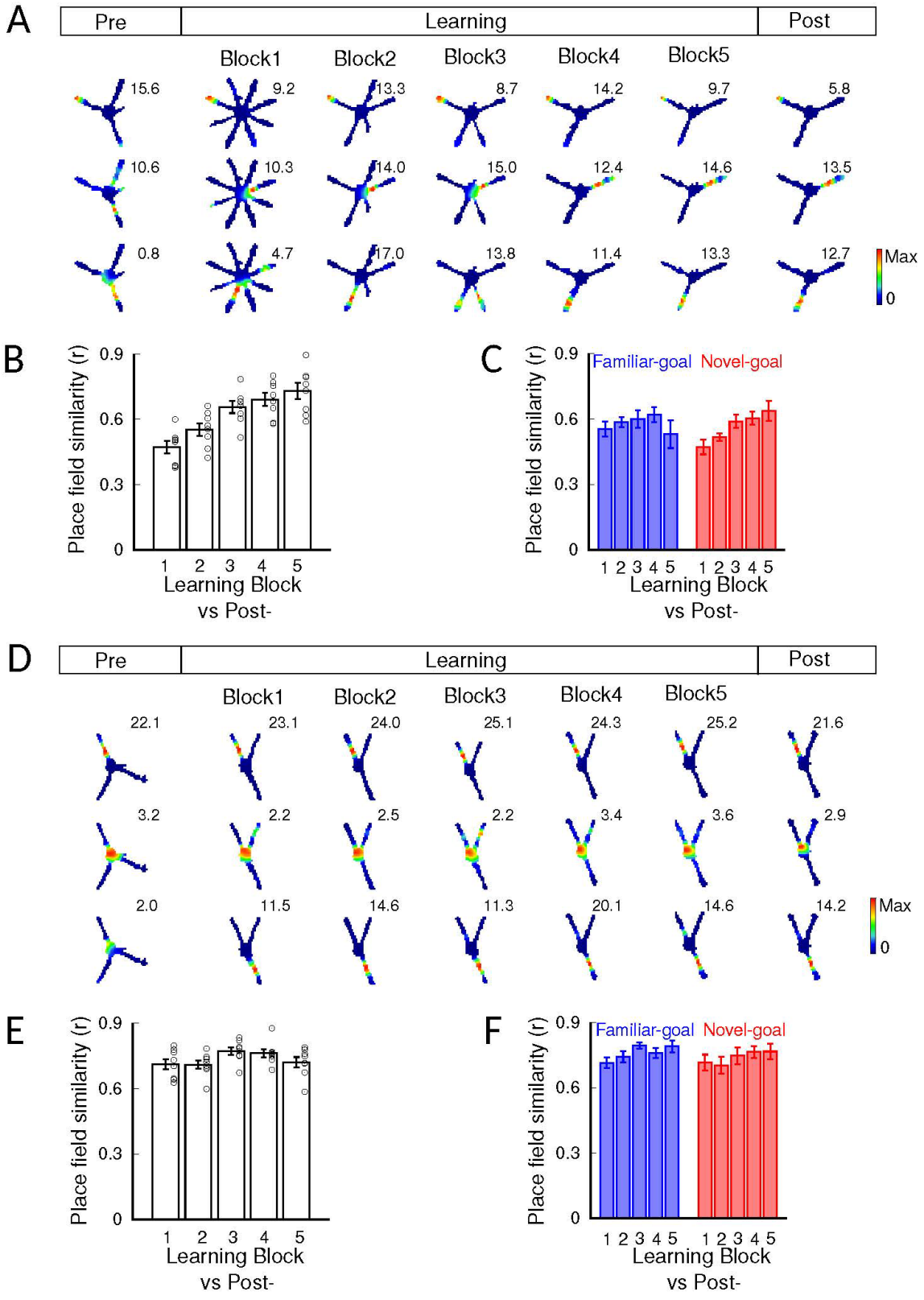

Figure 10 | Place fields reorganize gradually during the reference memory task but not the working memory task

(A, D) Firing fields of representative place cells at different trial blocks and during probe sessions for reference memory (A) and working memory (D) tasks. Numbers represent the maximum firing rate (Hz) of the cells.

(B-C, E-F) Place field similarity between fields at trial blocks during learning and that in the post-probe session for reference (B) and working (E) memory tasks for the entire field are compared. Regression line between block and place field similarity, Reference: n=40 learning blocks from 2 recording days in 3 rats, r= 0.6994, P<0.0001; Working: n=40 learning blocks from 2 recording days in 3 rats, r=0.1671, P=0.3028.

Same shown for fields on novel- and familiar-goal arms for reference (C) and working (F) memory tasks. Reference familiar: n=40 learning blocks from 2 recording days in 3 rats, r=0.1420, P=0.9256; novel goal: n=40 learning blocks from 2 recording days in 3 rats, r=0.5630, P<0.0001; Working familiar: n=40 learning blocks from 2 recording days in 3 rats, r=0.1834, P=0.1438; novel goal: n=40 learning blocks from 2 recording days in 3 rats, r=0.1238, P=0.8625.

3.4 Place fields gradually shift forward novel-goal arms during the combined memory task

Place cells tend to fire directionally (i.e. firing forward or backward direction only) on one dimensional track and that the proportion of neurons that exhibit directionality increases with experience (Markus et al., 1995; Navratilova et al., 2012). Therefore, to check for similar directional firing on the 8-arm maze I examined whether place cells fire on the arm either by approaching or returning from the goal locations. I first identified place fields separately on each arm, and then calculated their firing fields for inbound and outbound passes in the combined task. Many place cells fired unidirectionally on the arm, i.e. either inbound or outbound. Moreover, the proportion of unidirectionally firing cells increased across consecutive training days (**Figure 11A**). Signs of the reorganization of the hippocampal spatial map are also indicated by the fact that several place cells started to fire in their firing fields on an arm only in the second, third or even later trials (**Figure 11B-C**). Such an effect was more prominent in the combined and spatial reference memory tasks

than in the spatial working memory task. Moreover, more cells started to fire at later trials on the novel-goal arm than in the familiar-goal arm.

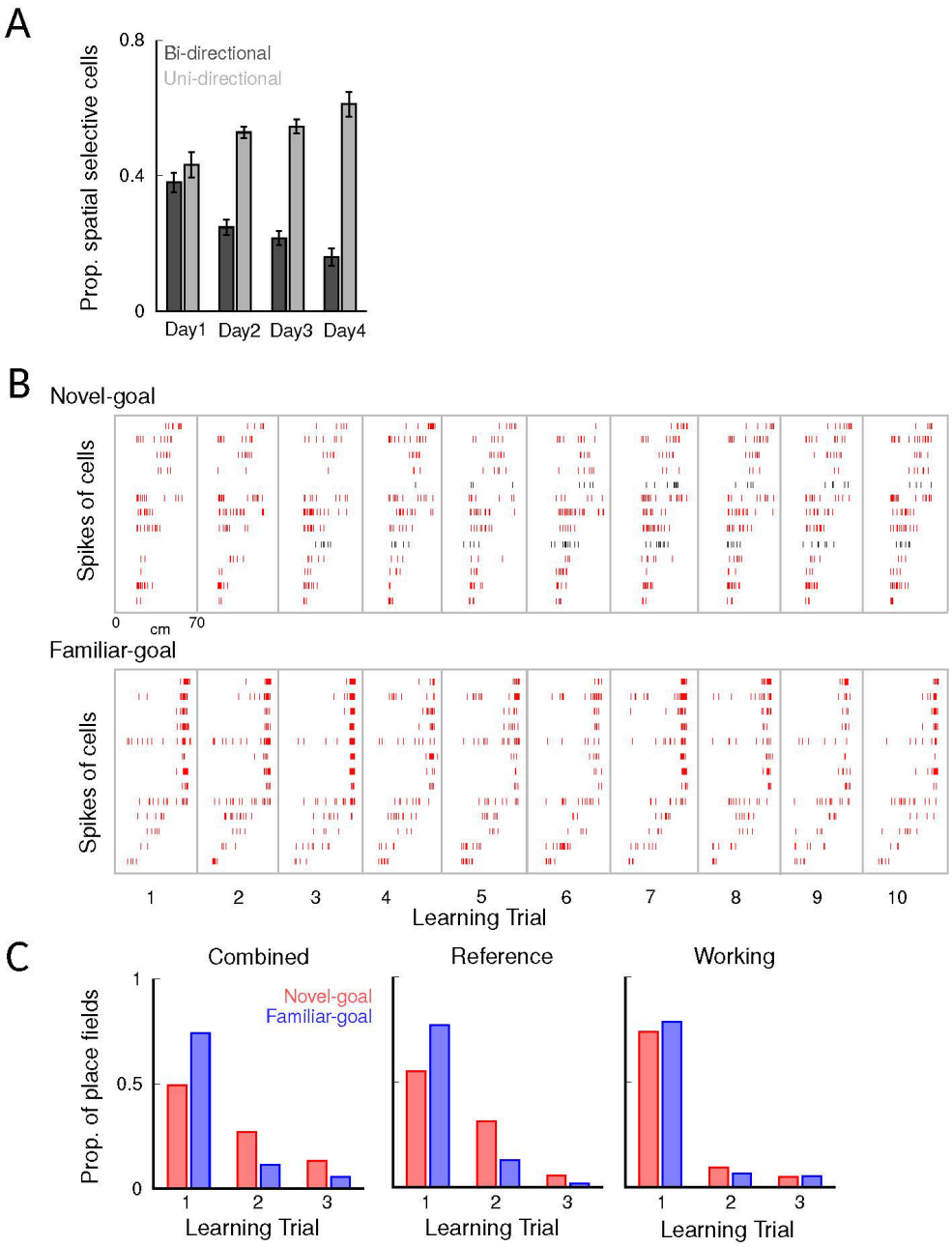

Figure 11 | Reorganization of place fields during learning

(A) Proportion of cells that exhibited directional firing at different learning days for the combined task.
(B) Example showing the firing patterns of different place cells on a novel-goal arm (top) and familiar goal arm (bottom). The raster shows the arm locations at which the displayed cells fired at different trials. Each line represents a different cell. Note that the majority of cells fired from the beginning (red) but some started to fire at later trials (black).

(C) Proportion of cells that started to fire in the first three trials in the combined, working and reference memory tasks. Note that only 50-55% of the cells fired in the first trial in the combined and reference memory tasks on the novel-goal arm, while 75-80% fired in the familiar-goal arms and in the working memory task.

During the learning session, however, an unexpected firing pattern was observed. By plotting the place fields of the inbound passes when animals moved towards rewards, I observed that they showed a gradual shift towards the goal locations on the novel-goal arms but not on the familiar ones nor in outbound passes when animals returned from an arm (**Figure 12A**). To quantitatively characterize this forward translocation of spatial firing, the shifting score of each place field was calculated by comparing place field locations in the first and last five trials. The shifting score compared the place field peak locations of the cells on the relevant arms during the first and the last five trials and difference of the positions were divided by the sum. First I examined the combined task where a significant shift towards the rewards was observed only for inbound novel-goal arms passes ($P<0.001$, binomial test, **Figure 12B**). Furthermore I compared the distribution of place field peak locations and compared these distributions in the first and last five trials I observed an increasing the proportion of cells firing near the rewards at the end of learning compared to the beginning ($P<0.001$, K-S test, **Figure 12C**).

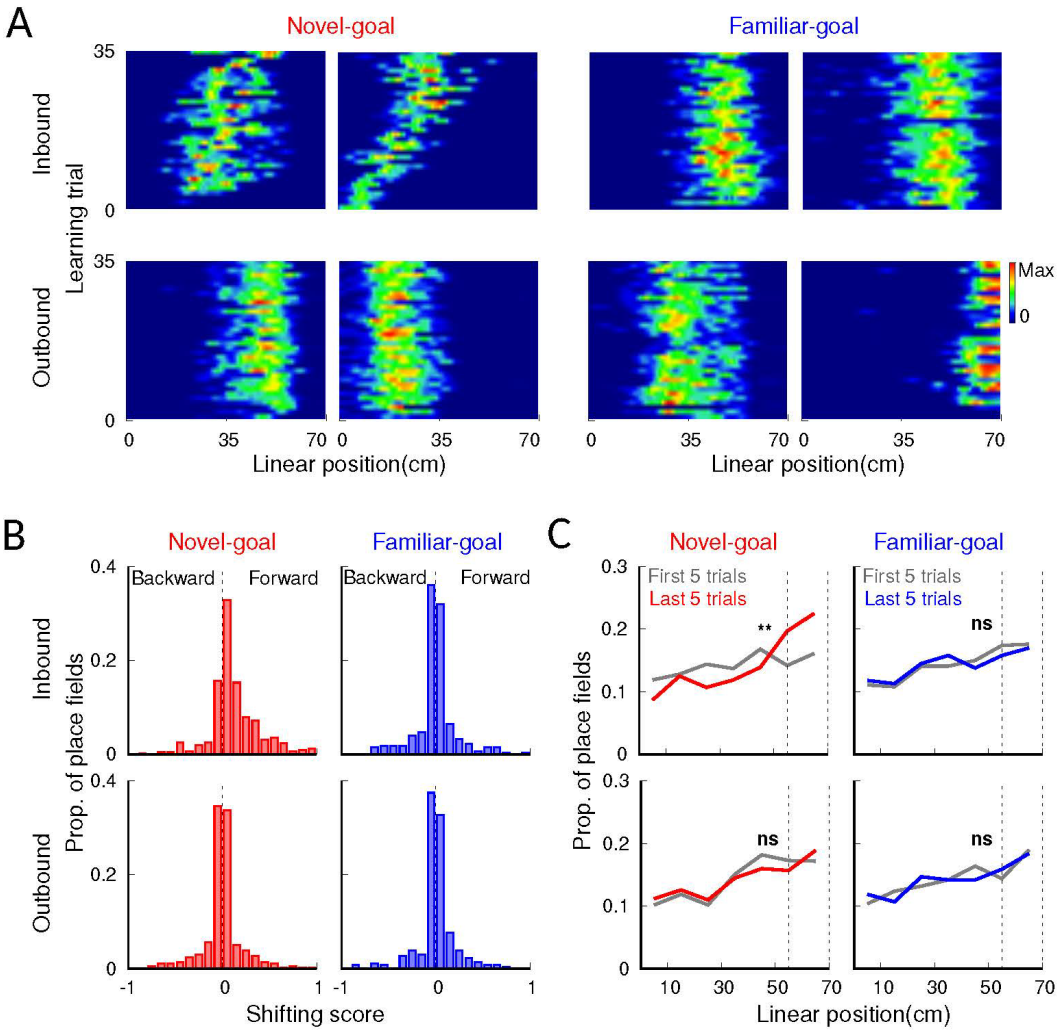

Figure 12 | Place fields gradually shift towards the reward locations in inbound trials of novel-goal arms during the combined task

(A) Example firing fields at different learning trials for inbound and outbound trials in familiar- and novel-goal arms. Two cells of each category are shown. Maps show the rate maps of the cells on the goal-arm at different trials. Note that shift towards rewards only occurs in inbound trials on the novel goal arms and the cell in the top-left starts to fire at later trials only.
(B) Distribution of shift scores comparing the place field peak positions in the first and last five trials. Shift scores measured the difference between the positions of place field peaks divided by the sum. Binomial test, novel-goal for inbound: n=417 place fields, P<0.001; novel-goal for outbound: n=432 place fields, P=0.879; familiar-goal for inbound: n=375 place fields, P=0.922; familiar-goal for outbound: n=359 place fields, P=0.630.
(C) Distribution of place field peak positions as measured in the first and last five trials for familiar and novel arms. Note that more cells fired near the goal in the last five trials than in the first five trials in inbound runs in novel goal arms only. Kolmogorov-Smirnov-test (K-S test), novel-goal for inbound: n=417 place fields, P<0.001; novel-goal for outbound: n=432 place fields, P=0.9575; familiar-goal for inbound: n=375 place fields, P=0.8595; familiar-goal for outbound: n=386 place fields, P=0.630. **P<0.001, Ns, not significant.

