Context Modulated Spatial Encoding and Memory Consolidation in the Rodent Hippocampus

Margot Fiona Tirole

A dissertation submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

of

University College London.

Department of Experimental Psychology

University College London

August 16, 2021

I, Margot Fiona Tirole, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Abstract

The recollection of daily events is inherently personal: episodic memories are defined by the recollection of one's sense of self during a particular event, within a surrounding context. Representations of such experiences are initially encoded in the hippocampus then consolidated by their repeated reactivation in synchrony with the cortex during sleep. After consolidation, memories are less prone to interference by similar experiences.

However, a day in one's life is usually constructed from multiple episodic experiences which can span multiple contexts. Little is known about the potential interference by previous memories on the construction of novel representations when contextual features are shared. Moreover, salient episodic memories are better remembered than neutral ones in the long term. Highly rewarding, traumatic or novel experiences can lead to intrusive (e.g. Post Traumatic Stress Disorder) or extremely vivid recall (e.g. Flashbulb memories) recall, and in general longer lasting memories. This phenomenon of prioritised memory consolidation is thought to ensure the storage of relevant memories, at the detriment of less important ones, and has been shown to correlate with an overall increase in their reactivation frequency during sleep. However, the temporal dynamics of memory triage during sleep have not yet been investigated.

Recording from many hippocampal neurons simultaneously in the rat, during both sleep and the exploration of three completely new environments each session, we tracked the encoding and consolidation of feature-sharing and salience modulated representations. We provide evidence for the presence of neural patterns of activity that may support generalisation with similar past experiences, as well as differentia-

tion of the novel representation during its initial stabilisation window. Furthermore, we show that the temporal dynamics of memory triage are not uniform, and instead exhibit a cyclic (time attributed to each memory) and an amplitude (relative proportion) component.

Impact Statement

One's ability to remember important information in the long term is contingent on getting enough quality sleep. However, more than a third of American adults sleep less than 7 hours (CDC), the average Briton sleeps 6 hours and 19 minutes (Sleep Council), and a study with 13,000 participants across 12 countries worldwide reports that 51% of adults are generally dissatisfied with their sleep (Phillips 5th annual global survery). Under such pressure, memory triage is an essential process with the aim of ensuring the retention of experiences with the highest learning capital. Investigating the fundamental mechanisms of memory triage, as well as finding ways to modulate it is directly relevant to public health and education.

More recently, with lockdown measures being instated for months at a time, a growing number of reports have been made of declining memory performance, even in healthy individuals. The lack of change of context, the lack of segmentation between one's professional and personal lives, and decreased opportunities for recall (through social interactions) are directly relevant to the working framework of this thesis.

The two results chapter of this thesis will be published in scientific journals, presented in large conferences and if possible the findings disseminated to the general public.

Acknowledgements

First, I would like to thank my supervisor, Daniel Bendor, for his continued support over the last four years, on both a professional and personal level.

I would also like to thank:
The BBSRC LIDo DTP for taking a chance on me and giving me a scholarship to pursue my dreams.

The members of the Bendor Lab who were most involved at the time of setting up the rat ephys: Juli, Lilia, Marta, Soraya, James and Sophie.

All of those at the IBN who have made it a welcoming environment: Zita, Will, Edd, James, Jo, Stefano, Fabio, Eleonore, Roddy, Tom and Tomaso.

More particularly I would like to thank those who have continuously listened, encouraged, taught, supported me and sometimes simply laughed with me over the last few years - Catherine, Ningyu and Merlin - thank you.

The friends I made when we were stranded in KCL's Denmark Hill campus: Azhaar and Jon

Vincent, Severa and Maisha for being my London family

My friends whose enduring friendship I am grateful for in spite of sometimes

moving countries and continents: Myriam, Aaron, Martin, Eva, Cécile, Annie and Antonia.

Most important of all, I would like to thank my family: Nathalie, Jean, Naïs (& William) and Romain. They support me unconditionally and there are not enough words to express my gratitude or to say how much they mean to me. Without them there is no doubt I would not be writing these fancy words today, and so I would like to dedicate this thesis to them !

The author acknowledges the use of the UCL Myriad High Performance Computing Facility (Myriad@UCL), and associated support services, in the completion of this work.

Contents

1 Introduction **23**

1.1 What Defines an Experience - The Case for Episodic Memory . . . 23

1.2 How to Build an Episodic Memory: Encoding 25

1.2.1 Spatial coding in the hippocampus 25

1.2.1.1 Anatomy of the Hippocampus 25

1.2.1.2 Place Cells 27

1.2.1.3 Other Neural Substrates of Space 28

1.2.2 Forming Cell Ensembles 29

1.2.2.1 The Hippocampus as a sequence learner 29

1.2.2.2 Pre-configured Ensembles 31

1.2.3 Explicit Features: Multi-Sensory Integration 32

1.2.3.1 Sensory Cues 32

1.2.3.2 Reward 34

1.2.3.3 Pain and Fear 35

1.2.4 Implicit Features: Internal States 35

1.2.4.1 Experience 35

1.2.4.2 Attention and Tasks 36

1.2.4.3 Motivation 37

1.2.4.4 Time 37

1.3 How to Build an Episodic Memory: Consolidation 38

1.3.1 The Hippocampus and Memory 38

1.3.2 The Role of Sleep 39

1.3.2.1 REM and SWS 39

1.3.3 Memory Consolidation Models 40
1.3.3.1 Standard Consolidation Model 40
1.3.3.2 Cognitive Map Theory 41
1.3.3.3 Multiple Trace Model 41
1.3.3.4 Homeostatic Model 43
1.4 How to Deal with Feature-Sharing Experiences 43
1.4.1 Segmentation of Experiences 44
1.4.2 Remapping 45
1.4.3 Pattern Completion and Separation 46
1.4.4 Schemas and Novelty Detection 48
1.4.5 Working Framework 50
1.5 How to Deal with Limited Storage: Memory Triage 51
1.5.1 Salient Memories 51
1.5.1.1 Emotion 52
1.5.1.2 Novelty 54
1.5.2 Mechanisms 54
1.5.2.1 Tagging 55
1.5.2.2 Cortical Feedback 56
1.5.3 Working Framework 58
1.6 Thesis Aims 59

2 General Methods 63
2.1 Animal Housing and Care 64
2.2 Surgeries 65
2.3 Electrophysiological Recordings 66
2.3.1 Microdrives 66
2.3.1.1 Independently Moveable Microarrays 66
2.3.1.2 Non-Independently Moveable Microarrays 67
2.3.2 Screening 67
2.3.3 Data Acquisition 68
2.4 Behaviour 69

2.4.1 Apparatus . . . 69
2.4.2 Food Preference . . . 69
2.4.3 Recording Protocol: Reward Experiment . . . 70
2.5 Histology . . . 73

3 Analysis Methods **75**
3.1 Behaviour . . . 75
3.1.1 Reward Preference . . . 75
3.1.2 Position Data . . . 76
3.1.2.1 Pre-Processing . . . 76
3.1.2.2 Sleep State Detection . . . 77
3.2 Electrophysiological Data Pre-Processing . . . 80
3.2.0.1 Single Unit Isolation . . . 80
3.2.0.2 Deletion of Dropped Samples . . . 80
3.2.0.3 Single Unit Characterisation and rate map calculation . . . 80
3.2.0.4 LFP Extraction and Filtering . . . 84
3.3 Decoding . . . 85
3.3.1 Detection of Candidate Replay Events . . . 85
3.3.2 Detection of Reactivations . . . 85
3.3.2.1 Split Events . . . 85
3.3.3 Bayesian Decoding . . . 86
3.3.3.1 Jump detection candidate replay events . . . 88
3.3.4 Shuffles . . . 89
3.3.4.1 Spike Train Circular Shift . . . 89
3.3.4.2 Rate map Circular Shift . . . 89
3.3.4.3 Decoded Position Bin Circular Shift . . . 89
3.3.5 Significance Testing . . . 89
3.3.5.1 Spearman Correlation . . . 89
3.3.5.2 Weighted Correlation . . . 90
3.3.5.3 Line Fitting . . . 90

3.3.6 Scoring of Replay Events . . . 91
3.3.7 Decoding Error . . . 93
3.4 Analysis . . . 95
3.4.1 Remapping Analysis . . . 95
3.4.2 Map Stabilisation . . . 96
3.4.3 Classification Accuracy and Decoding Errors . . . 97
3.4.4 Significance procedure for the proportion of replay events . 100
3.4.5 Statistical tests . . . 100
3.4.6 Summary of Data . . . 101

4 Generalisation vs Differentiation of Novel Maps 103
4.1 Brief Introduction . . . 104
4.2 Results . . . 107
4.2.1 Behaviour and Remapping Between Environments . . . 107
4.2.2 Temporal Dynamics of Map Differentiation . . . 111
4.2.3 Temporal Dynamics of Cell Participation . . . 116
4.2.4 Temporal Dynamics of Local and Remote Replay . . . 119
4.3 Chapter Discussion . . . 123

5 The effect of reward and temporal proximity to sleep on memory triage 129
5.1 Brief Introduction . . . 129
5.2 Results . . . 133
5.2.1 Reward Preference . . . 133
5.2.2 Behaviour and Cell Properties . . . 134
5.2.3 Recency and Reward Modulation of Candidate Replay Events 137
5.2.4 Recency and Reward Modulation of Awake and Sleep Replay 140
5.3 Chapter Discussion . . . 144

6 General Discussion 147
6.1 Evidence for Proactive Interference in the Hippocampus . . . 147
6.2 Temporal Dynamics of Memory Triage . . . 150

Appendices **153**

A Appendix Chapter 5 **153**

B Appendix Chapter 6 **169**

Bibliography **174**

List of Figures

1.1 Anatomy of the Hippocampus 27
1.2 Schematic illustration of place cells, theta and replay 32
1.3 Memory Consolidation Models 42
1.4 Synaptic Tag and Capture 56

2.1 Schematic of the recording setup 71
2.2 Histology: Location of the drives and tetrodes 74

3.1 Sleep detection procedure 78
3.2 Example of SWS and REM epochs in the sleep pot 79
3.3 Example of rate maps from the session with the least number of cells 82
3.4 Example of rate maps from the session with most cells 83
3.5 Power Spectral Density of the LFP for low and high speeds 86
3.6 Example of bayesian decoding on the tracks 88
3.7 Decoding and shuffling procedure for replay events 92
3.8 Schematics for decoding accuracy measures 94
3.9 Schematic of the single cell remapping analysis 96
3.10 Effect of shuffles on cell distribution 99
3.11 Summary of behavioural and recording data 102

4.1 Contexts are differentiated and cells remap between them 110
4.2 Incorrect Bayesian track classification decreases over the first 5 laps and the corresponding decoded positions are biased toward the end zones 115

4.3 Cells form place fields predominantly in the first lap, and a subset of cells from past environments are active then disappear in the first couple laps 118
4.4 Past cells differ from other cells by their lower firing rates 119
4.5 Remote replay of previous experiences occur at the beginning of a novel track then abate after a few Laps. Distinct sub-population of cells participate in each replay type 122
4.6 summary schematic of findings 124

5.1 Behaviourally confirmed reward preference translates to a higher number of laps but does not increase stopping time at end zones . . 136
5.2 Candidate replay event rate does not compensate for an increasing number of contexts to replay and is not modulated by reward 139
5.3 Awake replay is selectively modulated by recency while sleep replay is temporally modulated by both recency and reward 143

A.1 Reward Preference 153
A.2 Running speed as a function of laps 154
A.3 Reward preference, number of laps and stopping time for all 5 rats . 156
A.4 GLMM results for laps 157
A.5 GLMM results for running speed 158
A.6 GLMM results for stopping times 159
A.7 GLMM results for number of cells recorded 160
A.8 GLMM results for peak in field firing rate 161
A.9 GLMM results for Skaggs' information content 161
A.10 Classification Accuracy and Decoding Error 162
A.11 Only a major disruption of the distribution of cells on the track remove teleportation to the end zones effects - controls 163
A.12 Probability distributions of the absolute distance between real and decoded position when the track classification is accurate, for end zones and middle zone 164

A.13 Difference in percentage of cells per cm between the end zones and the middle zone. positive values indicate a higher density in the end zones. 165
A.14 Decoded position accuracy per lap 166
A.15 Between laps differences in decoded position accuracy 166
A.16 Between laps differences in track classification accuracy 167

B.1 Proportion of replay events before and after sleep for eacg track . . 170
B.2 Temporal evolution of the proportion of replay events during sleep: recency and reward for the most recent track 171
B.3 Temporal evolution of the proportion of replay events during sleep: reward modulation for the first two tracks 172
B.4 Distribution of stopping times 173

List of Tables

A.1 Summary statistics for reward preference tests 154
A.2 Summary statistics for the mixed Poisson model: number of laps ∼ reward + (rat|session), back transformed to response scale 155
A.3 Summary statistics for the mixed Poisson model: number of laps ∼ reward*recency + (rat|session), contrasts back transformed to response scale 155
A.4 Summary statistics for the mixed Poisson model: number of laps ∼ change in reward + (rat|session), back transformed to response scale 155
A.5 156
A.6 Summary statistics for the mixed Gaussian model: time spent < 5cm.s^{-1} at end zones ∼ reward + (rat|session) 158
A.7 Summary statistics for the mixed Gaussian model: time spent < 5cm.s^{-1} in middle zone ∼ reward + (rat) 158
A.8 Summary statistics for the mixed Poisson model: number of cells on track ∼ reward + (rat|session) 160
A.9 Summary statistics for the mixed Poisson model: Peak in field firing rate ∼ reward + (rat|session) 160
A.10 Summary statistics for the mixed gaussian model: skaggs information ∼ reward + (rat|session), estimated effect on the log scale. contrasts back transformed to the response scale. 162

B.1 Summary statistics of recency effects for each epoch. 169

Chapter 1

Introduction

1.1 What Defines an Experience - The Case for Episodic Memory

Our daily lives are constructed from episodic experiences, spanning multiple contexts. At the end of the day when we go to sleep, only some of these experiences will become long-lasting memories. Such 'episodic' memories are defined not only by a sense of self in time and space, but also by our ability to intentionally recall them.

Episodic and semantic memory are distinct forms of declarative memory: memories that can be explicitly and consciously recalled (Tulving, 1972). They differ in that semantic memory refers to the knowledge of facts: "London has a current population of 9 million inhabitants" (London Met) and is not rooted in time, space nor linked to one's sense of self. Contrary to this, episodic memories are commonly defined by *"What, Where and When?"*. Before becoming long term recollections, episodic occurrences are one's experience of certain set of external and internal states, or in other terms, of a context.

Defining context

A context can be defined by four main factors 1) sensory attributes (geometry, colour, objects, smell etc..), 2) internal states (hunger, pain, attention...), 3) contingencies (a specific succession of actions will lead to reward or punishment) and

4) previous experience (degree of familiarity and knowledge about all previously listed attributes) (Kentros et al., 2004; Nadel, 2008; Smith and Mizumori, 2006). Contextual changes can occur within an unchanged physical space when an internal state or contingencies changes, while two physically distinct spaces might be bound together by the same set of rules (driving on the left hand side of the road in England and Japan). Identifying what makes two contexts distinct, and the transition point from one to another is not always straightforward, as in the example of a slowly changing probability of success on a slot machine. However, given how strongly context influences behaviour and learning, it is important to recognise when an efficient strategy in one context (stopping to analyse the situation) might prove disastrous in another (doing so in the middle of the road).

Therefore, the brain needs to strike the delicate balance between encoding and storing different contexts as separate memories, and yet be able to retain the ability to generalise across these contexts to optimise behaviour. Because we have limited memory resources, the episodes experienced in different contexts must be compared, to determine which are more important to consolidate (and which are the least important and can be forgotten). While there may be a discrepancy between whether a memory is stored and whether it can be recalled, less striking experiences have been shown to be forgotten at a faster rate than important ones (see section 1.5): we tend to remember birthdays years and decades later, while we tend to forget what we had for lunch on a regular day a few weeks ago.

Identifying the Neural Substrates of Episodic Memories

As episodic memory is a form of declarative memory, their recall can be tested verbally in humans (Tulving, 1972), or through the correct choice of action (or lack thereof) in experimental settings probing the recall of temporal order, space, or items in humans (Tulving, 1972; Watkins and Tulving, 1975), non-human primates (Beran et al., 2016), rodents (Zhou and Crystal, 2009), and birds (Clayton and Dickinson, 1998; Raby and Clayton, 2012), among other animal models. Historically, lesion studies of patients with Medial Temporal Lobe (MTL) damage - which includes damage to the Amygdala (AMY), the Hippocampus (HPC) and parahippocampal,

entorhinal and perirhinal regions - have identified this brain lobe as a prime candidate for supporting encoding and retention of memory (Scoville and Milner, 1957). More recently, through the development of neural imaging techniques and electrophysiological recordings, the temporal dynamics of episodic memory formation and consolidation can also be studied at the level of individual or large ensembles of neurons.

If episodic memories can be studied by searching for the ”what, where or when” (items, space or time) or combinations thereof in the brain, the discovery of hippocampal place cells (O’Keefe and Dostrovsky, 1971) in an area identified as important for episodic memory, has strongly biased the last several decades’ research towards the ”where”. This thesis will likewise be focused on spatial memories as a means to understanding episodic memory.

1.2 How to Build an Episodic Memory: Encoding

Before they can be consolidated for the long term, spatial experiences need to be encoded into a neural representation, such that they can be accessed across memory systems and incorporate a variety of information about the current context.

1.2.1 Spatial coding in the hippocampus

The search for a cognitive map of space, partly incentivized by the work of Tolman and colleagues which demonstrated the ability of rats to learn about shortcuts and detours after the latent learning of space (Tolman and Honzik, 1930; Tolman, 1948), led to the discovery of place cells in the hippocampus (O’Keefe and Dostrovsky, 1971).

1.2.1.1 Anatomy of the Hippocampus

Anatomically, the hippocampus is part of a recurrent circuit with parahippocampal regions and neocortical areas. Neocortical association areas - including many somatosensory areas - project to the parahippocampal areas which themselves project back to the hippocampus. The hippocampus consists of three subregions that are mainly connected uni-directionally. This connectivity is summarised as a trisynaptic loop (Andersen et al., 1971): layer II of the Entorhinal Cortex (EC) $\rightarrow$ Dentate

Gyrus (DG) → Cornu Ammonis 3 (CA3) → Cornu Ammonis 1 (CA1). Few projections opposing this flow of information exist, but include recurrent connections in CA3, and some direct projections from layers II-III of the EC to CA3 and CA1. The output of this trisynaptic loop is then fed back to the neocortical areas via the subiculum and the layers V of the EC (see Figure 1.1 for more details). Importantly, this convergence then redistribution of information from the neocortex to the hippocampus is well conserved across mammalian species (Amaral and Witter, 1989; Manns et al., 2007; Witter et al., 2000).

Regions of particular interest for the scope of this thesis with connections to the hippocampus include:

1. the Prefrontal Cortex (PFC), a region involved in decision making and memory, which can be considered to contain the Orbitofrontal Cortex (OFC) and is thought to be involved in decision making, value learning, and more recently has also been posited to form cognitive maps of state spaces (Schuck et al., 2016; Wilson et al., 2014)
2. the Ventral Tegmental Area (VTA) with its dopaminergic projections that can encode reward prediction errors (Schultz et al., 1997)
3. the Locus Coeruleus (LC) which is part of the noradrenergic system and relates to arousal, surprise, novelty and attention (Duszkiewicz et al., 2019; McNamara and Dupret, 2017; Yamasaki and Takeuchi, 2017).

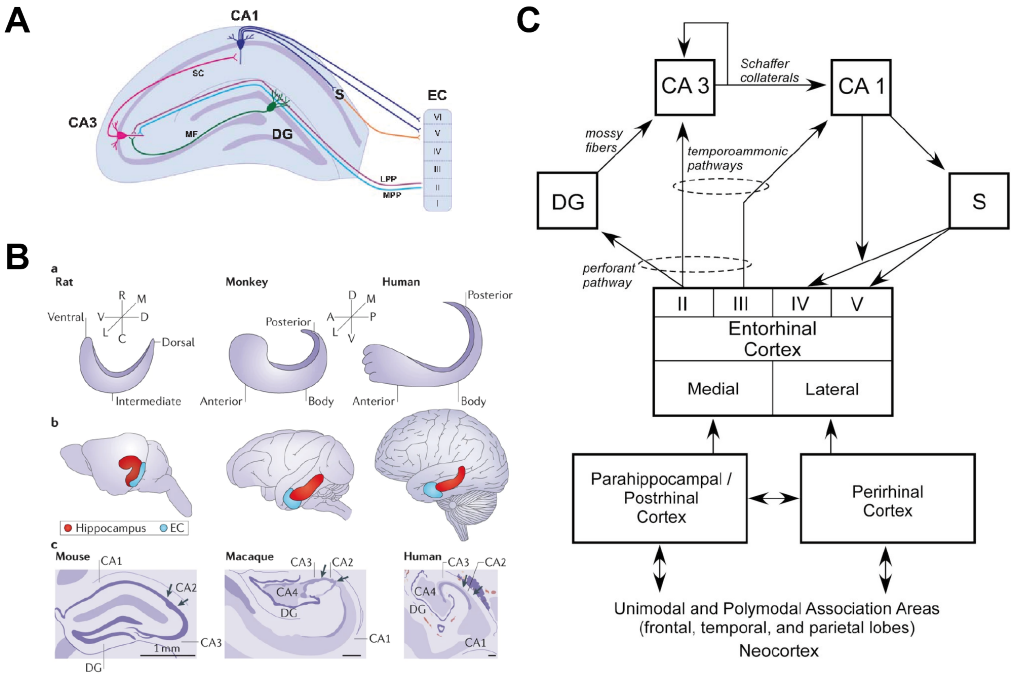

Figure 1.1: Anatomy of the Hippocampus

A: Schematic of the trisynaptic loop superimposed on a coronal slice of the dorsal hippocampus. Layer II of the EC projects to the granule cells of the DG via the the perforant paths (medial in light blue, lateral in purple), which continue and also project onto CA3. The DG projects onto CA3 via the mossy fibres. CA3 neurons then project to CA1 via the Schaffer collaterals. CA1 is the main output of the trisynaptic loop, and projects to the subiculum and deeper layers of the EC. adapted from Patten et al. (2016)

B: Schematic of the rat, rhesus macaque and human hippocampus illustrating their similarities. Top two rows: the orientation of the hippocampus and EC along the antero-posterior and ventro-medial axes. Bottom row: Nissl stained cross sections of the hippocampus revealing the conservation of the trisynaptic loop. adapted from Strange et al. (2014)

C: Schematic illustration of within MTL connections. adapted from Clark and Squirea (2013)

1.2.1.2 Place Cells

While recording pyramidal neurons in the dorsal CA1 of rats, O'Keefe and Dostrovsky (1971) made the observation that as the animal freely foraged through an environment, each neuron had a preferred firing location within the space. The locations of increased place cell firing are known as place fields: inside the place field, the cell exhibits high frequency bursting activity, and exhibit low firing activity outside of it (Fenton and Muller, 1998). Each place cell therefore codes for a

portion of the environment, which suggests that at a population level, a spatial map can be reconstituted from the combined activity of many place cells.

The importance of place cells for creating a 'cognitive map' of space is supported by various hippocampal lesion studies demonstrating that the spatial navigation abilities of rodents in the lesion group are impaired (Hollup et al., 2001; Redish and Touretzky, 1998; Zhang et al., 2004), and from the observation that the position of an animal can be accurately decoded from the spiking activity of a few tens of place cells (Davidson et al., 2009b; Fenton et al., 2008; Jensen and Lisman, 2000; Wilson and McNaughton, 1994; Zhang et al., 1998). Place cells are far from being the only spatially-tuned cells in the brain, but their high density within the hippocampal cell layer along with their ease of recording and higher spatial information content has led to decades of research linking them to memory, and making them a prime (if not the only) target to investigate spatial maps.

1.2.1.3 Other Neural Substrates of Space

Place cells are not the only discovered neurons with spatially modulated firing. For the sake of comprehensiveness, we will briefly cover the other cells that are thought to support spatial navigation:

1) Grid cells in the EC were discovered by Hafting et al. (2005). Like place cells, grid cells form fields in the environment, but do so in a regular hexagonal pattern covering the entirety of the space. They may support path integration (Chen et al., 2019) as the animal crosses the regularly spaced fields of each cell.

2) Head Direction cells, discovered by Ranck (1984) and characterised by Taube et al. (1990), are found in the subicular complex, retrosplenial cortex, the Anterior Dorsal, Lateral Mamillary thalamic nuclei (ADN, LMN), and Dorsal Tegmental Nucleus (DTN) to cite a few. HD cells fire maximally when the head of the animal is aligned with the preferred direction of the cell, and code for orientation in space.

3) Boundary Vector Cells discovered by Lever et al. (2009) in the subiculum have both a preferred direction and distance from boundaries, and may explain the sensitivity of place cells to geometrical constraints (see the BVC model of place cell

firing Hartley et al. (2000); O'Keefe and Burgess (1996)).

1.2.2 Forming Cell Ensembles

We have described how individual neurons can encode a subset of spatial features, but to obtain a map of space, the relational properties or transitions between cells need to also be encoded to form a representation. Knowledge of transitions between states is what ultimately constitutes a cognitive map, by allowing for trajectories to be planned and remembered.

1.2.2.1 The Hippocampus as a sequence learner

Through Hebbian learning, and more particularly Spike Timing Dependent Plasticity (STDP), place cells with neighbouring fields will tend to fire in close temporal proximity, strengthening their synaptic connections (D'Albis et al., 2015; Hebb, 1949). The asymmetry in the firing sequence between the pre-synaptic cell and the post-synaptic cell, resulting in either LTP or LTD, has been modelled to encode sequence formation and place field skewness in the hippocampus (Blum and Abbott, 1996; Mehta et al., 1997; Yu et al., 2006). Furthermore, the hippocampus displays two striking properties relating to sequences of place cell activation on shorter timescales (relevant to STDP) that may contribute to faster sequence learning and stronger representations:

Theta Sequences

Like in many areas in the brain, theta oscillations (6-10Hz in the rat) can be observed in the hippocampal Local Field Potential (LFP) during several types of behaviours including locomotion, exploratory behaviour and REM sleep. Place cell activity is directly modulated by this rhythm - as the animal moves through a place field, the spike timing of the cell will correspondingly shift from the late phase of the theta cycle to earlier phases, a phenomenon called phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996). Place cells start phase precessing very rapidly upon exploration of a novel environment (Foster and Wilson, 2006), and at a population level, the precession of each cell in conjunction with a still unelucidated temporal coordination process (Feng et al., 2015; Middleton and McHugh, 2016) leads to the

emergence of theta sequences (Buzsáki et al., 2003; Drieu et al.). Theta sequences form an ordered compressed representation of past, present and future positions of the animal on a short timescale (few hundreds of ms) and occur at each theta cycle.

Replay

The second mechanism by which the hippocampus is postulated to strengthen spatial trajectory transitions within an ensemble of place cells is the spontaneous reactivation (or replay) of place cells in a temporally compressed sequence. Unlike theta sequences, replay does not occur during the theta modulation of place cells during locomotion. Replay is the reactivation of previously experienced trajectories by place cells during periods of quiet rest/immobility, such as reward consumption and sleep. Replay events have originally been defined as occurring during Sharp Wave Ripples (SWRs), which are depolarising events in CA1 and consist of a large amplitude deflection in the LFP (the sharp wave) on top of which rides a fast oscillation (the ripple, 150-300Hz) (Buzsáki et al., 1992). The replayed trajectories can span longer distances than what is typically observed during theta sequences (Davidson et al., 2009b), and while theta sequences may support planning and allow trajectory encoding and retrieval (Dragoi and Buzsáki, 2006; Drieu et al.; Foster and Wilson, 2006; Hasselmo and Eichenbaum, 2005; Robbe and Buzsáki, 2009; Wang et al., 2015), they are tied to the current location and context. On the contrary, replay events show a greater degree of flexibility in what and how spatial trajectories can be represented, including the reactivation of trajectories in forward or reverse order, of previously experienced environments (Gupta et al., 2010; Karlsson and Frank, 2009a) and of potentially never experienced trajectories (Gupta et al., 2010). Thus, replay provides a representational flexibility that does not appear to be possible with theta sequences.

Crucially, both replay and theta sequences are necessary to stabilise spatial representations (Brandon et al., 2011; Koenig et al., 2011; Kovács et al., 2016; Theodoni et al., 2018; van de Ven et al., 2016), but also for spatial navigation (Jadhav et al., 2012; Roux et al., 2017) and memory consolidation (Ego-Stengel and

Wilson, 2009; Girardeau et al., 2009).

1.2.2.2 Pre-configured Ensembles

In 2011, Dragoi and Tonegawa (2011) reported replay of space that had not yet been experienced, and called this phenomenon de novo preplay. The implication of such preplay would be the pre-configuration of place cells in sequences, and experience of an environment would only serve as mapping spatial features to this pre-existing map. Preplay has been observed in a few studies since (Dragoi and Tonegawa, 2011, 2013; Farooq et al., 2019; Ólafsdóttir et al., 2015). Criticism for the existence of preplay as such comes from the difficulty to predict how long the sequence needs to be in advance, the topography of the environment that needs to be represented (e.g. linear track or open arena) and the choice of statistical methods used to quantify the significance of detected replay events. For a review and demonstration that preplay can be detected in noise when using incorrect statistics see Foster (2017); Silva et al. (2015). Furthermore, as will be described in a later section, place cells can participate in multiple representations, and preplay may be related to past, feature-sharing memories (Eichenbaum, 2015).

Evidence for some cells forming a pre-existing ”backbone” structure that can later be integrated into a novel representation was presented by Grosmark and Buzsáki (2016). In this study, they identified two sub-populations of cells with differing firing dynamics: fast-firing ”rigid” cells and slow-firing ”plastic” cells. The first category, rigid cells, presented sequential firing (replay) prior to, during and after the novel experience. They had broader place fields and higher firing rates than the other neurons, and did not refine their spatial tuning much during the novel experience. The second category, plastic cells, only participated in replay during and after the novel maze exploration. They had more sharply tuned place fields, and increased their involvement in replay over time. Again, rigid cells could be part of previous feature-sharing memories, but this hypothesis could not be tested in Grosmark and Buzsáki (2016).

Thus far, we have described how representations of space can emerge from the combined activity of place cells. We will next investigate how these representations

may be modulated by other factors than space and lead to the representation of context.

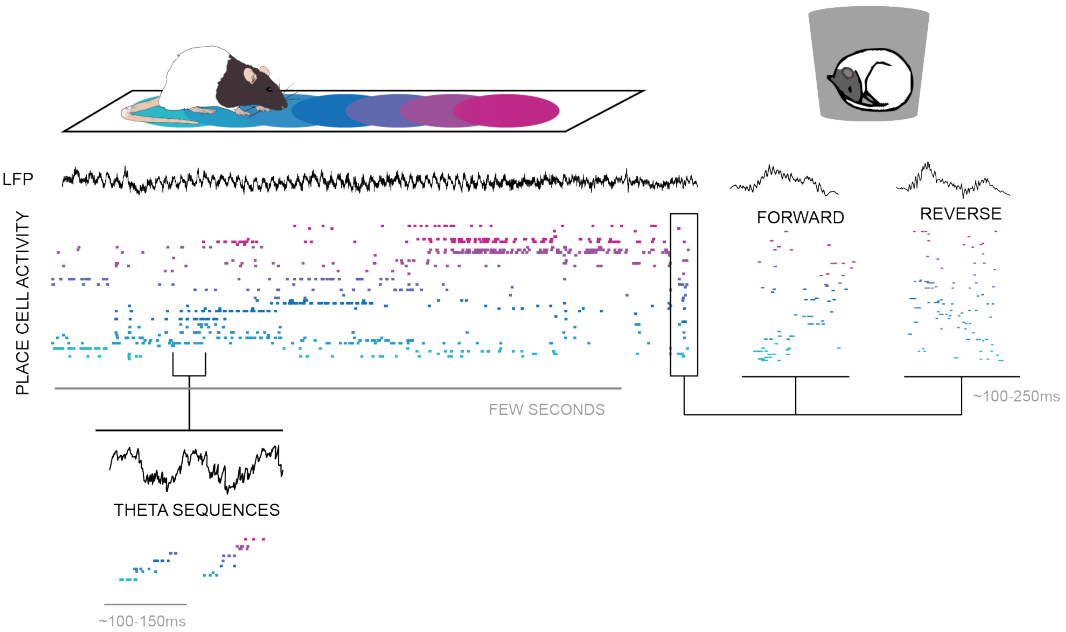

Figure 1.2: Schematic illustration of place cells, theta and replay
The preferred firing location of place cells on the track are represented as coloured disks, where each cell has its own colour. Below, the hippocampal LFP (in black) is shown as the animal runs down the track. When the animal reaches the end of the track, power in the theta band is greatly reduced. Synchronised to the LFP, the activity of place cells - ordered on the vertical axis according to their preferred firing position in space - forms a sequence over the timescale of a few seconds. Zooming on a couple of theta cycles, individual theta sequences can be observed, sweeping from previous positions to future ones. To the right, examples of forward and reverse replay events while the animal is sleeping. Sequences during theta and replay occur on much shorter timescales. Rat schematic adapted with permission from SciDraw.io (https://doi.org/10.5281/zenodo.3926077, https://creativecommons.org/licenses/by/4.0/)

1.2.3 Explicit Features: Multi-Sensory Integration

Place cells encode space through the combined inputs from neocortical and parahippocampal areas, including most sensory cortices. Early studies have focused on how the directly observable features of a context modulate place cell firing.

1.2.3.1 Sensory Cues

In the literature, the visual and geometrical (boundaries) properties of a context are the most frequently varied within an experiment, partly for their ease of ma-

nipulation, but also because changes in visual cues or boundaries elicit significant changes in the firing of place cells. Experiments testing the removal of subsets of visual landmarks from an environment show that place cells tend to be tuned to the conjunctive presence of multiple visual cues rather than that of single clues (Fenton et al., 2000; Muller and Kubie, 1987; O'Keefe and Conway, 1978; Shapiro et al., 1997). Place fields may rotate with visual cues, but do not depend on their presence (O'Keefe and Conway, 1978), and fields stay stable in the dark, given the environment has been sufficiently explored before (Quirk et al., 1990).

Fields are restricted by boundaries in the sense that they will not extend beyond an obstacle placed in the environment (Muller and Kubie, 1987). Elongation or compression of the boundaries of an environment elicits the elongation or compression of place fields accordingly (O'Keefe and Burgess, 1996). The insertion of barriers often creates a duplication of fields (Lever et al., 2002).

Olfactory cues can help stabilise maps (Save et al., 2000), disambiguate between environments (Anderson and Jeffery, 2003), and provide reliable landmarks in the absence of visual cues (Zhang et al., 2015).

Tactile cues have also been shown to help stabilise, refine and participate in the formation of spatial maps (Gener et al., 2013; Save et al., 1998). In addition to olfactory and tactile cues, idiothetic cues - self motion - can increase the stability of representations and prevent drift (Knierim et al., 1996; Ravassard et al., 2013; Sharp et al., 1995).

Non Spatial Sequence Learning

Aronov et al. (2017) recorded hippocampal and medial EC cells in rats learning to navigate a linear sequence of sounds to obtain a reward. Many of these cells formed a tuning response to a specific part of the soundscape. About 21% of these cells were place cells in physical space, and 34% were grid cells. While hippocampal non-place cells and MEC non-grid cells were more likely to be tuned to a sound frequency, this study showed that the connectivity of the hippocampus may putatively support different types of cognitive maps, but space is the most often encountered one. It also fits well with human hippocampal maps that are more prone to extend

beyond space (e.g. Schuck and Niv (2019); Tavares et al. (2015)).

We have seen that external cues can modulate spatial representations, and that the latter are robust to small changes in the environment and seem to encode for spatial context (you can recognise your backyard even after a tree has fallen). In the next sections we show that place cells indeed code for more than just space, and reflect context in a larger sense. One example is the modulation of representations by reinforcers and emotions.

1.2.3.2 Reward

The hippocampus receives indirect projections from the PFC, the OFC, and direct projections from the VTA. These regions are respectively involved in decision-making, value learning, and reward signalling, the latter through dopaminergic projections, suggesting that place cells may potentially be modulated by reward (see Kennerley and Walton (2011) for a review of PFC function and Hollerman and Schultz (1998); Schultz et al. (1997) for a review on reward and dopamine). The importance of the map-like properties of ensembles of place cells for spatial navigation (Hu and Amsel, 1995) supports the idea that some form of reward or goal coding - even if only conjunctive - might occur in the hippocampus. Place cells have been shown to over-represent reward and goal locations (Dupret et al., 2010; Hollup et al., 2001; Poucet and Hok, 2017; Sato et al., 2020) and fire in anticipation of reward at the goal locations (McKenzie et al., 2013; Poucet and Hok, 2017). However, their firing properties near reward and goal locations are confounded with changes in locomotion during approach behaviour. One recent study decoupled goal location and reward, and found no over-representation of goal locations or goal value coding in CA1 and CA3 in the absence of reward (Duvelle et al., 2019).
Furthermore, calcium imaging combined with virtual reality techniques led to the discovery of cells specifically coding for reward and reward anticipation, in the CA1 and the subiculum of mice (Gauthier and Tank, 2018).
Finally, the multi-unit activity of place cell during SWRs, as well as replay event frequency are increased at reward locations (Ambrose et al., 2016; Michon et al.,

2019; Singer and Frank, 2009), which is thought to reflect behavioural performance and learning (Dupret et al., 2010; Igata et al., 2021).

1.2.3.3 Pain and Fear

The importance of the ventral HPC - medial PFC - AMY network in fear conditioning is well established (Milad and Quirk, 2012). However, few studies examine how fear alters hippocampal representations because of the exploration-limiting freezing responses that accompany fear memory retrieval. Experience of a negative reinforcer such as an electric shock in an environment caused place cells to form a new representation of the context after it was associated with fear (Moita, 2004; Schuette et al., 2020). The presence of fearful stimuli such as predator urine also caused the formation of a new representation (Wang et al., 2012). Wu et al. (2017) showed that place cells with fields in the shock zone prior to the shock experience were still recruited in replay events but not theta sequences after the animals learnt to avoid the shock zone.

While we have discussed evidence that reward and fear shape hippocampal representations, demonstrating that those maps do not only convey spatial information and can also encode contextual changes, those changes are still rooted in the presentation of external stimuli (food or a shock). We now review evidence that hippocampal representations also can incorporate implicit features.

1.2.4 Implicit Features: Internal States

1.2.4.1 Experience

In a novel environment, hippocampal maps evolve as the animal explores and learns about the features of the environment. Examples of this include the increasing stability of the representation with exploration, which can take multiple exposures of the animal exploring a 2D environment (Cacucci et al., 2007; Feng et al., 2015; Foster and Wilson, 2006; Frank et al., 2004; Law et al., 2016; Leutgeb et al., 2004; McNaughton et al., 1983). Hippocampal intracellular recordings revealed that novel environments elicit a large amplification of input signals to CA1 neurons, support-

ing rapid place field emergence. The following decrease of such amplification with experience is also marked by a more reliable driving of CA1 neurons by their inputs (Cohen et al., 2017).

One consequence of exploring an environment through stereotyped routes - as is the case on linear tracks and in some 2D environments- is for place fields to become directional (Battaglia et al., 2004; Markus et al., 1995; McNaughton et al., 1983; Muller and Kubie, 1987). The development of calcium imaging methods has allowed experimenters to record cells over multiple days, and to show that after the initial stabilisation period, place fields usually form coherent representations across days in rats (Kinsky et al., 2018), therefore extending findings from standard extracellular recordings (Jeantet and Cho, 2012; Thompson and Best, 1990). Finally, replay has been shown to be more frequent in novel than familiar environments (Buhry et al., 2011; Cheng and Frank, 2008).

1.2.4.2 Attention and Tasks

Parallel to those findings, place fields in mice were shown to be less stable across days than in rats (Ziv et al., 2013), and may reflect the degree of attention paid to the cues available in the environment (Kentros et al., 2004). Tracking the activity of place cells of rats executing different tasks (random or directed search) in multiple environments (low or high complexity, single or multiple cues), revealed that not only cues, but also the task and behaviour affected hippocampal representations of the same space (Dupret et al. (2010); Markus et al. (1995); O'Keefe and Speakman (1987); Wood et al. (2000), Smith and Mizumori (2006) for a review). There is an entire corpus of literature on the role of awake replay during spatial navigation and how it may support planning or retrieval based on task demands. However, given this is outside the scope of this thesis, we will not discuss the potential role(s) of awake replay further (see Findlay et al. (2021); Foster (2017); Ólafsdóttir et al. (2018); Pfeiffer (2020) for reviews).

1.2.4.3 Motivation

To the best of our knowledge, only two papers address the role of motivation on hippocampal representations. Kennedy and Shapiro (2009) showed that hippocampal representations reflected the motivational state (food or water deprived) of the animal, and this encoding was strongest in goal directed behaviours, but still present during random foraging. Carey et al. (2019) built on these observations by tracking replay rates across food and water deprivation days during goal directed behaviour. Surprisingly, replay content was shifted away from the preferred outcome (turn left/right to obtain food/water), regardless of the behaviour reflecting the motivational state of the animal.

1.2.4.4 Time

Hippocampal damage impairs learning of temporal sequences of events in both humans and rats (see Eichenbaum (2013); Ranganath and Hsieh (2016) for reviews). The discovery of hippocampal Time cells, or at least some form of temporal coding in CA1, may provide the neural basis needed for the temporal organisation of episodic memories (Kraus et al., 2013; MacDonald et al., 2013; Mankin et al., 2012; Manns et al., 2007; Mau et al., 2018; Pastalkova et al., 2008; Paz et al., 2010; Umbach et al., 2020).

We have reviewed how the rodent hippocampus generates representations of space from the activity of populations of cells, and the internal and external variables that can also be encoded into those representations to create not only a map of space but of a context. We now review how those maps are stored in the long term.

1.3 How to Build an Episodic Memory: Consolidation

1.3.1 The Hippocampus and Memory

The link between the hippocampus and episodic memories originates from accounts of patients with MTL damage. The most famous account of said link between the hippocampal formation and episodic memory, is the anterograde and temporally limited retrograde amnesia of patient H.M., as reported by Scoville and Milner (1957). The importance of their report lies in the separation of episodic memory from other cognitive functions - importantly from working memory and other types of long term memory - and pinpointing the MTL as its origin. However it is not until accounts from other patients with more focused hippocampal lesions (Rempel-Clower et al., 1996; Spiers et al., 2001; Zola-Morgan et al., 1986) and lesions in monkeys (Zola-Morgan and Squire, 1990; Zola-Morgan et al., 1994) that the role of the hippocampus specifically was established.

In humans, hippocampal lesions cause retrograde amnesia for events experienced a few years earlier, while broader MTL lesions led to retrograde amnesia of the last decades (Manns et al., 2003). It was therefore assumed that long term memories gradually become independent of the hippocampus and MTL, and it was hypothesised that they become more strongly expressed in the neocortex instead.

In rodents, hippocampal lesions induce retrograde amnesia over days or weeks (see Frankland and Bontempi (2005) for a comprehensive review). One of the strongest pieces of evidence of the gradual disengagement of the hippocampus and parallel engagement of neocortical areas after learning was the observation that c-fos/zif268 expression (proxies of brain metabolic activity) shifted between those two brain regions when the retrieval of recent memories was contrasted with the retrieval of remote memories (Bontempi et al., 1999; Maviel et al., 2004). Conversely, mice with intact hippocampal but impaired cortical plasticity can form short term but not long term memories (Frankland et al., 2001; Hayashi et al., 2004).

Before we delve into the memory consolidation models that have been created

to try to explain how memories change locii, we examine the role of sleep in memory consolidation.

1.3.2 The Role of Sleep

Prior to H.M. and hippocampal lesion studies, the role of sleep for memory consolidation was already the focus of many studies. Research in the 1880s-1930s had already identified from personal accounts or studies with few participants that forgetting is reduced when sleep occurs sooner rather than later after learning, and that sleep deprivation was detrimental to memory retrieval (Jenkins and Dallenbach, 1924; Patrick and Gilbert, 1896; Schmidt, 1987; Van Ormer, 1933). These effects of sleep or lack thereof have since then been replicated in a myriad of studies (see Rasch and Born (2013); Sara (2017); Walker and Stickgold (2004) for reviews).

1.3.2.1 REM and SWS

In mammals, sleep is divided in stages of Rapid Eye Movement (REM) and Slow Wave Sleep (SWS), also termed Non-REM sleep (NREM). In humans, NREM has three stages, while in rodents the distinction is usually made only between SWS and REM sleep. The two stages are mainly differentiated by the frequency of the EEG oscillations and magnitude of EMG activity:

- SWS is characterised by slow delta waves (0.5-4Hz), which form alternating up and down states. During down states, neurons are hyperpolarised and the neocortex is 'silent'. During up states, neurons are depolarised and bursts of activity emerge. SWRs occur during SWS, but not REM.

- REM is characterised by an EEG signal close to that of wakefulness, with the exception of general muscle atonia and fast eye movements. Faster oscillations than delta waves are observed, such as theta (8-12Hz) in the hippocampus, and gamma waves/spindles (40-60Hz) in the cortex.

REM and SWS may contribute to memory in different ways. Mainly driven by research in humans, the Dual Process hypothesis postulates that SWS preferentially

supports the consolidation of declarative memory (of which episodic memories are a sub-type), while REM sleep is biased for the consolidation of non-declarative memories (which includes emotional aspects) (Gais and Born, 2004; Maquet, 2001; Rauchs et al., 2005; Smith, 2001). In opposition, the sequential hypothesis, mainly supported by work in rodents, but also in humans, gives complementary functions to SWS and REM. SWS leads to a potentiation of strong memories and a depotentiation of weaker ones, while REM sleep incorporates the 'surviving' memories, which are then strengthened and integrated or linked with previous networks and memories (Ambrosini and Giuditta, 2001; Giuditta et al., 1995). In this framework, the cyclic alternation of SWS and REM cycles is crucial, and has been shown to lead to better memory retrieval or performance than pure SWS sleep periods in humans and rats (Ambrosini and Giuditta, 2001; Mandile et al., 2000; Vescia et al., 1996). In an alternative viewpoint, REM sleep has been hypothesised to be primarily for forgetting (Poe, 2017).

Although the role of each stage of sleep, with their respective oscillatory rhythms and chemical balances, may still be the subject of much debate, the importance of sleep for memory consolidation processes is well established. We now give an overview of systems memory consolidation models.

1.3.3 Memory Consolidation Models

1.3.3.1 Standard Consolidation Model

In 1971, Marr was the first to formulate the idea that daily experiences would be stored in the hippocampus then transferred to the neocortex for reorganisation, through the reactivation of waking patterns (Marr, 1970, 1971). Buzsáki (1989) formalised the standard consolidation or 'two-stage' model by identifying SWRs and theta oscillations as the neural underpinnings of memory formation. In this model, sensory information about the current experience is encoded in neocortical areas, and the hippocampus integrates these incoming inputs into a neural representation, creating an initial memory trace. Concomitant reactivations of this trace in the hippocampus and cortical areas during SWRs strengthen and grow cortical traces until they are no longer dependent on the hippocampus and are integrated

with previous knowledge. In this scenario, the hippocampus is a rapid but transient learner, while the cortex is a slow but long-lasting learner. Slow integration in the cortex is viewed as a way to prevent inappropriate overwriting or degradation of previous memories, termed catastrophic interference. The discovery of the necessity for replay events during offline states (Girardeau et al., 2009; Pavlides and Wilson, 1989; Wilson and McNaughton, 1994), and in coordination with the cortex (Ji and Wilson, 2007; Maingret et al., 2016; Peyrache et al., 2009) further supports the consolidation of episodic memories during sleep via replay. In this model, all sub-types of memories are transferred to the neocortex, and no distinction is made between episodic and semantic memories.

Other models, which generally agree with the standard consolidation model, make different predictions depending on memory sub-types.

1.3.3.2 Cognitive Map Theory

In cognitive map theory, the hippocampus forms spatial, allocentric, representations of environments. These representations constitute the spatial basis of context, and continues to do so regardless of the recency of that representation (Burgess et al., 2002; O'Keefe and Nadel, 1978). Therefore even old episodic memories remain hippocampal-dependent, while semantic memories (in humans) never rely on the hippocampus.

1.3.3.3 Multiple Trace Model

Nadel and Moscovitch (1997) suggested that instead of a transfer from the hippocampus/MTL to the neocortex, all experiences are stored in both, the hippocampus acting as an index to cortical traces, and therefore memories require both structures. Furthermore, each time a context is re-experienced or retrieved, a new hippocampal trace is created leading to a ever-increasing number of traces for older memories. Hippocampal damage is therefore more likely to sever the link between the hippocampus and neocortex for recent memories than older ones.

Some evidence for semantic memories being independent from the MTL of exists in humans (Westmacott et al., 2004), while remote, highly detailed, spatial memories can still be dependent on or at least engage the hippocampus (Cipolotti

et al., 2001; Martin et al., 2005; Rosenbaum et al., 2000; Viskontas et al., 2002). That being said, an overwhelming majority of data supports a disengagement of the hippocampus/MTL for remote memories (reviews Frankland and Bontempi (2005); Fujii et al. (2000); Moscovitch et al. (2006); Rasch and Born (2013); Sutherland et al. (2020)), arguing against the cognitive map theory, and favouring the standard consolidation model.

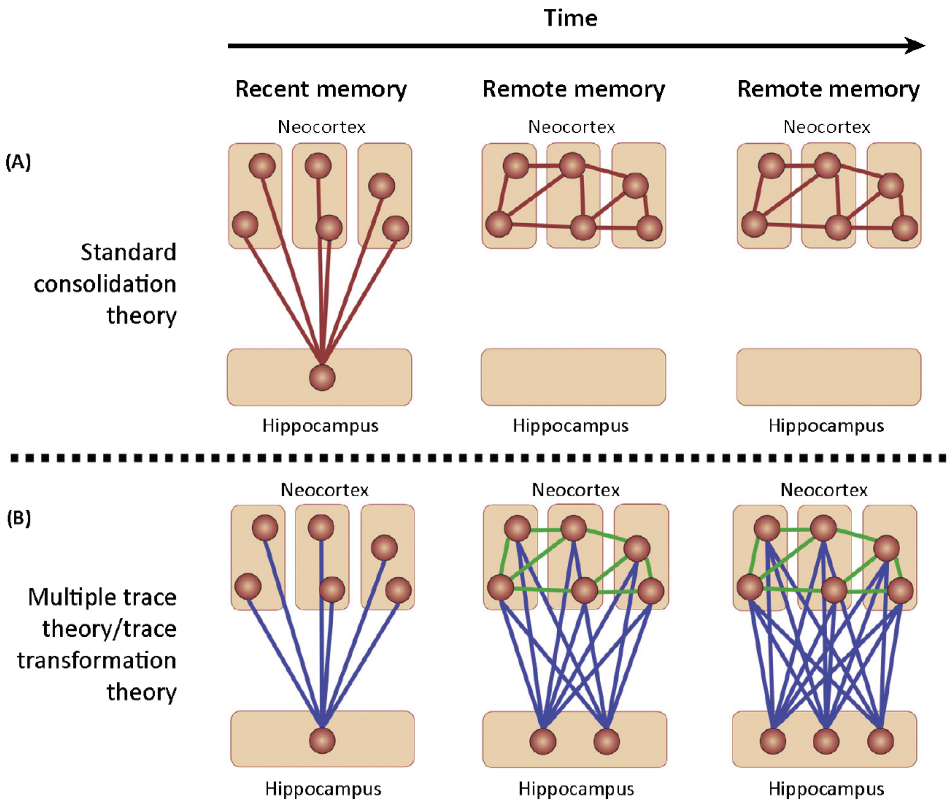

Figure 1.3: Memory Consolidation Models

A: The standard consolidation model. A representation is created in the hippocampus and is linked in parallel with all involved cortical areas. During sleep hippocampal and cortical traces are reactivated, enabling the creation of cortico-cortical connections. With time, the memory becomes independent from the hippocampus.

B: Multiple trace theory. Similar to the standard consolidation model, the memory is originally formed in the hippocampus, and reactivations lead to the strengthening of cortico-cortical traces. However, each time the memory is reconsolidated, a new hippocampal trace is integrated in this network, and these never subside, leading to an ever increasing number of traces for this memory. adapted from Barry and Maguire (2019)

1.3.3.4 Homeostatic Model

All of the above models rely on sustained synaptic potentiation, both during wake and sleep states. However, the need for synaptic downscaling or homeostasis is evident. Tononi and Cirelli (2003, 2006) hypothesised that sleep is needed to downscale the synapses back to a baseline level, before the heightened plasticity and synaptic potentiation that occurs during awake states. The homeostatic model is an independent, complementary function to that of memory consolidation models. Linear downscaling of synapses will prune weakly strengthened representations or connections, and therefore improve the signal to noise ratio for remaining memories. Downscaling of synapses is hypothesised to be mediated by slow wave oscillations and low concentrations of acetylcholine, norepinephrine, and serotonin during SWS. While there is evidence for such downscaling (Bellina et al., 2008; Bushey et al., 2011; Cirelli et al., 2005; Gilestro et al., 2009; Vyazovskiy et al., 2009), there is also some evidence against it (Chauvette et al. (2012); Grosmark et al. (2012), the literature on LTP inducing oscillations such as SWRs, spindles). Based on the available evidence, sleep is likely to be a combination of strengthening epochs (reactivation based) along with general downscaling.

1.4 How to Deal with Feature-Sharing Experiences

We have shown how the hippocampus creates a representation for experiences during awake states, integrating both spatial and non-spatial features into a map, which is then consolidated during sleep into long term memory storage through hippocampo-cortical interactions. However, we encounter multiple contexts and experiences during a single day, and in a continuous manner. We dedicate the following sections reviewing what we know about how these context and experiences may be segmented into distinct representations, and how multiple maps may interact with one another - through competition or cooperation - in awake and sleep states.

1.4.1 Segmentation of Experiences

Humans are usually able to give a temporally organised account of their daily experiences, which can only be done if they are capable of segmenting the continuous passage of time into events in the first place.

Early studies consisting of asking participants to segment sequences of daily actions (Newtson, 1973; Newtson et al., 1977) led to the hypothesis that event segmentation relied upon 1) large changes in perceptual stimuli 2) graded boundaries (more or less distinct) 3) the presence of a hierarchy in events, with higher level events being better segmented and remembered (Zacks et al., 2001).

However, because humans can segment experiences when asked to, this does not mean segmentation occurs spontaneously during daily activities. Zacks et al. (2001) tested this by showing movies to participants during fMRI. A movie was played passively first (no task), then a second time with the participants segmenting the movie. Transient changes in cortical BOLD signals correlated with event boundaries in both passive and active conditions. Although these changes may be correlated with significant changes, the involvement of non-sensory cortical areas suggests that event segmentation is part of normal perception. These result has been replicated (Swallow et al., 2009; Zacks et al., 2006), and extended to participants reading or listening to stories (Speer and Zacks, 2005; Speer et al., 2007; Whitney et al., 2009). The neural basis of event segmentation is still unknown to say the least, but from this corpus of literature we expect event boundaries to be defined by ”characters and their interactions, interactions with objects, spatial location, goals, and causes” (Zacks, 2010). Another, complementary, theory is that context segmentation and identity can be explained by a hidden state inference framework (Sanders et al., 2020). The underlying theory is that an animal needs to infer the posterior probability of each hidden state (or context) given the available observations using Bayes' rule. This posterior distribution represents the confidence or uncertainty the animal has about being in a hidden state/context. A trade-off has to be struck between segmenting the observations into states/contexts to best fit the data and keeping the complexity and number of states minimal. This framework is useful for not only

addressing context segmentation - which can be done in a hierarchical manner, but also to re-frame previous findings relating to the effect of sensory cues, experience and context changes on place cell activity.

1.4.2 Remapping

What constitutes a context and how events are segmented may remain elusive, but even over the duration of one day, we usually experience multiple contexts (home, work, public transport etc..). We have shown that the hippocampus creates a representation or map for a single context, so now we review how it deals with multiple maps: a phenomenon called remapping. First of all, at a single neuron level, place cells can adapt their place field tuning in multiple ways in response to changes in or of an environment (Colgin et al., 2008; Poucet et al., 2000). Consider a pair of environments, one that has been experienced and in which a place cell has a stable place field, and a second novel environment. This place cell can:

1. become silent, by not forming a place field in the novel environment.
2. form a place field in the novel environment:
    (a) in a similar location and keep its spatial tuning properties identical: this is the absence of remapping
    (b) change one or more of its spatial tuning properties: commonly quantified variables are the peak location, centre of mass or peak in-field firing rate.

The final possibility is for a cell to be silent in the first environment, and become spatially tuned to features of the novel one. At a population level this creates remapping continuum, with at one extremity identical maps for two contexts - hence the contexts are not perceptually differentiated - and at the other extremity of this continuum, where the populations of cells involved in the two contexts are mutually exclusive - and the contexts they represent do not share a single feature. These two ends of the spectrum are somewhat theoretical, and in many cases the remapping data will fall along the middle section of this continuum: partial remapping. In

this case, one may observe all three types of remapping behaviour between contexts (emerge or vanish, alter place field properties), and the populations of place cells are shared between contexts. Populations of cells being (efficiently) reused between maps has multiple implications. First, maps with a substantial number of shared features need to be differentiated in a way that their consolidation does not cause catastrophic interference. Second, the degree of similarity between maps determines the likelihood for this to occur. Third, this may be beneficial to generalise across maps, and link experiences together. We now review the potential underlying mechanisms used to strike this delicate balance.

1.4.3 Pattern Completion and Separation

Pattern separation is the process of trying to orthogonalise representations (removing any overlapping components) while pattern completion is the process by which an episode can be retrieved from partial or noisy information. Pattern completion can therefore also support generalisation between environments. Models identify the dentate gyrus (DG) granule cells as the mediators of pattern separation using inputs from the EC, and CA3 and its auto-associative recurrent collaterals to mediate pattern completion through attractor networks (Mcclelland et al., 1995; Norman and O'Reilly, 2003; Shapiro, 1984; Treves and Rolls, 1994).

Pattern Completion

The recurrent connections between CA3 neurons and their Hebbian plasticity (Bains et al., 1999; Pavlidis et al., 2000) have been hypothesised (Ribak et al., 1985; Treves and Rolls, 1992, 1994) to resemble the properties of a Hopfield network (Hopfield, 1982). Memories are learned and stored in a set of strongly connected CA3 cells. Later on, presentation of a cue belonging to this memory excites a subset of the cells from this memory. The recurrent connections in the network then in turn activates the rest of the cell ensemble leading to recall of the memory in its entirety. Importantly, the activity of this network is 1) persistent, even after removal of the cue (Wang, 2001), 2) present properties of an attractor network. Small perturbations do not degrade the ensemble as the large number of connections will reinstate the firing pattern. Large perturbations may lead to a shift of activity towards another attractor

state. Evidence for CA3 performing pattern completion includes impaired retrieval but not encoding after knocking out NMDA dependent plasticity in CA3 or lesioning CA3 (Gold and Kesner, 2005; Nakazawa et al., 2002), and electrophysiological studies (Leutgeb et al., 2007; Nakazawa, 2017; Neunuebel and Knierim, 2014).

Pattern Separation

Activation by a cue of an auto-associative network alone would lead to the activation of any memory containing said cue, which is obviously undesirable. Having a network that separates inputs based on the available observations prior to engaging the pattern completion network is one way to avoid such an effect. The DG is suited for this as it receives the cortical inputs from the EC. It is thought that the combined input of the EC, the DG via the mossy fiber pathway and/or via the perforant path is used to regulate the excitability of CA3 neurons and respectively privilege creation of new patterns in CA3 or recall of past experiences (Leutgeb et al., 2007; Neunuebel and Knierim, 2014). The inactivation of DG inputs to CA3, including mossy fibres, impairs encoding but not recall (Lassalle et al., 2000; Lee and Kesner, 2004), while severing the direct input from EC to CA3 via the perforant path impairs recall selectively (Lee and Kesner, 2004).

There is a significant amount of evidence for the DG and CA3 being at the epicentre of pattern separation and completion - even if some debate remains as to the underlying model and potential non-linearity of these functions (see (De Almeida et al., 2007; Madar et al., 2019; Yassa and Stark, 2011)) - but they are not the only structures that have been shown to be able to do it. Examples include pattern separation in the amygdala (Gilbert and Kesner, 2002), the piriform cortex (Sahay et al., 2011; Wilson, 2009) and both completion and separation in the perirhinal cortex (Bartko et al., 2007; Gilbert and Kesner, 2003).

CA1 is neither performing pattern completion nor separation but rather reflects linear changes in inputs. That being said, alteration of place fields properties by remapping can be viewed as a form of pattern separation (perceptual change in inputs results in a change in the output), while the absence of remapping and stability of place fields in the face of overlapping features can be related to pattern

completion.