3.5 The forward shifting of spatial representation toward the reward locations in the reference memory task, but not in the working memory task

Next I asked whether the shifting of place field locations was related to the presence of reward or the learning process per se involving specific type of memories. I found that place fields gradually shifted towards upcoming reward location during the spatial reference memory task but not in the spatial working memory task (**Figure 13**). The linear place firing map of each place cell revealed that most place fields were spatially stable across learning session; only those firing in inbound direction at the newly-rewarded arms shifted gradually their place fields towards the end of the arms, and only in the reference memory task (**Figure 13A-B**). Similar tests were used to assess whether significant place fields shift took place as for the combined task. Firstly, I calculated the shifting score of place fields. Similar significant shift was seen during the spatial reference but not in the spatial working memory task as for the combined task, and shifting was observed only for inbound novel-goal arms passes not for familiar-goal arm (Reference memory inbound runs $P<0.001$, all other $P>0.5$; Binomial test, **Figure 13C-D**). Secondly the distribution of place field peak locations also exhibited a shift and more cells fired near to goals in the end of the learning than in the beginning, again this effect was significant only for inbound trials of the reference memory task (Reference memory inbound runs $P<0.0001$, all other $P>0.24$; K-S test, **Figure 13E-F**).

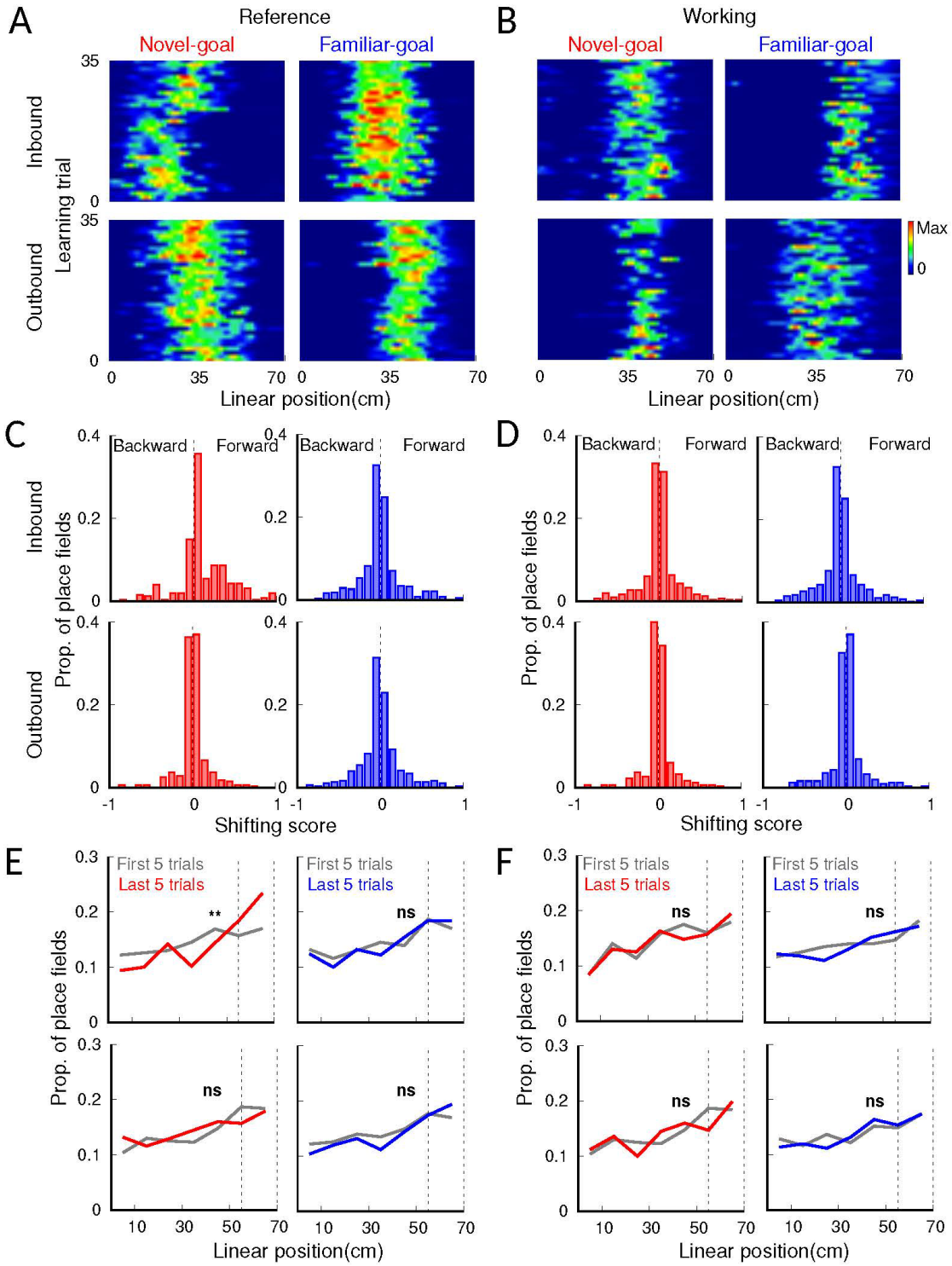

Figure 13 | Place fields shift towards the reward locations in the reference memory task but not in the working memory task

(A-B) Example firing fields at different learning trials for inbound and outbound trials in familiar- and novel-goal arms. One cell of each category is shown for the reference (A) and the working (B) memory tasks. The rate maps show the firing rate of the cells on the goal-arm at different trials. Note that shift towards rewards only occurs in inbound trials on the novel-goal arms in the reference memory task.
(C-D) Distribution of place field shift scores comparing the place field peak positions in the first and last five trials for reference (C) and working (D) memory sessions. Shift scores measured the difference between the positions divided by the sum. Binomial test, Reference: novel-goal for inbound n=253 place fields, P<0.001; novel-goal for outbound n=275 place fields, P=0.517; familiar-goal for inbound n=353 place fields, P=0.819; familiar-goal for outbound n=379 place fields, P=0.907; Working: novel-goal for inbound n=312 place fields, P=0.830; novel-goal for outbound n=328 place fields, P=0.717; familiar-goal for inbound n=382 place fields, P=0.678; familiar-goal for outbound n=305 place fields, P=0.522.
(E-F), Distribution of place field peak positions as measured in the first and last five trials for reference (E) and working (F) memory session. Note that more cells fired near the goal in the last five trials than in the first five trials but only in the inbound runs in novel-goal arms. K-S test, Reference: novel-goal for inbound n=253 place fields, P<0.0001; novel-goal for outbound n=275 place fields, P=0.7935; familiar-goal for inbound n=353 place fields, P=0.4757; familiar-goal for outbound n=379 place fields, P=0.2421; Working: novel-goal for inbound n=312 place fields, P=0.9358; novel-goal for outbound n=328 place fields, P=0.8384; familiar-goal for inbound n=382 place fields, P=0.3174; familiar-goal for outbound n=305 place fields, P=0.8456. **P<0.001, Ns, not significant.

3.6 Firing rate modulation of cells depending on past or future arm choices

Hippocampal place cells were recorded as animals often followed different arm-sequences to complete the task Therefore, when I examined all the trials, I found that in many instances the animal reached an arm from either of the remaining arms and also once it returned from an arm it went to either of the remaining arms. Accordingly, as seen on other mazes, such as the T-maze, place cell firing may be modulated by the past or future choice of the animal. While place cells exhibited location-specific activity throughout the maze, the focus of the current analysis was on those cells with place fields on the arm that animals traversed on every trial, i.e. the goal arms. Here, I examined cases when the animal had already visited one arm in a session and tested its firing rate while returning from that arm depending on which arm it went to next or when approaching an arm whether the rate depended on the previous arm visited (**Figure 14, A-B**). To identify cells that exhibited future or past choice-dependent firing I compared the within trial rate of cells in five spatial

bins and used ANCOVA analysis to compare rates across the two trial conditions when speed at the appropriate spatial bin was compensated for. The inbound firing of the place cells was significantly modulated in 43% of the place cells by the past arm choice (P<0.05, ANCOVA) for the combined task (**Figure 14A**). Similar modulation was observed for outbound firing of cells, firing rate modulation depended on which arm the animal visited next (42% ANCOVA p<0.05) (**Figure 14B**). Significant rate modulated cells were seen not only in the combined but in the spatial reference and working memory task as well, all showing rate dependence on the past or future arm visits (**Figure 14C-D**).

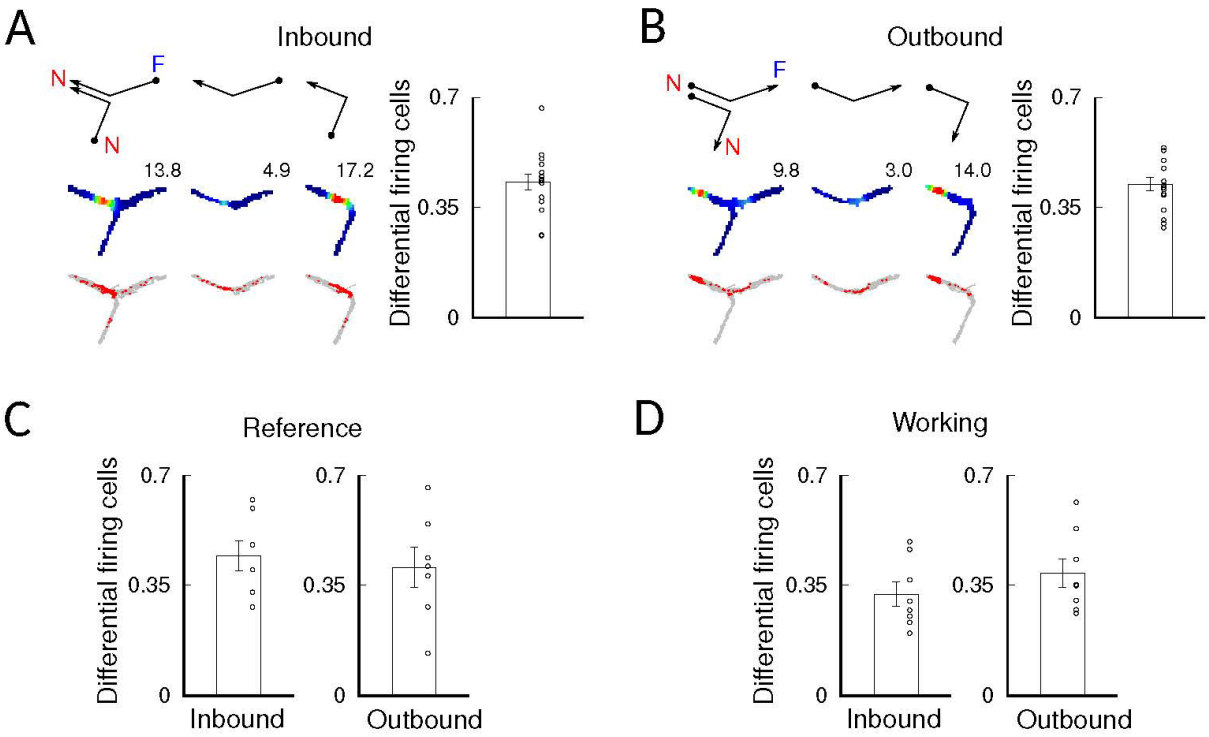

Figure 14 | Different patterns of activity preferentially associated with future and past choices

(A-B) Firing rate modulation of place cells in inbound trials may depend on their previous arm choice (A) while, in outbound trials, it may predict their future choice (B). Left maps illustrate the place field of an inbound and an outbound firing cell depending on passes involving the other two goal-arms. The cells fired on a novel-goal arm stronger when other segment of the paths ere also a novel-goal arms as compared to a familiar-goal arm. Right histogram shows the proportion of place cells exhibiting significant, speed-compensated rate modulations (P<0.05, ANCOVA).

(C-D) The proportion of place cells showing significant, speed-compensated rate modulations (P<0.05, ANOCA) on the reference (C) and working (D) memory task. Means of the sessions (±SEM) are shown with individual session values.

Although cells exhibited conditional firing depending on future or past arm choices in all memory tasks; however these might depend on goal novelty. We know that place cells fire stronger in a novel environment; therefore it is possible that such goal novelty may be reflected in their conditional firing as well. This rate modulation did not show goal novelty related changes in the working memory task. In contrast, the other two tasks involving spatial reference memory exhibited a firing rate bias when the previous or future arms were novel-goal arms (**Figure 15A-B)**. Moreover, this firing rate modulation bias was not seen in the beginning of the trial only in the later trials. Accordingly, in the second half of the learning session the firing rate of cells was always higher in the inbound passes if the animal approached from a novel-goal arm as compared to a familiar-goal arm (**Figure 15A**). Similarly, in outbound passes firing was stronger when animal went to a novel-goal arm next as compared to a familiar goal (**Figure 15B**).

However, this conditional firing related with novel-goal arms was not seen in the beginning of trials, only in later trials once the animal learned the task (**Figure 15A-B**). To quantify firing rate modulation of cells depending on the novelty of the goal the animal visited before or after, the firing rate score of each cell was calculated to compare the rate of the cells when the previous or next visit was a familiar-goal arm or a novel-goal arm. Rate score was measured as the difference of the scores divided by the sum and this rate score was calculated separately for the first half and second half of learning trials. I found that during reference and combined memory tasks firing depended on goal-novelty, and the rate score distribution of cells showed a positive bias (all $P<0.001$, Binomial test) for the rate scores calculated in the second half of learning but not in the first half of learning (all $P>0.64$, binomial test) . (**Figure 15 C-D**). In the working memory task I did not see such bias (all $P>0.5$, Binomial test). Therefore, in the spatial working memory task place cells showed conditional firing on the past or future arm choices, and these did not depend on goal novelty before or after (**Figure 15E-F**).