1.4.4 Schemas and Novelty Detection

As mentioned above, inputs from the the parahippocampal, postrhinal and perirhinal cortices via the EC will determine the hippocampal representation of the current context. And for each experience, the overlap in the current contextual features with previous knowledge and experiences will shape the current representation. Feature overlap can alternatively be thought of as the current context's degree of novelty. This novelty can be stimulus based (e.g. a novel object is encountered), or associative (e.g. oddball paradigm or an object being moved withing a known spatial environment). There is significant evidence that the perirhinal cortex supports stimulus novelty detection (novel vs familiar) (Brown and Aggleton, 2001; Miller et al., 1993; Xiang and Brown, 1998), with 25% of its neurons coding for novel items (Xiang and Brown, 1998) regardless of the item's behavioural relevance (Brown and Bashir, 2002; Zhu and Brown, 1995). As a consequence of the anatomical circuitry illustrated in Figure 1.1, the perirhinal novelty signals are then propagated to the hippocampal subfields. However, hippocampal neurons have been shown to rarely respond to stimulus novelty (Xiang and Brown, 1998). Instead, evidence points toward the hippocampus as coding for associative novelty such as stimulus-location mismatches or new associations of familiar objects and what is more generally is considered as contextual novelty (Brown and Aggleton, 2001). One mechanism thought to potentially underlie associative mismatch novelty in the hippocampus is a comparator model: violations of prior predictions (recall in CA3) by sensory inputs generates novelty signals (Gray and McNaughton, 1982; Lisman and Grace, 2005; Sokolov, 2003). In this model, overlap in contextual features will elicit a hippocampal recall of previous representations in CA3 in conjunction with the generation of a novelty signal in CA1. Another model of associative novelty is a familiarity mechanism, triggering hippocampal novelty signals proportionally to the amount of novelty present, without the need for recall (Bogacz et al., 2001; Henson et al., 2003). Empirically, the comparator model would be favoured if there was ev-

idence for 1) reactivation of prior contexts in CA3 and 2) novelty signals exclusive to associative mismatch novelty, while the familiarity model would be supported by 1) the absence of hippocampal recall and 2) novelty signals for any associative novelty. The comparator model is supported by a few studies which found hippocampal novelty signals solely in the presence of a contextual mismatch paradigm, and not pure associative novelty (Fyhn et al. (2002); Kumaran and Maguire (2006); Long et al. (2016), Kumaran and Maguire (2007) for a review) .

The need to retrieve prior predictions and check these against current sensory inputs by a comparator model directly relates to and calls for a link with the corpus of literature on pre-existing associative networks, termed schemas. Originating from the human literature, the definition of schemas varies across reviews and authors, but generally refer to 1) networks of neurons, sometimes posited as neocortical, 2) which form the basis of memory traces of acquired knowledge over a significant amount of past experiences and 3) influence memory encoding, consolidation and retrieval (Alonso et al., 2020; Bartlett and Kintsch, 1995; Fernández and Morris, 2018; Ghosh and Gilboa, 2014; Van Kesteren et al., 2012). At the encoding stage, if the current experience triggers the recall of a schema, said encoding activates, if not directly occurs, in cortical networks such as the mPFC (Cooper et al., 2019; Coutanche and Thompson-Schill, 2014). Concurrently, the hippocampus is inhibited and hippocampo-mPFC co-activity weakened (Berkers et al., 2017; Bovy et al., 2020; Roediger and McDermott, 1995; Van Kesteren et al., 2010, 2013). Conversely, if the experience is very novel and doesn't fit with previous schemas, hippocampal activity and hippocampo-mPFC co-activity are increased (Bein et al., 2014; Van Kesteren et al., 2013). Importantly, schemas have been shown to hasten memory consolidation in both humans (Van Kesteren et al., 2014) and rats (Tse et al., 2007). A study measuring IEG expression in several brain regions revealed that retrieval of schemas involves cortical areas (Prelimbic, ACC, RSC) and the hippocampus (Tse et al., 2011), while novel experiences lead to a greater amount of synaptic plasticity in the hippocampus compared to cortical areas (Lesburguères et al., 2011).

1.4.5 Working Framework

While we have models of how pattern separation, completion, associative novelty and schema retrieval may occur in and affect the hippocampus, substantially less is known about how novel representations are built when overlapping features may trigger the recall of past memories. The extent of our knowledge on this can be summarised to:

- The DG may depolarise CA3 via the mossy fibers to allow for a new representation to be encoded
- Sub-populations of CA1 rigid and plastic place cells may respectively contribute to generalisation and differentiation when building a novel representation
- Remapping / the stabilisation of novel maps is experience dependent, reflecting knowledge accumulation
- Replay of remote experiences can happen in a novel environment. This may relate to associative mismatch novelty detection and the retrieval of schemas

The presence of remote replay and rigid cells hint at the possibility that past memories may interfere with the creation of novel one, a process called proactive interference, which has been shown to be supported by the rodent hippocampus (Han et al., 1998). Whether proactive interference occurs during learning of a novel environment, and if so, what the temporal dynamics of such a process are, have been overlooked and remain open questions. We posit a framework where 1) the contextual uncertainty is high at the onset of exploration of a new environment. 2) The brain needs to determine whether this new space has previously been encountered before or not. 3) We hypothesise that the hippocampus can rapidly extrapolate from a restricted set of observations to create a coarse map of this new environment and inform behaviour appropriately. 4) This mechanism of extrapolation is dependent on a ”recall and compare” of feature-sharing contexts for simultaneous generalisation and differentiation 5) Knowledge accumulation reduces this uncertainty about the context and stabilises the representation.

Within this framework, recall of previous experiences will need to occur from the very first moments of the novel experience. This requires the DG to depolarise CA3 enough for a new attractor network to be created but in an intermittent manner. Supposing that rigid cells are indeed cells representing features shared with previous experiences - possibly features most often encountered - then these high firing place cells should create a stable representation faster than plastic cells that are integrated in the network. Shared features of the context should trigger the remote replay (recall) of previous contexts, helping stabilise the new representation, and creating a link between memories needing to be generalised across during consolidation. Consequently, the need for recall is expected to decrease with knowledge accumulation.

1.5 How to Deal with Limited Storage: Memory Triage

Another challenge that comes with experiencing multiple contexts each day is the impossibility to continually accumulate and consolidate all of this information. Even in the case of hyperthymesic individuals (from the ancient Greek *hyper-* 'excessive' and *thymesis* 'remembering', an extraordinarily rare condition), one does not have a perfect memory of every day of one's life, implying that only a small fraction of experiences are consolidated. We here acknowledge that the absence of recall may not be the absence of consolidation, but it is a reasonable hypothesis that every single moment of the life of a 70-year-old might not be represented in their brain. From an ethological point of view, contexts with the highest learning value or future expected value should be preferentially consolidated over others.

1.5.1 Salient Memories

There is a growing body of evidence for salient memories, regardless of valence, to be tagged during the awake states for prioritised consolidation during sleep. The mere instruction to participants that sets of information were either "to be remembered" or "to be forgotten" is sufficient to create a difference in the recall ability

or amount of consolidation between each set (Rauchs et al., 2011). Similarly, the disclosure post-training by the experimenter to participants that an improvement in recall performance on the test phase the next day would be rewarded monetarily, led to better recall (Fischer and Born (2009) and Walter and Meier (2014) for a review on prospective memory). By separating participants into sleep-deprivation and control groups, the effect of explicit instructions 'to remember' or 'to forget' was shown to be time sensitive: a 24hr sleep deprivation nullified any memory gain from the instructions, and could not be recovered, even after two full nights of recovery sleep (Rauchs et al., 2011).

However, implicit rather than explicit instructions of what needs to be remembered are a more common occurrence in our daily lives.

An example of extreme prioritisation of salient events is the formation of "Flashbulb memories", an unusually detailed and "vivid" autobiographical memory of the circumstances surrounding a particular event (Brown and Kulik, 1977), which can be recalled even years later. The cause for the creation of flashbulb memories can be positive: fall of the Berlin Wall (Bohn and Berntsen, 2007), negative: Marmara and Loma Prieta earthquakes (Er, 2003; Neisser et al., 1996), the 9/11 events (Kvavilashvili et al., 2003, 2010), fall of the Berlin Wall (Bohn and Berntsen, 2007), or elements of surprise: a majority of UK residents had flashbulb memories of Margaret Thatcher one year after her resignation (Conway et al., 1994). We now review the factors that are known to trigger prioritised memory consolidation.

1.5.1.1 Emotion

Presentation of emotional or neutral images to participants divided in sleep or sleep deprivation groups is one of the most commonly used paradigms to test emotional memories in humans. Consistently, emotional content is better remembered than neutral items (Atienza and Cantero, 2008; Feld et al., 2014; Fischer and Born, 2009; Hu et al., 2006; Liu et al., 2008; Nishida et al., 2009; Wagner et al., 2001). When presented with a single picture, emotional components are remembered in greater detail at the expense of neutral components (Payne et al., 2008). Crucially, this prioritisation effect was also shown to be sleep dependent in these studies, with the

saliency 'tag' of emotional memories eroding as a function of waking time.

Reward

Anticipation of reward following explicit instructions increases memory retention (Fischer and Born, 2009; Oyarzún et al., 2016). As described in section 1.2.3.2, reward modulates hippocampal activity, increasing the reactivation frequency of rewarded portions of the environment (Singer and Frank, 2009), of reverse replay at higher reward sites (Ambrose et al., 2016) and of replay during sleep (Igloi et al., 2015; Michon et al., 2019). With both awake and sleep replay being necessary for memory trace strengthening and consolidation (Girardeau and Zugaro, 2011; Maingret et al., 2016), an increase in their frequency by reward suggests reward-based memory prioritisation. This prioritisation is expected to be graded within context, with a higher need for items or location closer to the reward compared to those further away (Payne et al., 2008; Singer and Frank, 2009). Braun et al. (2018) demonstrated this by asking participants to memorise virtual grid maps of object picture states, and learn to navigate these maps to find a hidden reward. After a period of sleep, object/state recall was inversely correlated with distance from the reward. The existence of ramping dopamine signals as a function of proximity to the reward in mice (Fiorillo et al., 2005; Howe et al., 2013), may support this recall gradient (Guru et al., 2020).

Fear

Just like reward anticipation bolsters recall, the threat of punishment upon failure to recall in humans triggers better memorisation of fear associated items (Murty et al., 2012; Oyarzún et al., 2016). Negative reinforcers such as pain and their consequent aversive/fear component lead to persistent fear memories (Maren et al., 2013), of which Post Traumatic Stress Disorder (PTSD) is an unfortunate example, and are consolidated with a higher priority than neutral stimuli (Cahill and Alkire, 2003; Cahill et al., 2003). Interestingly, just like reward, fear of punishment activates the mesolimbic dopaminergic system, including the VTA (Adcock et al., 2006; Carter,

2009; Delgado et al., 2011).

1.5.1.2 Novelty

Finally, anticipation of novelty and novelty itself also increases recall performance in humans (Wittmann et al., 2007). In flashbulb memories, not only is the unexpected novel event remembered in detail, but so are contiguous low-salience items/events, which would not have been memorised otherwise. This prompted studies examining whether novelty could create a 'grace period' for preceding and subsequent events. Indeed temporally proximal memories were also strengthened (Dunsmoor et al., 2015b; Salvetti et al., 2014) and novel environments are replayed preferentially compared to familiar ones (Kudrimoti et al., 1999; McNamara et al., 2014; O'Neill et al., 2008).
Distinct types of novelty have been postulated to exist (Duszkiewicz et al., 2019). Spatially novel environments engage VTA dopamine neurons projecting to the hippocampus (McNamara et al., 2014), while surprise and more unusual novelty engage the LC. Recently it has been discovered that the LC also has dopaminergic projections to the hippocampus, and in larger numbers than the VTA (Kempadoo et al. (2016); Takeuchi et al. (2016), reviews: Duszkiewicz et al. (2019); McNamara and Dupret (2017); Yamasaki and Takeuchi (2017)). We will describe how those projections have been postulated to lead to the presence or not of a 'grace period', as well as their importance for memory consolidation in more details in section 1.5.2.

We have shown how reward, punishment, novelty and motivation bias replay content and memory consolidation, determining the fate of memory traces by prioritising the consolidation of salient experiences during sleep. We now delve into the underlying mechanisms of such prioritisation, during both awake and sleep states.

1.5.2 Mechanisms

Memory triage happens in two steps: tagging during or shortly after encoding, and preferential consolidation during sleep.

1.5.2.1 Tagging

From the known factors inducing memory prioritisation during sleep, reward and novelty are both linked to dopamine release in the hippocampus (Schultz (2007) and Duszkiewicz et al. (2019) for reviews). The origin of such dopamine release is either from VTA-TH+ neurons or LC-TH+ neurons. Dopaminergic projections from the VTA have been shown to help stabilise hippocampal maps and increase reactivation frequency (McNamara et al., 2014). The postulated underlying mechanism for this is the ”synaptic tagging and capture (STC) hypothesis of protein synthesis-dependent long-term potentiation” (Frey and Morris, 1997, 1998). Hippocampal plasticity in the encoding stage is NMDA dependent, with postsynaptic depolarisation leading to transient LTP and tagging of the synapse.

However, the strength of the synapse decays rapidly in a few hours. Dopaminergic projections, and notably onto the D1/D5 receptors of hippocampal neurons, leads to persistent LTP in already tagged synapses, giving those synapses a comparative advantage during consolidation. Because this STC mechanism will capture any tagged synapse indiscriminately, it explains the “grace period” of rescuing temporally proximal experiences when exposed to highly novel situations, mediated by strong LC dopaminergic projections.

There is emerging evidence that dopamine may also play a role in contextual fear conditioning and extinction, but it is unclear how it would participate in STC in the encoding stage (Fadok et al., 2009; Luo et al., 2018; Pezze and Feldon, 2004). The basolateral amygdala, a key structure of the fear conditioning network, has been shown to enhance the production of LTP related genes (the immediate early gene Arc) in the hippocampus via noradrenergic projections (McReynolds et al., 2014). Electrically stimulating the BLA around neutral, novel objects led to better recall, likely due to an increase in coordinated plasticity-inducing oscillations (slow gamma, 30-55Hz) with the hippocampus (Bass and Manns, 2015).

Fast oscillations and reactivations are likely to help determine (or at least correlate with) the fate of memories by further strengthening synapses. However, the causality of these interactions is difficult to determine - between increased replay and

captured synapses. Nevertheless, two studies, one in humans and one in rats, show that awake replay of less often experienced contexts (Gupta et al., 2010) and of weakly learned information right after learning (Schapiro et al., 2018) may prevent the forgetting of selected experiences.

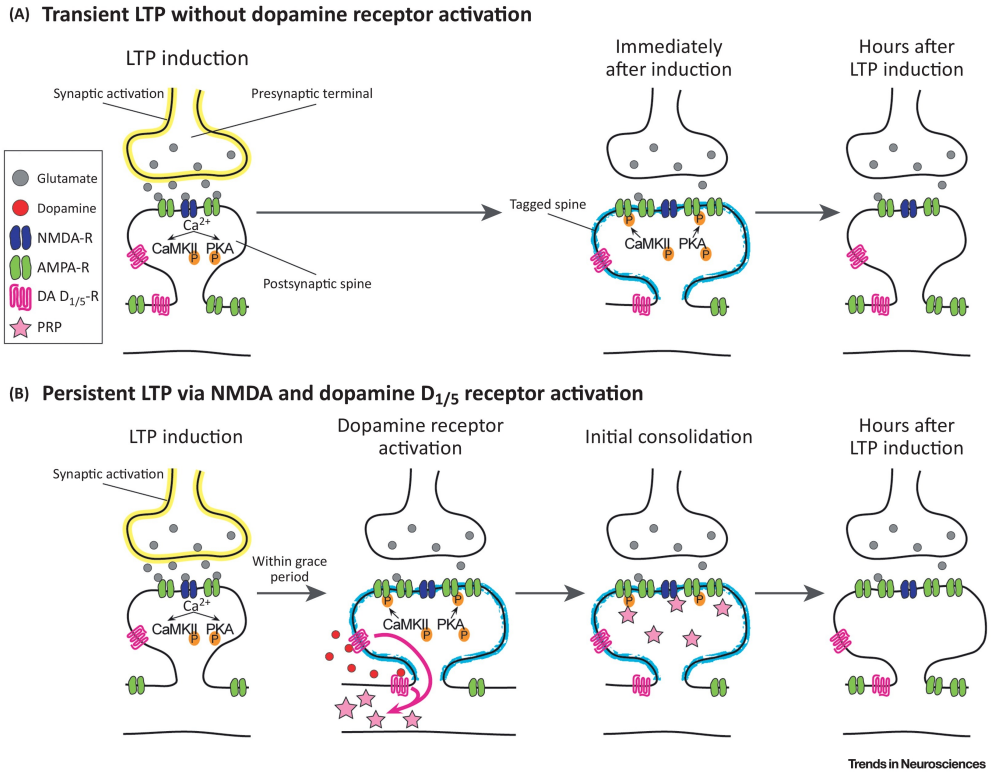

Figure 1.4: Synaptic Tag and Capture

A: Concurrent release of pre-synaptic glutamate and depolarisation of the post-synaptic synapse induces transient LTP in the postsynaptic spine. The synapse is 'tagged'. In the absence of plasticity-related proteins (PRP) this potentiation returns to baseline after a few hours.

B: Dopaminergic activation of D1/D5 receptors leads to PRP synthesis. If this occurs within the grace period after the initial transient LTP induction of the synapse, the PRPs are captured by tagged synapses maintaining LTP levels hours later.

adapted from Duszkiewicz et al. (2019)

1.5.2.2 Cortical Feedback

Synapses are therefore tagged during encoding - or shortly after - for prioritised consolidation. One may assume that the fate of each memory is then sealed. However, the consolidation stage engages a hippocampo-cortical dialogue. The content of hippocampal replay predicting subsequent cortical replay and vice versa (Roth-

schild et al., 2017), which includes the possibility for the neocortex to bias the content of hippocampal replay (Bendor and Wilson, 2012). Tagging may also occur in the neocortex during encoding, ensuring that memories that have been tagged in both structures are preferentially consolidated. Neocortical tagging would also support non-declarative memory consolidation. We now briefly review the neocortical areas potentially involved in memory triage.

Neural plasticity associated with the consolidation of memories, including LTP, is associated with an increase in Immediate Early Gene (IEG) expression (Alberini, 2009; Cruz et al., 2013; Minatohara et al., 2016). Mukherjee et al. (2018) systematically tested IEG expression after 13 different experiences of varying valence, salience and experience/familiarity (cocaine, sucrose, feeding post food deprivation, lithium chloride injection, saline injection, mild foot shock, novel environment) in multiple brain regions. The transcriptional signatures of each type of experience could be near-perfectly decoded and revealed shared attributes between experiences. Notably, expression levels were higher for salient experiences compared to neutral ones, with distinct expression targets depending on valence. Rewarding experiences increased gene expression in the frontal cortex (mPFC, ACC, Nucleus Accumbens, Dorsal Striatum and VTA), aversive experiences targeted the Amygdala, and the hippocampus always presented minimal IEG expression levels.

Imaging techniques (fMRI) show increased hippocampal activation for “to be remembered” compared to “to be forgotten” items (Rauchs et al., 2011). Fear of punishment activates the amygdala, the parahippocampal areas and the orbitofrontal cortex, but not the dopaminergic midbrain (Murty et al., 2012). Furthermore, while dopamine plays a crucial role during encoding, Gomperts et al. (2015) observed a decrease in the activity of reward responsive VTA neurons during NREM sleep. Therefore, the memory triage process is unlikely to rely on VTA dopamine activity during sleep. While LC neurons become silent during cortical spindles (Aston-Jones and Bloom, 1981), the activity of LC-TH+ neurons during NREM sleep has not been studied yet to the best of our knowledge.

Prioritisation of salient experiences is therefore engaging distinct cortical areas

based on valence, consistent with cortical consolidation and reorganisation, while preserving hippocampal representations. Whether neocortical activity influences memory triage during sleep remains an open question.

1.5.3 Working Framework

Memory triage allows for the retention of important memories at the cost of forgetting less relevant ones. This preferential consolidation is sleep dependent. Declarative memories, and more specifically episodic memories have been shown to be encoded by the emergence of context-specific cell ensembles in the hippocampus. During sleep, repeated reactivation of these hippocampal cell ensembles, coordinated with reactivations in distributed cortical areas allows for those representations to be consolidated as long term memories. Memory triage is a two step process: 1) relevant memories are tagged during awake states, jump-starting LTP processes. At a systems level these are observable through an increase in reactivation and ensemble coordination during wake. 2) These memories are better consolidated during sleep, as marked by an increase in reactivation frequency and a higher coherence between the hippocampus and neocortex.

Multiple factors can gate the consolidation of a memory trace. In the absence of variation in salience between memories, temporal proximity to sleep is advantageous (Payne et al., 2012; Talamini et al., 2008), most likely due to the decay in hippocampal NMDA-dependent synaptic strength with time. Salience, in the form of reward, fear/pain, or novelty bolsters synaptic LTP protein synthesis in the hippocampus. The specificity of this boost is neuromodulator and projection dependent: VTA dopaminergic projections and fear conditioning alone may be more specific than LC dopamine projections in the presence of strong novelty (novelty can also be coupled with an emotional component). Salience is therefore dampened by habituation and repetition, leading familiar experiences to not be prioritised against novel ones.

Therefore we posit that the sequential experience of different contexts of equivalent salience should lead to a decline in reactivation prevalence during sleep, as determined by the decay dynamics of NMDA dependent plasticity. Differing salience

between contexts should lead to an interplay between those temporal decay dynamics and selective synaptic strength enhancement. The magnitude of this salience (reward, punishment strength or novelty, surprise) will mediate whether an earlier, but more salient memory will be preferentially, or equally consolidated compared to a later but less salient experience.

These hypothesis can be tested behaviourally, molecularly through IEG expression or other LTP quantification methods, and at a systems level by tracking the proportions of reactivations for each context. Of note, all of the studies investigating the role of various factors on memory triage did not investigate the dynamics of prioritised consolidation during sleep other than a general increase in reactivation frequency and or strength. For example, whether consolidation of relevant memories occurs in parallel or in succession is unknown. Sleep stages (REM or NREM) may also play distinct roles in memory triage.

1.6 Thesis Aims

The focus of this thesis is on how the sequential experience of multiple contexts in a day influences episodic memory encoding and consolidation. To obtain a systems-level understanding, we chose to make use of the contextual encoding and reactivation properties of hippocampal place cells in the rat to track those memories during both wake and sleep states.

This thesis is divided into two main axes of research:

1. What are the encoding dynamics of generalisation versus differentiation of novel maps ? Investigating proactive interference in the hippocampus.
2. What are the temporal dynamics of prioritised memory consolidation ? More specifically, what are the effects of reward and temporal proximity to sleep on subsequent replay?

To this end we designed an experimental protocol that could address both questions. We recorded the extracellular signal of dorsal CA1 pyramidal neurons of rats exploring three completely novel contexts each day, followed by sleep. The salience of each novel context could be further modulated by an increase in reward quality.

The spatial component of the contexts was chosen to be variations of linear tracks to ensure that we could decode and track replay event proportions for each context given the expected number of place cells that we would be able to record from. Single unit hippocampal recordings allowed us to explore amongst other things: the precise temporal dynamics of 1) place cell formation and remapping 2) cell ensemble reactivation and replay during wake and sleep. Armed with these tools we sought to address the following questions:

1. **Chapter 4: Generalisation vs differentiation of novel maps: proactive interference in the hippocampus**

   Novel contexts can share features - whether external (e.g. sensory) or internal (e.g. motivation) - with previous contexts. While the representation for this new context is still juvenile, proactive interference is in theory possible: recall of previous feature-sharing contexts may influence how the new experience is encoded. There is some evidence that this may be the case, through 1) the activity of a sub-population of CA1 neurons (rigid cells) almost instantly forming a backbone structure of the new representation, and these neurons may belong to previous maps, and 2) the presence of remote replay. To the best of our knowledge no one has investigated either the possibility of proactive interference in the formation of hippocampal representations, nor its associated temporal dynamics. If proactive interference exists during encoding we expect:

   (a) for place cells from previous maps and emerging cells to have different stabilisation dynamics on the novel track

   (b) The need for recall, in the form of remote replay, to decrease with exploration and stabilisation of the new representations

2. **Chapter 5: The effect of reward and temporal proximity to sleep on memory triage**

   The presence of multiple experiences (or contexts) is required to tax memory consolidation processes, and create the need for memory triage to occur. Here

we modulate two factors known to create prioritisation, reward and recency, to investigate the temporal dynamics of memory triage during sleep, and the interaction between said factors. At the time of data collection for this thesis, reward had not yet been shown to increase replay frequency during sleep. Comparing replay event proportions for each context we will investigate:

(a) whether memory prioritisation of salient memories occur in parallel (absence of temporal dynamics) or in an ordered fashion

(b) the interaction between reward and temporal proximity to sleep given our experimental parameters

Those two axes of research together are expected to highlight the complex interactions between overlapping and competing memory traces, from the instant they are created to their consolidation in the long term.

Chapter 2

General Methods

2.1 Animal Housing and Care

All experimental procedures and postoperative care were approved and carried out in accordance with the UK Home Office, subject to the restrictions and provisions contained within the Animal (Scientific Procedures) Act of 1986 and the European Communities Council Directive of 24 Nov 1986 (86/609/EEC). Prior to surgery, 5 male Lister-Hooded rats (Charles River) were housed in pairs and kept at 90% of their free-feeding weight with free access to water. Their housing room was maintained at a temperature of (22 ± 2)°C, a humidity level of (55 ± 10)%, and on a 11am:11pm light:dark cycle, with 1h of simulated dusk/dawn. Following surgery, animals were singly housed under the same conditions, with their weight and condition checked daily.

2.2 Surgeries

Animals were anaesthetised in an induction chamber with isoflurane (Piramal Healthcare UK Ltd, 3-5%, O_2 flow rate of 2L per min) while analgesia was administered intra-peritoneally with an injection of Carprofen (0.1mL of 10v/v% per 100g animal weight). They were then shaved and positioned in a stereotaxic frame with ear bars, and body temperature was kept constant throughout surgery with a heating pad. Anaesthesia was maintained under isoflurane at a reduced dose (1-2.5%, O_2 flow rate of 2L per min). Surgical drapes were placed, and the surgical site cleaned with successive applications of iodine (povidine-iodine, WHO, 2009) and sterile saline. The skull was then exposed by a mid-sagittal incision along the dorsal axis, using vaseline-coated haemostatic forceps to hold the fascia and skin away from the site of interest. Successive applications of diluted hydrogen peroxide (10% in phosphate buffered saline (PBS), etching gel agent (Kerr) and 30% ethanol dilution were used to ensure cleanliness and dryness of the skull before implantation. Craniotomies were performed with a burr drill to insert the anchoring screws as well as ground and reference screws (above the cerebellum). Metabond was applied on the skull and around the screws, and left to dry. Then, craniotomies and durotomies were done above the regions of interest: HPC (AP: -3.48mm, ML: +/-2.4mm from Bregma). The implant(s) was(were) aligned vertically above the center of the craniotomies with the help of custom made attachments to the stereotaxic arms, and lowered to the desired DV coordinate as measured from the dura (HPC: 1-1,5mm DV). Sterile vaseline was placed around any remaining exposed brain within the craniotomy to protect it from dental acrylic, which was slowly applied over the skull and microdrive to hold it in place. Finally, the ground and reference wires were soldered to the microdrive and the skin was sutured. The animal was injected saline intra-peritoneally and allowed to recover in a heated cage until fully awake. All animals were given Meloxicam for three days after surgery and left to recover under careful monitoring for a week before the start of experiments.

2.3 Electrophysiological Recordings

2.3.1 Microdrives

Two types of microdrives were used for this project, each with their own advantages and limitations. While the 'Poor-lady' drives (Axona) provided greater stability and shorter building time although they tended to have a lower cell yield. On the other hand, the 'Wilson-lab' microdrives (designed in the Wilson lab, MIT) were more time consuming and difficult to build, but when used correctly, yielded a higher number of recorded cells. Their full potential has not yet been reached in this project. All animals were either implanted with: two non-independently moveable drives above left and right HPC; or with one independently moveable drive, in both dorsal hippocampi.

2.3.1.1 Independently Moveable Microarrays

We modified an existing protocol to build micro-drive arrays from Kloosterman et al (2009). The 3D CAD files for twenty-four tetrode micro-drives were customised to accommodate for bilateral HPC stereotaxic coordinates. The microdrive's body was printed using a FormLabs 3D printer, rinsed in isopropanol and cured in UV light. Supports were then detached from the base and any undesirable resin removed. 2x5mm of 15G metal cannula were cut, inserted at the bottom of the drive and fixed with superglue to create the output cannulae. Top pieces were prepared by 3D printing upper and lower rings, one of each were then superglued to custom screws (1.2mm x 14.41mm, AMT) and 14.5mm 23G cannula and left to dry. All twenty-four top pieces were then placed inside the drive body, before the oiled AMT screws were covered in either epoxy or dental acrylic, to create grooves for the screw to go up and down in. Outer polyimide tubes (HPC medical products: inner diameter 0.071" / outer diameter 0.116") were fed inside each top piece, and glued in place with epoxy, before being cut flush with the output cannulae. These provide a passage for inserted inner polyimide tubes (HPC medical products inner diameter 0.035" / outer diameter 0.053"), which were attached to the top pieces' cannulae, to go up and down. Ground and reference wires were soldered to an Elec-

tronic Interface Board (EIB), which was then screwed to the drive's body. Hardened and shielded plastic was shaped into a cone to create a faraday cage around the drive. 17μm tungsten wire was twisted (Twister, Open Ephys) and gently heated into twenty-four tetrodes (bundle of four closely spaced electrode sites), each placed inside an inner polymide tube, secured in place with superglue, and connected to the EIB via a gold pin - ensuring electrical contact by removing the wire's insulation (scraped off by the gold pin when it was inserted into the EIB). Finally, tetrodes were cut at the desired length (HPC: 4mm) and plated with a gold solution (Neuralynx) until they reached an impedance of around 200kOhms at 1kHz (NanoZ).

2.3.1.2 Non-Independently Moveable Microarrays

Poor Lady microdrive bare frames (Axona Ltd, St Albans, UK) were fitted with two strips of 2x10 MillMax pins connected to thirty-four wires, of which thirty-two were fixed with dental acrylic around a section of the screw and two were left exposed for ground and reference. A 7mm long, 17G cannula was attached at the desired distance from the screw with the help of custom 3D-printed holders. Eight 17μm platinum-iridium tetrodes (see paragraph above) were inserted inside the cannula and wound around each of the wires, soldered and shielded with plastidip (PlastiDip UK Ltd., Hampshire, UK). The tetrodes were then cut at the desired length (HPC: 4mm) and plated with a gold solution (Neuralynx) until they reached an impedance of around 200kOhms at 1kHz (NanoZ). Custom MillMax to Omnetics 44pins adaptor were made to have the correct mapping from Poor Lady microdrives to the Neuralynx headstages that were used during experiments.

2.3.2 Screening

Animals were screened inside the sleep pot for familiarisation purposes. Based on the presence of sharp-wave ripples in the hippocampal LFP, the amplitude of spikes in the cluster space, and the number of distinct clusters, tetrodes were moved between 25-125μm every day, or leaving 8h between screening sessions.