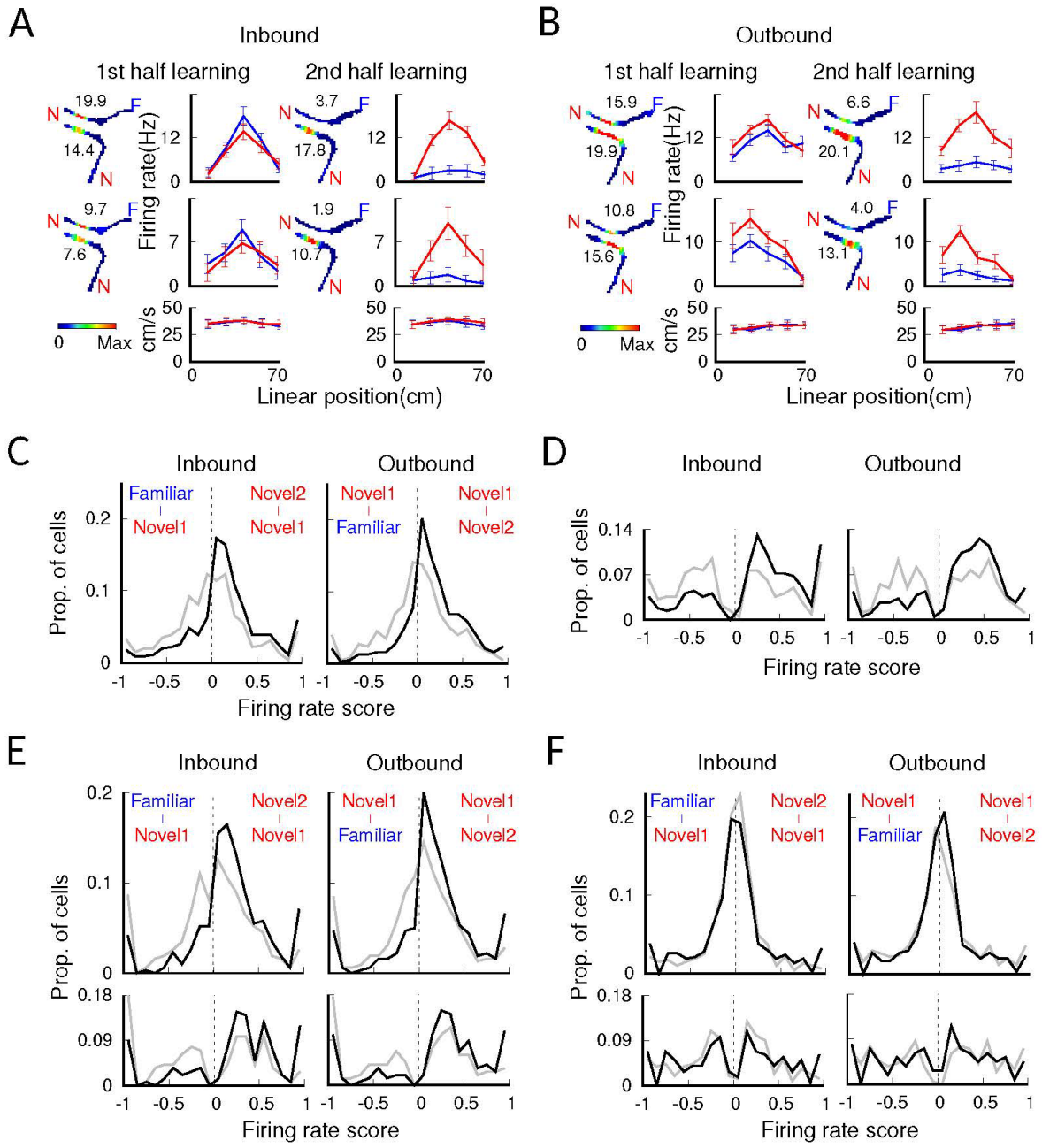

Figure 15 | Firing rate modulation of cells depends on the object novelty of past or future arm choices

(A-B) Examples illustrate the past (A) or future (B) arm choice-dependent rate modulation of representative cells in the first and second half of the learning trials. Firing fields and the mean (±SEM) firing rate of different spatial bins of the arm are shown in the top two rows. Bottom histogram: mean (±SEM) speed at different spatial bins. Blue curves show passes including a familiar- and a novel-goal arms while red curves covered passes across novel-goal arms. Note that rate differences are stronger in the second half of learning. N, novel-goal arm, F, familiar-goal arm.

(C) Rate modulation of cells on a novel-goal arms on inbound (left) and outbound (right) passes depending on the past or future arm choices respectively. Distribution of firing rate scores comparing passes in which the previous or future arms were either a familiar-goal arm or another novel-goal arm. Rate scores were calculated by the difference of the rates dived by their sums, positive rate score reflect higher rates in novel-novel passes as compared to passes involving a familiar- and a novel-goal arm. Rate score distributions were calculated in the first half (grey) and second half (back) of the learning trial. Binomial test, inbound for the first half (1st): n=457 cells, P=0.644; inbound for the second half (2nd): n=457 cells, P<0.001; outbound for 1st: n=376 cells, P=0.986; outbound for 2^{nd}: n=376 cells, P<0.001

(D) Same as (C) only cells with significant, speed compensated rate modulation (P<0.05, ANCOVA) are included. Binomial test, inbound for the 1st: n=182 cells, P=0.515; inbound for the 2nd: n=182 cells, P<0.001; outbound for 1st: n=151 cells, P=0.428; outbound for 2nd: n=151 cells, P<0.001

(E-F) Rate modulation histograms during the reference (E) and working (F) memory task. Rate modulation of cells on a novel-goal arms on inbound (left) and outbound (right) passes are shown depending on the past or future arm choices respectively. Top curves show all cells while the bottom ones represent those with significant, speed-compensate rate modulation (P<0.05, ANCOVA). Binomial test, Reference, top histograms: inbound for the 1st n=310 cells, P=0.909; inbound for 2nd n=310 cells, P<0.001; outbound for 1st : n=318 cells, P=0.753; outbound for 2nd: n=318 cells, P<0.001; bottom histograms: inbound for the 1st: n=143 cells, P=0.071; inbound for the 2nd: n=143 cells, P<0.01; outbound for 1st : n=127 cells, P=0.255; outbound for 2nd: n=127 cells, P<0.001;

Working, top histograms: inbound for 1st: n=299 cells, P=0.644; inbound for the 2nd: n=299 cells, P=0.860; outbound for 1st : n=334 cells, P=0.568; outbound for 2nd: n=334 cells, P=0.741; bottom histograms: inbound for the 1st: n=109 cells, P=0.722; inbound for the 2nd: n=109 cells, P=665; outbound for 1st : n=126 cells, P=0.584; outbound for 2nd: n=126 cells, P=0.769

3.7 Hippocampal sequence replay

In the previous section I showed that place cells on the eight-arm maze exhibit conditional firing depending on the past and future paths in all of my tasks. I also demonstrated such conditional firing changes on the novel arms during the course of learning. I showed this for the combined and reference memory tasks and I demonstrated that goal novelty on the previous or the next arms influenced the conditional firing of the cell and this developed gradually, being seen in later trials. Next, I set out to investigate whether place cell assembly activity always encoded the current location of the animal, or if it reflected other locations or indeed entire paths. Finally, if such replay or movement paths are be observed, to analyze whether such out-of-place coding is correlated with the behavior of the animal and

related to its previous arm visit or future arm choice. Because I recorded the population activity of place cells in the CA1 region while animal ran on the maze (from one reward location to another on a linear track), I could probe whether this assembly activity expresses the current location of the animal or some other location on the maze. During a run, each place cell's activity is tuned at a particular location along the track. These locations defined a temporal sequence for the firing place cell assemblies on the timescale of seconds (**Figure 16**). I then detected high synchrony events (HSE) where many cells intensively fired action potential together transiently in a time period lasting from approximately 100ms or more, while animals performed the task. As expected from past work examining the reactivation of movement trajectories, I often observed that place cell assembly firing sequences seen in an arm during task running can also be seen during the HSEs but in a temporally compressed form, preserving the same order as these fired on the arm either in a forward or reverse temporal order. Such HSEs tend to occur while the animal was at the center or the reward location (**Figure 16**). In the combined task, HSEs near the reward location typically contained place cell firing patterns representing the animal returning from that arm, but in a reverse temporal order; i.e. cells close to the end of the arm fire towards the end of HSE whereas those firing close to the center of the maze fire in the beginning. In contrast, HSEs that occurred in the center often incorporated place cells that fire in the next arm to be visited by the animal, but this time with cells firing in a forward order.

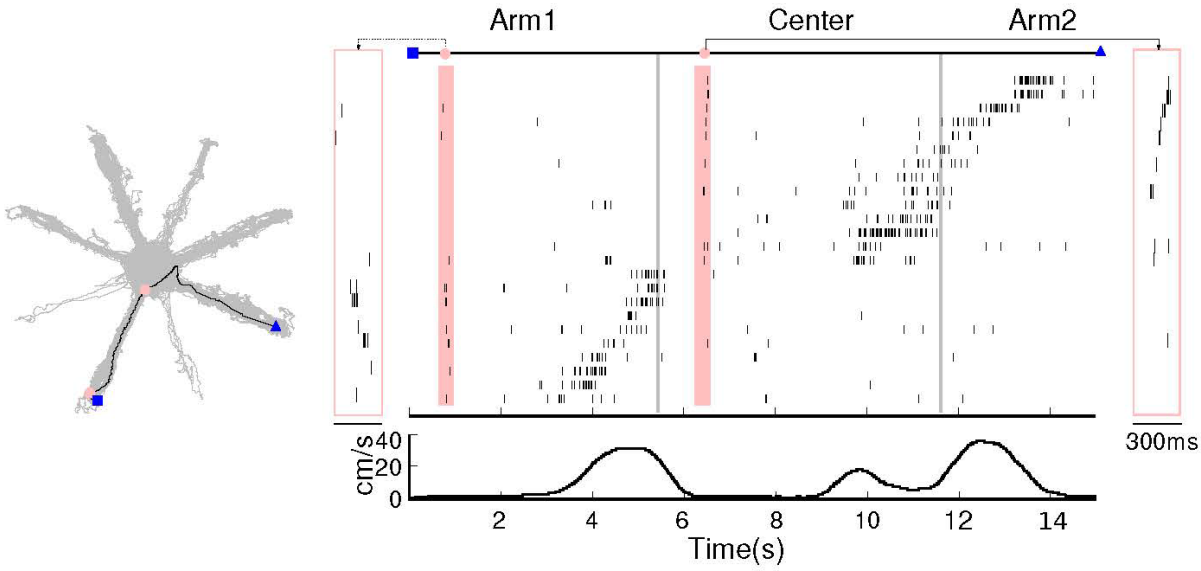

Figure 16 | Reactivation of assembly sequence representative maze trajectories

Example showing place cell assembly activity during a pass covering movement from one goal-arm to the next in the combined task. Left traces: Grey traces show all the movement during all the learning trials while the black trace show the pass for which the network activity is displayed on the right. Pink circles mark the location of the 2 HSEs highlighted on the right. Top right raster plot: firing times of 24 place cells sorted according to their place field locations on the arms. Pink areas highlight the two HSEs which are expanded on the left and the right boxes (300-ms sections of the spike train). Note that the first HSE in the beginning of the pass reactivates the sequential activity of place cells firing while the animal returns from that arm to the center. But cells fire in a reverse temporal order; i.e. cells near the current location of the animal fire last. In contrast, the HSE in the center reactivate the activity of the cells in next arm the animal selects in forward temporal order, i.e., cells near the current location of the animal fire first. Bottom right curve shows the speed of the animal during the pass.

To detect and quantify these replay events, I identified HSEs as a brief increase in population spiking activity and then divided these candidate events into 20ms time windows. By using a Bayesian prediction method I calculated the probabilities at different locations of the maze according to which place cells were active in a given time window. Separate Bayesian probability maps (composed of probabilities of positions as derived separately for each time window of the HSE) were calculated for inbound and outbound runs of each goal arm (**Figure 17A-B**). Using these maps I calculated the arm in which the trajectory showed the maximum summed probabilities, allowing for both forward and reverse trajectories on inbound our outbound passes (see methods). Thus, the selected maximum probability trajectory held information about sequences of positions that are part of the trajectory, whether these positions represent an inbound or outbound trajectory and also whether these positions represent a forward or reverse order replay (**Figure 17C**).

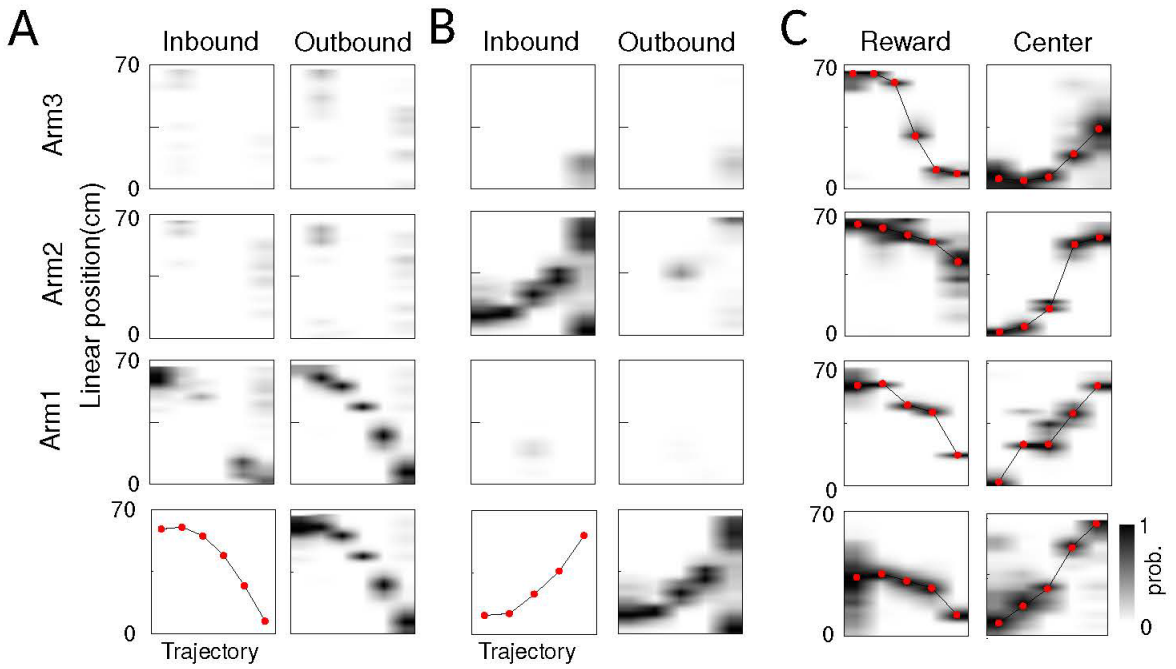

Figure 17 | Reactivation of maze trajectories during HSEs

(A-B) Examples illustrating how the replayed trajectories were calculated using two HSEs, one near a reward location (A) and the other at the central stem (B). Bayesian probability maps for both inbound and outbound runs are shown for all three goal-arms (darker grey colors represent higher probabilities). The map composed from inbound and outbound maps of the selected arm is shown on the bottom right while the reconstructed trajectory is shown on the bottom left (see Methods).
(C) Examples displaying reactivated trajectories in recordings during the combined task that occurred near the reward location and in the center stem. Bayesian maps are overlaid with the reconstructed trajectory. All examples near the reward represented outbound passes of that arm (reverse order) while at the center these were inbound passes of the next arm (forward order). On the probability maps distance relative to the HSE location was displayed, i.e., zero marks the end of the arm for HSEs near reward locations and beginning of arm for HSEs in the central stem.