2.3.3 Data Acquisition

All electrophysiological recordings were made using a 96 channel digital Neuralynx system (Digital Lynx SX, Neuralynx). The animal was tethered to either two 32 channels or one 96 channels digital multiplexing headstage(s), depending on the number of microdrives and tetrodes. Neural signals were digitised at the headstage using a fixed reference - in our case the reference screw on the head of the animal - AC coupled, unity gained and multiplexed before being sent down a 5m tether to the acquisition system. A custom built 96 channel passive commutator (made by Lilia Kukovska) was magnetically attached to the ceiling to allow the experimenter to untangle the tether with minimal disturbance to the animal's behaviour. Signals were further processed in the system and sent to the Cheetah interface as 30kHz raw LFP signal, bandpass filtered LFP and single unit activity. The animal's behaviour was recorded by an overhead camera. The video feed was synchronised by the system to the neural signal, and the animal's position was tracked by setting a colour-specific intensity threshold to a green and red LEDs' signal. Manually configured TTL pulses were sent from the liquid dispensers to the system to log start and end activation times. Highpass filtered (0.1Hz) local field potentials and the position data were stored for all further analysis.

2.4 Behaviour

2.4.1 Apparatus

A recurrent problem in chronic electrophysiology experiment is the need to rebuild the apparatus as experimental designs evolve and change. We have chosen to design a setup which allows for not only a very large number of 1D and 2D maze configurations, but also for multiple mazes to be present at the same time, and for instruments - such as sensors, liquid or pellet dispensers - to be placed anywhere within the experimental room with minimal disruption. This modular maze consists of rectangular pieces of cut Medium Density Fibreboard (MDF), painted black for tracking purposes. Each piece can be attached to any other piece with removable dowels. In a subset of them, a circular hole was drilled in the middle to fit both the tubing of the liquid dispensers from below, and the liquid receptacles. Maze pieces were attached to height-adjustable tripods with velcro. Infusion pumps (dual Aladdin, WPI) were used to dispense 0.1mL liquid reward at a rate of 21.36mL/min. Custom Bonsai and an Arduino code were used to run the behavioural task by activating the pumps upon the animal's entry in regions of interest set near the reward wells.

2.4.2 Food Preference

Unlike many other studies, reward quality rather than quantity was modulated to create a contrast between environments. Prior to any electrophysiological recordings, but after surgical implantation of the microdrives, the following food preference test was made to assess each animal's preference to the different rewards that would later be used during recording sessions. Animals were placed on a (20 x 80) cm platform with two ceramic bowls filled with 15mL of pure or 1:1 dilution of a chocolate flavoured soy milk. Each trial consisted of 2 minutes where the animal could freely sample the liquids. The animal's position and time spent near each bowl was recorded using Bonsai. At the end of each trial, the animal was removed from the platform, the remaining amount of liquid was measured, the bowls were refilled and placed back in a pseudo-random manner (random number generator,

MATLAB, MathWorks) at either end of the platform (6 trials, 3 on each side). 12 trials were done for each liquid reward combination. As a positive control, water was used instead of the 1:1 dilution. The animals were exposed to all tested dilutions in their home cages beforehand.

chocolate vs 1:1 dilution	chocolate vs water
12 trials	12 trials

2.4.3 Recording Protocol: Reward Experiment

A crucial goal for this experiment was to create very distinct contexts. Black curtains were placed around the recording area in a 2m by 3m room, and a large number of textured fabrics and high contrast cues were available to choose from to create distinct visually and tactile experiences. Furthermore, large black cards could be used as moveable partitions to occlude the other mazes from the animal's sight, creating compartments within the room.

MDF maze pieces of varying lengths were assembled on top of tripods to create three 2m tracks of varying geometry within the recording area (see table 2.4.3), at a height of roughly 35cm. Cues and partitions were placed in the environment, as well as a black plastic flower pot (diameter 20cm) with a folded tall (1m) black plastic sheet as a sleeping pot, removing any visual cues from the animal's line of sight during rest sessions. The room was illuminated by concealed blue LEDs, and either chocolate or 1:1 diluted chocolate was fed into the liquid dispensers. Liquid dispensers only activated on the condition that the animal travelled the entirety of the track. At the beginning of the recording, the animal was put in the sleep pot for about 1 hour before being placed at one end of the first maze for 15 minutes. It was left free to run to get a 0.1mL reward at both ends of the track by visiting each site in turn. The animal was then put back in the sleep pot for 10 minutes, as the experimenter fitted the next track with the liquid dispensers and if necessary changed the reward. Similarly the animal ran for 15 minutes on the second track, had another 10 minutes rest session before the third track, ran for 15 minutes on the third track, and was finally placed back in the sleep pot for a longer 1h30 to 2h period. If necessary, tetrodes were adjusted at the end of the session, before unplugging the headstage.

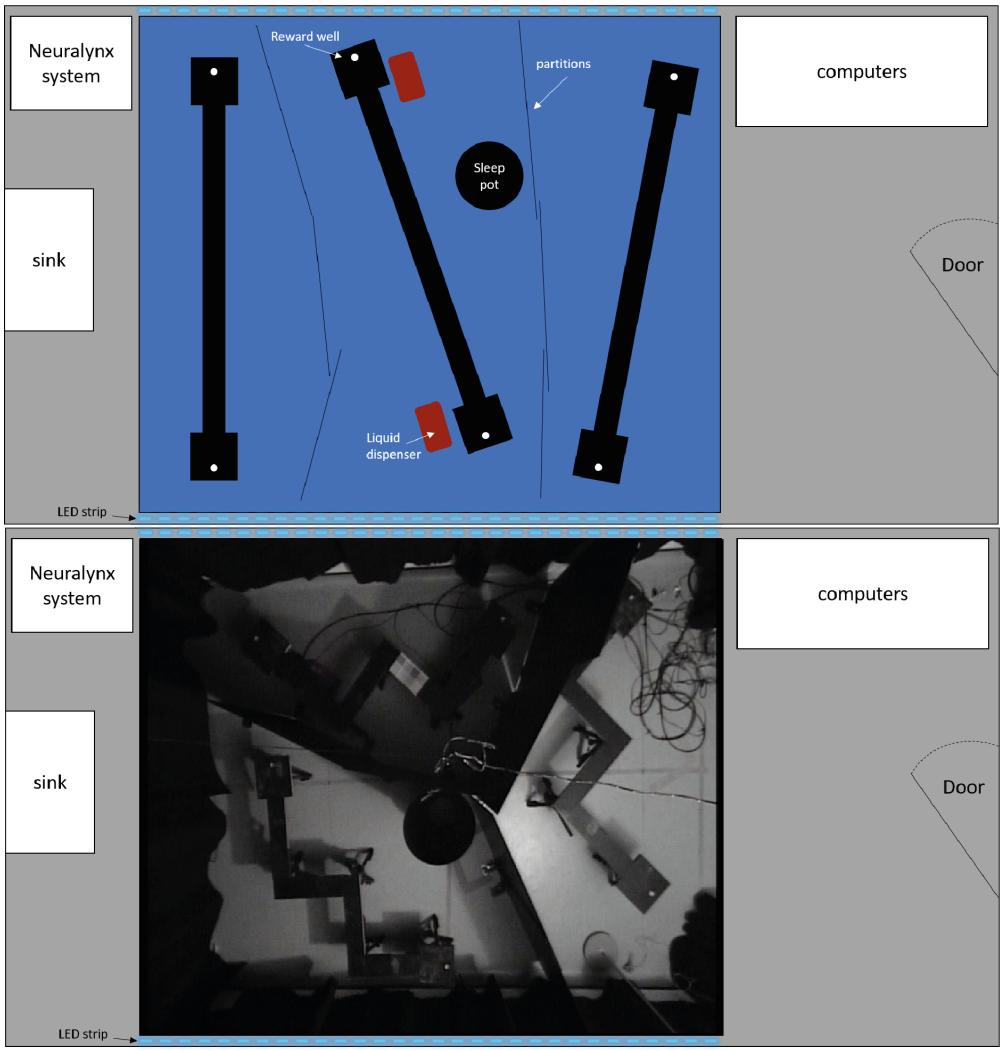

Figure 2.1: Top: Schematic of the recording setup **Bottom:** Schematic of the recording setup, with a picture of the area used for video tracking

The mazes were then cleaned with an ethanol/chlorhexidine spray, and dismantled before the next session.

Each day, two of the mazes were similarly rewarded (pure chocolate or 1:1 dilution). The order of the mazes, reward and maze shape were pseudo-randomised for each rat using MATLAB. For the rat Navi, human error led to two sets of conditions to be repeated twice (see data summary 3.11).

Day	Maze1	Maze2	Maze3	Shape
1	chocolate	diluted chocolate	diluted chocolate	
2	diluted chocolate	diluted chocolate	chocolate	
3	diluted chocolate	chocolate	diluted chocolate	
4	chocolate	chocolate	diluted chocolate	
5	diluted chocolate	chocolate	chocolate	
6	chocolate	diluted chocolate	chocolate	

2.5 Histology

Animals were anaesthetised in an induction chamber with isoflurane (Piramal Healthcare UK Ltd, 3-5%, O_2 flow rate of 2L per min, reduced to 2% after 5 minutes). Small electroloytic lesions were made at the tip of each tetrode to mark their emplacement by passing a 30mA current for 15s between tetrode wires. The tetrodes were then lifted all the way up if possible, and the animals were overdosed with an intra-peritoneal injection of pentobarbitone (Pentoject, pentobarbitone sodium). Immediately after breathing stopped, the animals were transcardiacally perfused with saline at a rate of 5 mL/min followed by a perfusion of 10% neutral buffered formalin, thus removing blood and fixing the tissues.

The carefully extracted brains were stored for a minimum of 24h in formalin, then placed in 30% sucrose for at least 72h for cryoprotection. They were then mounted in OCT and cut in 30μm slices with a LEICA CM1850 UV cryostat and mounted on slides.

The mounted slices were left to dry for at least 24h, Nissl stained (see protocol below) and imaged with a bright field microscope.

Cresyl Violet	6-12 min
dH2O 1	1 minute
dH2O 2	1 minute
70% EtOH	30 seconds
95% EtOH	30 seconds
100% EtOH	20-10 seconds Leave less in EtOH if understaining
Histoclear 1	1 minute
Histoclear 2	1 minute - until gluing

Glue coverslips with DPX

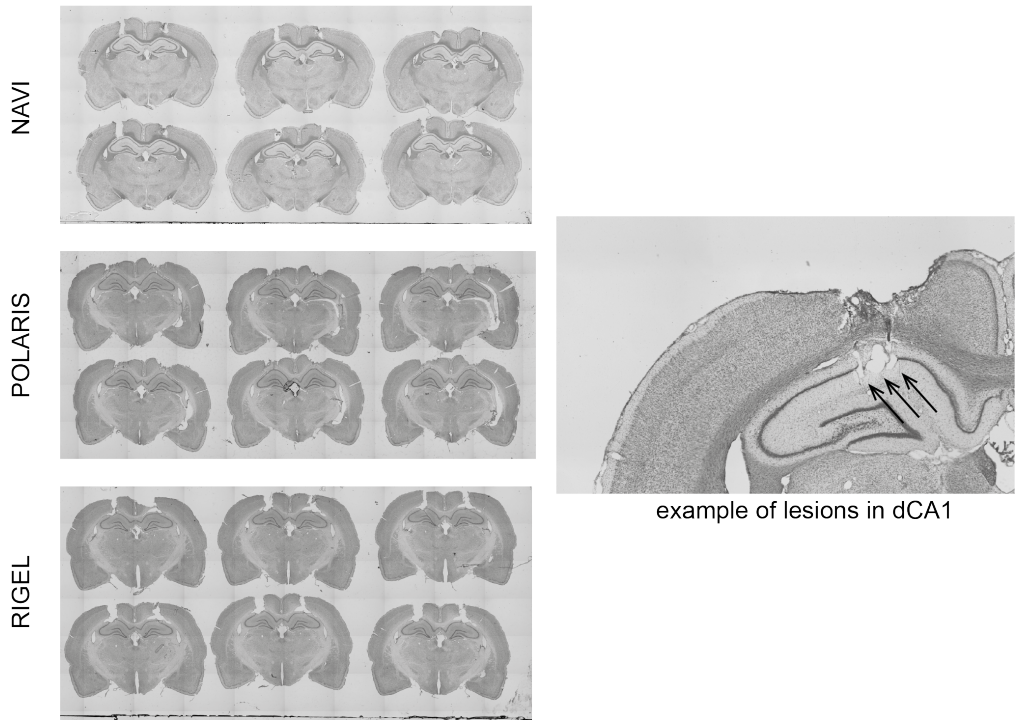

Figure 2.2: Histology: Location of the drives and tetrodes **Left:** hippocampal coronal slices for each of the rats that contributed to the ephys data. All drives were correctly positioned at the desired coordinates. Lesions and tetrode tracks are not always visible. **Right:** example of successful lesions in dorsal CA1

Chapter 3

Analysis Methods

3.1 Behaviour

3.1.1 Reward Preference

The magnitude of the reward preference of each animal for either the pure chocolate or its 1:1 diluted version was quantified by a preference index defined as:

$$preference\ index = \frac{\%\ volume\ consumed\ chocolate - \%\ volume\ consumed\ 1:1\ dilution}{\%\ volume\ consumed\ chocolate + \%\ volume\ consumed\ 1:1\ dilution} \tag{3.1}$$

with:

$$\%\ volume\ consumed\ (i) = \frac{volume(end\ of\ trial\ i) - volume(start\ of\ trial\ i)}{volume(start\ of\ trial\ i)} \tag{3.2}$$

The preference index measure described above in equation 3.1 will detect differences in the volume consumed of each reward, while by being weighted by the total amount of reward consumed. A preference index of 1 indicates a strong preference for chocolate while an index of -1 indicates a strong preference for the 1:1 dilution.

3.1.2 Position Data

3.1.2.1 Pre-Processing

Cleaning in time and space: The raw position data was loaded into MATLAB. The instantaneous position was defined as the middle point between the largest clusters of pixels with the highest light intensity for each LED colour, giving one X,Y coordinate at each timestamp. The following cleaning procedure was then applied to each subset of tracking data: The tracking data was plotted against time, and the period of interest was manually cropped (e.g. track 1). This selection was then plotted as an X,Y scatter plot, and a polygon was drawn around the track to eliminate false detections (e.g. reflective surfaces). The refined data was once more cleaned in the time domain before a track mask was defined for the purpose of linearisation. Data during rest and sleep epochs were not linearised. Missing data points during the run or rest periods were linearly interpolated in 2D.

Track linearisation: The distance from each data point to the corresponding track mask was calculated. Points further than 50 pixels away from any part of the track were discarded. A weighted average of the distance from the track was used to determine the animal's current location. This weighted average method ensures smoother tracking around corners. Now having a linear position for each timestamp on the current track, any large jumps in position (more than 40 pixels) were removed. The position data was aligned to timestamps with an exact inter-timestamp interval of 40ms (25Hz sampling rate), and any missing points interpolated to the nearest position. Finally, the position data was converted from pixels to cm.

Rest periods: Similarly, timestamps during periods in the sleep pot were interpolated to an exact inter-timestamp interval of 40ms (25Hz sampling rate), and the instantaneous velocity of each timestamp was calculated over the entire recording. Any points were the velocity inside the sleep pot exceeded 300cm/s were removed, after which the position data was interpolated once more to the nearest position and the velocity smoothed with a 4s moving average filter.

Lap Detection: A 10th order median filter was applied to the linearised positions. Laps were segmented as trajectories from one end of the track, to the other end, and back to the first zone, regardless of whether the animal retraced its steps at any point. Because each rat had their own approach and consummatory behaviour at the end zones, the exact location of stopping to collect the reward would change (more or less far from the edge). Therefore we implemented an automatic detection of end zones for each track. The dwell map was used to calculate the average dwell time in the middle 90% of the track. From each edge of the track, the first crossing of the dwell curve with this average value was set as the boundary delimiting the end zone.

Offline periods on the tracks: To detect immobility on the track, the instantaneous velocity was smoothed with a moving average filter of length 1s. Periods where the velocity was less than 5cm.s^{-1} were classified as immobility periods.

3.1.2.2 Sleep State Detection

Our sleep detection algorithm takes advantage of both tracking data and multi-unit activity. The smoothed instantaneous velocity was downsampled to 1Hz, and a time histogram of multi-unit activity over 60s bins was computed. Thresholds for the zscored number of spikes per time bin and zscored velocity were manually adjusted after visual inspection for each session, but the default values used were a zscore of 0 for the multi-unit count and a zscore of 4 for speed. Offline periods were defined as periods where the zscored multi-unit activity and velocity where respectively above and below their corresponding thresholds. This method was effective in detecting both SWS and REM epochs (see Figures 3.1 and 3.2), but did not provide a distinction between SWS and REM, partly due to the absence of Electromyographic (EMG) data.

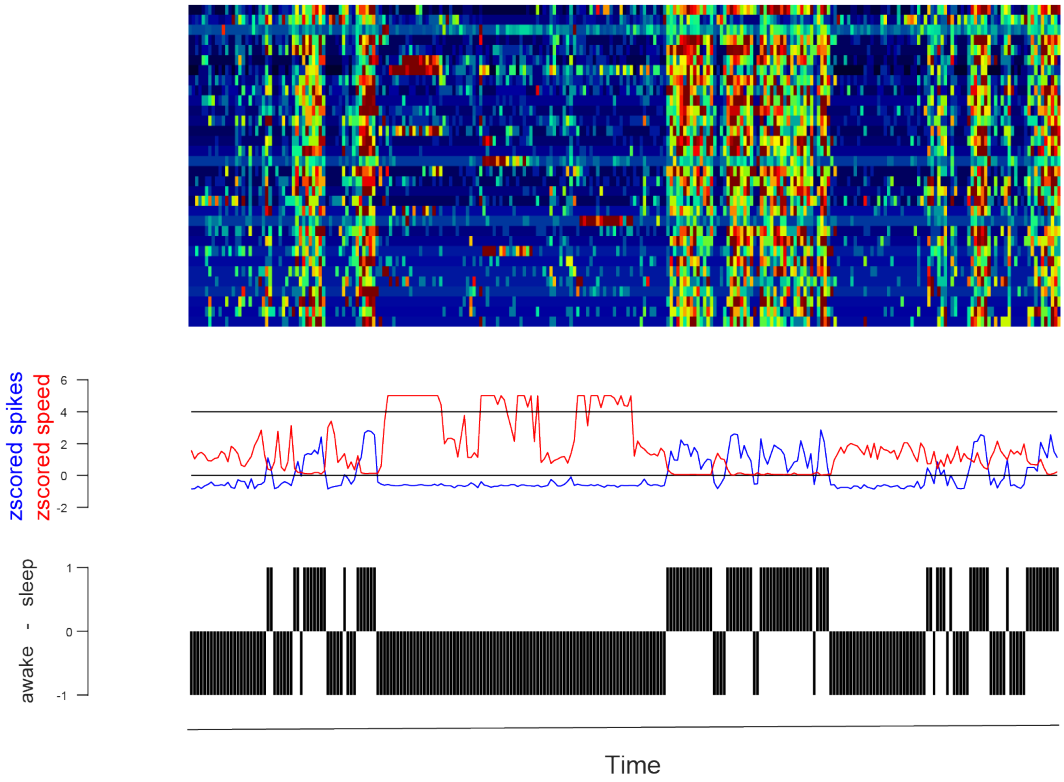

Figure 3.1: Sleep detection procedure. Example from one session.
Top: Multi-unit activity, disinhibition of the cells during offline periods are easily visible
Middle: Whenever the zscored velocity (red line) is below the threshold (0), and the zscore multi-unit activity (blue line) is above the threshold, sleep is detected.
Bottom: classified stages: sleep (1) or wake (-1)

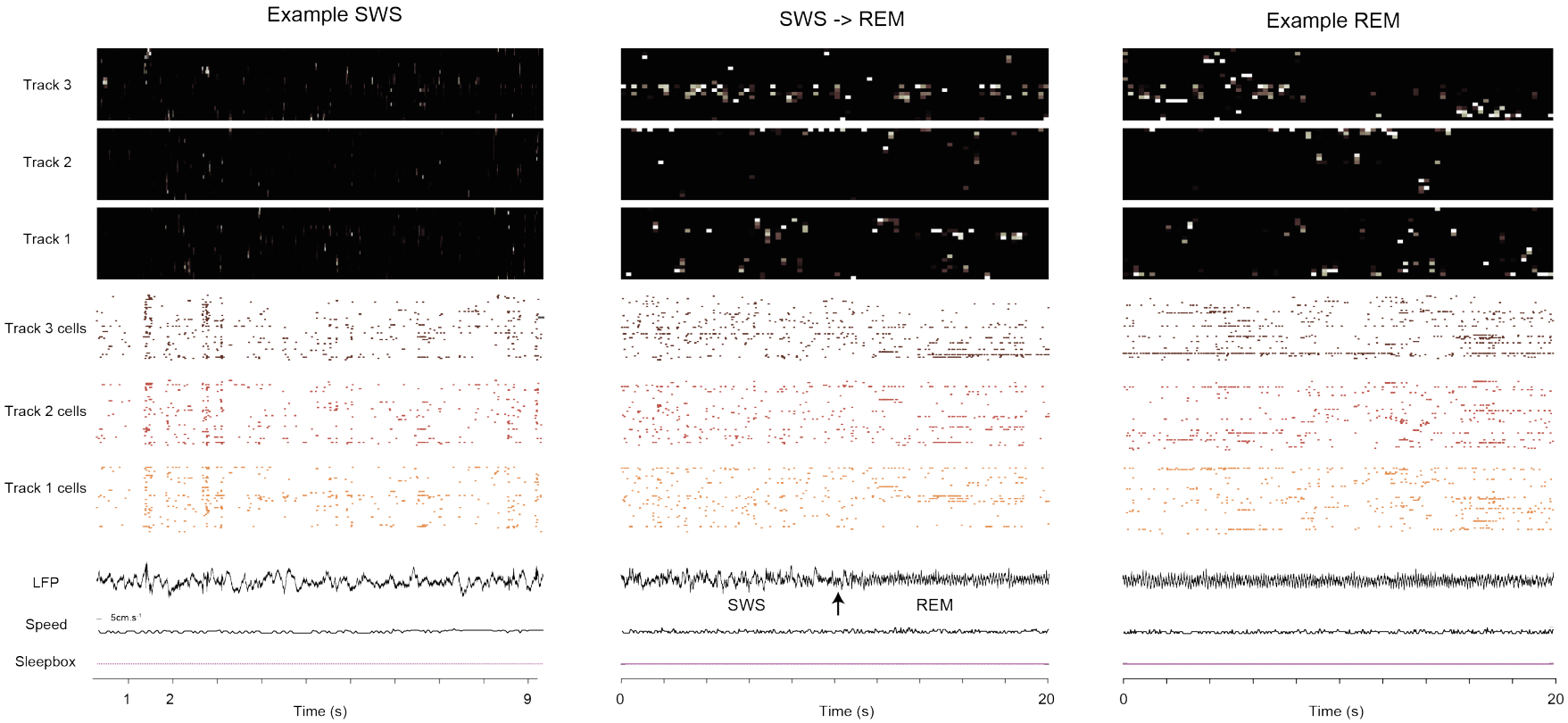

Figure 3.2: Example SWS and REM epochs in the sleep pot.
Top: Decoded probability matrices for each track. The time bins are different based on the time window at the bottom of the plot (250ms in the plots with REM, 20ms for SWS)

3.2 Electrophysiological Data Pre-Processing

3.2.0.1 Single Unit Isolation

Custom scripts were written to convert the recorded data from .csc (Neuralynx) to .dat, a format used by the semi-automatic clustering software KlustaKwik2. This algorithm clusters similar spiking activity over the entire recording session, in a coordinate system defined by the first three principal components of the waveforms' PCA (Principal Component Analysis) We used the open source Klusta Suite package and Klustaviewa for manual classification of the clusters as noise, multi-unit activity (MUA) or single units. A subset of sessions were clustered on UCL's Myriad HPC.

3.2.0.2 Deletion of Dropped Samples

In several sessions, some samples were erroneously dropped during recording by the Neuralynx recording system. However, a log of the samples dropped is automatically generated within the acquisition system to account for these errors. Based on this, raw wideband data and classified unit data were imported in MATLAB, any data from dropped epochs were removed and the remaining wideband data corrected by linear interpolation.

3.2.0.3 Single Unit Characterisation and rate map calculation

Single unit, multi unit spiking activity and their respective waveforms were loaded into MATLAB. Pyramidal cells were identified as units with a Half Width Half Max (HWHM) value larger than 500μs, and interneurons as units with an average firing rate on all tracks above 5Hz. All tracks were divided into either 2cm bins for finer rate map calculations or 10cm bins for bayesian decoding. The animal's position and each unit's spiking data were restricted to periods where the animal's velocity was between 5cm.s^{-1} and 50cm.s^{-1}. A histogram of both datasets for each position bin were then calculated to respectively create a dwell map and a spike histogram. Dividing the spike histogram by the dwell map gives the raw firing map for each cell. Position bins where no spikes occurred were set to 0. Next, a 10 point gaussian filter of width factor 2.5 (MATLAB's gausswin function) was applied to smooth the

finer resolution rate maps. No smoothing was applied to the rate maps used for bayesian decoding. Spatially tuned cells were selected according to the following criteria: a HWHM of a pryamidal cell, a minimum smoothed firing peak of 0.5Hz, a minimum raw firing peak of 1Hz, an overall mean firing rate lower than 5Hz on the tracks, and a non-zero information content (Skaggs Information). This subset of cells was ordered according to their peak location on the track for following analyses.

Skaggs information is calculated as:

$$I = \int_x \lambda(x) log_2 \frac{\lambda(x)}{\lambda} p(x) dx$$

where I is the information rate of the cell, x is the position bins, p is the dwell map - or probability for the animal to be at each position, and $\lambda(x)$ is the firing map. The mean firing rate of the cell is then $\lambda = \int_x \lambda(x) p(x) dx$ (Skaggs et al., 1994).

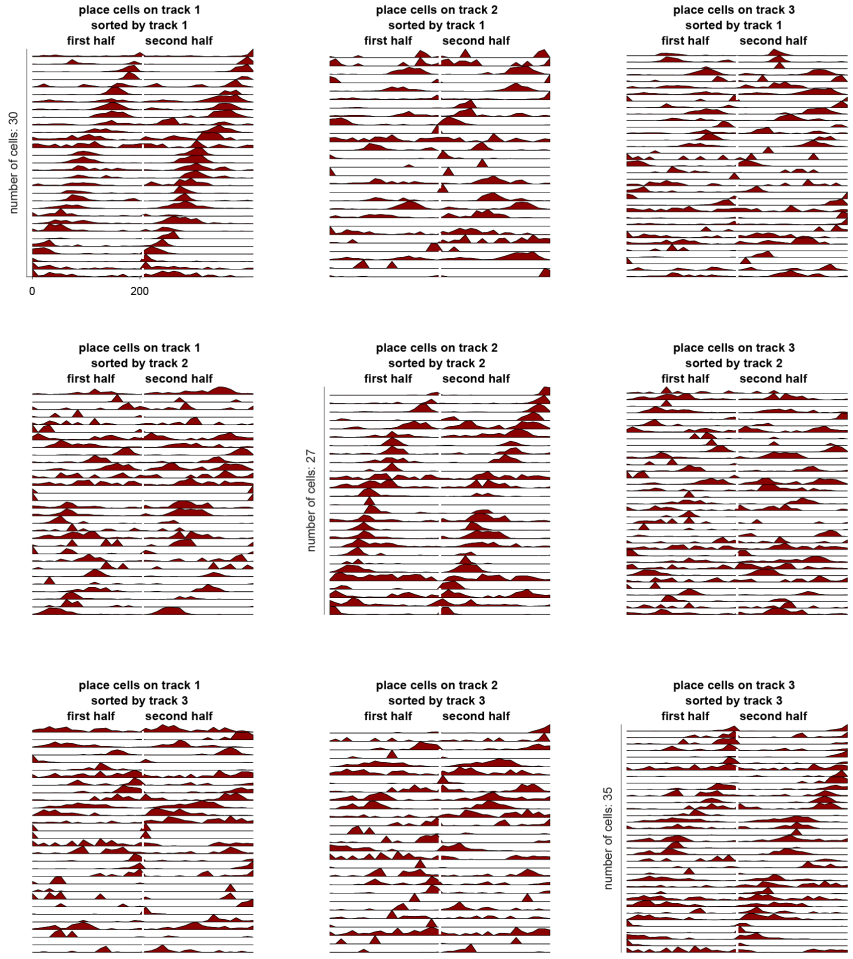

Figure 3.3: Example of rate maps from the session with least number of cells.
Normalised rate maps ordered by peak firing rate location, divided in the first and second half of exploration of each track to demonstrate within representation stability. Sorting order based on peak location of one track is applied to the rate maps of other tracks to demonstrate between representation remapping

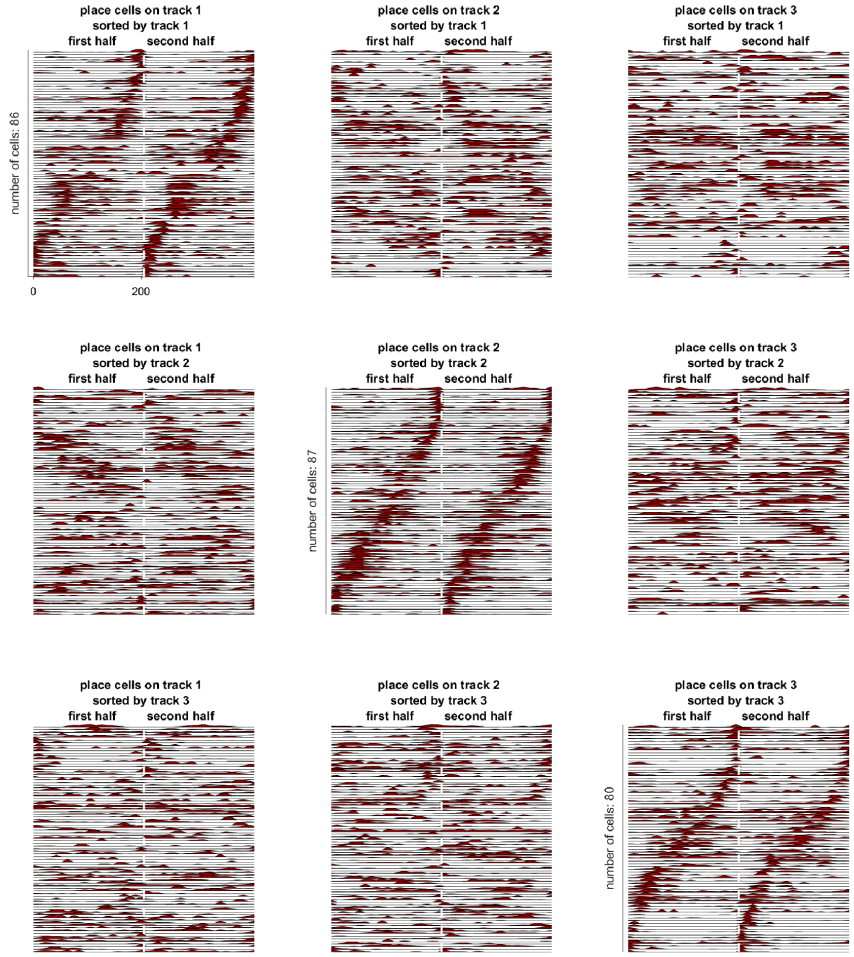

Figure 3.4: Example of rate maps from the session with most cells.
Normalised rate maps ordered by peak firing rate location, divided in the first and second half of exploration of each track to demonstrate within representation stability. Sorting order based on peak location of one track is applied to the rate maps of other tracks to demonstrate between representation remapping

3.2.0.4 LFP Extraction and Filtering

Power Spectral Density: The raw LFP signal was lowpass filtered ($<$ 500Hz), downsampled to 1kHz, and whenever possible, divided into offline and online sets (see 3.1) . Welch's power spectral density estimate (MATLAB's pwelch) of the signal using an Hanning window of 1024 samples and no overlap was calculated for each channel (and each state), and converted into dB/Hz: $power = 10log_{10}(PSD)$.

Selection of channels: The power spectrum was divided into frequency bands:

Oscillation	Frequencies (Hz)	Behavioural state
theta	[4 12]	online
ripple	[125 300]	offline
delta	[1 4]	offline
spindle	[9 17]	offline
high gamma	[40 100]	online
low gamma	[17 40]	online

To find the peak power for each channel for each band, the median power over the band was compared to the $1/f$ decrease in power over the frequency range, as estimated by the line drawn between the minimum and maximum power values for that range. If a type of oscillation occurs on this channel, the median will be above the $1/f$ slope. This was only computed for the relevant behavioural state, e.g. online periods for theta oscillations. The channel with the highest power for each oscillation was selected for further processing. In addition to the bands described above, we also selected the channel with the largest difference in normalised theta to ripple power, which is later used to inform on our detection of candidate replay events.

Filtering: Finally, the channels with the highest signal in each of the bands detailed above were bandpass filtered with a Finite Impulse Response (FIR - MATLAB's fir1) zero-phase digital filter (filtfilt) of order $round(\frac{6*sampling\ rate}{filter\ width})$ and a Hamming window with a cutoff frequency at the nyquist frequency $\frac{sampling\ rate}{2}$. The amplitude

of hilbert transform of the filtered signal was also zscored (MATLAB's zscore).

3.3 Decoding

3.3.1 Detection of Candidate Replay Events

Similarly to (Davidson et al., 2009a), we chose to detect candidate replay events using multi-unit activity. MUA activity was binned in 1ms bins, smoothed with a gaussian kernel (gausswin) of length 41ms and width factor of 2, and then zscored. A burst was defined as periods where the zscored MUA activity and ripple envelope amplitude exceeded a threshold of 3, with its edges defined by an adaptive MUA zscore threshold of 0, 0.25 or 0.5 within 300ms of its peak. The edge threshold was iteratively increased if the MUA did not fall down to 0 within the search window, up to 0.5, after which the burst was discarded. Bursts shorter than 100ms were discarded and bursts within 50ms of another neighbouring burst were grouped together and classified as a single event. Finally, bursts occurring when the animal's velocity was above 5cm.s^{-1} and with less than 5 spatially tuned cells active were discarded.

3.3.2 Detection of Reactivations

Reactivations were detected using the same method as candidate replay events, but with a minimum duration of 50ms instead of 100ms. They were not merged together, and no restriction was imposed on the number of neurons active.

3.3.2.1 Split Events

In an effort to optimise detection of replay events, and avoid a minority of events that were discarded due to noisy probability decoding at the beginning or the end of the event, we split candidate replay events in half. To do so, the minimum MUA activity in the middle third of the candidate replay event was used determine a natural midpoint to split the event in two segments. Both segments were decoded and tested for significance independently following the same procedure as 'intact' candidate replay events (i.e. same criteria including minimum duration, etc.), for the exception of an adjusted p-value threshold (see scoring section).

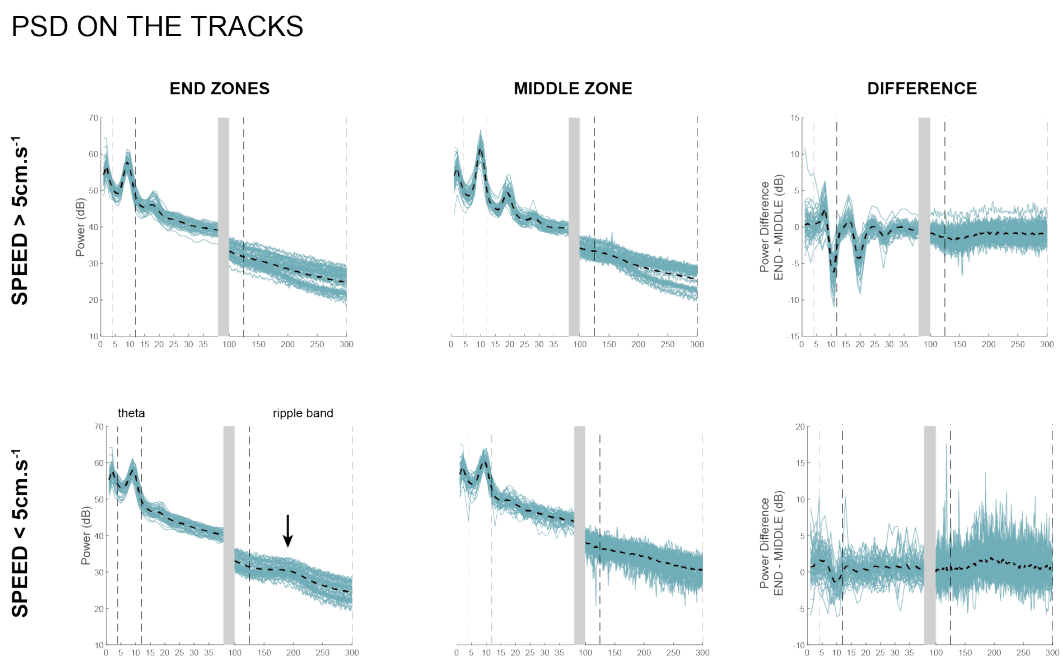

Figure 3.5: Power Spectral Density of the LFP for low and high speeds.
Top: locomotion speeds $\geq$ 5cm.s^{-1}, for the end and middle zones as well as the difference between the two. Theta is at a slightly higher frequency in the middle as the rats tend to run faster there, there is no power in the ripple band
Bottom: locomotion speeds $<$ 5cm.s^{-1}, for the end and middle zones as well as the difference between the two. Power in the theta band is reduced compared to higher speed, and an increase in ripple band can be seen, especially at the end zones where the rats consume the reward

3.3.3 Bayesian Decoding

Epochs where the animal was running (velocity $>$ 5cm.s^{-1}) were divided into 250ms bins, while candidate replay events were divided into 20ms bins. A histogram (MATLAB's histcounts) of the spikes from cells classified as spatially tuned cells (whose fields were binned more roughly into 10cm chunks) was calculated over those binned epochs, and along with the rate maps of those cells fed into a bayesian decoding algorithm: We take Bayes formula

$$P(A|B) = \frac{P(B|A) * P(A)}{P(B)}$$

which for our purpose translates to

$$P(position|spikes) = \frac{P(spikes|position) * P(pos)}{P(spikes)}$$

where $P(position|spikes)$ is the posterior, or the probability of the animal being at a specific position given the current observed spikes. $P(spikes|positions)$ is the likelihood, or the probability of observing these spikes at a specific position. $P(position)$ is the prior, or probability of occupying a specific position: which is set to 1 as we assume the animal is equally likely to be anywhere on the available tracks. $P(spikes)$ is the marginal likelihood, or probability of observing this number of spikes. For cells, this follows a Poisson distribution $P(n\ spikes\ in\ interval\ \tau) = \exp^{(}-\lambda\tau\frac{\lambda\tau^n}{k!})$, with λ the average firing rate of the cell. Hence 3.3.3 becomes:

$$P(position|spikes) = constant\ term * (\prod_{i=1}^{N} firing\ maps^{n\ spikes}) \exp^{-}(\tau \sum_{i=1}^{N} firing\ maps)$$

for $cell\ i \in 1,N$

Therefore for run epochs, τ is 250ms, while for replay events τ is 20ms. This algorithm was run separately for each track using all spatially tuned cells active on that track. Finally, the resulting estimated position $P(position|spikes)$ was normalised across environments, so that the summed probability for each time bin and across all three tracks together was equal to 1. Normalising the probability sum to 1 across all three tracks together rather than each track individually, allowed us to decode both which track and where on that track the animal was based on hippocampal activity.

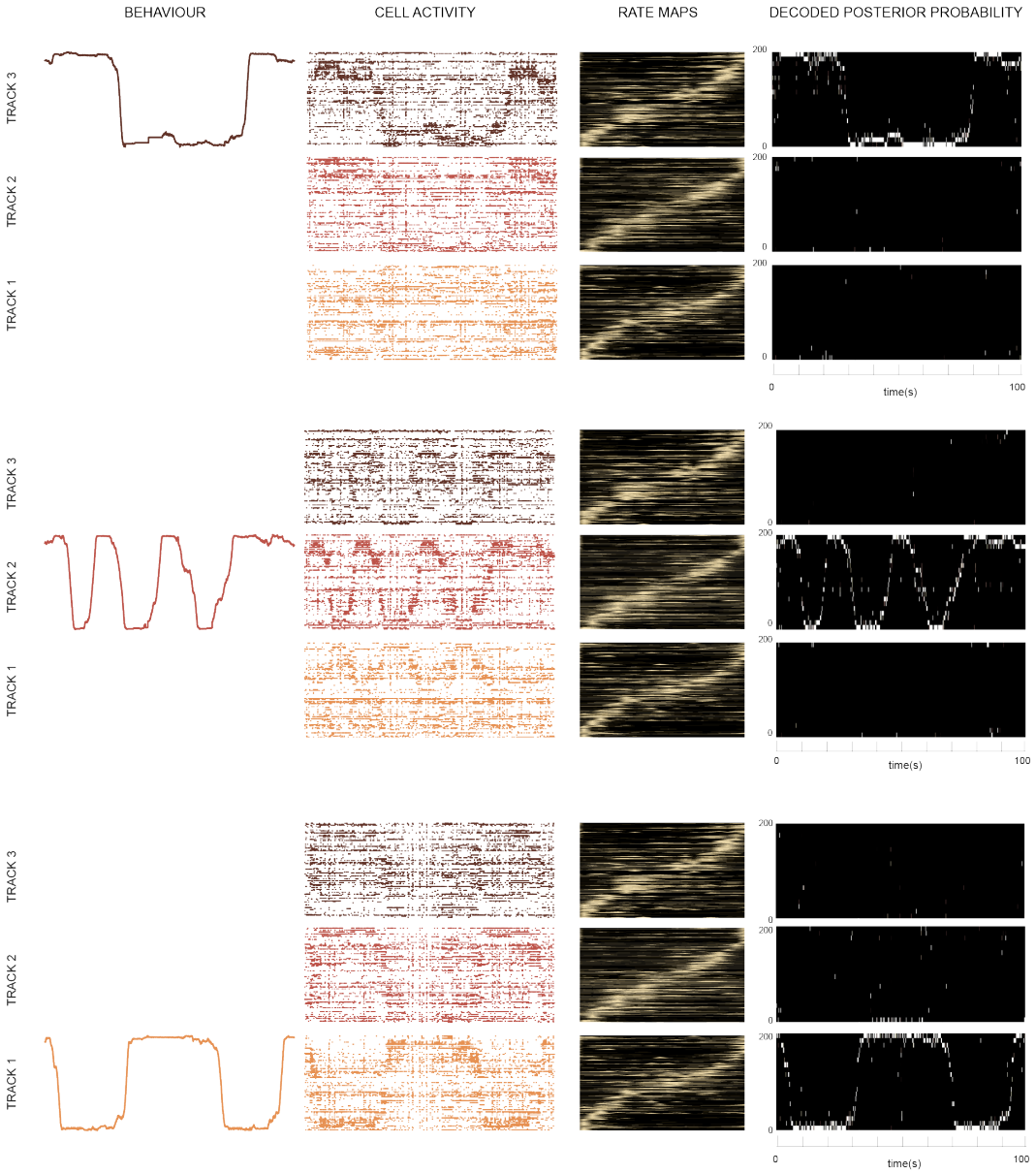

Figure 3.6: Example of bayesian decoding on each track.
The spiking activity and ratemap of each place cell is fed into a bayesian decoded to obtain a distribution of probabilities for each decoded time bin (250ms). The maximum probabilities (lighter pixels) provide an accurate representation of the behaviour on the track. For these plots, all running speeds are included, and bursts corresponding to candidate replay events can be observed.

3.3.3.1 Jump detection candidate replay events

To eliminate decoded events with very large jumps and only a few high probability decoded positions at the ends of the diagonal, we implemented a maximal jump criterion. First, very low probability bins ($p < 0.02$) were set to 0, then the maximum

decoded position for each time bin was identified. Any jumps larger than half the track that were not situated at the beginning or the end of the event (which can just be caused by an imprecise detection of even onset/offset) were identified. Events with two or more large jumps and less than 5 time bins with a maximum decoded probability > 0.02 were excluded. These criterion are quite lenient, but proved efficient at removing a large number of events which might otherwise display high correlation values.

3.3.4 Shuffles

To assess significance, the following three shuffles were run 1000 times on candidate replay events and their respective split candidate replay events.

3.3.4.1 Spike Train Circular Shift

For each candidate replay event, the spike count vectors for each cell (prior to decoding) were independently circularly shifted in time prior to decoding.

3.3.4.2 Rate map Circular Shift

Each rate map was circularly shifted in space by a random amount of position bins prior to decoding. There was a chance for a field to be split in two, with one part at one end of track and the rest at the other end of the track with this shuffle.

3.3.4.3 Decoded Position Bin Circular Shift

For each candidate replay event, the posterior probability vectors for each time bin were independently circularly shifted by a random amount.

3.3.5 Significance Testing

Candidate events and shuffled events were then scored using three different methods. The significant replay events displayed in the results chapter of this thesis were scored using a weighted correlation, but all candidate replay events were also scored using the remaining two methods as a sanity check.

3.3.5.1 Spearman Correlation

For each cell active during a replay event, only its median spike was kept for evaluating Spearman's correlation (MATLAB's corr).

3.3.5.2 Weighted Correlation

Weighted correlation is an adapted form of the Pearson's correlation, using the decoded posterior probabilities at each position i and time j as weights:

weighted mean:

$$m(x;prob) = \frac{\sum_{i=1}^{M}\sum_{j=1}^{N} prob_{ij}\, x_i}{\sum_{i=1}^{M}\sum_{j=1}^{N} prob_{ij}}$$

weighted covariance:

$$cov(x,t;prob) = \frac{\sum_{i=1}^{M}\sum_{j=1}^{N} prob_{ij}\ (x_i - m(x;prob))(t_j - m(y;prob))}{\sum_{i=1}^{M}\sum_{j=1}^{N} prob_{ij}}$$

weighted covariance:

$$cov(x,t;prob) = \frac{\sum_{i=1}^{M}\sum_{j=1}^{N} prob_{ij}\ (x_i - m(x;prob))(t_j - m(y;prob))}{\sum_{i=1}^{M}\sum_{j=1}^{N} prob_{ij}}$$

weighted correlation:

$$corr(x,t;prob) = \frac{cov(x,t;prob)}{\sqrt{cov(x,x;prob)cov(t,t;prob)}}$$

where x_i is the ith position bin, t_j is the jth time bin and $prob_{ij}$ is the probability at the position bin i and time bin j.

3.3.5.3 Line Fitting

A line-fitting algorithm similar to that of Ólafsdóttir et al. (2017) was implemented. 2D kernels representing all possible slopes between 100 cm.s^{-1} and 5000 cm.s^{-1} in 70 cm.s^{-1} increments (and their opposite, negative values) were created, given the temporal and position dimensions of the event to be scored. Those kernels were then convolved with the decoded posterior matrix, effectively testing all possible intercepts for all possible slopes. The sum of the probabilities lying within 10cm above or below each fitted is used as a goodness of fit score. The slope and intercept with the highest score defines the line of best fit. Mathematically it can be defined

as:

$$R(slope, intercept) = \frac{1}{n}\sum_{t=0}^{n-1} Prob(|pos(t) - (slope \times t \times T + intercept)| \leq d)$$

where t is each time bin, prob is the decoded posterior, pos is the position bin, t the time bin, d the maximum distance from the line of fit. Line fitting of candidate replay events was run on UCL's Myriad HPC.

3.3.6 Scoring of Replay Events

To determine whether a candidate replay event is significant or not, the score of the decoded event (whether it was weighted correlation, line fitting score or spearman correlation) was compared to the corresponding score distributions of the shuffled events. If the score of the candidate event was greater than the 95^{th} percentile of the distribution for all three shuffles then the event was considered to be significant. To account for multiple comparisons in the case of split replay events, segment scores had to be above 97.5^{th} percentile of the shuffled distributions. If a replay event was significant for more than one track the following measures were applied:

- if both segments are significant, but each for a different track, the event was divided into two events, one for each segment
- if the whole replay event was not dividable, the bayesian bias $\sum_i \sum_j prob_{ij}$ for each significant track was used to assign the event as significant for either track:
  - for 2 tracks: if the bayesian bias for one track is larger than 60%, it is selected as significant for that track
  - for 3 tracks: the bayesian bias for one track needs to be above 40% to be selected
  - if no track can be selected as the bayesian bias does not meet the conditions above, the event was discarded as non significant

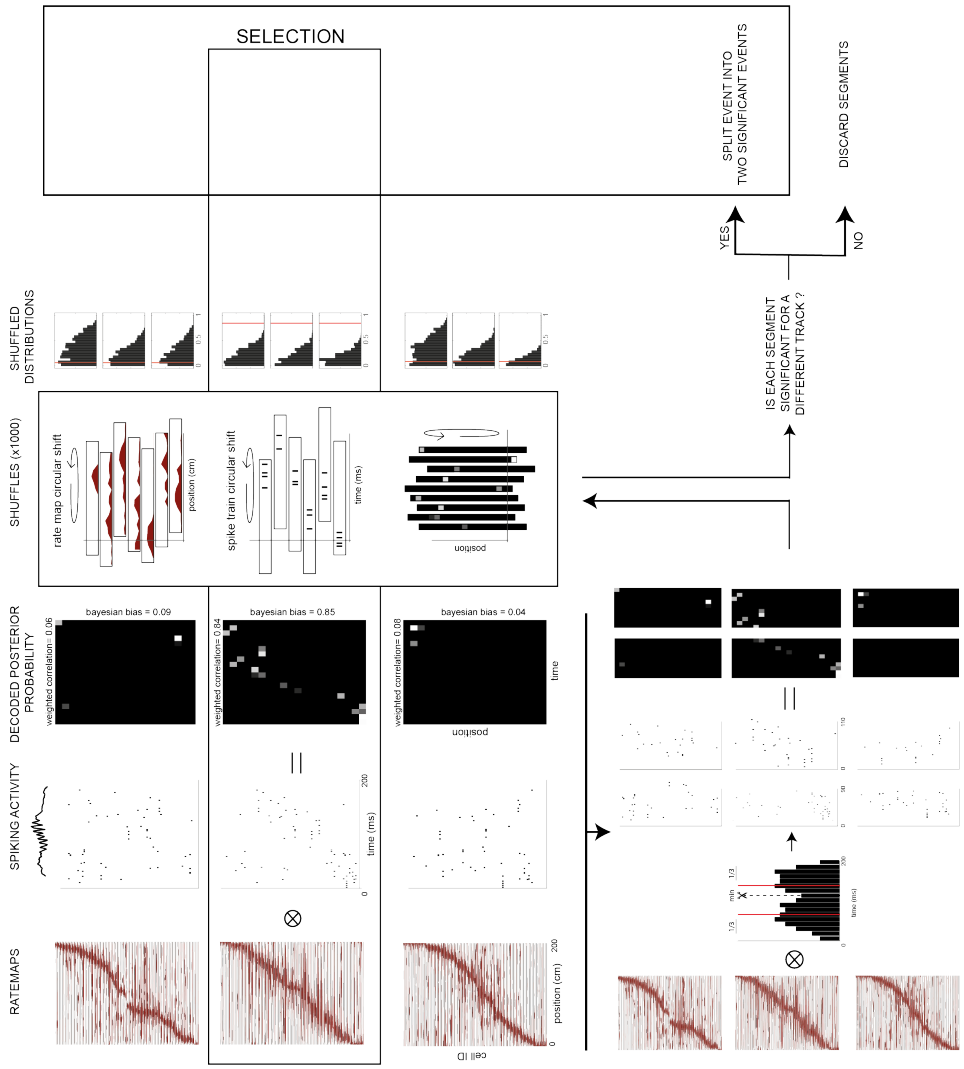

Figure 3.7: Decoding and shuffling procedure for replay events

3.3.7 Decoding Error

To assess the quality of our decoding algorithm, we used two quantification methods. The first one was aimed at determining how often the decoder correctly identified the current track, and the second method described how precisely the decoder identify the position of the animal on the current track.

Within track accuracy: percentage of small errors We compared the estimated position to the real position of the animal using a 'leave one out' procedure (van der Meer et al., 2016). Iteratively, rate maps were calculated for all laps except one (see 3.1.2.1 for lap detection), used to train the bayesian decoder along with the spiking activity (locomotion speed $\geq$ 5cm.s^{-1}) of the left out lap, to estimate the location of the animal on that lap. The decoding error was then calculated as the sum of the distance from the true position to the decoded position with maximum probability (see schematic 3.8). The percentage of time bins with a decoding error $\leq$ 20cm averaged over all laps was used as the quantification measure for within-track accuracy.

Between tracks accuracy: classification accuracy The rate maps calculated from all laps on each track were used to decode the spiking activity on other tracks to provide an estimate of the position of the animal (locomotion speed $\geq$ 5cm.s^{-1}). For each time bin, track identity was determined by the track with the maximum decoded probability. The percentage of time bins where the decoded track was the current track provided a measure of between tracks classification accuracy.
See Figure 3.11 for a summary of the values for these two measures for each animal, session and track.

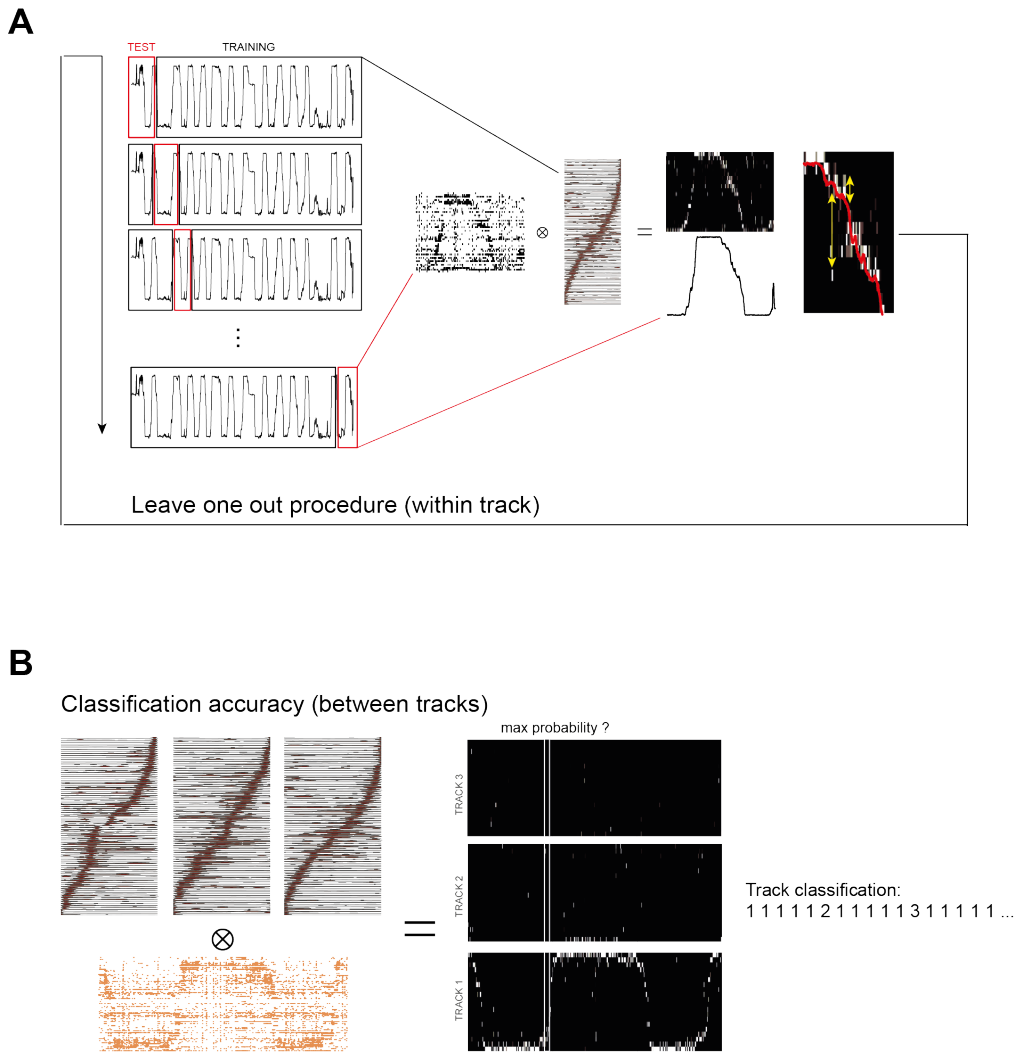

Figure 3.8: Schematics for decoding accuracy measures

3.4 Analysis

3.4.1 Remapping Analysis

Remapping analyses are usually carried out by comparing the correlation or overlap between the rate map of one cell and of another randomly chosen cell many times to create a distribution or correlations/overlap. If the correlation of the same cell's rate maps between epochs/environments/laps exceeds the 5^{th}/95^{th} percentile of that distribution, then it is globally remapping. Using these methods, rate remapping can only be quantified in cells that were not classified as globally remapping (Fuhs et al., 2005). In this scenario, a similar technique is used, but comparing values of the following difference metric:

$$D = \frac{\sum_x |f_1(x) - f_2(x)|}{\sum_x |f_1(x)| + |f_2(x)|}$$

where $f_1(x)$ and $f_2(x)$ are individual rate maps with their mean firing rate subtracted.

Such methods can be problematic for two reasons. 1) First, they depend on the population of cells recorded. Not only will a low number of cells will create large variations in such shuffling procedures, but also any bias in cell selection will be amplified. 2) Second. peak location and firing rate modulation cannot be individually quantified. In older studies, remapping is often visually assessed.

We designed a bootstrapping procedure to circumvent some of the issues from traditional remapping analysis methods. Our reasoning is that remapping between epochs should be assessed as a change in the selected property that exceeds the cell's intrinsic variability in the reference epoch. In other words, by creating a distribution of the values taken by said property (e.g. peak firing rate) during the reference epoch (e.g. on track 1), we can compare this distribution to the one built during the target epoch (e.g. on track 2). With this method, a cell that fires consistently with a median of 6Hz 95%CI [5-7]Hz on track 1 and 11Hz 95%CI [10-12]Hz on track 2 will be classified as peak firing rate modulated, whereas a cell that has a peak firing rate median of 6Hz 95%CI [2-15]Hz on track1 and 11Hz 95%CI [5-16]Hz on track 2

will not be classified as being rate modulated. Such an analysis can be conducted on any quantification measure of interest: peak firing rate, location, centre of mass, overlap... We implemented such an approach by resampling laps in a bootstrapping procedure. From the total number of laps N on a track, a random subset of N randomly laps (with replacement) was selected, and the rate maps of each cell as well as the desired measure (e.g. peak firing rate) were calculated from this subset of data. Repetition of this resampling a hundred times for each track led to robust parameter distributions. The medians of these distributions were compared to the 5^{th}/95^{th} percentiles of the other for each track pair. Either median exceeding either percentile led to the classification of the parameter being modulated.

This bootstrapping technique can also be applied in 2D, but we expect that it would require ample exploration of the environment, or stereotyped trajectories.

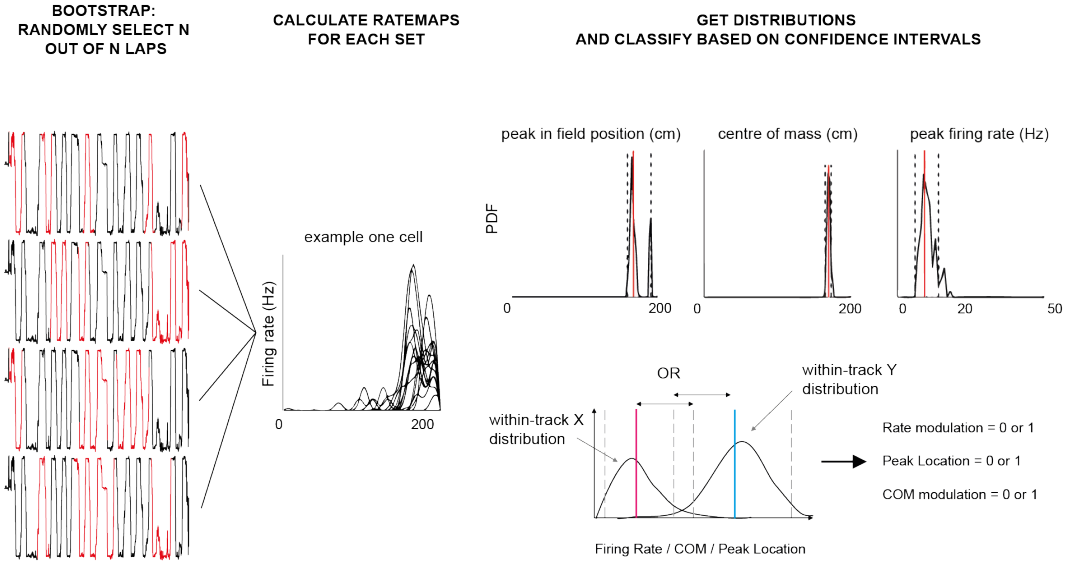

Figure 3.9: Schematic of the single cell remapping analysis

3.4.2 Map Stabilisation

To evaluate the rate of stabilisation of each representation with exploration, we computed the between-lap spearman correlation of single-lap computed rate maps. First we conducted an omnibus Friedman test, followed by post-hoc Conover tests with Holm-Sidak correction to identify when the difference between laps no longer was significant. Upon visualisation of these growth curves and based on Michon

et al. (2020), we decided to fit a sigmoid growth function:

$$corr(lap_i, lap_{i+1}) = \frac{b1}{1 + b2 \times \exp^{-(\lambda \times lap_{i+1})}}$$

where the correlation value evolves towards the asymptotic value b1 with an increasing number of laps, b2 helps set the starting value or offset of the curve, and λ is the stabilisation rate. Sigmoid curve fitting was done using R's nls (nlstools package), and the bootstrapped (ten thousand repetitions, nlsBoot) estimated values of the mean and confidence intervals were calculated for each between-lap correlation distribution. Between groups comparisons in the values of b1,b2, and λ were done using nlme.