Each replayed trajectory was quantified by a measure called the replay score which is measured by the summed Bayesian probability of the trajectory locations divided by the number of time window frames. To test whether the probability that detected trajectories occurred by chance, I rotated the place field of each active cell to see whether similar replay scores of the replayed trajectories can occur when using the same spike temporal patterns but with de-correlated place maps. The reconstructed trajectory events were not random (All $P<0.0000001$, K-S test **Figure 18**). My trajectory searching procedure generated significantly weaker probabilities with place field rotated probability maps than with the

original maps. Moreover, the z-score of the reactivated trajectories as measured relative to the corresponding shuffled distributions was significantly larger than zero (All P<0.0001, binomial test, **Figure 18**).

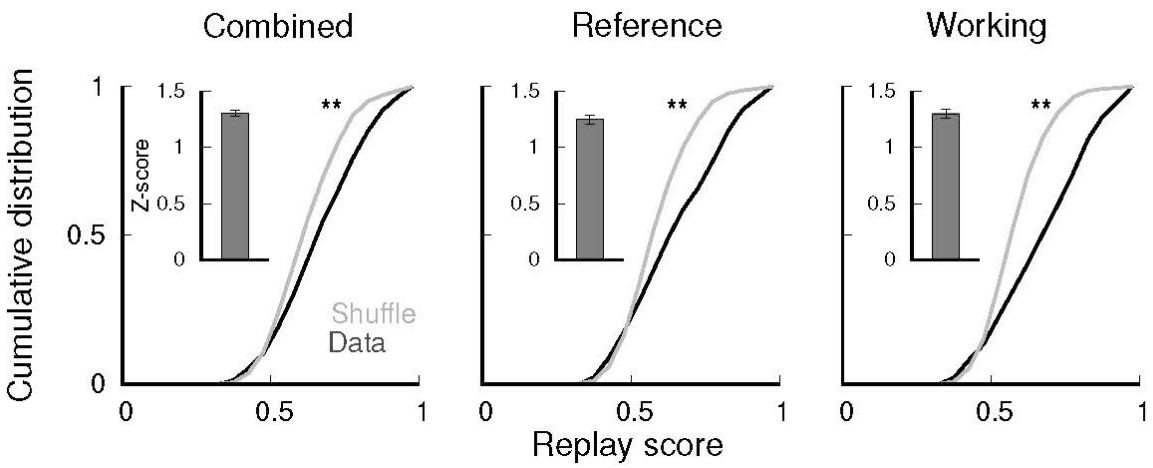

Figure 18 | HSEs represent trajectories with significantly better replay scores than their shuffled equivalents

The cumulative distribution of replay scores for the original events (data) and those of the shuffled events in which the place field relationship between cells was randomized by randomly rotating them to a different degree for each cell. For each original event 100 random shuffled events were calculated, each involving different place field rotations. Inset shows the average z-score of original events relative to the mean and SD of their corresponding 100 shuffled events. K-S test for cumulative distribution, Combined: data n= 1200 events, shuffle n=120000 events, P<0.0000001; Reference: data n=605 events, shuffle n=60500 events, P<0.0000001; Working: data n= 691 events, shuffle n=69100 events, P<0.0000001. **P<0.001. Binomial test for z-score, Combined: n=1200 events, P<0.0001; Reference: n=605 events, P<0.0001; Working: n=691 events, P<0.0001

Given that reactivation is closely associated with SWR events, I also examined whether the detected HSE reactivation were associated with SWRs. The cross-correlation between HSE times and SWR times were calculated for all sessions and averaged. The sharp peak on the mean cross-correlation curve demonstrates the close association of HSE to SWRs (**Figure 19**).

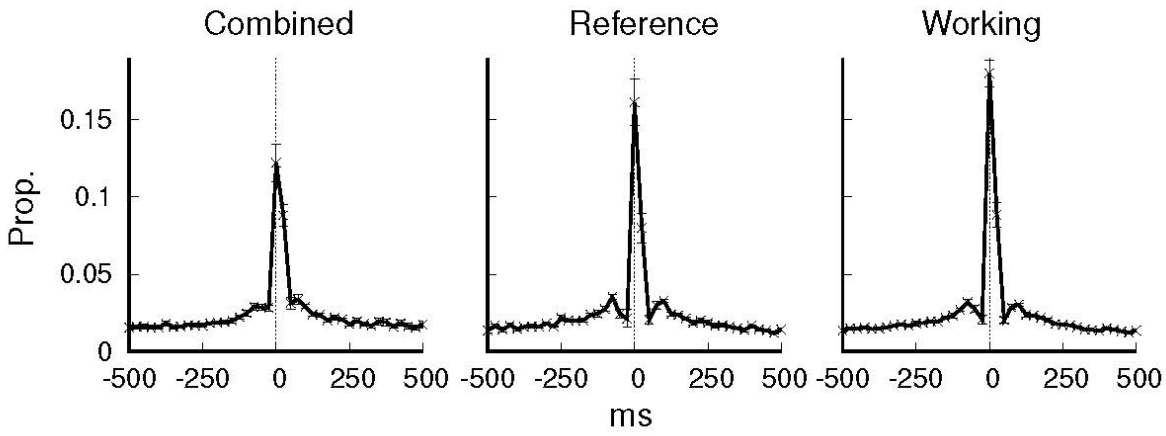

Figure 19 | Temporal association between HSE and SWR events

Mean (±SEM) cross correlation curves between SWR times with HSE peak times were averaged across sessions (Combined, n=16 recording days in 4 rats. Reference: n=8 recording days in 3 rats; Working N=8 recording days in 3 rats).

Previous studies on the linear track demonstrate that spiking sequences can be replayed in either the forward or reverse temporal order (Diba and Buzsaki, 2007; Foster and Wilson, 2006; Davidson et al., 2009; Silva et al., 2015). However, it is not clear whether the replay order reflects the experience of the animal running on the maze. Therefore, for each HSE I determined which arm it will encode in relation to the location of the HSE. In the combined and reference memory tasks reconstructed trajectories of HSEs that occurred in the center of the maze had a preference to encode trajectories on the future arm that the animal visited next and less the previous arm that the animal visited before (**Figure 20A**). However, at the reward location the current arm of the animal was preferentially encoded (all P <0.0001, ANOVA, **Figure 20B**). In the working memory task at the reward locations the current arm was encoded as well, but the previous visited arm was encoded in the central stem (P <0.0001, ANOVA, **Figure 20A-B**). I further tested whether inbound vs outbound trajectories were preferentially reactivated and whether forward vs reverse order reactivation was seen. In the combined and reference memory tasks in the central stem forward replay of inbound direction trajectories were seen encoding preferentially the next arm (i.e. forward passes in forward replay). At the reward locations reverse order replay trajectories encoding outbound passes were detected (outbound passes in reverse order). Hence in these conditions replay always preferentially encoded the upcoming movement of the animal but at the rewards on a reverse direction. By contrast in the working memory task reverse order replay was seen encoding outbound trajectories and in the central stem

these represented the previous arm and at the reward location these encoded the current arm (**Figure 20C**).

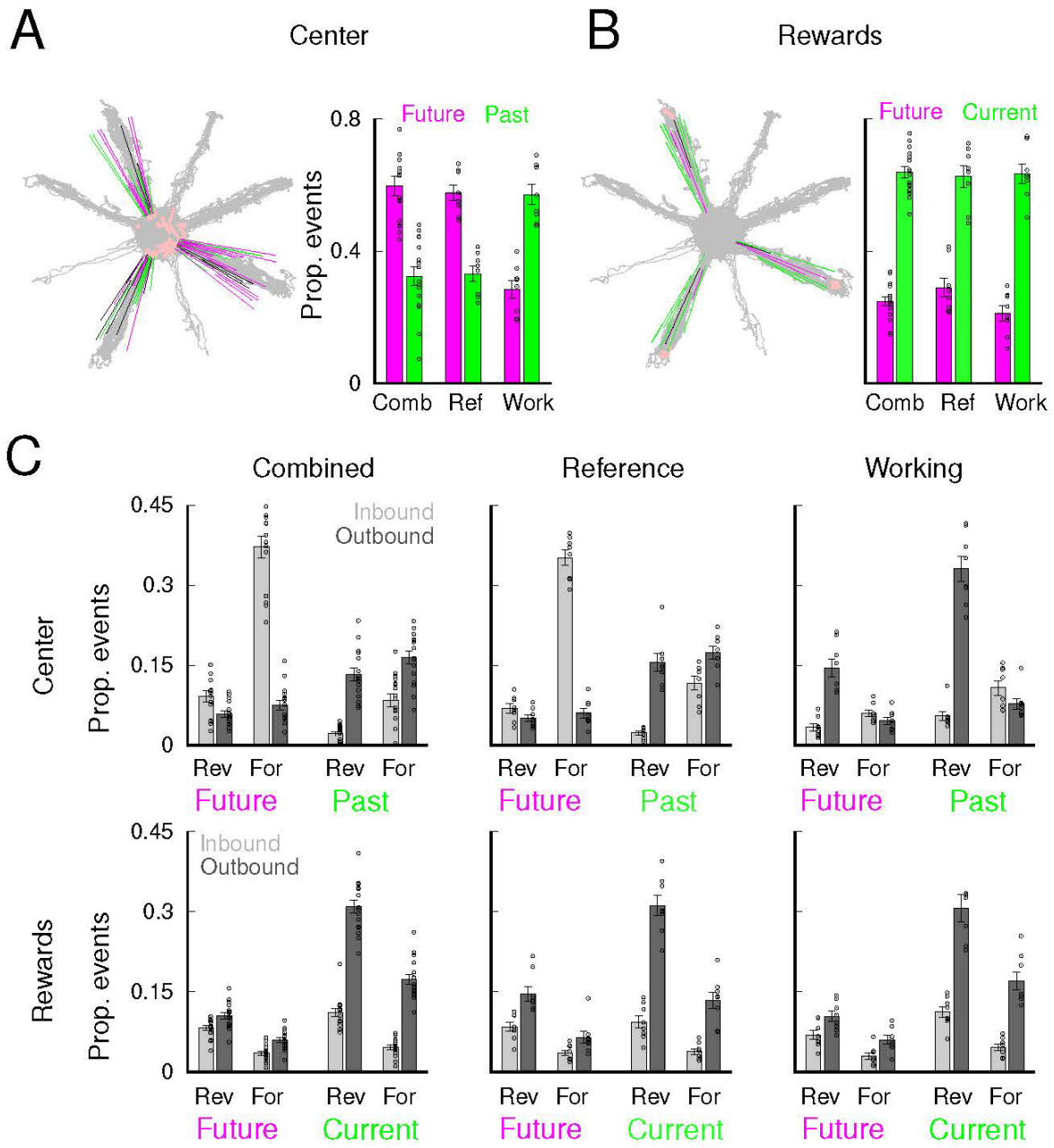

Figure 20 | Reactivated trajectories predicting the behavior of the animal

(A-B) Left: Example showing all the reactivated trajectories of HSEs occurred on the central stem in a single learning session in a combined task. Trajectories predicted the next arm choice of the animal (purple), the previous choice (green) and the rest of the events (black) are all shown. Reactivated events are illustrated as a line showing the two extreme ends of the trajectory. Trajectories of the same arms are all displayed by different relative angles from each other so that all of them can be visible. Right: Percentage (mean ±SEM and individual session values) of trajectories predicting the future arm choice of the animal and

those displaying its past arms for HSEs in the center stem. Comb: combined task, Ref: reference memory task, Work: working memory task (B) same as (A) but HSE near reward location are shown predicting current and future arms. One-way ANOVA between future and past/current choice, Combined: n=16 recording days in 4 rats; Reference: n=8 recording days in 3 rats; Working: n=8 recording days in 3 rats, all P <0.0001.
(C) Percentage (mean ±SE and individual session values) of HSEs reactivating in forward and reverse order trajectories of future, past/current trajectories of inbound and outbound movement of the animal. Note that the combined and reference memory HSEs in the center stem predicted the future arm choice of the animal in the form of forward order inbound movement while in the rest of the cases the previous/current arm choices were predicted, in replay events representing outbound movement in a reverse temporal order. Three-way ANOVA with Tukey Post hoc, (Top) Combined and Reference: Future-Forward-Inbound group is significantly different from other groups, all P<0.0000001; Working: Past-Reverse-Outbound group was significantly different comparing to other groups, all P<0.0000001; (Bottom) All three task: Current-Reverse-Outbound group vs. other groups, all P<0.0000001.

Similar results were seen when I used the probability maps of all eight arms (**Figure 21**). These results could be calculated for the combined and reference memory tasks only because only three arms were always visited in the working memory task. I observed that trajectory replay in the center of the maze predicted the future arm choice that the animal visited next (**Figure 21A**). At the reward location, replay was associated with the current arm (**Figure 21B**). Trajectories at the center encoded preferentially inbound passes representing in forward replay while reverse replay was seen near the rewards encoding outbound passes (**Figure 21C**). Moreover, the reconstructed trajectories allowing replayed trajectories on all eight arms were not random, by rotating the place field of each cell the rotated map replay scores resulted in weaker repay scores than the original events (**Figure 21D**).

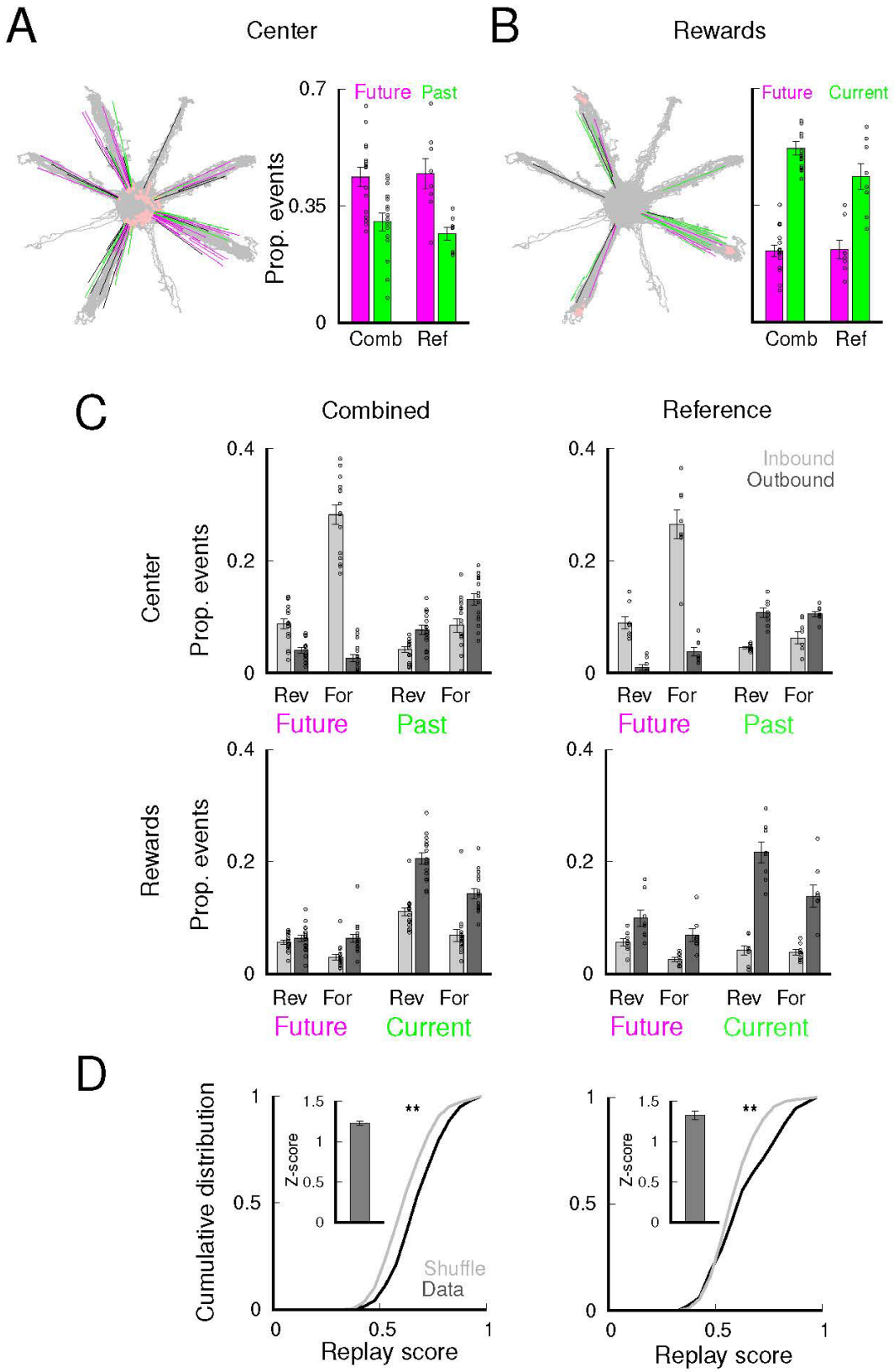

Figure 21 | Reactivated trajectories predict the behavior of the animal testing for reactivation of all eight arms

(A-B) Left: Example showing all the reactivated trajectories of HSEs occurred on the central stem in a single learning session in a combined task. Trajectories predicted the next arm choice of the animal (purple), the previous choice (green) and the rest of the events (black) are all shown. Reactivated events are illustrated as a line showing the two extreme ends of the trajectory. Trajectories of the same arms are all displayed by different relative angles from each other so that all of them can be visible. Note that some of the reactivated trajectories predicted not only the correct choices of the animal to the current goal-arms but some also to other goal arms such as those that the animal learned the day before. Right: Percentage (mean ±SEM and individual session values) of trajectories predicting the future arm choice of the animal and those displaying its past arms for HSEs in the center stem. Comb: combined task, Ref: reference memory task, Work: working memory task (B) same as (A) but HSE near reward location are shown predicting current and future arms. One-way ANOVA test comparing future vs. past/current choice, Combined: n=16; Reference: n=8; all $P < 0.0001$.
(C) Percentage (mean ±SEM and individual session values) of HSEs reactivating in forward and reverse order trajectories of future, past/current trajectories of inbound and outbound movement of the animal. Note that some of the reactivated trajectories not only predicted the correct choices of the animal to the current goal-arms but some also to other goal arms such as those that the animal learned the day before. Three-way ANOVA with Tukey Post hoc, (Top) Future-Forward-Inbound group significantly different from other groups, all $P<0.0000001$; (Bottom) Current-Reverse-Outbound group vs other groups, all $P<0.0000001$.
(D) The cumulative distribution of replay scores for the original events (data) and those of the shuffled events (shuffle) in which the place field relationship between cells were randomized by randomly rotating them to a different degree for each cell. For each original event 100 random shuffled events were calculated, each involving different place field rotations. Inset shows the average z-score of original events relative to the mean and SD of their corresponding 100 shuffled events. K-S test for cumulative distribution, Combined: data n= 908 events, shuffle n=90800 events, $P<0.0000001$; Reference: data n=529 events, shuffle n=52900 events, $P<0.0000001$. Binomial test for z-score, Combined: n=908 events, $P<0.0001$; Reference: n=529 events, $P<0.0001$.

4 Discussion

In this thesis I examined CA1 place cell activity during a task in which animals had to explicitly update their spatial reference memory and, at the same time, utilize spatial working memory. In addition, I compared this cell activity to that during two other tasks, this time requiring only the update of spatial reference or the use of spatial working memory. I found that many task-dependent place cell activity patterns took place only when spatial reference memories were updated. Firstly, place cells that fired on a novel-goal arm gradually moved their place fields towards the reward locations at the end of the arm while the animal learned the task. Secondly, place cells gradually developed modulated firing rates at an arm depending on the novelty of goal locations on their previous and future arm choices. That is that during runs towards the goal firing on a novel-goal arm was stronger when the previous arm was also novel-goal arm as opposed to a familiar-goal arm, and firing during runs from the goal to the center showed a similar dependence with the next arm choice. In the spatial working memory task place cells never showed such place field shift during learning, and, although cells exhibited conditional firing on future or past arm choices, these did not depend on goal novelty before or after. I also examined whether assembly firing predicted the future behavioral choice of the animal during trajectory replay in high synchrony periods. In tasks requiring spatial reference memories the trajectory replay in the center of the maze predicted the future arm choice of the animal while in the spatial working memory task it preferentially encoded its past arm choice. At the reward locations, in all three tasks replay was associated with trajectories of the current arm showing the trajectory that the animal took next to return to the center. At reward locations trajectories were replayed preferentially in reverse temporal order. Moreover, in the center reverse replay was seen in in the working memory task but in the other tasks forward replay was seen.

4.1 Goal-related remapping of place cells

Several studies have demonstrated that following goal learning a disproportional number of place cells have place field near the learned goal locations (Markus et al., 1995; Hok et al., 2007; Hollup et al., 2001; Dupret et al., 2010). Such disproportional representation of reward-associated goals can be observed also while the animals are performing very familiar tasks in simple maze environments as well (Allen et al., 2012). In my case I also observed a higher number of place cells having a place field at the end of the arms where the reward was located, even at the familiar goal-arms and during the working memory task.

Dupret at al. (2010) showed that on the cheeseboard maze CA1 place cells remap their firing fields when goals are changed and they represent the new goals. This goal-oriented remapping only takes place when animals have to use allocentric strategies to locate these goals without the use of local cues making them. My task also involved a change of goal locations. I observed a gradual remapping of place fields during learning in tasks requiring reference memory update but not in the working memory task. In the working memory task I cannot determine from our data whether remapping took place given that I have not recorded from the same cells in the novel-goal arms before. At least the majority of these cells had stable firing fields from the first trial suggesting that these place cells did not remap, given that the animal visited these arms before, at least during the training sessions.

Like during the first exposure to a novel environment (Wilson and McNaughton, 1993), remapped place field emerge rapidly during goal learning on the cheeseboard maze when animals learn new goals quickly (Dupret et al., 2010) However, previous and the newly-formed place representations initially flicker for the first 10-20 trials on the cheeseboard (Durpet et al., 2013). Unlike during the cheeseboard learning, in our tasks requiring reference memory updates many place cells did not immediately fire in the first trials on the novel-goal arms, but once they started to fire, their place fields gradually moved closer to the goal. Such gradual remapping in our case may be attributed to the fact that it took over 10-15 trials for the animal to reliably locate the rewards on the novel-goal arms. Place fields in the familiar-goal arm were unchanged by learning, though this location was rewarded as well. The stability of the familiar-goal arm-related firing patterns could be explained by the fact that the place reward association for the familiar arm remained constant from previous day to the current recording day while novel-goal arms changed daily. Therefore, the partial

update of reference memory representations did not lead to the full reorganization of the hippocampal cognitive map, only part of the map related to the novel-goals were updated.

Learning novel-goal locations in an environment depends on the induction of synaptic plasticity. In the hippocampal pyramidal cells NMDA receptors, mediate most known forms of synaptic plasticity (Bliss and Collingridge, 1993). Infusion of an NMDA receptor antagonist, AP-V, impairs spatial learning over consecutive training days on the water maze task (Morris et al., 1986). However later it was shown that induced abolition of GluN1 receptors in the CA1 region and the dentate gyrus did not show such impairment in learning (Bannerman et al., 2012). However when the escape platform was shifted these GluN1 knockouts exhibited an impairment in learning the new locations and these animals also shown reference memory deficit on the 8-arm maze. The global injection of the NMDA receptor antagonist CPP did not impair the initial learning of new goal locations on the cheeseboard, but did impair later recall of those baited locations (McDonald et al., 2005; Dupret et al., 2010). Here the animal also had to suppress the previously learned goals and learn a new set of goals similar to the change of the escape platform.

Reactivation results in the Dupret et al., 2010 paper may highlight why NMDA receptors in CA1 are needed for the update of spatial reference memories. They found that NMDA receptor blockade did not prevent the reactivation of new goal locations, however the previous day's goals were also reactivated with equal strength, which latter were suppressed in the drug-free animals. Hence NMDA receptors may have a crucial role in updating spatial memories and in consolidation, suppressing old conflicting representations. Note that another study found that under a similar drug to CPP, CPPene place cells were unable to organize in a sequential pattern reflecting the spatial memory of the running trajectory (Silva et al., 2015). Given that my data suggest that sequence replay can play a role in decision making in tasks requiring reference memory on the eight-arm maze, NMDA receptor-associated impairment of sequence replay could also contribute the learning impairment on the radial eight-arm maze (Bannerman et al., 2012).

NMDA receptors are also needed for the stabilization of newly established place fields but new place fields can be transiently formed even under NMDA receptor blockade (Kentros et al., 1998; Dupret et al., 2010). This indeed explains why animals can quickly learn but cannot remember after a long delay a new set of goal locations or an updated escape platform

under NMDA receptor blockade. Taking these results together, it is possible that goal-related remapping is needed when spatial reference memories are needed to be updated and this process require NMDA receptors to enable the stabilization of the newly formed goal-maps. However in a familiar environment where a stable map of the environment already exists, that stable map is sufficient for the learning of a fixed goal, and therefore this may not require NMDA receptors.

4.2 Conditional place cell firing

Previous studies have shown that when a well-trained rat runs through the central or common segment of a maze on its way to or from different locations, hippocampal place cell exhibit differential firing depending on their past and future arm choices on the maze (Wood et al., 2000; Frank et al., 2000; Ferbinteanu and Shapiro, 2003; Bower et al., 2005; Ji and Wilson, 2008; Pastalkova, 2008; Ferbinteanu et al., 2011; Allen et al., 2012; Catanese et al., 2014; Ito et al., 2015; Grieves et al., 2016). The results of these previous studies have varied in the characteristics how hippocampal neurons distinguish path-choices in spatial working memory tasks on the maze. This firing is related to spatial working memory demands given that in error trials this conditional firing is disrupted (Ferbinteanu and Shapiro, 2003; Allen et al., 2012) or these may not be seen when animals only decide about alterative choices later at the choice point (Ainge et al., 2007b). In my case, trial type-dependent firing was observed even in a reference memory maze task not requiring working memory. This suggests that conditional firing may be related to arm choices not exclusive to working memory but can occur in reference memory choices as well.

Findings from Ferbinteanu and Shapiro (2003) indicate that retrospective coding as manifested by the firing modulation of place cells may not reflect trajectories. They trained rats on a plus maze task and showed that even when the rats took indirect trajectories to a goal, differential retrospective coding was observed depending not on the detoured arm, but the original starting arm. However the effect of the detour on the firing of the cells was not quantified. In my data I also observed retrospective firing and many place cells modulated their firing depending on the past arm visits. Importantly in my case not a task-

rule but the animal itself decided which order it will visit the three goal arms. Unlike Ferbinteanu and Shapiro (2003) work, I have seen examples of place cells where firing was modulated by the order of all three arm visits. However there were too few arm visits to demonstrate the significance of these events using ANCOVA.

Given that retrospective coding does not help to solve the task in our case, or e.g. in the Ferbinteanu and Shapiro (2003) work, such task demand-independent coding could indeed transiently encode the past experience of the animal, more reminiscent of episodic-like coding. The fact that such coding reflected in the rate remapping of place cells further suggest episodic like coding properties (Allen et al., 2012, O'Neill et al., 2017; Leutgeb et al., 2005). Such task dependent rate modulation may or may not be needed for decision making however. A likely possibility is that the hippocampus represents both where the animal is going and where it has been. Recent work by Ito et al. (2015) has suggested that trajectory dependent coding is found in the nucleus reuniens, which projects to the lacunosum moleculare of CA1. Moreover, the nucleus reuniens receives input from the medial prefrontal cortex (mPFC). Ito et al. (2015) also suggests that the nucleus reuniens is necessary for the task-contingent firing in CA1 place cells. This implies that conditional firing may arise in the mPFC and may be passed through the nucleus reuniens to the CA1 layer of the hippocampus. However, another study showed that in the encoding phase CA1 input to the mPFC is needed for the animal to correctly perform the delayed non-match-to-sample task on the T-maze (Spellman et al., 2015). This indicates that the mPFC and the hippocampus exhibit bidirectional interactions during spatial memory tasks in which the nucleus reuniens may play a role as a relay.

4.3 Interaction of novel reward with dopamine

One of the primary hippocampal inputs that can regulate the reward association processing is the ventral tegmental area (VTA) (Lisman and Grace, 2005). Single-unit recording studies have revealed that the firing rate of dopaminergic neurons is increased by unexpected reward and such firing is also reduced when an expected reward is omitted (Mirenowicz and Schultz, 1994). The firing rates of VTA dopaminergic neurons are increased by exposure to

novel stimuli (Ljungberg et al., 1992). VTA dopaminergic input inputs may play a role in spatial leaning. Indeed, intra-hippocampal injection of D1 and D2 agonists improves performance in the eight arm radial maze (Packard and White, 1991). Furthermore, optogenetic activation of dopamine terminals in CA1 during learning results in increased recall of trajectories in a "crossword" maze and enhances post-learning reactivation of place cells (McNamara et al., 2014). According to these previous studies, the dopaminergic projection from the VTA has modulatory effects on hippocampal functions like those related to spatial learning and novelty detection.

Given that dopamine cells increase their firing as a result of novel, unexpected rewards and reduce it with expected rewards (Mirenowica and Schultz, 1994), I expect that in the early trials while the animal is learning the task dopamine cells in the VTA are active leading to extra levels of dopamine in the hippocampus while the animal is approaching the reward. Indeed voltammetry results showed that dopamine levels in the striatum increase steadily as animals approach rewarded goals on mazes (Howe et al., 2014). Therefore, dopamine levels can be modulated even within single arm approaches. Such increased dopamine levels may be a factor that enables the shifting of place fields during learning. Such an effect may be directly caused by dopamine but it is possible that this is indirect, it occurs due to changes of inputs to place cells that might be modulated by dopamine. The fact that the animal learns the working memory task fast indicates that the animal expects a reward at the end of all arms it visits. Hence dopamine cells may be only weakly active, and the reduced dopamine levels could not induce place field shift in the working memory task.