Quantifying map stabilisation through correlations is only a partial assessment. Correlations track changes in the shape of place fields (location and distribution), but are agnostic to the scaling of firing rates. Place cells are known to be speed modulated (Huxter et al., 2003), and to track between-lap changes in firing rates, the rates need to be corrected for running speed first (Michon et al., 2020). This may be implemented in future work.

3.4.3 Classification Accuracy and Decoding Errors

Models

To provide a qualitative intuition of how decoding errors in position and track classification can lead to the results in chapter 4, we constructed models of three artificial decoders: an accurate decoder, a teleporting decoder and an uniform (random) decoder. For the specified number of position bins (20 in our case corresponding to 10cm bins tiling out the 2m tracks), ten thousand decoded positions were calculated for each 'real' position bin according to the specified model. The absolute distance between the decoded and real position bins were then used to generate probability distributions.

1. **Uniform:** for each position bin the decoded positions are uniformly distributed on the track
2. **Accurate Decoder:** for each position bin ***i***, the decoded positions are a sam-

pled from a normal distribution with a standard deviation of 0.1 and mean of

(a) $\boldsymbol{i} \pm \boldsymbol{1}$ for the middle 16 bins

(b) $\boldsymbol{i}$ for the end bins (2 bins each end)

A higher uncertainty in the decoder for the middle bins reflects what is observed in our data. We acknowledge that the parameter space has not been optimised for fitting the data and therefore other means and standard deviations for each bin may be better suited.

3. **Teleporting Decoder:** for each position bin i, the decoded positions are a sampled from a normal distribution with a standard deviation of 0 and mean uniformly distributed over all end positions bins, regardless of whether the current position bin i is in the middle or end. Therefore, middle bins are decoded at either ends, and end bins can be at the same or opposite end.

Normal distributions were truncated not to exceed the available position bin space. Confusion matrices were constructed by calculating the 2D probability distribution over combinations of decoded positions from different models.

Shuffling Controls

In chapter 4, we tested the effect of three different shuffles on decoding errors in the first few laps of exploration of a new track, aiming at selectively disrupting the distribution of cells on the current or alternate track:

1. **Cell ID shuffle:** The identity of the rate map corresponding to each spatially tuned cell was randomly shuffled for each alternate track independently, keeping the current track intact.

2. **Circular shuffle alternate tracks:** The rate map of each spatially tuned cell was circularly randomly shifted for each alternate track independently, keeping the current track intact.

3. **Circular shuffle current track:** The rate map of each spatially tuned cell was circularly randomly shifted for the current track, keeping the alternate tracks intact.

The cell ID shuffle conserves the over-representation of cells at the ends of the track but separated the spiking activity of a cell from its rate map, and allows us to test if a subset of cells is responsible for those decoding errors. Both circular shuffles change the distribution of place fields within the specified track, while keeping the spiking activity and rate map correspondence fixed. Given more computing time, this procedure could be repeated a thousand times for each session to effectively create a distribution, or a brute force approach could be implemented to enforce a uniform (or as closely as possible) rate map distribution on each track. However the current solution was satisfactory (see Figure 3.10).

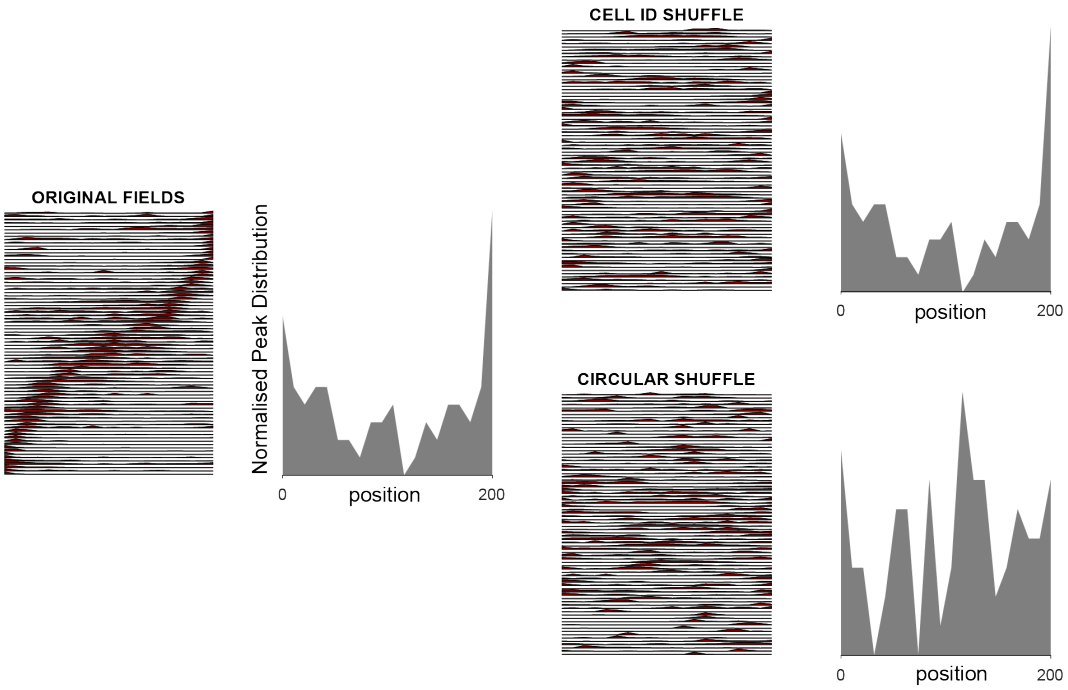

Figure 3.10: Effect of shuffles on cell distribution.
Plot of the rate maps sorted by their maximum firing rate in the original setting. The structure is disrupted in both shuffles, but the underlying distribution of peak firing rates in only disrupted in the circular shuffle condition

3.4.4 Significance procedure for the proportion of replay events

Comparing replay rates within and across sessions is non trivial. The number of detected replay events is not only dependent on the number of cells recorded, the spiking properties of those cells, and other recording or animal specific variability that are not of interest. Two approaches have been used in previous studies to circumvent those issues. The first one, used by Ambrose et al. (2016) is to fit Poisson GLMM to the replay rate with nested [sessions within rats] random intercepts. However, Ambrose et al. (2016) not only had a higher number of subjects and sessions (5 rats, 7 repetitions of each condition) than us, but also only had one track to decode from, with changes in conditions occurring within-day and track. We tried implementing a similar approach in R, but more data is required for the GLMM to provide reliable estimates. It is also unclear if it would be sufficient in compensating for small differences between tracks in the same session. The alternative approach that we implemented has been used by Carey et al. (2019), who also needed to compare replay rates between different portions of an environment, and changes in conditions occurred between days. In this case, comparing replay proportion for one section of the environment or track is more meaningful. The effect of the specified factor: reward (HIGH vs LOW) or recency (Track_M vs Track_N) was assessed by comparing the average observed difference between conditions to a bootstrapped distribution of randomly permuted labels. The zscore of the observed compared to the shuffled distribution of differences determined the significance level: $zscore(difference_{observed}) = \frac{difference_{observed} - mean(difference_{shuffled})}{std(difference_{shuffled})}$, using either a one-tailed ($normcdf(|zscore|)$) or two-tailed test ($2 \times normcdf(|zscore|)$) depending on the hypothesis. Importantly, significance testing is done across rats, not sessions.

3.4.5 Statistical tests

Statistical tests were done either using MATLAB or R, depending on the test's complexity and availability in both softwares. MATLAB was used for ttests, Mann-Whitney U, Wilcoxon tests and simple correlations, while Friedman tests, GLMMs, curve fitting and post-hoc comparisons including p-value adjustments for multiple

comparisons were done in R.

GLMM

To quantify the effect of experimentally-specified factors (reward, recency) on behavioural correlates (number of laps, speed...) we fitted GLMMs using the *afex* package in R. We used the function *mixed*, which estimates mixed models using *lme4* and calculates p-values for fixed effects. We used either Poisson models with a log link function or gaussian models using *lmer*. To establish which combination of factors best described the data, anovas were run on nested models. Estimated means and ratios were calculated with the *emmeans* package.

3.4.6 Summary of Data

Two rats (Ogma and Toliman) had a lower number of place cells recorded on the tracks and a poor decoding quality (percentage of within track errors $\leq$ 20cm: 30-40%, classification accuracy: 50-60%), and therefore were excluded from any electrophysiological analyses, but were still included for behavioural quantification. See Table 3.11 below for a summary.

Rat	Day	Maze Shape	Reward			Sleep PRE (min)	Number of Laps			Sleep POST (min)	Number Spatially Tuned Cells				Track Classification Accuracy (%)			Position Accuracy (%)		
							Track1	Track2	Track3		Total	Track1	Track2	Track3	Track1	Track2	Track3	Track1	Track2	Track3
Navi	1	linear	HIGH	LOW	LOW	0	27	10	12	65	56	37	27	27	84	83	87	68	47	54
Navi	2	W	LOW	LOW	HIGH	18	11	9	13	64	52	35	27	29	87	79	77	70	65	66
Navi	3	U	LOW	LOW	HIGH	12	16	16	19	64	50	33	28	26	80	86	79	71	57	63
Navi	4	inverted S	HIGH	HIGH	LOW	15	17	16	12	61	49	30	27	35	93	92	78	73	67	62
Navi	5	unequal U	HIGH	HIGH	LOW	10	29	17	14	70	52	30	38	26	83	79	91	74	73	59
Navi	6	L	HIGH	LOW	HIGH	19	12	15	16	69	44	30	25	29	85	80	69	65	64	64
							0	0	0											
Polaris	1	L	LOW	LOW	HIGH	29	9	11	11	91	63	48	49	53	83	85	80	68	66	71
Polaris	2	Linear	HIGH	LOW	LOW	34	12	19	10	82.5	110	86	87	80	92	92	93	77	68	71
Polaris	3	unequal U	LOW	HIGH	LOW	37	12	13	13	62	57	40	44	38	86	86	91	69	68	67
Polaris	4	W	HIGH	LOW	HIGH	8	11	10	15	92.5	57	43	40	40	85	86	89	69	68	70
Polaris	5	inverted S	HIGH	HIGH	LOW	20	14	9	13	96	97	67	73	72	86	91	91	78	68	74
Polaris	6	U	LOW	HIGH	HIGH	12	12	13	11	90	77	55	65	54	87	86	93	67	80	69
Rigel	1	Linear	LOW	LOW	HIGH	8	8	9	13	48	104	73	81	86	88	87	85	65	64	63
Rigel	2	unequal U	LOW	HIGH	LOW	20	9	11	11	43	106	68	74	67	93	88	92	71	68	78
Rigel	3	W	HIGH	LOW	LOW	29	13	13	11	46	82	52	50	57	92	93	90	75	73	75
Rigel	4	U	HIGH	HIGH	LOW	39	6	9	9	48	100	72	61	77	96	95	90	70	74	78
Rigel	5	inverted S	LOW	HIGH	HIGH	26	9	13	19	33	102	70	71	67	90	92	93	74	78	78
Rigel	6	L	HIGH	LOW	HIGH	23	15	13	25	30	98	62	71	58	93	86	84	69	75	78
Ogma	1	inverted S	LOW	HIGH	LOW		6	9	12											
Ogma	2	Linear	HIGH	LOW	LOW		12	8	9											
Ogma	3	U	LOW	LOW	HIGH		8	13	10											
Ogma	4	L	HIGH	HIGH	LOW		14	15	13											
Ogma	5	W	HIGH	LOW	HIGH		13	11	17											
Ogma	6	unequal U	LOW	HIGH	HIGH		11	13	27											
Toliman	1	inverted S	LOW	HIGH	LOW		13	8	9											
Toliman	2	Linear	HIGH	LOW	LOW		15	14	14											
Toliman	3	U	LOW	LOW	HIGH		13	10	15											
Toliman	4	unequal U	LOW	HIGH	HIGH		7	21	23											
Toliman	5	L	HIGH	LOW	HIGH		25	19	30											
Toliman	6	W	HIGH	HIGH	LOW		25	29	20											

Figure 3.11: Summary of behavioural and recording data

Chapter 4

Generalisation vs Differentiation of Novel Maps

4.1 Brief Introduction

While there is much theory and some evidence on how distinct regions of the hippocampal formation may contribute to differentiation and generalisation of hippocampal maps through pattern separation and completion, less is known as to how past memories may interact with novel experiences within the critical time window where they are formed.

A novel environment may have overlapping features with previous ones, whether because of its close temporal proximity, common sensory inputs, or identical task rules. One way to assess differences between their hippocampal representations is to look at place field remapping: the process by which place cells form, withhold forming, or see key properties of their place field altered - such as peak firing rate or position - when a new environment is encountered.

Geometry-morphing experiments between environments by Leutgeb et al. (2005, 2004); Lever et al. (2002), measured the remapping behaviour of place cells to show that the neural representation of highly overlapping environments become distinct with familiarity and experience. However, it was also shown that those representations resembled more closely the most familiar environment when experience on the novel one was limited (Leutgeb et al., 2004; Lever et al., 2002; Wills et al., 2005).

This initial, labile period when representations are being formed is short lived. Place fields quickly emerge and stabilise for the long term. Work by Feng et al. (2015) demonstrated that fields emerge in the first couple of laps on a linear track, and only take another few laps before stabilising. Cells are also rapidly recruited in processes that are thought to increase their co-activation and are necessary for the formation of memories: namely, theta sequences and replay. Place cells start to independently precess on the first lap of a novel environment, and precess in sequence by the second lap. Local replay has been observed as early as the first lap. Further supporting the idea that previous memories are not left in the past, awake non-local replay has been reported, whether it is of remote parts of the environment (Davidson et al., 2009b; Ólafsdóttir et al., 2017), of previous strategies (Carey et al.,

2019; Gupta et al., 2010), of never-experienced paths (Gupta et al., 2010), or of previous physically-separate environments (Karlsson and Frank, 2009a). However, these studies did not repeatedly test series of novel environments. The latter was tested in an study by Frank et al. (2004), but it did not include replay analysis.
Finally, it has been suggested that the hippocampal sub-populations of slow-firing 'rigid' and fast-firing 'plastic' cells (as described in Grosmark and Buzsáki (2016)) may respectively contribute to generalisation and differentiation of experiences. Plastic cells are recruited to build on a skeleton structure of co-activating rigid cells which exists already during sleep prior to the experience, and see their participation in replay after learning to be selectively increased.

In light of all of the findings reviewed above, we set the following aim: **Can we find evidence of hippocampal proactive interference at a systems level: the process by which previous memories shape the representation of novel experiences ?**

- Contextual uncertainty is highest at the onset of exploration of a novel environment, and may be reduced by knowledge accumulation through exploration. Therefore, if representations are initially more similar to one another because of shared environment features, and only later evolve into distinguishable entities: could this crucial period at the beginning of a new experience be the time window for generalisation between memories to occur during awake states?

  Sub-Aim1: Identify the time window where the novel representation is not yet stable.

- We hypothesise that "recall and compare" of previous overlapping contexts - thus supporting differentiation and generalisation - should occur more frequently in this initial time window.

  Sub-Aim2: Quantify the ratios of local to remote replay as a function of exploration.

- If rigid cells participate in generalisation, they should participate in multiple

contextual representations. We expect for place cells from previous maps (remapping) and emerging cells (cells integrated into the new representation) to have different dynamics on the novel track.

Sub-Aim3: What are the emergence and stabilisation dynamics of place cells based on their remapping properties ?

Sub-Aim4: Are rigid cells, place cells from previous representations, and do they encode most commonly encountered features ?

In this chapter we present data from a large number of novel environments, with multiple experiences being recorded each day. We take advantage of a high place cell yield to study both remapping and replay, to investigate how past and present may interact during novel map creation.

4.2 Results

We recorded dCA1 pyramidal cells in three rats while they successively explored three novel tracks per day by running back and forth to collect a small amount of liquid at the ends of the track. Each animal was exposed to a total of 18 novel environments over 6 days. The geometry of the tracks (each 2m long) was identical within days but dissimilar across. Therefore, a total of 6 different geometries were used, and bends on the track formed from 0 to 3 corners depending on the geometry (see Figure 4.1 A). Global and local cues, location within the recording room, partitions between tracks, as well as reward quality were used to create contrasting sensory environments. The animals were placed for 10 minutes in a view-shielding sleep pot between exposures (see Figure 4.1 A). None of the results in this chapter were affected by the change in reward quality between tracks. For a description of the influence of reward on memory encoding and consolidation, see 5. For a summary of the data, including the number of cells recorded, see Table 3.11.

4.2.1 Behaviour and Remapping Between Environments

First, we quantified the degree of remapping between the environments, and therefore the whether the experimental protocol successfully led to the creation of distinct, yet overlapping, neural representations. We compared the rate map correlations of all cells (2cm bins) between even and odd laps, within and between environments (see Figure 4.1 B). As expected, the within-track correlation value (mean 0.77 ± 0.01) was higher than between-track (mean 0.30 ± 0.007), and the latter was comparable across all track pairs, giving a first hint that the representations were indeed neurally distinct. For a more thorough analysis, all cells with at least one place field on any track were processed through our remapping classification algorithm (see 2) and were classified as either: 1. only active on one track, 2. undergoing peak in-field rate modulation between tracks, 3. undergoing place field Centre Of Mass (COM) modulation between tracks, 4. a mixture of both (2) and (3), or 5. not modulated between tracks. In short, a bootstrapping procedure to calculate rate maps of a thousand randomly chosen subsets of laps led to a distribution of peak firing rate, COM and overlap for each cell on each track. If the median of either

track parameter distribution was above/below the $95^{th}/5^{th}$ percentile of the other, that parameter was classified as modulated.

Our recording protocol led to ample remapping between environments: 46% of cells did not create a new place field when transitioning from one track to another. Of these cells, 50% were unique to one track out of three. The remaining 54% of the total population remained spatially tuned after transitioning to a novel track. The near-entirety of cells active on both tracks underwent either peak firing rate, COM location modulation or a mixture or both: less than one percent exhibited neither form of modulation (see Figure 4.1 C). Change in COM and peak rate was comparable across track transitions and centred around zero (see Figure 4.1 D). We made use of a bayesian decoding approach (see 2) to estimate the probability of the animal being at a particular location anywhere on any of the tracks for each 250ms time bin of exploration given the cells' activity and the rate maps calculated from all laps on each track. After normalising across all three tracks, the maximum decoded probability indicated which track and at which location the decoder estimated the animal to be on. We observed an accurate track classification on 85% of all time bins, while a leave-one-out procedure using rate maps from the current track only (see 3) revealed that on 80% of time bins the decoded location was less than 20cm away from the animal's true position (see Figure A.10). Therefore, if more than three quarters of the recorded cells were shared between multiple tracks, their peak rate and COM shifted sufficiently to create distinct representations that we were then able to use to infer the animal's position accurately.

Consistent with the literature on over-representation of salient locations (Bourboulou et al., 2019; Danielson et al., 2016; Dupret et al., 2010; Gauthier and Tank, 2018; Hollup et al., 2001; Sato et al., 2020), the distribution of cells within each environment was not uniform, and place fields tended to be more densely distributed near the ends of the track. The density of fields at the end and corners was compared against the remainder of the track (any linear portion not at the ends nor within 10cm of a corner). The percentage of cells per cm at the ends was statistically higher than at corners and the rest of the track (kruskal-Wallis test followed by multiple com-

parisons with Dunn-Sidak correction, see Figure 4.1 E). There was no difference between corners and the rest of the track. Ends and corners representing a smaller portion of the track (20% and 10%-30% depending on the number of corners), there were more fluctuations in the cell density estimate, an effect further accentuated by the number of spatially tuned cells recorded on said track. In order to make stronger inferences about these effects, the percentage of cell per cm was regressed against the number of cells recorded. If for end zones there was a significant positive correlation between the two (quasibinomial glm, estimated effect= 0.01. s.e.= 0.00, t val= 3.19, $p < 0.001$), this correlation broke down for corners (quasibinomial glm, estimated effect= -0.01. s.e.= 0.00, t val= -1.55, p=0.13), going against the idea that low sampling may be the cause for not observing corner over-representation.

Experimental data suggests that place fields are not stable from the first lap. Rather, it takes some amount of experience not only for cells to hone their spatial tuning, but also for their coordinated firing to lead to the emergence of theta sequences and replay (Feng et al., 2015; Foster and Wilson, 2006). To assess the amount of experience needed for the representation of each track to stabilise, we calculated the Spearman correlation of all rate maps between consecutive laps. Friedman and post-hoc Conover tests revealed that after the fourth or fifth lap, there was no longer any significant difference in correlation values (see Figure 4.1 F), indicating a representative amount of experience required for representation stability - keeping in mind that any peak rate changes cannot be revealed by a such an analysis.

To summarise the findings of this section, our protocol was efficient in creating distinct yet overlapping representations between tracks, as shown by the presence of both globally remapping and track-specific cells and our ability to individually decode each track. We observed a bias in the density of place fields towards the ends of the track. Each representation took about five laps to become stable, and in the few next sections we further investigate what happens within this initial window of time.

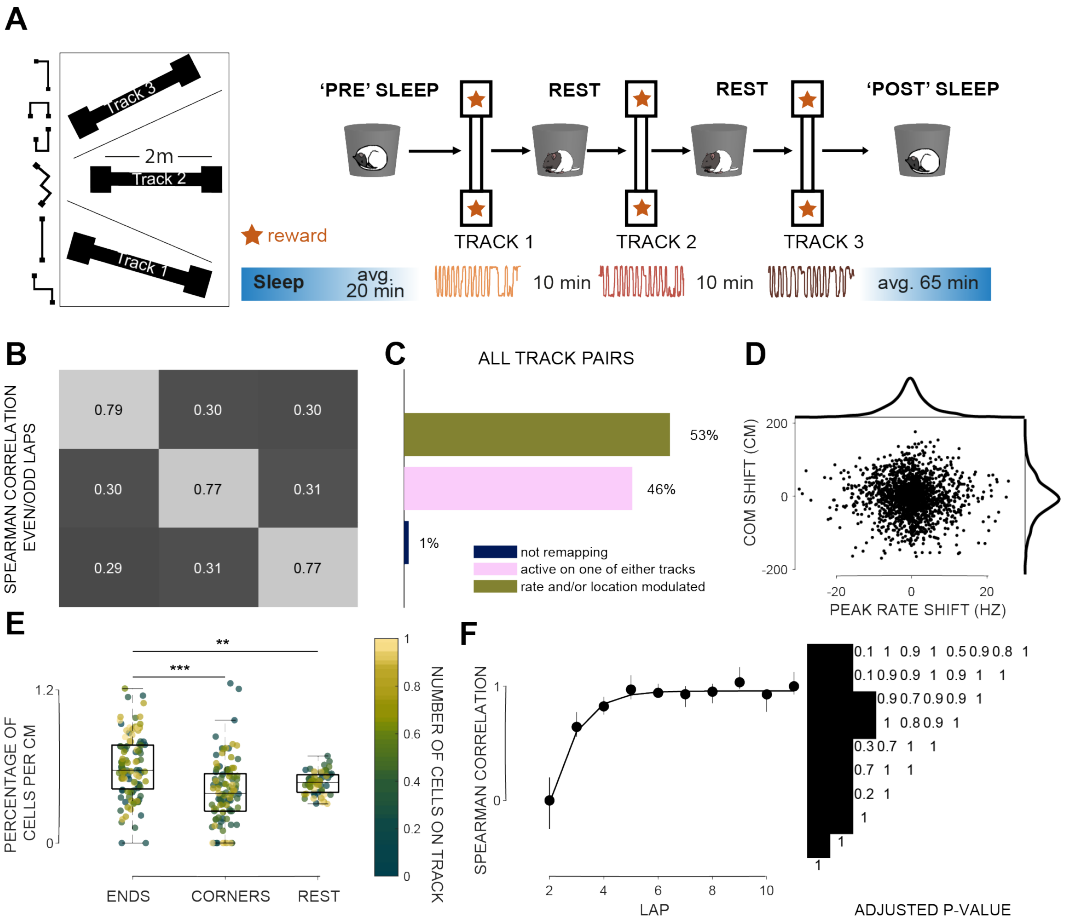

Figure 4.1: Contexts are Differentiated and Cells Remap Between Them

A: Schematic of the protocol each day.

B: Average ratemap correlation between all possible track pairs: within-track comparison of even vs odd laps on the diagonal, and between-track comparison of even vs odd laps (upper triangle) or odd vs even (lower triangle)

C: Cells active on either or both tracks for each possible track pair, categorised depending on the presence or absence of rate and peak location modulation as well as peak activity $>$ 1Hz on track, leading to a percentage of active cells (%) for each category

D: scatter and histograms of COM shift and peak rate change for each cell spatially tuned on at least two tracks. Cells active on three tracks appear twice.

E: Percentage of cells recorded per cm on one track, divided into end zones, corners and the rest of the track

FLeft: Spearman correlation between laps for all rate maps as a function of the number of laps so far. Right: Holm-Sidak adjusted p-values for between lap differences in Spearman correlation, Friedman with post-hoc Conover tests

4.2.2 Temporal Dynamics of Map Differentiation

As a first approach to dissect how maps stabilise within the first few laps, we focused on our ability to decode the different tracks (250ms time bins, locomotion speed $>$ 5cm.s^{-1}). We focused on two types of decoding errors : wrong track classification and location errors on the current track. The percentage of incorrect track classifications (i.e. the maximum decoded probability after normalising across all tracks lies on another track than the current one being experienced) decreased during the first three laps before reaching a stable value (see Figure 4.1 F and Figure A.16). Interestingly this decay was slower at the ends of the track than in the middle (see Figure 4.2 A, Wilcoxon signed rank test $p < 0.001$), even if the rats spent more time in there. On the other hand, the percentage of accurate location decoding (decoded location is within 20cm of true location) increased over the first three laps before reaching steady state (see Figure A.15, Friedman test with posthoc Conover test and Holm-Sidak multiple comparison adjustment). From the first lap onward, end zones have a higher location accuracy than the middle portion of the track (Wilcoxon sign rank test $p < 0.001$, see Figure A.14). The ability to distinguish between tracks and being able to locate oneself within a track therefore seems to precede the stabilisation of individual rate maps.

Because all tracks shared the same geometry, the corresponding maximum decoded position on alternate tracks can be compared to that of the current tracks and the actual position of the animal for each time bin, regardless of the track classification. The start and end value of the tracks (0 to 200cm) were chosen to maximise the population vector correlation values between tracks and minimise orientation errors.

We looked at time bins with a classification error, and retrieved what was the maximum decoded position on the alternate track compared to the animal's true position. Time bins where the real position fell within the end zones or the middle zone were separately analysed.

The decoded position during track classification errors clustered near the end zones (decoded position on the track that the rat was not currently on). This was observed for both errors generated where the rat was in either the end zones or middle re-

gion of the track (see Figure 4.2 B and C). We are confident that those results are not due to the spurious inclusion of replay events: as assessed by the lack of ripple band power above 5cm.s^{-1} (see Figure 3.5) and the replication of those results with a minimum speed threshold of 10cm.s^{-1}. Looking at the absolute distance between the real position and the maximum decoded positions on the current and alternate track (Figure 4.2 C), the decoded position on the current track was a short distance away from the real position, but the decoded position on the alternate track "teleported" the animal to either ends of the track, regardless of whether the real position was in the end zones or the run zone. A small amount of teleportation to the ends also occurred to the decoded position on the current track.

The average bayesian bias (sum of decoded probabilities on desired track divided by the sum of decoded probabilities across all tracks, see 3) of the detected track equaled 80% for incorrectly classified time bins and 90% for correctly classified time bins. There was no difference in the number of spikes emitted or active cells per time bin with classification, suggesting that - combined with a high bayesian bias - the shift of activity towards the end zones is not the result of very few cells suddenly bursting (see Figure 4.2 D). Unlike for replay analysis, track classification is not further informed by testing for the sequential firing of cells, therefore there is an increased probability of 'decoding' tracks that have not yet been experienced. To account for this, we fed our bayesian decoder the rate maps for each track in an iterative manner so that it did not have access to future representations. The proportion of time bin classifications for the current or remote (past) tracks respectively increased and decayed over the first few laps, leading to an overall decrease in errors. Remote track classification was comparable for tracks experienced right before (n-1) or 2 tracks before (n-2).

To better understand this finding and aid visualisation, we generated artificial decoded positions from three models: an accurately decoding model, a 'teleporting to the ends' model and a random decoder (see full model description 3). Combining the different models with the aim to reproduce the confusion matrices in Figure 4.2 C, we found that the data can be explained by combinations of the accurate and tele-

porting model on the current track with a combination of teleporting and random model for the alternate track in the end zones. For the middle zone the data was best explained by a combination of accurate, random and teleporting models for the current track and a teleporting model for the alternate track (see Figure 4.2 F). These mixtures of models, if they provide an acceptable qualitative description of the data, can be further refined and future work will focus on calculating an estimate of the contribution of each.

We have shown that the activity of cells during the first few laps is biased in an unexpected way, leading to windows of "teleportation" where the activity of cells, regardless of the animal's current position, resemble that of the end zones of previous tracks and sometimes the current one. This puzzling phenomenon might be the result of similarities between past representations and novel ones during the labile period of the first few laps. We hypothesised that over-representation of the end zones by place cells might be a good candidate contributing to our observation: more cells are active in these zones, which are more experienced and are characterised by a better position decoding accuracy during correct track classifications (see Figure A.12, two sample Kolmogorov-Smirnov test: $p < 0.001$). A preliminary analysis also suggests that over-representation of the end zones is already present during the first few laps (see Figure A.13), a property consistent with a previous study (Sato et al., 2020).

We shuffled our data in three different ways to test our hypothesis. The first shuffle, a cell ID shuffle of the alternate tracks, disrupts the association between the spiking activity of cells and their rate maps, while preserving the distribution of place fields on the track. The percentage of track classification errors over the first 5 laps was scaled down, but the 'teleporting to the ends' property of both the alternate and current tracks was kept intact (Figure A.11 A). The second shuffle circularly shifted the position of the place fields within each alternate track by a random amount, disrupting the distribution of place fields (Figure A.11 B). The percentage of track classification errors was again scaled down, this time removing teleportation to the ends effects on the alternate track (but not the current one). In-

stead, the distribution of decoded positions became uniform, as would be expected from a random decoder. The third shuffle was a circular shuffle of rate maps of the current track, keeping the alternate tracks unchanged (Figure A.11 C). The percentage of errors at the end zones increased, but stayed similar for the middle zone. As expected, teleportation to the ends was abolished for the current track but not the alternate tracks.

These results exclude the attribution of teleportation to the ends effects to a small set of cells and confirms the necessity of over-representation of place fields at the end zones on both tracks for it to occur.

The hippocampus may not function as a bayesian decoder, yet this approach reveals that there may be some experience-dependent confusion between tracks and positions during the first few laps, caused by similarities between representations. We further investigate how place cells change during this crucial time window in the following section.

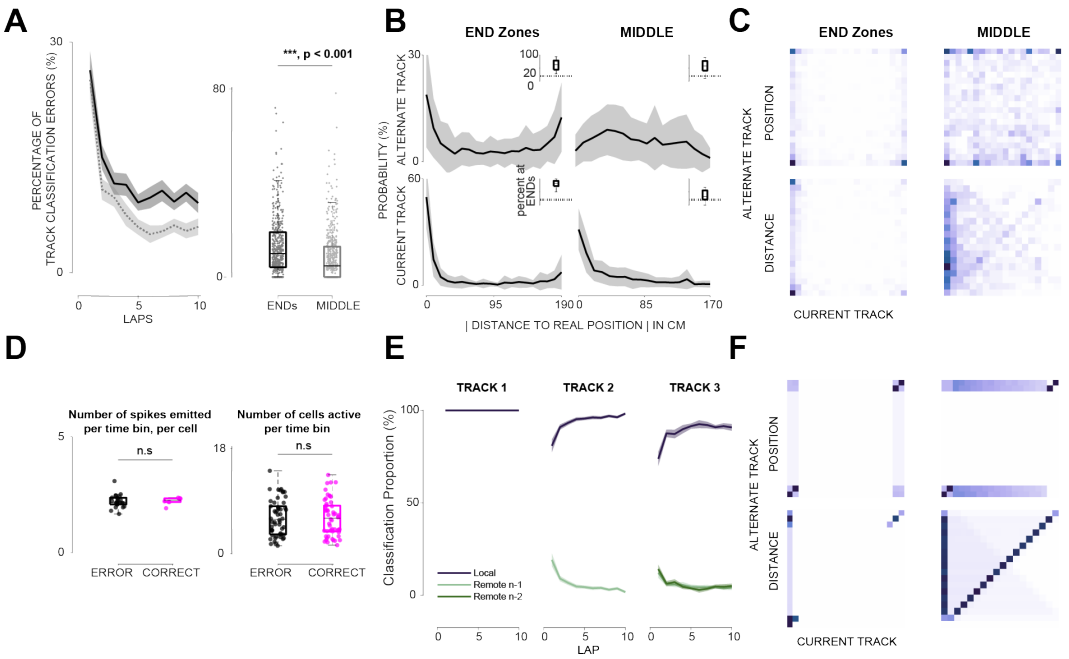

Figure 4.2: Incorrect Bayesian Track Classification Decreases over the First 5 Laps and the Corresponding Decoded Positions are Biased Toward the End Zones

A: Left: Percentage of incorrect track classification for each lap, divided by end and middle zones. Right: boxplot and raw percentage of errors across all laps for end and middle zones

B: Absolute distance between decoded and real positions during incorrectly classified time bins for end zones and middle zone, on the alternate track (track with maximum probability) and current track. Inserts: percentage of time bins where the decoded position falls within the end zones. A random distribution leads to approximately a value of 20% **C:** Top: probability matrices of decoded positions for the current versus alternate tracks, for end and middle zones Bottom: probability matrices for the distance from the real position, for the current versus alternate track

D: Left: Number of spikes emitted in an incorrectly classified time bin versus in a correctly classified time bin Right: Number of cells active in an incorrectly classified time bin versus in a correctly classified time bin

E: Proportion of time bins classified as current or previous tracks as a function of the number of laps

F: probability matrices of decoded positions for the current versus alternate tracks, for end and middle zones created from mixtures of accurate, random and teleporting to the ends models. The end zones can be represented by a combination of teleporting and random models for the alternate track, and accurate and teleporting models for the current track. The middle zone can be represented by a teleporting to the ends for the alternate track, and accurate, random and teleporting models for the current track

4.2.3 Temporal Dynamics of Cell Participation

We have shown that cells will take approximately five laps to stabilise their spatial response function on a track, and that there is a variety of responses for cells on a novel track: they can form a place field, keeping or modulating their peak rate and/or location of their place field compared to previous tracks, but they can also not form a stable place field and not participate in the novel representation. We examined the emergence pattern of place fields with experience: place fields were calculated for each cell and for each lap. Cells were then classified as either stable between consecutive laps, emerging or vanishing. Strikingly, most cells (80%) emerged on the first lap and about 70% of those remained stable from lap 2 onwards (not shown). Perhaps more interestingly, a small proportion (10-15%) of cells vanished on lap 2 (see Figure 4.3 A and E). We therefore repeated the analysis, dividing into 3 cell populations: cells that are spatially tuned on at least one previous track as well as the current one (Figure 4.3 B and E), cells that formed a place field for the first time on the current track (Figure 4.3 C and E), and cells that were spatially tuned on a previous track, but not on the current one - termed 'past cells' (Figure 4.3 D and E). While all cell categories predominantly formed place fields on the first lap, the proportion of vanishing fields on lap 2 for cells that will end up having a stable place field on the novel track was comparable to all other laps. Conversely, more than 40% of past cells vanish specifically on lap2, revealing a sub population from previous tracks mainly active in the first lap that gets pruned from the representation afterwards. As our previous field stabilisation analysis considered all place cells at once (Figure 4.1 F), recalculating for each sub-population separately validated that fields will move to their final location over the first five laps, with the exception of past cells - which never achieve a stable representation.

To investigate what the determining factors underlying the pruning or integration of cells participating in previous representations might be, we calculated the mean and peak in-field firing rate of all three groups of cells in the first ten laps (see Figure 4.4). Strikingly, the mean and peak in-field firing rates of past cells were from the first lap much lower than of previous cells that get integrated and novel

cells (kruskalwallis test on the mean over all laps $p < 0.001$, posthoc Tukey-Cramer adjusted multiple comparisons, mean of peak in field for past cells significantly different from the other two groups $p < 0.001$). Furthermore, cells that were previously spatially tuned had higher rates than novel cells (posthoc Tukey-Cramer adjustment $p = 0.003$), and while the starting peak in field firing rate are different, they seem to converge to similar rates after 10 laps, potentially denoting a higher stabilisation rate for cells that were previously active. These differences in peak in field firing rates could be explained by the degree of overlap of shared features between the pairs of environments, with the cells tuned to strongly present features being reused, while cells tuned to more weakly present features get pruned, resulting in generalisation.

In summary, the emergence and vanishing of cells occurred primarily during the first and second lap, while stabilisation of place fields increased until reaching steady state on the fifth lap. Whether a cell will be integrated into a novel representation is therefore determined using a small amount of experience, putatively based on the strength of their tuning to current features, resulting in a population of past cells being active at the beginning of the experience of a novel track.

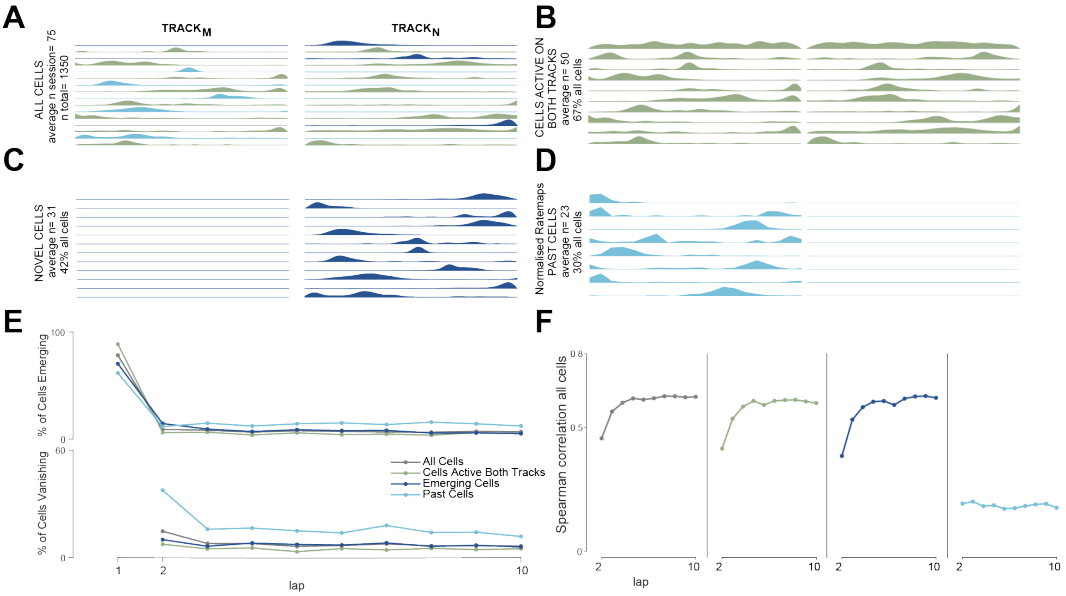

Figure 4.3: Cells Form Place Fields Predominantly in the First Lap, and a Subset of Cells From Past Environments Are Active then Disappear in the First Couple Laps

Panels (A,C,E,G): Examples of normalised rate maps in two distinct environments (N>M), Panels (B,D,F,H): Left, Percentage of selected cells with an emerging place field on a specific lap. Right, Percentage of selected cells which had a place field on the previous lap, and no longer do on the current lap.

A: Cells with a place field on either or both tracks

B: Cells with a place field on both tracks

C: Cells with a place field on the novel track only

D: Cells with a place field on a previous track (calculated from all laps), with a place field on some laps of the novel track, but when averaging over all laps do not show robust spatial tuning

E: Percentage of specified cell population with an emerging (top) or vanishing (bottom) place field for each lap

F: Between lap correlation of rate maps for each cell population. From left to right: all cells, cells spatially tuned on both tracks, newly tuned cells, past cells

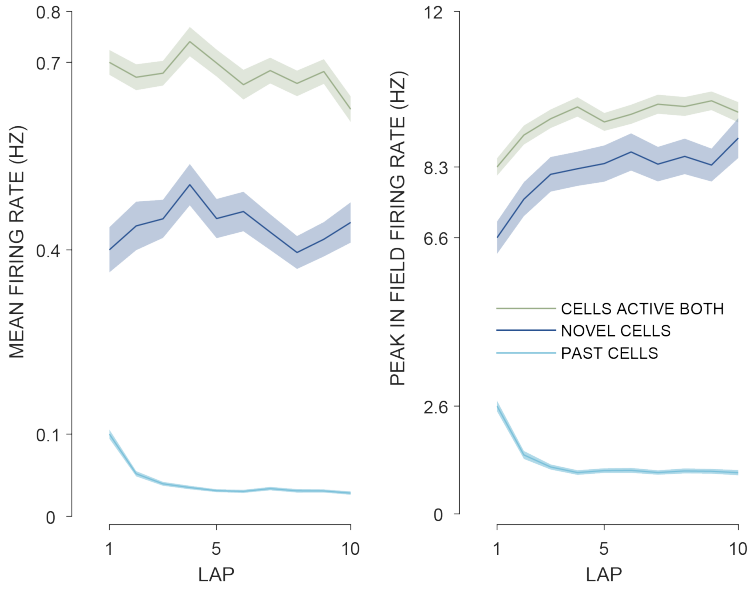

Figure 4.4: Past Cells Differ From Other Cells by Their Lower Firing Rates
Evolution of firing rates over laps for novel cells, past cells and cells active on both. **Left:** Mean firing rate for each lap, which includes periods of running and immobility.
Right: Peak in-field firing rate for each lap

4.2.4 Temporal Dynamics of Local and Remote Replay

Different populations of place fields emerge and disappear in the first five laps. Place fields that remain form a stable representation of the current track by refining their spatial tuning. As there are cells from previous representations active during this initial window of novel map creation, we looked for other neural correlates associated with previous representations. We identified the presence of remote replay (replay of previous tracks) during exploration of a novel track. More importantly, the rate of those remote replay events was not uniform over laps, and decreased from representing about half of all significant replay events in the first lap to about 20% on the fifth lap, while the proportion of local replay events symmetrically increased (see Figure 4.5 A). Remote replays from track 1 and 2 were equally likely on track 3, indicating that this remote replay is not modulated by recency. The rate of remote replay events were above noise levels, as their proportion by far exceeded that of replay events for not yet experienced tracks. Furthermore, remote replay was not the result of sparse firing from a few cells, as 1) the average number of spikes

emitted per cell was similar to that of local replay events, and 2) the number of cells involved even slightly larger than for local replay events (Wilcoxon sign rank test $p < 0.001$, Figure 4.5 D).

To account for a potentially reduced detection ability of local replay events due to unstable place fields during the first laps, on top of local replay events detected from the entire experience of the track, we included local replay events obtained from single lap generated rate maps (each of the first five laps). This procedure rescued a few local replay events, the combined number of events is shown in Figure 4.5 A. The percentage of significant replay events cells were involved in- either remote or local - was calculated for each of our place cell sub-populations (see Figure 4.5 B). Past cells preferentially participated in remote replay events (cell average remote=28%, local= 5% of events) and those active in both remote and local replay events emitted more spikes (as a percentage of the total number of spikes emitted by all cells during the replay event) during remote than local replay events. Newly tuned cells preferentially participated in local replay events (cell average local=28%, remote= 8% of events), increasing their participation over time - a trend correlated with the increasing number of local replay events. The percentage of spikes emitted by newly tuned cells active during both remote and local events was higher for local replays. Cells spatially tuned on both tracks equally participated in local and remote replay events (cell average local=36%, remote= 40% of events). Cells active in both types of replay emitted a similar percentage of spikes for each. Interestingly, these results suggest that while remote replay is the consequence of the activity of cells previously tuned on another track, local replay gradually emerges, first recruiting previously spatially tuned cells, then incorporating newly tuned cells. Furthermore, cells that are spatially tuned on both previous and the novel track do not see their activity gradually being dampened during remote replay to the advantage of local replay, but are capable of robustly participate in both representations, regardless of the current sensory inputs.

Establishing a causal link between the activity of all three types of cells and the emergence and disappearance of local and remote replay is difficult. Past cells

represent a proportion of cells active on the track equivalent to that of newly tuned cells, but both populations constitute only half of cells that remap between tracks, which is potentially the main driving force for both types of replay. As a test to see whether past cells were crucial for remote replay, we abolished their activity on novel tracks by artificially removing their spikes from the data. The amount of significant remote replay events decreased but did not disappear, indicating that past cells contribute to, but do not bear the sole responsibility for the presence of remote replay events (Figure 4.5 C). Abolishing the activity of past cells did not have an impact on the amount of incorrect track classifications during exploration (locomotion speed >5 cm.s^{-1}) nor teleportation to the ends effect of the previous section.

Further analysis may shed a better light on the exact contribution of each cell population to the emergence and disappearance of remote replay, and how cell ensembles reconfigure from previous representations to novel ones.

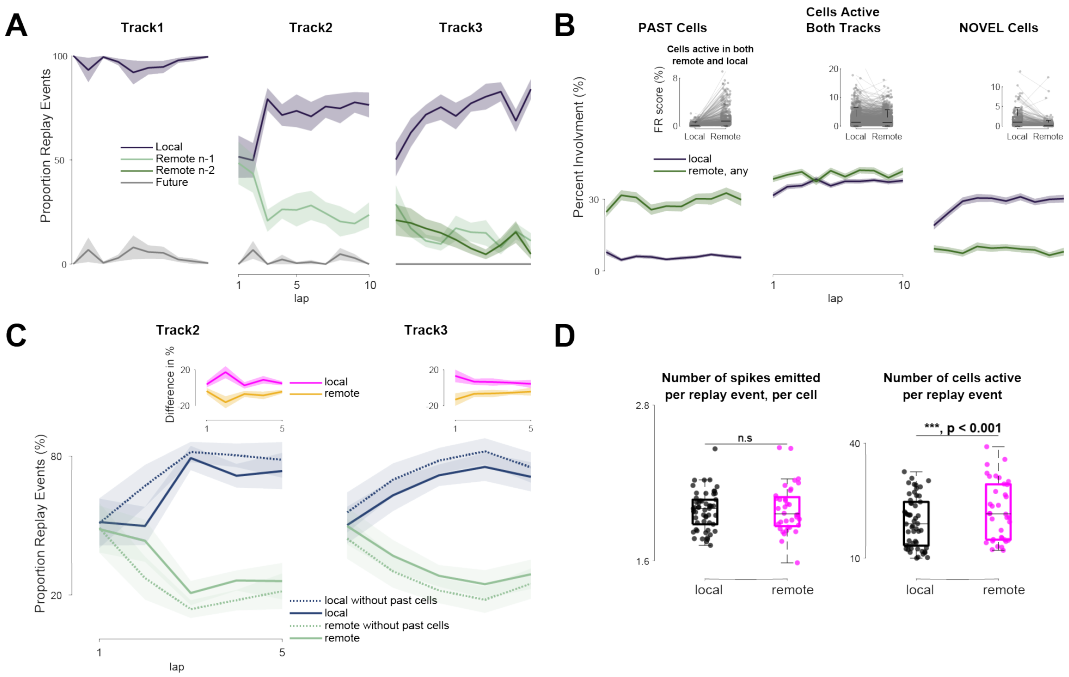

Figure 4.5: Remote Replay of Previous Experiences Occur at the Beginning of a Novel Track then Abate after a Few Laps. Distinct Sub-Population of Cells Participate in each Replay Type

A: Percentage of local, remote (one and two tracks beforehand) and future replay events during exploration of each novel track, including single lap decoded local events for the first five laps

B: Percentage of remote or local replay events cells participate in, per lap. inserts the average percentage of spikes of a replay event the cells emit. From left to right: Past cells, cells spatially tuned on both tracks and newly tuned cells

C: percentage of significant replay events classified as local or remote when the activity of past cells is abolished. Inserts: change in percentage of each replay type due to cessation of past cell activity

D: Left: average number of spikes emitted per cell in local and remote replays. Right: average number of cells active in local and remote replays. statistical tests: Wilcoxon sign rank.

4.3 Chapter Discussion

We recorded dCA1 extracellular data from rats running back and forth on sets of novel tracks. Exploration of each environment led to the creation of distinct hippocampal representations through remapping. We observed over-representation by place cells of the ends of the tracks, a key location where reward was delivered. Place fields took five laps before becoming stable, revealing a crucial time window for the shaping of the representation of novel tracks. We found that multiple processes were occurring during this unstable, labile period:

- The majority of incorrect track classification errors produced by our bayesian decoder happened in these first five laps. The preponderance of those errors decreased as the animal's experience of the track grew, and became stable by the third lap. The associated decoded positions were biased towards either end zone, especially on the remote track and sometimes on the current track. This phenomenon is most likely a consequence of end zones over-representation rather than the work of a few cells or low spiking activity.

- Cells that will end up forming a stable place field on the novel track predominantly emerged on the first lap, and took five laps to fully refine their spatial tuning. Intriguingly, past cells - cells from previous representations that will not end up forming a stable place field on the novel track - were spatially tuned on the first lap and then returned to sub-threshold activity (maximum firing rate lower than 1Hz at any location) shortly after.

- The division between past cells and the other cells may be predicted by their firing rates in the first lap, and the latter may be a measure of the strength of their tuning to features of the environment. This may be consistent with a BCM learning rule (Bienenstock et al., 1982), which has been successfully used to model pattern separation and completion in the hippocampus (Fuhs and Touretzky, 2000).

- Remote replay of past experiences occurred during immobility periods of the first few laps on the novel track. The proportion of remote compared to local

replay decreased with experience, as both the number of remote replay events diminished, and local replay became more frequent.

- Different sub-populations of cells were active during local and remote replay. Past cells participated in remote replay, while newly tuned cells fired during local replay. Cells that end up being part of both representations, while keeping an equal probability of participation in both types of replay events, end up participating in local replay more often, as the frequency of remote replay events decreases.

Together, these results are the first pieces of evidence for hippocampal proactive interference at a systems level. They very specific temporal dynamics of recall of past representations, cell selection and stabilisation during the creation of novel maps. Those processes are thought to enable both generalisation and differentiation.

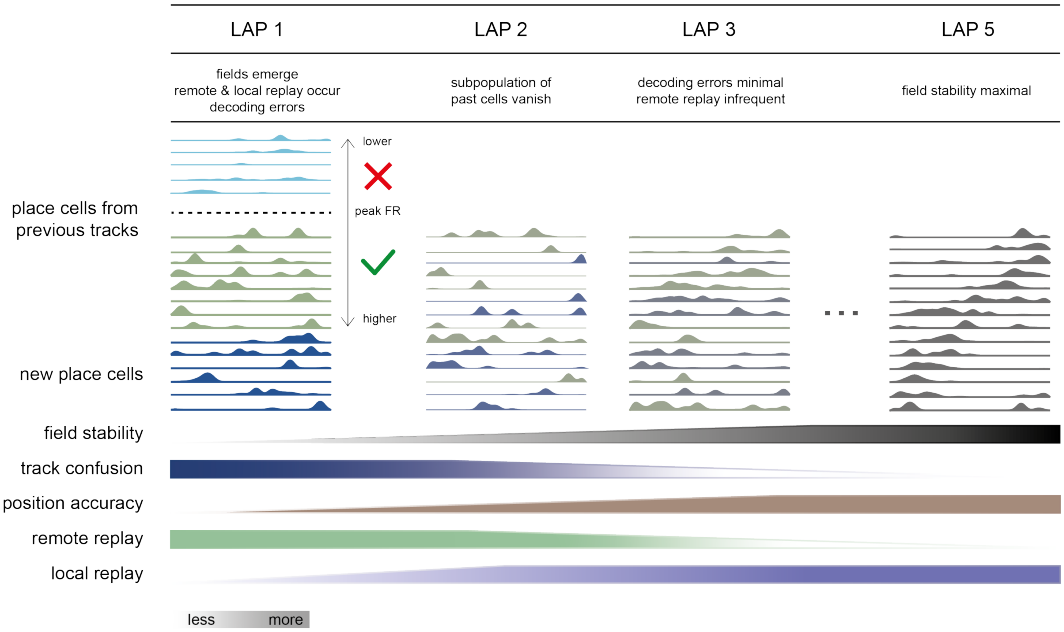

Figure 4.6: summary schematic of findings

These findings point to several research directions, and raise questions about their mechanisms and putative functions:

Could common environmental features in conjunction with overlapping cell ensembles assist generalisation across experiences?

It has been widely reported that hippocampal pyramidal cells over-represent salient

features of an environment, namely reward and/or goal as well as landmark locations (Bourboulou et al., 2019; Danielson et al., 2016; Dupret et al., 2010; Duvelle et al., 2019; Gauthier and Tank, 2018; Hollup et al., 2001; Sato et al., 2020). Overrepresentation of salient features emerges rapidly, especially when reward is involved, as shown in our data and Sato et al. (2020). If there is a function associated with the anchoring of maps to those locations, can the presence of similar features in a novel environment help create the initial scaffolding to start building the representation? Rigid and plastic cells (Grosmark and Buzsáki, 2016) are thought to respectively contribute to generalisation and differentiation. Classification of our cell populations into plastic and rigid sub-populations did not end up being done for this thesis, and therefore we have not tested whether they tend to encode most commonly encountered features. In our experiment, these would likely be the end zones with the reward ports. We hypothesise that salient landmarks might be represented by a higher percentage of rigid than plastic cells. This would entail a prioritised distribution of rigid cells to salient landmarks, which may require some learning before being categorised as such.

Is remote replay a consequence devoid of function because of place cells being active in multiple environments, or does it participate in creating new cell ensembles?

We have shown that different populations of cells are initially active in a novel environment: previous place cells that will either be incorporated into the new representation or not, and cells that were not previously spatially tuned that become place cells specific to this environment. However, a map is more than separate representations of local sub-spaces. Place cells need to be 'linked' together and all possible transitions mapped out. Theta sequences and awake replay are the two key mechanisms thought to underlie this process. Theta precession and local replay have been shown to appear as soon as the first lap on a novel linear track, while theta sequences developed with experience after the first lap (Feng et al. (2015); Foster and Wilson (2006) and our own observations of local replay emergence). Awake remote and non-local replay has previously been observed (Davidson et al., 2009b;

Gupta et al., 2010; Karlsson and Frank, 2009a; Ólafsdóttir et al., 2017). We have now shown that it is most frequent at the beginning of novel experiences. While remote replay outlasts the integration or removal of previous place cells in the new representation, the vanishing of past cells on the second lap could be linked to the emergence of theta sequences. Concurrent presence of local and non-local/remote replay may prevent catastrophic interference between memories and safekeeping of alternatives (Carey et al., 2019; Gupta et al., 2010). However, we show that there is a temporal evolution of remote replay occurrence which could not have been tested for in past studies. We posit that there may be competition between remote and local replay in the first laps to shape the activity of previous place cells (but not past cells, which are rapidly pruned from the representation) which could help generalise but also differentiate the two cell ensembles, by incorporating newly tuned cells and reordering previous place cells while keeping some of the pre-existing structure. Stabilisation of cells on lap 5 then dramatically reduces the need for remote replay for this purpose. It would be interesting to test whether the preponderance of remote replay would follow similar temporal dynamics if we recorded from wildly different environments, with different geometries, task, cues etc..

Does awake remote replay constitute active recall: would there be a behavioural advantage if there was a task ?

Ólafsdóttir et al. (2017) observed non-local replay during periods of task disengagement, while Karlsson and Frank (2009b) did not see a link between truly remote replay and longer immobility periods. Our data also goes against this view. Instead, we suggest that there may be a behavioural advantage to be able to extrapolate from a previous map what the rules of a new environment may be. In our experiment, the rats knew what they had to run full half-lap to get a reward from the moment they were placed on the track, and did not have to relearn that they cannot go back to the same end to receive a reward sooner. With such a simple behaviour we unfortunately cannot link remote replay, recall and learning. In this framework, remote replay would do more than help re-arrange cells into distinct ensembles, and also serve the cognitive function of active recall. Furthermore, it would be interesting to

study the influence of memories that have been consolidated in the long term (post sleep, across days), to test for an added recall benefit from perhaps stronger cell ensembles.

How are experiences temporally linked ?

Finally, the rates of remote replay reflected the recency of the replayed environment: the more recent the track, the higher the rate. Novelty is known to cause representations to be more excitable (Cheng and Frank, 2008; Duszkiewicz et al., 2019; Li et al., 2003; Ribeiro et al., 2004), and with experience, familiarity and an increasing total number of replay events, the need to replay a track decreases (Kudrimoti et al., 1999; McNamara et al., 2014; O'Neill et al., 2008). However, a decrease in replay rates does not necessarily reflect the memory of temporal order, and how the hippocampus may be involved in the relative and absolute ordering of separate experiences remains an open question.

Chapter 5

The effect of reward and temporal proximity to sleep on memory triage

5.1 Brief Introduction

Every day we go through a multitude of experiences, and then at the end of the day we go to sleep. Sleep is crucial for long term memory, as it is thought to be a period where the newly formed memories undergo various processes, from consolidation (Diekelmann and Born, 2010; Stickgold, 2005; Walker and Stickgold, 2004), to generalisation (Stickgold and Walker, 2013; Witkowski et al., 2020), or alternatively, pruning (Li et al., 2017; Poe, 2017). As we do not remember every single minute of every day, it implies that some form of memory prioritisation must occur. Given the importance of Slow Wave Sleep (SWS) and Rapid Eye Movement (REM) sleep for memory consolidation (Gais et al., 2006; Poe, 2017; Sara, 2017; Stickgold and Walker, 2009), we expect that those states, and sleep in general, will play a role in memory prioritisation. Pre-emptive tagging and triage during awake states before sleep is most likely to also be a contributing factor (Redondo and Morris, 2011; Wang et al., 2010). We will go back to this aspect in a few paragraphs.

Exposing mice to various salient experiences has been shown to lead to unique immediate early gene (IEG) transcription signatures in various parts of the brain (Mukherjee et al., 2018). IEG transcription has long been posited to be a marker of Long Term Potentiation (LTP) (Alberini, 2009; Lanahan and Worley, 1998; Okuno,

2011) and play a role in synaptic plasticity and memory formation of recent experiences. Transcription magnitude is higher for salient compared to neutral experiences, and valence determines which brain areas have this increase in gene expression. Rewarding experiences increased gene expression in the frontal cortex (Limbic cortex, Nucleus Accumbens, Dorsal Striatum and Ventral Tegmental Area (VTA)), while aversive experiences targeted the Amygdala instead.

From a behavioural approach, salient experiences are also better recalled, whether positive or negative. Post-learning memory is enhanced for positive and negative stimuli but not neutral ones (Feld et al., 2014; Fischer and Born, 2009; Liu et al., 2008). Memories of neutral objects are prioritised based on their distance from reward (Braun et al., 2018). Contextual fear conditioning leads to persistent memories (Maren et al., 2013) sometimes leading to conditions such as Post Traumatic Stress Disorder (PTSD), and the presence of aversive stimuli enhance consolidation of emotionally arousing but not neutral stimuli (Cahill and Alkire, 2003; Cahill et al., 2003).

At a systems level, salient memories are often studied by comparing the reactivation frequency of neurons tuned to salient stimuli to that of neurons tuned to non-salient stimuli. Place cells are often used for this type of analysis as they have been shown to code for specific locations in an environment (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976), allowing for the study of episodic memory. Place cells have also been shown to reactivate according to previously experienced behavioural trajectories, but in a temporally compressed manner: a phenomenon called replay (Foster and Wilson, 2006; Lee and Wilson, 2002).

We will focus on positive valence only for the rest of this chapter. A few studies have shown that reward locations are preferentially replayed or reactivated during awake states (Ambrose et al., 2016; Michon et al., 2019; Singer and Frank, 2009), and during and quiet rest/sleep states (Igloi et al., 2015; Michon et al., 2019). But reward is not the only factor that can lead to enhanced memories: experiencing a novel environment has been shown to strengthen temporally proximal memories (Dunsmoor et al., 2015a; Salvetti et al., 2014). Novel environments are preferen-

tially replayed over more familiar ones (Kudrimoti et al., 1999; McNamara et al., 2014; O'Neill et al., 2008).

Given the above evidence that memories are prioritised during sleep, what are the underlying mechanisms of memory triage and prioritisation? In awake states, both reward and novelty have been shown to trigger dopamine release in the hippocampus, respectively originating from VTA and Locus Coeruleus (LC) projections (see Duszkiewicz et al. (2019) for a review). Stimulation of dopaminergic projections from VTA to CA1 during spatial learning has been shown to improve memory and heighten reactivation frequency of novel and rewarded locations (Cheng and Frank, 2008; McNamara et al., 2014). Therefore, dopaminergic release coupled with a synaptic tagging and capture mechanism is a plausible system to tag memories during awake states and help determine the order of priority of memories during sleep.

Interestingly, during slow wave sleep (SWS) VTA-HPC coordination is diminished (Gomperts et al., 2015), and the pharmacological inhibition of dopaminergic projections does not alter the prioritisation of high over low rewards (Asfestani et al., 2020), indicating that dopaminergic projections are not required after the tagging step. Hinting at more complex dynamics than a prioritisation of memories purely based on the dopaminergic tagging of awake states, other brain structures can also influence the triage process. Indeed, coordination between the hippocampus and several cortices is elevated during SWS (Ji and Wilson, 2007; Ólafsdóttir et al., 2017; Shin et al., 2019), and may influence the content of replay (Bendor and Wilson, 2012). Further painting a complex and incomplete picture, short experiences or weakly learned information can also be prioritised during sleep (Schapiro et al., 2018), but not always (unpublished data from the Bendor Lab).