Dopamine may not be the only nonspecific neurotransmitter that can influence hippocampal place cells during goal learning. The unexpected reward at the novel-goal arms may trigger changes in the environmental cortex and it could be associated with similar network responses to that we see in novel environments. Novel environments are associated with a variety of nonspecific neurotransmitters that increase their firing in novel environments. In addition to dopamine acetylcholine has been also shown to increase in novel environments (Pepeu and Giovannini, 2004). Moreover, a recent study showed the increased activation of the locus coeruleus in novel environments, but the hippocampal effect in learning was dopamine-dependent (Takeuchi et al., 2016). Given that VTA cells also increase their activity during environmental novelty, it may be difficult to separate out

the effect of specific dopamine release from the VTA and that originating from the locus coeruleus.

In novel environments pyramidal cells on average exhibit a higher firing rate than in familiar environments (Nitz and McNaughton, 2004). Such a rate increase may be caused by an increase of any of these neurotransmitters. Similar to the novel environment-mediated firing increase, in my tasks in which spatial reference memory was needed to be updated, the firing rate of the cells was modulated by novel-goal locations in the previous or next arms. In our case the conditional, goal novelty-related firing increase has been seen in both inbound and outbound trials. However, place field shift has been seen in approaching a goal on an arm but no shift occurred in in returning from an arm while animals approached a goal in another arm. This suggests that the conditional rate modulation and place field shift are linked to different mechanisms, and perhaps different subcortical areas. For example dopamine from VTA may cause the place field shift while acetylcholine or perhaps locus coeruleus activation may cause the increased firing related to novel goal locations.

Novel goal arm-related rate modulation or place field shift was not seen in the working memory task. Although animals did not have to remember the location of rewarded arms, the working memory errors certainly indicate that animals detected the new task configuration involving partially updated arms. Yet goal shift or novel-goal arms-related rate changes were not seen here suggesting that these occur only during the update of reference memories and are triggered by novel context-related network responses and the extra release of nonspecific neurotransmitters in this case.

4.4 Sequence reactivation

Several studies have examined whether trajectory replay predicts the future behavioral choice of the animal. Early studies observed the reactivation of both alternative trajectories at the choice point of a T-maze during theta oscillations (Johnson and Redish, 2007). This has been observed in animals which were hesitant at the choice points and stopped to decide which arm to take next. Theta sequence replay was examined further in a task in which animals had to decide between reward locations with varying reward amount and

delays on a circular track (Wikenheiser and Redish, 2014). In such cases theta sequences replayed longer trajectories when a more distant goal was selected. The length of the theta sequence trajectory was predictive of the behavioral choice of the animal but they were not directly related to the selected goal. In this latter study it is possible that short sequences reflected theta phase precession-related replay whereas longer sequence may occur during HSEs that can occur during theta oscillations as well (O'Neill et al., 2017). Such HSEs could be generated through behavioral state-dependent mechanisms, e.g. the animal may have stopped more frequently before undertaking a longer run on the maze.

Indeed other work suggested that not theta periods but SWR and perhaps trajectory replay during SWR-associated HSEs are important for decision making related to goal locations. This was first shown by revealing differences in SWR firing in error trials as compared to correct trials on a spatial task on a W maze (Singer et al., 2013). However, replayed trajectories did not predict the behavioral choice of the animal. The blockade of SWR on the same W maze task caused working but not reference memory deficits suggesting that SWR associated trajectory replay may be involved in working memory recall (Jadhav et al., 2012). Another study again using varying stimulus delays associated with varying reward amounts on a continuous T-maze showed that more SWRs occur at the reward locations when the animals do not stop at a decision point after as compared to cases when it stops (Papale et al., 2017). In this study they also compared the Bayesian place probabilities expressed by the cell assemblies at the decision point. As expected the highest probabilities encoded the decision point itself. However when the two reward location were compared, the probabilities encoding the chosen reward location were higher than those encoding the unchosen one. This finding suggests that some of the place cells encoding the next reward may have also fired, on occasions, at the decision point. Taking these studies together, the SWRs at reward locations may be involved in the decision to reach the next goal.

Even in 2D environments, SWR-associated replay may play a role in goal selection: it was shown that trajectory reactivation predicts the direction in which animals move to reach a goal in a 2D environments in which goals are placed in many possible locations along a grid arrangement, similar to the cheeseboard (Pfeiffer and Foster, 2013). However, the goal location itself could not be directly predicted, given that several alternative fixed-placed goals can align with the predicted heading of the animal. In our case the radial eight-arm

maze offered fewer possible goals, enabling us to identify which arm and thus which goal is to be reached by a reactivated trajectory. Indeed, at the central arm, just before the animal made a decision, sequence replay predicted the future arm choice of the animal in tasks requiring spatial reference memories. Such prediction worked when we tested for the three possible arm choices or even when tested for trajectories representing all eight arms. These reactivated trajectories preferentially encoded the next inbound trajectory of the animal in the forward temporal order. At the same time at the reward location reactivated trajectories encoded the movement of the animal returning from the arm to the center but in a reverse temporal order. Therefore our finding suggests that sequence replay at the decision point guide the animals' future choice when spatial reference memory was needed for the task.

In the working memory task at the decision point the previously visited arm was replayed preferably, the return trajectory of the animal from the arm in a reverse temporal order. This is identical to the trajectory replayed previously at the reward locations at the end of the arm. Hence replay in the central stem did not reflected alternatives of the future arm-selection but the experience of returning from the last rewarded arm. How can our findings be explained in the light of the SWR blockade experiments that caused reference but not working memory errors on the W maze (Jadhav et al., 2012)? In fact the maze running task used on the W maze both had a working and reference memory component. In this condition our replay indeed predicted the future behavioral choice of the animal. Note, however, that blockade of the SWRs during cheeseboard learning only caused mild behavioral impairments in learning the cheeseboard task in mice experiments (Roux et al., 2017). The cheeseboard maze task is however much easier to learn and we do not see trajectory reactivation in this task (Stella and Csicsvari, unpublished observation). In our working memory task it is likely that the hippocampus was not involved in arm selection per se. Indeed, the hippocampus may only signal the visited arms to the mPFC, which information may be retained there in pure working memory tasks (Spellman et al., 2015).

Hence our findings suggest that hippocampus may involve actively in goal selection through sequence replay when alternative goal locations are needed to be localized at the decision, i.e. when reference memory is needed. In contrast, in agreement with past work (Spellman et al., 2015), during pure spatial working memory tasks the hippocampus may only signal

previous arms visits to the mPFC and the mPFC is keeping track of the arm visits of a trial and is involved in future goal selection.

The conditions when we observed forward or reverse replay do not agree with a previous study. Diba and Buzsaki (2007) suggested that just before the animal leaves for a track, forward replay of the next trajectory may be replayed whereas just after the animal arrived to a place a reverse replay could be seen. In our case reverse replay of the next outbound trajectory was seen at the reward location unlike the predicted forward order trajectory. A more recent study (Silva et al., 2015) suggested that change of reward amount can modulate the propensity of reverse but not forward replay events so that an increase of reward amount is accompanied by an increase of reverse replay while decrease of rewards is associated with fewer reverse replays. In our case, at the reward location reverse replay was always more frequent than forward replay, in all of our tasks. Although reward was fixed in our task, reward expectancy varied across tasks and was expected to be higher in the working memory task. Moreover, in the center, the temporal order of the replay (i.e. forward or reverse) predicted whether the task on the maze required reference memories or only working memory.

5 Future work

My results revealed that place cell assemblies are influenced by spatial reference memory and their gradual reorganization is linked to novel-goals. Moreover, the reactivation of hippocampal assemblies at the decision point predicted the future arm chosen by the animal next. However, some other observations raise further questions about the behavioral factors that might influence place cells assemblies, and associated replay sequences. Some of these related topics of future research are outlined below.

5.1 Place coding in CA1 versus CA3 regions

According to my results, many CA1 cells in the hippocampus showed conditional firing; i.e., they showed changes in firing patterns depending on the past and future arm choices of the animal. It is unclear, however, whether such conditional firing can be observed in in CA3 region. Nucleus reuniens do not project to the CA3 area only to CA1 (Griffin, 2015). Therefore, if indeed the nucleus reuniens input is needed for conditional firing of hippocampal cells (Ito et al. 2015) we may not see such firing in CA3. Yet, considering that superficial layer medial entorhinal cortex cells also exhibit conditional firing (Lipton et al., 2007; O'Neill et al., 2017), CA3 cells may exhibit conditional firing in using inputs from the medial entorhinal cortex.

5.2 Gamma synchronization across the CA3 and CA1 regions

Previous modeling studies suggested that gamma oscillation has been implicated in working memory process (von Stein et al., 2000; Fries et al., 2001) and in particular it may play a role in segregating and maintaining items in working memory (Lisman and Idahrt, 1995). Experimental support has been also provided for this, CA3-CA1 gamma frequency synchronization selectively increases on the center of a modified T-maze where the animal makes a choice (Montgomery and Buzsaki, 2007). Indeed other studies have also implicated

CA3-CA1 slow-gamma synchronization to memory recall (Colgin et al., 2009; Zheng et al., 2016). Gamma synchronization may not be related to working memory recall only, it may occur during reference memory recall as well. Parallel recordings in the CA3-CA1 regions can reveal conditions in which gamma synchronization might increase between these regions and also which task can modulate such firing.

5.3 Awake versus sleep replay

In this study, forward and reverse replay has been examined during the awake state. However, I have not checked the replay during sleep SWRs or HSE periods. Early work has suggested that only forward sequences are present during sleep (Lee and Wilson, 2002). More recent work using Bayesian encoding-based methods however showed that both forward and reverse replay takes place in sleep as well (Dragoi and Tonegawa, 2011; Olafsdottir et al., 2016; O'Neill et al., 2017). It is unclear however whether in our conditions sleep replay would exhibit similar bias for forward and reverse replay as waking replay. Similar bias would suggest a similar mechanism behind both types of replay. It is possible that sleep replay is more literal reflections of experience, serving mainly a memory consolidation function, whereas awake replay represents all possible paths supporting learning or search function or navigation on the maze. Accordingly, unlike in waking replay where replay sequences were restricted to single arms sleep replay may involve multi-arm trajectories. It has been shown that during consecutive SWR long sequences may be replayed (Davidson et al., 2009). Therefore it is possible that during sleep sequences involving consecutive arm choices can be seen, particularly those combinations that the animal has a bias in taking during behavior. Finally it was shown that novel environments are relayed stronger than familiar ones (Cheng and Frank, 2008; O'Neill et al., 2008). Therefore, it is possible that sequences involving novel-goal arms are replayed more often than those of the familiar-goal arm.

5.4 Interaction of hippocampus with other brain regions

Recently, a few studies have utilized dual multichannel recordings in the hippocampus and reward processing areas such as the ventral tegmental area (VTA), ventral striatum and or other cortical regions such as the entorhinal cortex, prefrontal cortex (Ji and Wilson, 2007; Lansink et al., 2009; Gomperts et al., 2015; Olafsdottir et al., 2016; O'Neill et al., 2017). In the context of my findings on the eight-arm maze, multi-region recording can enable an understanding of the interaction between these areas, particularly to check how hippocampal interactions with other brain areas contribute to the place fields shifting, task-dependent firing modulation or to sequence replay. For example, in order to test whether some of the effects are originated from the medial entorhinal cortex, once can test whether gird cells behave similarly as described on relation to hippocampal place cells. Grid cells have been shown to show task parameter-related rate modulation and medial entorhinal cells also exhibit waking sequence replay during a working memory task (O'Neill et al., 2017). Hence, goal-related shift of grid fields, novel-goal arm related firing increase and behavioral choice dependence of replayed sequences can all be tested in the media entorhinal cortex. Prefrontal hippocampal interactions are also interesting to test, for example during memory encoding theta synchronization was seen between mPFC and hippocampus (Jones and Wilson, 2005). In my task it would be also possible to test at which stages of the task one may see such synchronization

Past work has relied examining on oscillatory synchronization of local field potentials across regions, which is useful tool for establishing functional connections between regions (Chrobak and Buzsaki, 1996; Fujisawa and Buzsaki, 2011) or between cell pairs in different regions (Gomperts et al., 2015; Lansink et al., 2009; van der Meer et al., 2010). However, simultaneous monitoring of replay events and neuronal assembly activity in other regions will help us understand how reward-related activity or replay sequences are influenced by different hippocampal inputs. This can ultimately reveal how spatial learning and spatial decision take place through the coordinated activity of assemblies in different brain areas.

6 Reference

Acharya, L., Aghajan, Z.M., Vuong, C., Moore, J.J., and Mehta, M.R. (2016). Causal Influence of Visual Cues on Hippocampal Directional Selectivity. Cell 164(1-2):197-207.

Ainge, J.A., Tamosiunaite, M., Woergoetter, F., and Dudchenko P.A. (2007b). Hippocampal CA1 place cells encode intended destination on a maze with multiple choice points. J Neurosci 27(36):9769-79.

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

Allen, K., Rawlins, J.N., Bannerman, D.M., and Csicsvari, J. (2012). Hippocampal place cells can encode multiple trial-dependent features through rate remapping. J Neurosci 32(42):14752-66.

Amaral, D., and Lavenex, P. (2007). “Hippocampal neuroanatomy”, in The hippocampus Book eds Andersen P., Morris R., Amaral D., Bliss D. T., O’Keefe J., editors. (New York: Oxford University Press) 37–114.

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

Ambrose, R.E., Pfeiffer, B.E., and Foster, D.J. (2016). Reverse Replay of Hippocampal Place Cells Is Uniquely Modulated by Changing Reward. Neuron 91(5):1124-36.

Bannerman, D.M., Bus, T., Taylor, A., Sanderson, D.J., Schwarz, I., Jensen, V., Hvalby, Ø., Rawlins, J.N., Seeburg, P.H., Sprengel, R. (2012). Dissecting spatial knowledge from spatial choice by hippocampal NMDA receptor deletion. Nat Neurosci 15(8):1153-9.

Bannerman, D.M., Good, M.A., Butcher, S.P., Ramsay, M., and Morris, R.G. (1995). Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. Nature 378, 182-186.

Bannerman, D.M., Yee, B.K., Good, M.A., Heupel, M.J., Iversen, S.D., and Rawlins, J.N. (1999). Double dissociation of function within the hippocampus: a comparison of dorsal, ventral, and complete hippocampal cytotoxic lesions. Behav Neurosci 113(6):1170-88.

Barnes, CA. (1979). Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. J Comp Physiol Psychol. 93:74-104

Bird, C.M., and Burgess, N. (2008). The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 9, 182-194.

Bliss, T.V., and Collingridge, G.L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361(6407):31-9.

Braak, H., and Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82(4):239-59.

Brzosko, Z., Schultz, W., and Paulsen, O. (2015). Retroactive modulation of spike timing-dependent plasticity by dopamine. Elife 4. pii: e09685.

Brun, V.H., Otnass, M.K., Molden, S., Steffenach, H.A., Witter, M.P., Moser, M.B., and Moser, E.I. (2002). Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. Science 296, 2243-2246.

Burgess, N., and O'Keefe, J. (1996). Neuronal computations underlying the firing of place cells and their role in navigation. Hippocampus 6(6):749-62.

Buzsaki, G. (1986). Hippocampal sharp waves: their origin and significance. Brain Res 398, 242-252.

Buzsaki, G. (1989). Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31, 551-570.

Buzsaki, G., Horváth, Z., Urioste, R., Hetke, J., and Wise, K. (1992). High-frequency network oscillation in the hippocampus. Science 256(5059):1025-7.

Buzsaki, G., Leung, L.W., and Vanderwolf, C.H. (1983). Cellular bases of hippocampal EEG in the behaving rat. Brain Res 287, 139-171.

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

Cave, C.B., and Squire, L.R. (1992). Intact verbal and nonverbal short-term memory following damage to the human hippocampus. Hippocampus 2, 151-163.

Cheer, J.F., Aragona, B.J., Heien, M.L., Seipel, A.T., Carelli, R.M., and Wightman, R.M. (2007). Coordinated accumbal dopamine release and neural activity drive goal-directed behavior. Neuron 54, 237-244.

Cheng, S., and Frank, L.M. (2008). New experiences enhance coordinated neural activity in the hippocampus. Neuron 57, 303-313.

Collingridge, G.L., Kehl, S.J., and McLennan, H. (1983). Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. J Physiol 334, 33-46.

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

Chrobak, J.J., and Buzsaki, G. (1996). High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. J Neurosci 16(9):3056-66.

Crusio, W.E., Schwegler, H., and Lipp, H.P. (1987). Radial-maze performance and structural variation of the hippocampus in mice: a correlation with mossy fibre distribution. Brain Res. 3;425(1):182-5.

Csicsvari, J., Dupret D. (2013). Sharp wave/ripple network oscillations and learning-associated hippocampal maps. Philos Trans R Soc Lond B Biol Sci. 69(1635):20120528.

Csicsvari, J., Hirase, H., Czurko, A., Mamiya, A., and Buzsaki, G. (1999). Fast network oscillations in the hippocampal CA1 region of the behaving rat. J Neurosci 19(16):RC20.

Csicsvari, J., Hirase, H., Mamiya, A., and Buzsaki, G. (2000). Ensemble patterns of hippocampal CA3-CA1 neurons during sharp wave-associated population events. Neuron 28(2):585-94.

Csicsvari, J., O'Neill, J., Allen, K., and Senior, T. (2007). Place-selective firing contributes to the reverse-order reactivation of CA1 pyramidal cells during sharp waves in open-field exploration. Eur J Neurosci 26, 704-716.

Davidson, T.J., Kloosterman, F., and Wilson, M.A. (2009). Hippocampal replay of extended experience. Neuron 63, 497-507.

Deacon, R.M., and Rawlins, J.N. (2006). T-maze alternation in the rodent. Nat Protoc 1(1):7-12.

Diba, K., and Buzsaki, G. (2007). Forward and reverse hippocampal place-cell sequences during ripples. Nat Neurosci 10, 1241-1242.

Dolorfo, C.L., and 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.

Dragoi, G., and Tonegawa, S. (2013). Distinct preplay of multiple novel spatial experiences in the rat. Proc Natl Acad Sci U S A 110, 9100-9105.

Dupret, D., O'Neill, J., and Csicsvari, J. (2013). Dynamic reconfiguration of hippocampal interneuron circuits during spatial learning. Neuron 78(1):166-80.

Dupret, D., O'Neill, J., Pleydell-Bouverie, B., and Csicsvari, J. (2010). The reorganization and reactivation of hippocampal maps predict spatial memory performance. Nat Neurosci 13, 995-1002.

Ego-Stengel, V., and Wilson, M.A. (2010). Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20, 1-10.

Eichenbaum, H., and Cohen, H.J. (2001). From conditioning to conscious recollection. New York, Oxford University Press.

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

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

Foster, D.J., and Wilson, M.A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature 440, 680-683.

Foster, D.J., and Wilson, M.A. (2007). Hippocampal theta sequences. Hippocampus 17, 1093-109

Fox, S.E., and Ranck, J.B.Jr.(1975). Localization and anatomical identification of theta and complex spike cells in dorsal hippocampal formation of rats. Exp Neurol 49:299-313.

Freund, T.F., and Buzsaki G. (1996). Interneurons of the hippocampus. Hippocampus 6(4):347-470.

Fries, P., Reynolds, J.H., Rorie, A.E., and Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291:1560–1563.

Fujisawa, S., and Buzsaki, G. (2011). A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. Neuron 72, 153-165.

Fyhn, M., Molden, S., Witter, M.P., Moser, E.I., and Moser, M.B. (2004). Spatial representation in the entorhinal cortex. Science 305, 1258-1264.

Gabrieli, J.D., Brewer, J.B., Desmond, J.E., and Glover, G.H. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 276, 264-266.

Gilbert, P.E., Kesner, R.P., and DeCoteau, W.E. (1998). Memory for spatial location: role of the hippocampus in mediating spatial pattern separation. J Neurosci 18, 804-810.

Girardeau, G., Benchenane, K., Wiener, S.I., Buzsaki, G., and Zugaro, M.B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12, 1222-1223.

Girardeau, G., Cei, A., and Zugaro, M. (2014). Learning-induced plasticity regulates hippocampal sharp wave-ripple drive. J Neurosci 34, 5176-5183.9.

Gomperts, S.N., Kloosterman, F., and Wilson, M.A. (2015). VTA neurons coordinate with the hippocampal reactivation of spatial experience. Elife 4: e05360.

Green, J.D., and Arduini A (1954). Hippocampal activity in arousal. J Neurophysiol. 17 (6): 533–57.

Griffin, A.L. (2015). Role of the thalamic nucleus reuniens in mediating interactions between the hippocampus and medial prefrontal cortex during spatial working memory. Front Sys Neurosci 9:29.

Grosmark, A.D., and Buzsaki, G. (2016). Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences. Science 351(6280):1440-3.

Gupta, A.S., van der Meer, M.A., Touretzky, D.S., and Redish, A.D. (2010). Hippocampal replay is not a simple function of experience. Neuron 65, 695-705.

Hafting, T., Fyhn, M., Molden, S., Moser, M.B. and Moser, E.I. (2005). Microstructure of a spatial map in the entorhinal cortex. Nature 436(7052):1248-52.

Hock, BJ. JR., and Bunsey, M.D. (1998). Differential effects of dorsal and ventral hippocampal lesions. J Neurosci 18(17):7027-32.

Hok, V., Lenck-Santini, P.P., Roux, S., Save, E., Muller, R.U., and Poucet, B. (2007). Goal-related activity in hippocampal place cells. J Neurosci 27(3):472-82.

Hollup, S.A., Molden, S., Donnett, J.G., Moser, M.B., and Moser, E.I. (2001). Accumulation of hippocampal place fields at the goal location in an annular watermaze task. J Neurosci 21(5):1635-44.

Howe, M.W., Tierney, P.L., Sandberg, S.G., Phillips, P.E.M., and Graybiel, A.M. (2014). Prolonged Dopamine Signalling in Striatum Signals Proximity and Value of Distant Rewards. Nature 500(7464):575-579.

Huxter, J.R., Senior, T.J., Allen, K., and Csicsvari, J. (2008). Theta phase-specific codes for two-dimensional position, trajectory and heading in the hippocampus. Nat Neurosci 11(5):587-94.

Ishizuka, N., Weber, J., and Amaral, D.G. (1990). Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. J Comp Neurol 295:580–623

Ito, H.T., Zhang, S.J.,Witter,M.P., Moser, E.I. and Moser, M.B. (2015). A prefrontal-thalamo-hippocampal circuit for goal-directed spatial navigation. Nature 522(7554):50-5.

Jackson, J.C., Johnson, A., and Redish, A.D. (2006). Hippocampal sharp waves and reactivation during awake states depend on repeated sequential experience. J Neurosci 26, 12415-12426.

Jadhav, S.P., Kemere, C., German, P.W., and Frank, L.M. (2012). Awake hippocampal sharp-wave ripples support spatial memory. Science 336, 1454-1458.

Jarrard, L.E. (1993). On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol 60:9-26.

Jarrard, L.E., Davidson, T.L., Bowring, B. (2004). Functional differentiation within the medial temporal lobe in the rat. Hippocampus 14:434-449.

Ji, D., and Wilson, M.A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10(1):100-7.

Johnson, A., and Redish, A.D. (2007). Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. J Neurosci 27(45):12176-89.

Jones M.W., and Wilson M.A. (2005). Theta Rhythms Coordinate Hippocampal–Prefrontal Interactions in a Spatial Memory Task. PloS Biol 3(12):e402.

Jung, M.W. and Wiener, S.I. (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. J Neurosci 14(12):7347-56.

Karlsson, M.P., and Frank, L.M. (2009). Awake replay of remote experiences in the hippocampus. Nat Neurosci 12, 913-918.

Kemere, C., Carr, M.F., Karlsson, M.P., and Frank, L.M. (2013). Rapid and continuous modulation of hippocampal network state during exploration of new places. PLoS One 8(9):e73114.

Kentros, C.G., Agnihotri, N.T., Streater, S., Hawkins, R.D., and Kandel, E.R. (2004). Increased attention to spatial context increases both place field stability and spatial memory. Neuron 42, 283-295.

Kentros,C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., and Muller, R.V. (1998). Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science 280(5372):2121-6.

Kesner, R.P., Farnsworth, G., and Kametani, H. (1991). Role of parietal cortex and hippocampus in representing spatial information. Cereb Cortex 1, 367-373.

King, C., Henze, D.A., Leinekugel, X., and Buzsaki, G. (1999). Hebbian modification of a hippocampal population pattern in the rat. J Physiol 521(Pt 1): 159–167.

Kjelstrup, K.G., Tuvnes, F.A., Steffenach, H.A, Murison, R., Moser, E.I., and Moser, M.B. (2002). Reduced fear expression after lesions of the ventral hippocampus. Proc Natl Acad Sci U S A 99(16):10825-30.

Klausberger, T., and Somogyi, P. (2008) Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. Science 321(5885):53-7.

Knierim, J.J., Kudrimoti, H.S., and McNaughton, B.L. (1998). Interactions between idiothetic cues and external landmarks in the control of place cells and head direction cells. J Neurophysiol 80, 425-446.

Kudrimoti, H.S., Barnes, C.A., and McNaughton, B.L. (1999). Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19,4090-4101.

Lansink, C.S., Goltstein, P.M., Lankelma, J.V., McNaughton, B.L., and Pennartz, C.M. (2009). Hippocampus leads ventral striatum in replay of place-reward information. PLoS Biol 7, e1000173.

Lavenex, P., and Amaral, D.G. (2000). Hippocampal-neocortical interaction: a hierarchy of associativity. Hippocampus 10(4):420-30.

Lee, A.K., and Wilson, M.A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36, 1183-1194.

Lee, I., Jerman, T.S., and Kesner, R.P. (2005). Disruption of delayed memory for a sequence of spatial locations following CA1- or CA3-lesions of the dorsal hippocampus. Neurobiol Learn Mem 84, 138-147.

Lenck-Santini, P.P., Fenton A.A., and Muller, R.U. (2008). Discharge Properties of Hippocampal Neurons during Performance of a Jump Avoidance Task. J Neurosci 28 (27) 6773-6786.

Lipton, P.A., White, J.A., and Eichenbaum, H. (2007). Disambiguation of overlapping experiences by neurons in the medial entorhinal cortex. J Neurosci 27(21):5787-95.

Leutgeb, S., Leutgeb, J.K., Barnes, C.A., Moser, E.I., McNaughton, B.L., and Moser, M.B. (2005). Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. Science 309, 619-623.

Li, S., Cullen, W.K., Anwyl, R., and Rowan, M.J. (2003). Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. Nat Neurosci 6, 526-531.

Li, X.G., Somogyi, P., Ylinen, A., Buzsaki, G. (1994). The hippocampal CA3 network: an in vivo intracellular labeling study. J Comp Neurol 339:181–208.

Lisman, J.E., and Grace, A.A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46, 703-713.

Lisman, J.E., and Idiart, M.A. (1995). Storage of 7 +/- 2 short-term memories in oscillatory subcycles. Science 26 J Neurophysiol 67(1):145-63.

Ljungberg, T., Apicella, P., and Schultz, W. (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. J Neurophysiol 67(1):145-63.

Louie, K., and Wilson, M.A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29, 145-156.

Markus, E.J., Qin, Y.L., Leonard, B., Skaggs,W.E., McNaughton, B.L., and Barnes, C.A. (1995). Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J Neurosci 15(11):7079-94.

McDonald, R.J., Hong, N.S., Craig, L.A., Holahan, M.R., Louis, M., and Muller, R.U. (2005). NMDA-receptor blockade by CPP impairs post-training consolidation of a rapidly acquired spatial representation in rat hippocampus. Eur J Neurosci 22(5):1201-13.

McKenzie, S., Frank, A.J., Kinsky, N.R., Porter, B., Riviere, P.D., and Eichenbaum, H. (2014). Hippocampal representation of related and opposing memories develop within distinct, hierarchically organized neural schemas. Neuron 83(1):202-15.

McKenzie, S., Robinson, N.T., Herrera, L., Churchill, J.C., and Eichenbaum, H. (2013). Learning causes reorganization of neuronal firing patterns to represent related experiences within a hippocampal schema. J Neurosci 33(25):10243-56.

McNamara, C.G., Tejero-Cantero, A., Trouche, S., Campo-Urriza, N., and Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. Nat Neurosci 17, 1658-1660.

McNaughton, B.L., Barnes C.A., and 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):41-9.

McNaughton, B.L., and Morris, R.G.M. (1987). Hippocampal Synaptic Enhancement and Information-Storage within a Distributed Memory System. Trends in Neurosciences 10, 408-415.

Mehta, M.R., Quirk, M.C., and Wilson, M.A. (2000). Experience-dependent asymmetric shape of hippocampal receptive fields. Neuron 25, 707-715.

Milner, B. (1958). Pyschological defects produced by temporal lobe excision. Res Publ Assoc Res Nerv Ment Dis 36:244-57.

Mirenowicz, J., Schultz, W. (1994). Importance of unpredictability for reward responses in primate dopamine neurons. J Neurophysiol 72(2):1024-7.

Mizuseki, K., Sirota, A., Pastalkova, E.,and Buzsáki, G. (2009). Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. Neuron 64(2):267-80.

Montgomery, S.M., Buzsáki, G. (2007). Gamma oscillations dynamically couple hippocampal CA3 and CA1 regions during memory task performance. Proc Natl Acad Sci U S A 104(36):14495-500.

Morris, R.G. (2006). Elements of a neurobiological theory of hippocampal function: the role of synaptic plasticity, synaptic tagging and schemas. Eur. J. Neurosci 23, 2829–2846.

Morris, R.G. (1989). Synaptic plasticity and learning: selective impairment of learning rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5. J Neurosci 9, 3040-3057.

Morris, R.G., Anderson, E., Lynch, G.S., and Baudry, M. (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319, 774-776.

Morris, R.G., Garrud, P., Rawlins, J.N., and O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. Nature 297, 681-683.

Morris, R.G., Schenk, F., Tweedie, F., and Jarrard, L.E. (1990). Ibotenate Lesions of Hippocampus and/or Subiculum: Dissociating Components of Allocentric Spatial Learning. Eur J Neurosci 2(12):1016-1028.

Moser, E.I., Moser, M.B., and Andersen, P. (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. J Neurosci 13, 3916-3925.

Moser, E.I., Krobert, K.A., Moser, M.B., and Morris, R.G. (1998). Impaired spatial learning after saturation of long-term potentiation. Science 281, 2038-2042.

Mott, D.D., and Lewis, D.V. (1991). Facilitation of the induction of long-term potentiation by GABAB receptors. Science 252, 1718-1720.

Muller, R.U., and Kubie, J.L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci 7, 1951-1968.

Muller, R.U., and Kubie, J.L. (1989). The firing of hippocampal place cells predicts the future position of freely moving rats. J Neurosci 9, 4101-4110.

Nakashiba, T., Young, J.Z., McHugh, T.J., Buhl, D.L., and Tonegawa, S. (2008). Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. Science 319, 1260-1264.

Nakazawa, K., McHugh, T.J., Wilson, M.A., and Tonegawa, S. (2004). NMDA receptors, place cells and hippocampal spatial memory. Nat Rev Neurosci 5, 361-372.

Nakazawa, K., Quirk, M.C., Chitwood, R.A., Watanabe, M., Yeckel, M.F., Sun, L.D., Kato, A., Carr, C.A., Johnston, D., and Wilson, M.A. (2002). Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 297, 211-218.

Navratilova, Z., Hoang, L.T., Schwindel, C.D., Tatsuno, M., and McNaughton, B.L. (2012). Experience-dependent firing rate remapping generates directional selectivity in hippocampal place cells. Front Neural Circuits. 21;6:6.

Neves, G., Cooke, S.F., and Bliss, T.V. (2008). Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nat Rev Neurosci 9:65-75.

Niewoehner, B., Single, F.N., Hvalby, O., Jensen, V., Borgloh, S.M., Seeburg, P.H., Rawlins, J.N., Sprengel, R., Bannerman, D.M. (2007). Impaired spatial working memory but spared spatial reference memory following functional loss of NMDA receptors in the dentate gyrus. E J Neurosci 25:837-846.

Nitz, D, and McNaughton, B. (2004). Differential modulation of CA1 and dentate gyrus interneurons during exploration of novel environments. J Neurophysiol. 91(2):863-72.

O'Carroll, C.M., Martin, S.J., Sandin, J., Frenguelli, B., and Morris, R.G. (2006). Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. Learn Mem 13, 760-769.

O'Keefe, J. (1976). Place units in the hippocampus of the freely moving rat. Exp Neurol 51, 78-109.

O'Keefe, J., and Conway, D.H. (1978). Hippocampal place units in the freely moving rat: why they fire where they fire. Exp Brain Res 31, 573-590.

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34, 171-175.

O'Keefe, J., and Nadel, L. (1978). The Hippocampus as a Cognitive Map (Oxford, Clarendon Press).

O'Keefe, J., and Recce M.L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3(3):317-30.

O'Neill, J., Boccara. C.N., Stella, F., Schoenenberger, P., and Csicsvari, J. (2017). Superficial layers of the medial entorhinal cortex replay independently of the hippocampus. Science 355(6321):184-188.

O'Neill, J., Senior, T.J., Allen, K., Huxter, J.R., and Csicsvari, J. (2008). Reactivation of experience-dependent cell assembly patterns in the hippocampus. Nature Neurosci 11:209-215.

O'Neill, J., Senior, T., and Csicsvari, J. (2006). Place-selective firing of CA1 pyramidal cells during sharp wave/ripple network patterns in exploratory behavior. Neuron 49, 143-155.

Olafsdottir, H.F., Carpenter, F., and Barry, C. (2016). Coordinated grid and place cell replay during rest. Nat Neurosci 19(6):792-4.

Olson, I.R., Page, K., Moore, K.S., Chatterjee, A., and Verfaellie, M. (2006). Working memory for conjunctions relies on the medial temporal lobe. J Neurosci 26, 4596-4601.

Olton, D.S., Becker, J.T., and Handelmann, G.E. (1979). Hippocampus, Space, and Memory. Behavioral and Brain Sciences 2, 313-322.

Olton, D.S., and Branch, M. (1978). Spatial correlates of hippocampal unit activity. Exp Neurol 58(3):387-409.

Olton, D.S., and Samuelson, R.J. (1976). Remembrance of Places Passed - Spatial Memory in Rats. J Exp Psychol Anim B 2, 97-116.

Packard, M.G., and White, N.M. (1991). Dissociation of hippocampus and caudate nucleus memory systems by posttraining intracerebral injection of dopamine agonists. Behav Neurosci 105, 295-306.

Papale, A.E., Zielinski,M.C., Frank, L.M., Jadhav, S.P., and Redish, A.D. (2016). Interplay between Hippocampal Sharp-Wave-Ripple Events and Vicarious Trial and Error Behaviors in Decision Making. Neuron 92(5):975-982.

Pepeu, G., and Giovannini, M.G. (2004). Changes in acetylcholine extracellular levels during cognitive processes. Learn Mem 11(1):21-7.

Pfeiffer, B.E., and Foster, D.J. (2013). Hippocampal place-cell sequences depict future paths to remembered goals. Nature 497, 74-79.

Potvin, O., Allen, K., Thibaudeau, G., Dore, F.Y., and Goulet, S. (2006). Performance on spatial working memory tasks after dorsal or ventral hippocampal lesions and adjacent damage to the subiculum. Behav Neurosci 120:413-422.

Quirk, G.J., and Muller, R.U. (1992). The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. J Neurosci 12(5):1945-63.

Ramos, J.M., and Vaquero, J.M. (2000). The hippocampus and flexible spatial knowledge in rats.J Physiol Biochem 56, 313-320.

Ranck, J.B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Exp Neurol 41(2):461-531.

Ranck, J.B., Jr. (1984). Head-direction cells in the deep cell layers of dorsal presubiculum in freely moving rats. Soc Neurosci 10:599.

Rawlins, J.N., and Olton, D.S. (1982). The septo-hippocampal system and cognitive mapping. Behav Brain Res 5, 331-358.

Redish, A.D., and Touretzky, D.S. (1998). The role of the hippocampus in solving the Morris water maze. Neural Comput 10, 73-111.

Reisel, D., Bannerman, D.M., Schmitt, W.B., Deacon, R.M., Flint, J., Borchardt, T., Seeburg, P.H., and Rawlins, J.N. (2002). Spatial memory dissociations in mice lacking GluR1. Nat Neurosci 5, 868-873.

Roux, L, Hu, B., Eichler, R., Stark, E., and Buzsaki, G. (2017). Sharp wave ripples during learning stabilize the hippocampal spatial map. Nat Neurosci 20(6):845-853.

Rumpel, S., LeDoux, J., Zador, A., and Malinow, R. (2005). Postsynaptic receptor trafficking underlying a form of associative learning. Science 308, 83-88.

Sargolini, F.M., Fyhn, M., Hafting, T., McNaughon, B.L., Witter, M.P., Moser, M.B. and Moser, E.I. (2006). Conjunctive representation of position, direction, and velocity in entorhinal cortex. Science 312(5774):758-62.

Saucier, D., and Cain, D.P. (1995). Spatial learning without NMDA receptor-dependent long-term potentiation. Nature 378, 186-189.

Schmitt, W.B., Deacon, R.M., Seeburg, P.H., Rawlins, J.N., and Bannerman, D.M. (2003) A within-subjects, within-task demonstration of intact spatial reference memory and impaired spatial working memory in glutamate receptor-A-deficient mice. J Neurosci 23:3953-3959.

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol 7, 191-197.

Schultz, W., Dayan, P., and Montague, P.R. (1997). A neural substrate of prediction and reward. Science 275, 1593-1599.

Scoville, W.B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20, 11-21.

Shapiro, M.L., and Caramanos, Z. (1990). NMDA Antagonist Mk-801 Impairs Acquisition but Not Performance of Spatial Working and Reference Memory. Psychobiology 18, 231-243.

Shapiro, M.L., and Ferbinteanu, J. (2006). Relative spike timing in pairs of hippocampal neurons distinguishes the beginning and end of journeys. Proceedings of the National Academy of Sciences of the U S A 103:4287-4292.

Silva, D., Feng, T., and Foster, D.J. (2015). Trajectory events across hippocampal place cells require previous experience. Nat Neurosci 18, 1772-1779.

Singer, A.C., Carr, M.F., Karlsson, M.P., and Frank, L.M. (2013). Hippocampal SWR activity predicts correct decisions during the initial learning of an alternation task. Neuron 77, 1163-1173.

Skaggs, W.E., and McNaughton, B.L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271, 1870-1873.

Smith, E.E., and Kosslyn, S.M. (2007). Cognitive psychology: mind and brain. Upper Saddle River, N.J., Pearson/Prentice Hall.

Spellman, T., Rigotti, M., Ahmari, S.E., Fusi, S., and Gordon, J. (2015). Hippocampal-prefrontal input supports spatial encoding in working memory. Nature 522:309–314.

Squire,L.R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99(2):195-231.

Steffenach, H.A., Witter, M., Moser, M.B., and Moser E.I. (2005). Spatial memory in the rat requires the dorsolateral band of the entorhinal cortex. Neuron 45(2):301-13.

Sutherland, R.J., Whishaw, I.Q., and Kolb, B. (1983). A behavioral analysis of spatial localization following electrolytic, kainite- or colchicine-induced damage to the hippocampal formation in the rat. Behav Brain Res 7(2): 133-153.

Swanson-Park, J.L., Coussens, C.M., Mason-Parker, S.E., Raymond, C.R., Hargreaves, E.L., Dragunow, M., Cohen, A.S., and Abraham, W.C. (1999). A double dissociation within the hippocampus of dopamine D1/D5 receptor and beta-adrenergic receptor contributions to the persistence of long-term potentiation. Neuroscience 92, 485-497.

Takeuchi, T., Duszkiewicz, A.J., Sonneborn, A., Spooner, P.A., Yamasaki, M., Watanabe, M., Smith, C.C., Fernandez, G., Deisseroth, K., Greene, R.W., and Morris, R.G. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. Nature 537(7620):357-362.

Taube, J.S., and Muller, R.U. (1990). Head-direction cells recorded from the postsubiculum in freely moving rats. J Neurosci 10(2):436-47.

Treves, A., and Rolls, E.T. (1992). Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 2, 189-199.

Tsien, J.Z., Huerta, P.T., and Tonegawa, S. (1996). The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87, 1327-1338.

Tsodyks, M. (1999). Attractor neural network models of spatial maps in hippocampus. Hippocampus 9, 481-489.

Tulving, E. (1983). Elements of episodic memory (Oxford Oxfordshire New York, Clarendon Press; Oxford University Press).

Tulving, E. (2002). Episodic memory: from mind to brain. Annu Rev Psychol 53, 1-25.

Vanderwolf, C.H. (1969). Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr Clin Neurophysiol 26, 407-418.

van der Meer, M.A., Johnson, A., Schmitzer-Torbert, N.C., and Redish, A.D. (2010). Triple dissociation of information processing in dorsal striatum, ventral striatum, and hippocampus on a learned spatial decision task. Neuron 67, 25-32.

van der Meer, M.A., and Redish, A.D. (2009). Covert Expectation-of-Reward in Rat Ventral Striatum at Decision Points. Front Integr Neurosci 3:1.

Vandecasteele, M., Varga, V., Berenyi, A., Papp, E., Bartho, P., Venance, L., Freund, T.F., and Buzsaki, G. (2014). Optogenetic activation of septal cholinergic neurons suppresses sharp wave ripples and enhances theta oscillations in the hippocampus. Proc Natl Acad Sci U S A 111, 13535-13540.

von Stein, A., Chiang, C., and Konig, P. (2000). Top-down processing mediatedby interareal synchronization. Proc Natl Acad Sci USA 97:14748–14753.

Wikenheiser, A.M., and Redish, A.D. (2011). Changes in reward contingency modulate the trial-to-trial variability of hippocampal place cells. J Neurophysiol 106, 589-598.

Wikenheiser, A.M., and Redish, A.D. (2014). Hippocampal theta sequences reflect current goals. Nat Neurosci 18,289-294.

Wilson, M.A., and McNaughton, B.L. (1993). Dynamics of the hippocampal ensemble code for space. Science 261, 1055-1058.

Wilson, M.A., and McNaughton, B.L. (1994). Reactivation of hippocampal ensemble memories during sleep. Science 265, 676-679.

Witter, M.P., Canto, C.B., Couey, J.J, Koganezawa, N., and O'Reilly, K.C. (2013). Architecture of spatial circuits in the hippocampal region. Philos Trans R Soc Lond B Biol Sci 369(1635):20120515.

Wood, E.R., Dudchenko, P.A., and Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. Nature 397:613-616.

Wood, E.R., Dudchenko, P.A., Robitsek, R.J., and Eichenbaum, H. (2000) Hippocampal neurons encode information about different types of memory episodes occurring in the same location. Neuron 27:623-633.

Zhang, K., Ginzburg, I., McNaughton, B.L., and Sejnowski, T.J. (1998). Interpreting neuronal population activity by reconstruction: Unified framework with application to hippocampal place cells. J. Neurophysiol 79, 1017–1044.

Zheng, C., Bieri, K.W., Hsiao, Y.T., and Colgin, L.L. (2016). Spatial Sequence Coding Differs during Slow and Fast Gamma Rhythms in the Hippocampus. Neuron 89(2):398-408.

7 Curriculum vitae

GENERAL INFORMATION

Email: hxu@ist.ac.at

Address: IST Austria, Am Campus 1, 3400 Klosterneuburg, Austria

Phone: +43 (0)2243 9000-4306

Nationality: China

EDUCATION

2011 - Ph.D Student in Neuroscience
IST Austria
PhD supervisor: Prof. Jozsef Csicsvari

2008 – 2011 M.S. in Neuropharmacology, School of Pharmacology
Nanjing Medical University
Thesis supervisor: Prof. Dong-Ya Zhu

2003 – 2008 B.S. of Medicine,
Nanjing Medical University

CONFERENCE PRESENTATION

2016 Society of Neuroscience (SFN), San Diego – Poster
Mnemonic coding of place cells on the 8-arm maze

2015 IST Austria, Neuroscience community data presentation – Speaker
Mnemonic coding of CA1 place cells on the 8-arm maze

2014 Federation of European Neuroscience Forum (FENS), Milan – Poster
CA1 Place Cell Coding during a Spatial Memory Task on the Eight-arm Maze

2012 Federation of European Neuroscience Forum (FENS), Barcelona

PUBLICATIONS

Xu H, O'Neill J, Csicsvari J. (2017). Assembly responses predict learned behaviour in goal-directed spatial tasks on the radial eight-arm maze. **In preparation**

Zhou L*, Li F*, **Xu H*,** Luo CX, WuHY, Zhu MM, Lu W, Ji X, Zhou QG, Zhu DY. (2010). Treatment of cerebral ischemia by disrupting ischemia-induced interaction of nNOS with PSD95. **Nature Medicine.** 16, 1439–1443 ***Equal contributions**