In this chapter, we present hippocampal data of latent learning of reward quality, occurring while rats ran back and forth on three successive novel environments to collect rewards prior to sleep. Building on the existing corpus of literature, we aim to address the following questions:

1. When multiple experiences need to be consolidated during sleep, are consolidation processes happening in equal measure and in parallel, or are experiences consolidated in turn?

2. Does temporal proximity to sleep play a role in the replay prioritisation of an experience?

3. Are experiences that have been replayed more during awake states replayed less during sleep, or the opposite ?

5.2 Results

We recorded dCA1 pyramidal cells in rats as they ran back and forth on linear tracks to obtain a drop of reward at each end. The identity of the liquid reward for each of the three novel tracks presented each day was pseudo-randomly allocated, drawn from a set of two rewards of distinguishable palatability (see Figure 5.1 A). All possible combinations of reward sequences were presented over the course of six recording sessions, with the exception of one rat, where human error led to the repeating of two combinations. The rats were allowed to run for 15min on each track and placed for 10min in a view-shielding pot in between exposures. This pot was also used to record neural activity during sleep at the beginning and at the end of the recording session.

5.2.1 Reward Preference

First, we behaviourally tested for a set of two rewards that would robustly lead to a preference of one reward over the other. Rats were repeatedly placed on a platform for two minutes during which they could freely sample both liquids placed pseudo-randomly at opposite extremities of the platform. After the first choice trial during which both rewards were usually sampled, the rats decisively sought out only one of the two liquids: their behaviour marked a clear preference for pure chocolate milk over its 1:1 dilution with water (Wilcoxon signed rank test $p < 0.001$ for all rats, see Figure 5.1 B for the three rats with dCA1 recordings, Figure A.3 and Table A.1 for all rats), and of chocolate over water, a liquid without calorific value and freely accessible in their home cages (Figure A.1, Wilcoxon signed rank test $p < 0.001$ for all rats). A comparison test between the 1x chocolate dilution and water was not run, but since the rats were still willing to run for the 1x dilution during recordings, we argue that this liquid was considered as rewarding, if less so than the pure chocolate. From this point onwards, we will refer to pure chocolate as the **HIGH** reward, and the 1x chocolate dilution as the **LOW** reward.

5.2.2 Behaviour and Cell Properties

To test for any changes in behaviour due to the presence of either reward we fitted three nested Generalised Linear Mixed Models (GLMM) to the number of laps on each track (one lap= traveling to one end of the track and returning back to the starting point) as a function of (1) reward on the current track, (2) reward and track presentation number (recency) without interaction and (3) reward and recency and their interaction term. A 4^{th} model was also fitted using the difference in reward between the current and the previous track as a predictor, to test whether reward change rather than reward value best accounted for the observed behaviour. HIGH reward was a significant predictor of an increase in the average number of laps (estimated means HIGH= 15.3 and LOW= 11.6 laps respectively, z= 4.68, $p < 0.001$, see Figure 5.1 C) and Figure A.3 C), as well as reward difference, but only the interaction term between reward and recency was significant (no main effect of recency). See Tables A.2, A.3 and A.4 for summary of statistics. A Chi-Squared test between the nested models (1) and (3) indicated that the more complex model with interactions was not significantly better (p= 0.06) than the simpler model using only reward as a predictor.

This increase of a few laps for HIGH reward translated in an increase in locomotion speed on HIGH reward tracks (see Figure A.5 B and Table A.5 for summary statistics with n=5, same result for n=3 with only the rats used for ephys recordings as shown in 5.1), but reward did not influence the average time spent at the reward wells at the end of the tracks per lap (estimated mean LOW= 18.56s, HIGH= 16.57s, t= -1.6, d.f.= 66, p= 0.11, see Figure A.3 D, left). The average time spent immobile in the middle of the track per lap increased by approximately two seconds for the LOW reward tracks (estimated mean LOW= 3.36s, HIGH= 1.58s, t= -3.35, d.f.=88, p= 0.001, see Figure A.3 D, right). Recency did not influence stopping times at the end zones (estimated means T1=18.2s , T2=17.8s , T3=16.7s , F= 0.52, p= 0.59) nor the run zone (estimated means T1=2.4s , T2=2.33s , T3=2.7s , F= 0.17, p= 0.84). Consistent with previous reports, locomotion speed gradually increased with experience of each track (Feng et al. (2015); Frank et al. (2004); Mehta et al.

(2002), see A.2).

In order to quantify the effect of reward and recency on cell activity, we calculated a rate map for each recorded pyramidal cell on each track. Cells with a Half-Width at Half-Max HWHM $> 50\mu s$), a peak in-field firing rate higher than 1Hz, a mean session firing rate lower than 5Hz and a non-zero Skaggs information content were classified as spatially tuned and used for all following analyses. Neither reward nor recency were associated with a significant difference in the number of spatially tuned cells (total= 1356 cells [Navi:303/Polaris:461/Rigel:593], average of 48 cells per track, z ratio= 0.45, p= 0.65 see Table A.8 and Figure A.7), information content (z ratio= 1.28, p= 0.23), but there was a small increase in peak firing rate with HIGH reward (estimated means: 5.9Hz for LOW, 6.6Hz for HIGH, z ratio= 20.35, $p < 0.001$) which may be a by-product of the increase in locomotion speed on HIGH reward tracks.

Our protocol was successful in not only ensuring an even coverage of space but also an equivalent amount of time spent at reward sites across reward conditions, thereby guaranteeing equal replay opportunities and decoding accuracy between conditions. We did unexpectedly observe a slight increase in the number of laps for HIGH reward. However, given that all tracks were sufficiently experienced for place cells to stabilise their rate maps and for the decoding accuracy to be very high (see Chapter 4), this difference in laps experienced was unlikely to have had a significant impact on the frequency or fidelity of subsequent replay.

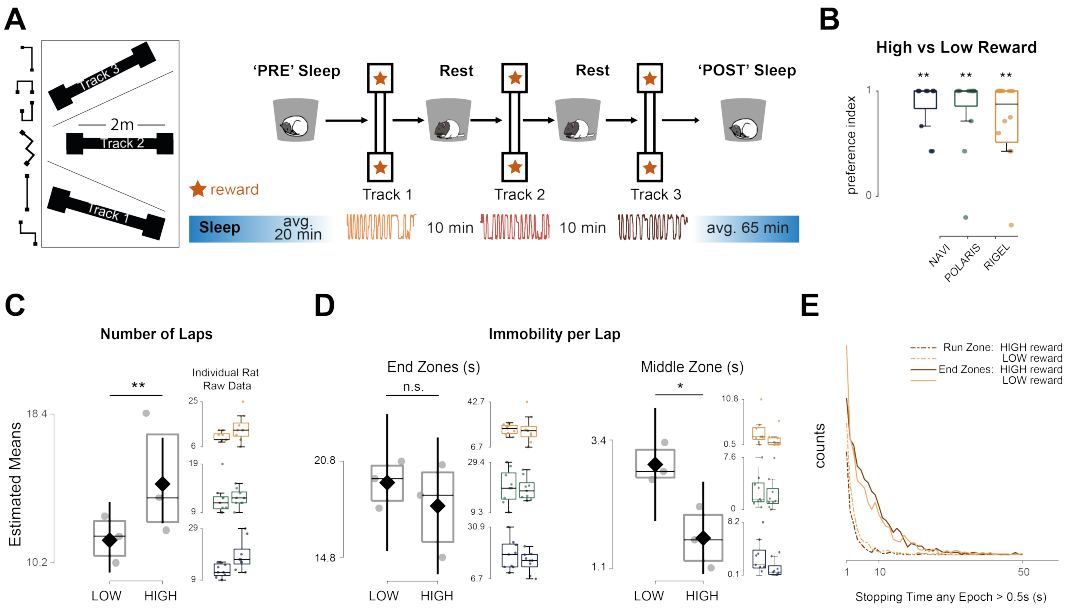

Figure 5.1: Behaviourally confirmed reward preference translates to a higher number of laps but does not increase stopping time at end zones

A: recording protocol. Each day, the rat is placed in a sleep pot before experiencing three novel tracks on which it runs back and forth to collect a drop of reward at the end. On one track, the reward will be different than on the other two tracks. This odd-one-out reward can be either High or Low (e.g. [LOW, HIGH, LOW] or [LOW, HIGH, HIGH]). All possible combinations are tested (6 combinations) pseudo-randomly across days. The rat is then placed back into the sleep pot for non REM and REM data to be collected.

B: Rats behaviourally demonstrate a preference for pure chocolate milk (High reward) over its 1x dilution with water (Low reward) when given the opportunity to freely sample either (n=3, Wilcoxon signed rank test $p < 0.001$ for all rats, see Table A.1). Each dot is a 2min trial, data points with a preference index near zero tend to occur in the very first trial

C: The number of laps is higher in High reward environments. Left: estimated means of poisson GLMM as a function of reward, with nested random effects Right: raw data of number of laps for each rat and session (n=3)

D: Reward does not modulate the time spent at the reward sites, but rats will stop more in the middle of the track on Low reward tracks. Left: estimated means from a GLMM with reward as a predictor and nested random effects. Right: Raw data for each rat and session

E: Distribution of every stopping epoch longer than half a second at either the end or middle zones, and for either High or Low rewarded tracks.

5.2.3 Recency and Reward Modulation of Candidate Replay Events

Having established how recency and reward affect behaviour in our protocol and basic place cell firing properties, we then went on to test how these factors may affect processes thought to be crucial for memory consolidation. Candidate replay events were identified based on an increase in zscored multi-unit activity (MUA) and ripple band amplitude above 3 (see full detection method based on Davidson et al. (2009a) in 3).

We normalised candidate event rates for each epoch (during sleep, on tracks, in the sleep pots between exposures) as a proportion of the candidate event rate during sleepPRE. Ratios were higher during active behaviour on the track and sleepPOST compared to quiet states during rest (Wilcoxon signrank test $p<0.001$, see Figure 5.2 A), consistent with previous reports (Karlsson and Frank, 2009a). The period in the sleep pot after the third track and before the animal fell asleep - labelled rest3 - was included in following analyses but varied in length from 48s to 14min30s (median just under 3min).

As described in chapter 4, as the rat explore more environments, an increasing number of remote tracks are replayed during each epoch, including during active behaviour (see Figure 5.2 B). We asked whether candidate replay event rate would compensate for this phenomenon to preserve the amount of local replay (on the tracks). To detect significant replay events, we used a Bayesian inference approach to decoding neuronal ensemble activity, normalised the posterior probabilities for each time bin so that the sum of probabilities over all possible positions (all three tracks) was equal to 1, then calculated the weighted correlation of the decoded posterior probability of each candidate replay event for a given track. Events satisfying minimal jump requirements were compared against the distribution of correlation values obtained from a thousand repetitions of three shuffling methods (see 3 for replay detection analysis) 1) circular spike train shuffle 2) circular ratemap shuffle and 3) circular timebin shuffle of the posterior decoded matrix. Events that achieved significance (correlation higher than 95% of distribution) on all three shuffles were

classified as significant replay events. If an event was significant on multiple tracks, the bayesian bias (fractional sum of probability for that track) determined whether the replay event was classified as significant for 1) the only track with a bias higher than 40% or 2) multiple tracks with a bias higher than 40% and the event was not included in further analysis.

Comparing the observed difference in proportion of candidate events between track pairs to a resampled distribution of shuffled track labels (analysis and plots based on Carey et al. (2019)) indicated that there was no increase in candidate replay events from the first to the third track. As a consequence, the percentage of local replay (current track) to candidate replay event rate per epoch was lower for track two and three ($p_{T3-T1} = 0.011$, $p_{T2-T1} = 0.005$, see figure 5.2 C, middle). Candidate replay events were neither modulated by recency nor reward (see figure 5.2 C, left and right), the latter contrasting with results from Ambrose et al. (2016).

In relation to previous findings in studies varying reward quantity rather than quantity, the time spent at the HIGH reward locations is always significantly longer than at LOW reward locations. It is then argued that normalising by time or the number of SWR irons out any differences (Ambrose et al., 2016; Michon et al., 2019), as SWR or replay rate is a linear function of time. However, by looking at our own data, one can quickly assess that stopping duration does matter (see Figure B.4). In fact, the rate of candidate replay events follows a sharp increase from 1s to 7s before very slowly decreasing over the next 20s. Our dataset does not have different stopping time distributions for HIGH and LOW reward, and yet gives some evidence that replay rate is not simply a linear function of time. However, even if it may not necessarily invalidate previous findings, we argue that sampling from distant parts of this distribution is likely to affect the output of any GLMM or group comparison test in unexpected ways and should be an acknowledged confounding factor.

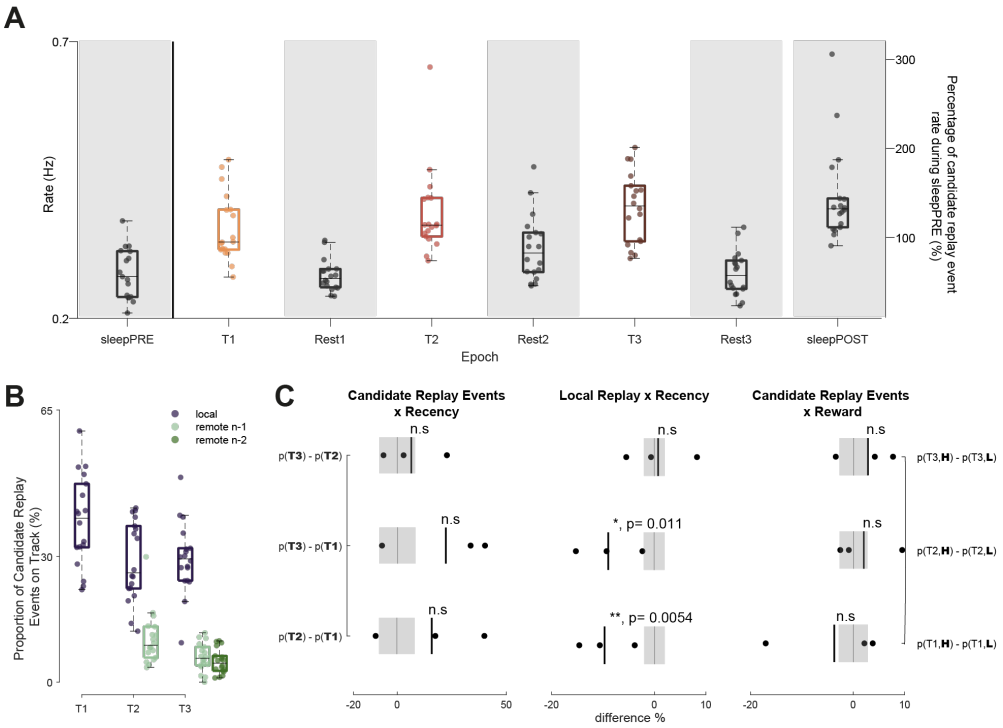

Figure 5.2: Candidate replay event rate does not compensate for an increasing number of contexts to replay and is not modulated by reward

A: Candidate replay event rate or proportion for each epoch. During sleepPRE, candidate replay event rates are shown. For the remaining epochs, event rate is normalised by the rate during sleepPRE. For one session where the animal did not sleep during sleepPRE, rates are normalised by the rate of the first track.

B: Proportion of the number of candidate replay events occurring on each track for each type of replay. As the number of tracks experienced during the day increases, more tracks are being replayed leading to a decrease in the proportion of local replay.

C: from left to right: Difference in the candidate replay events proportion between tracks pairs, difference in the proportion of local replay events between tracks pairs and difference in the proportion of candidate replay events with reward for each track. each dot is the observed average difference in proportion for each rat (n=3), the black line is the observed difference averaged across rats, and in grey is the bootstrapped distribution of differences obtained by resampling from shuffled labels (recency or reward). Asterix and p-values are obtained from a two tailed test on the zscore of observed vs resampled data.

5.2.4 Recency and Reward Modulation of Awake and Sleep Replay

We did not observe an increase in candidate replay events with recency nor reward. This observation combined with an increase in remote replay with recency led to a reduction in local replay events on the last two tracks as a result. In this section we investigate how the rate of significant replay events during awake states prior to sleep are influenced by reward and recency, and whether memory prioritisation is a function of valence, recency and awake replay.

The most prominent observation when looking at the evolution of the most replayed track over the course of a session was the prioritisation of the local track during active behaviour, and of the most recently experienced track during rest periods (see Figure 5.3 A,E and summary statistics in Table B.1). As a consequence of the presence of remote replay, there was a clear gradation with recency of how many times a track will have been replayed right before sleepPOST: the first track will have been replayed in all subsequent epochs (50+ minutes) while the third track will have only been replayed locally and in the awake period before sleep in the pot (median= 2min58s, min= 47s, max= 14min30s). By the end of sleepPOST (median= 60min, min= 30min, max= 1h35min), the overall amount of replay for the last two tracks was significantly lower than of the first (ratio T1/T2= 1.17 p= 0.003, ratio T1/T3= 1.22 p=0.008 ,see B.1).

We then looked at the relationship between the amount of replay during awake states and sleepPOST. While there was a clear positive correlation between the total proportion of replay events during awake and sleep states for less replayed tracks (second and third tracks), this wasn't the case for the first track (Spearman correlations: track1 rho= 0.10, p= 0.7, track2 rho= 0.8 $p<0.001$, track3 rho= 0.65 p= 0.003, see Figure 5.3 B). There was also a very clear segregation based on recency, indicating that sleep replay is not a simple function of how much an environment has been replayed before, but also reflects temporal discrimination. We repeated the analysis using only local events or remote events in the awake states. Both graphs showed the same trend.

To test for recency or reward effects at varying time points, we proceeded with the same analysis as in the previous section: obtaining the zscore of the observed data relative to the bootstrapped shuffled label distributions for each comparison of interest. If multiple time points were tested in the same epoch, Holm-Sidak's multiple comparison correction was applied to the p-values. For sleepPOST, the first, middle and last time points were tested for significance in the case of recency comparisons. The first, peak difference and last time points were tested during sleepPOST when comparing reward conditions. Visual inspection revealed that recency was the main factor driving how much an environment was prioritised during sleep. Figure 5.3 E, shows that the cumulative proportion (total number of events since beginning of sleep) of replay events for the third track was significantly higher than any other track for periods up to 50-60min of sleep (mean ratio to track1= 1.72 ± 0.27, mean ratio to track2= 1.67 ± 0.20). After 60min, the proportion of events for the first track drops, and the proportion for the second track increases (see Figure B.2). However, the number of sessions with a sleep duration longer than 60min is considerably lower (4-12), and decays rapidly with sleep duration. As a consequence, this latter observation merits some additional recordings session to be confirmed.

Recency being the main driving force for replay prioritisation, we focused on reward effects on the proportion of replay events for the current track, the most recent during rest or the third track only during sleep. In contrast with previous studies Ambrose et al. (2016); Michon et al. (2019), we did not see an effect of reward on the number of local replay events, nor of the most recent track during rest epochs. However, to our surprise given those initial findings, but in accordance with Braun et al. (2018); Feld et al. (2014); Michon et al. (2019) the HIGH rewarded tracks were prioritised during sleepPOST. Prioritisation only lasted the initial 20-30min of sleep (see Figure 5.3 F, Figure B.2), after which the proportions were no longer different between reward conditions. Since this first-pass analysis does not take into

account potential interaction effects with past reward, we plotted the cumulative proportion of replay events for the third track as a function of reward history (Figure 5.3 G). Interestingly, it seems that the combination [HIGH-HIGH-LOW] has proportions more comparable with that of HIGH ending combinations after 30min: potentially pointing to more complex factors than just reward or recency. Interactions due to the temporal ordering of rewards require more sophisticated analyses, and is an interesting future direction of this work.

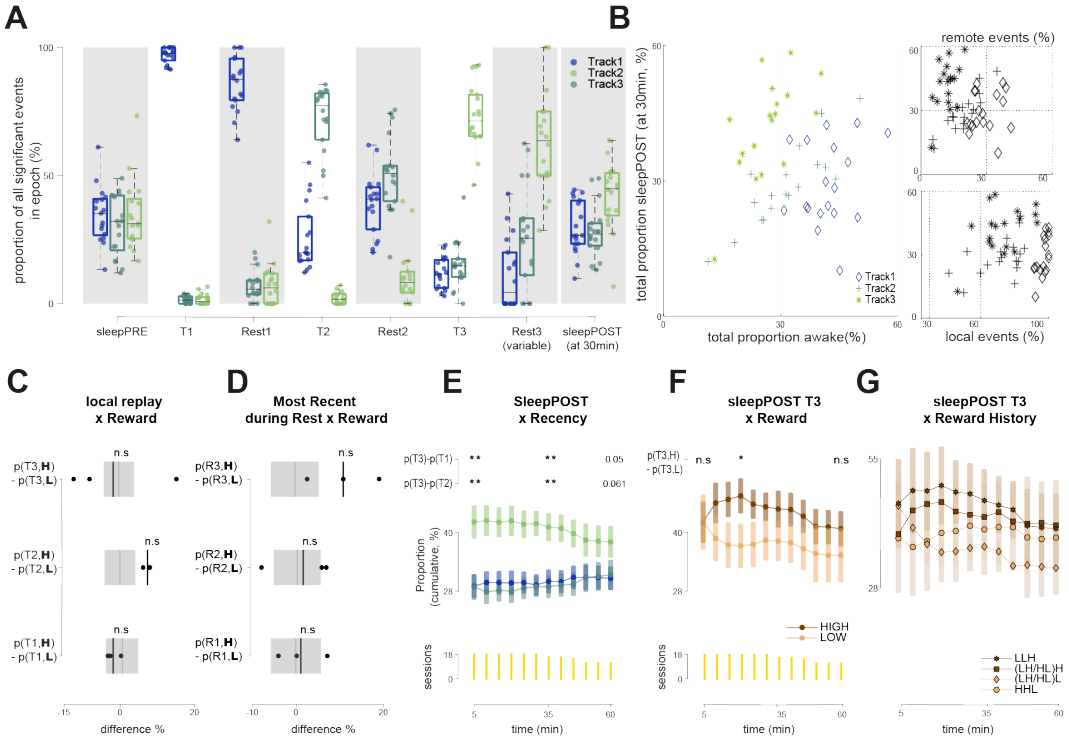

Figure 5.3: Awake replay is selectively modulated by recency while sleep replay is temporally modulated by both recency and reward

A: Proportion of the total number of significant replay events during an epoch, for each track.

B: Left: Scatter plot of the proportion of replay events during awake epochs (includes rest epochs) versus sleepPOST. Bottom right: scatter plot of the proportion of local replay events during awake epochs (track epochs only) versus sleepPOST. Top right: scatter plot of the proportion of remote replay events during awake epochs (includes rest epochs) versus sleepPOST.

C: Proportion of replay events during sleepPOST as a function of reward history. The six possible combinations are grouped as a function of the third track's reward, and the sum of rewards on the previous two tracks. There is no linear correlation with reward history (Spearman correlation, p= 0.81)

D: from left to right: difference in the proportion of local replay events with reward, difference in the proportion of the most recently experienced track during rest periods with reward, difference in the proportion of replay events for the third track with reward and recency. Each dot is a rat average (n=3), black lines indicate the average across rats, and grey rectangles represent the corresponding bootstrapped distribution.

E-G: Cumulative proportion of replay events as a function of time spent sleeping during POST and the corresponding number of sessions contributing to each time point. **E:** for each track based on proximity to sleep

F: for the most recent track (Track 3) based on reward quality

G: based on four types of reward successions: 1) when there is one high reward track and it closest to sleep 2) the most recent track has a high reward, but a previous track also had a high reward, 3) the most recent track has a Low reward and a previous track had a high reward and 4) the most recent track has the only low reward in the session.

5.3 Chapter Discussion

We have presented our findings from a corpus of analysis aimed at dissecting the effects of reward and recency on memory prioritisation during sleep. Reward and recency were modulated while keeping keeping novelty constant between environments. The use of reward quality instead of quantity minimised differences in behaviour and exploration between reward conditions.

Candidate replay event and replay event rates are unaffected by reward during awake states

Contrasting with Michon et al. (2019) and Ambrose et al. (2016), we did not observe an increase in candidate replay events or significant replay events on the tracks in the presence of the HIGH reward compared to the LOW reward. The preference for the HIGH over the LOW reward was behaviourally demonstrated in this study, and the absence of a need to learn reward locations is also present in Ambrose et al. (2016), and therefore are unlikely to be the reason for this discrepancy. Although we did not look at forward and reverse replay rates in this chapter, the increase in reverse replay rate and lack of change of forward replay rates reward found by Ambrose et al. (2016) would still result in an overall increase in replay rate. The main differences between those two studies and ours are 1) a possible greater preference magnitude/saliency for the HIGH reward in the other manipulations, 2) unaccounted effects due to longer waiting times at the HIGH reward sites, 3) differences in significance testing for replay events: we used a robust set of criteria by including 3 different shuffles and 4) awake replay only codes for direct reward changes or comparisons within an environment and not reward magnitude.

Multiple environments decreases the reactivation capital of experiences later in the day

The exploration of multiple tracks during the same recording session revealed the absence of compensation of candidate replay event rate with the growing number of environments to replay. As a consequence, tracks presented later in the session

were replayed less often prior to sleep compared to earlier tracks, which could mean weaker representations. The quality (or fidelity) of the different representations prior to sleep is an important future direction of this work.

Experiences are consolidated in sequence during sleep, in the reverse order of presentation

During both awake and sleep states, the most recent or local track was always preferentially replayed. During sleepPOST, this prioritisation lasted for the first half-hour of sleep, with cumulative effects lasting up to 50min. Despite a smaller amount of data available after one hour of sleep, the amount of replay for the second track then increases, also sustaining replay for the third track, at the detriment of the first track. Longer sleep recordings would give the evidence necessary to confirm this reverse temporal ordering of experiences. Reward further increased the prioritisation of the most recent track over the other tracks - but seemingly only for the time window associated with that environment's preferential consolidation. Additional, longer sleep recordings might also inform whether reward acts a prioritisation booster only for the currently prioritised track or in a continuous fashion. Separating sleep into SWS and REM epochs may also create some insight on why prioritisation of the most recent track ends when it does.

Temporal proximity or rescuing of less replayed environments?

For the least replayed environments, we observed a positive correlation between the total amount of replay during awake states and during sleep. This correlation was not conserved for the first track, which, even by the end of sleepPOST, was overall replayed more than the other two. However, the amount of awake replay did not solely determine which track was prioritised during sleep. The presentation order of the context or temporal distance from sleep - factors near-indistinguishable in our experiment - was the main driver determining the amount of replay of an environment during sleep. Those two processes are consistent with previous studies in humans demonstrating that temporal proximity to sleep is beneficial while a

longer wake period between encoding and sleep is detrimental (Payne et al., 2012; Talamini et al., 2008). Local and remote replay may not serve the same purpose, nor present the same reconstruction quality. We hypothesise that remote replay may be play a role in both generalisation and preventing catastrophic interference between experiences (see chapter 4), and this may be at the expense of eroding/simplifying the original representation. Assessing the quality of each track's representation over the course of the session may further inform why the most recent track is prioritised.

Open Questions:

We wish to end this chapter with a list of open-ended questions, some of which can be addressed with further analysis on this data set, others requiring the acquisition of new data.

- Is the temporal window of preferential prioritisation a function of the average number of experiences one goes through between sleep periods?
- How is the balance between ensuring the consolidation of salient experiences (during SWS) and generalisation (putatively during REM) struck? Is the interleaving of states arbitrary or dependent on some amount of consolidation ?
- Is prioritisation also reflected by a targeted increase in the fidelity of replay sequences of an environment prior to and during sleep?

Chapter 6

General Discussion

This thesis sought to address how the experience of multiple contexts influence episodic memory encoding and consolidation in the rat. We chose a systems level approach and made use of the known contextual mapping and reactivation properties of hippocampal place cells to modulate the similarity and salience of spatial contexts. Recording from many hippocampal neurons simultaneously, during both sleep and the exploration of three completely new environments each session, has given us unprecedented insights into episodic memory formation and consolidation. Notably, we have provided evidence for the presence of neural patterns of activity that may reflect generalisation and disambiguation between contextual representations in the awake states, giving the first systems-level account of how past experiences can shape new ones. Furthermore, taxing memory resources with multiple new experiences each recording session revealed the temporal dynamics of prioritised memory consolidation during sleep. Together, these findings highlight the complex interactions between memory traces in wake and sleep states.

6.1 Evidence for Proactive Interference in the Hippocampus

Proactive interference is the influence of previously learned experiences on the acquisition of new ones. While interference is often associated with a deficit in performance, this thesis focuses solely on its underlying implication: previous experiences can shape the encoding of new representations in the presence of shared

features, which create ambiguity. This process may serve both generalisation and differentiation purposes, and as a consequence have an overall positive or negative effect on behavioural performance.

In our experimental setup, in which each spatial context was defined by both distinctive (visual, tactile, gustatory) and shared (geometry, gustatory, task) features, we demonstrated that neural correlates of previous experiences could be observed during the stabilisation period of novel environments. More specifically, place cells from past environments not only formed place fields in that period, but also actively participated in the recall of these past contexts. The cells associated with previous contexts were either pruned or integrated and reorganised into the new representation on the timescale of a few complete exploration runs of the environment by the rat.

Replay of the current experience is thought to help strengthen and stabilise the hippocampal representation (Brandon et al., 2011; Koenig et al., 2011; Kovács et al., 2016; Theodoni et al., 2018; van de Ven et al., 2016), while remote replay is thought to be better suited for the prevention of catastrophic interference (Carey et al., 2019; Gupta et al., 2010). We showed that remote replay is most frequent in the first few laps when the new representation is being refined and stabilised. This suggests that remote replay plays a role in generalising and differentiating between contexts, although our experiment was not designed to provide causal evidence. Given that the task was the identical across contexts in our experimental design (running back and forth between the ends of the track to collect rewards), there is by definition no context-dependent task learning. Consequently, we do not have a behavioural readout of the animal's ability to disambiguate feature-sharing contexts, and the link between behavioural performance, replay frequency and other neural correlates cannot be made on that level. However, such context-dependent tasks have been considered in the design stage of this thesis, through the learning of different reward locations on the track for example, but this implementation would have been at the cost of longer recording sessions - the length of which are limited by our animal license - and an initial concern for the stability of cells over extended periods

of time.

Controlling for shared features between environments along with contextually distinct task requirements would provide the means to gather evidence for or against improved behavioural performance when some previous knowledge of shared features has already been acquired. Our findings call attention to the role of remote replay in the generalisation and disambiguation of contextual information. The presence of remote replay during our paradigm which modulates associative novelty provides additional evidence for the hippocampus being an associative mismatch novelty detector (comparator model, see General Introduction). Indeed, it points to a recall of feature-shearing representations in the hippocampus, perhaps triggered by pattern completion in CA3. It is however also possible that remote replay may concurrently be triggered by the retrieval of cortical schemas (running back and forth on linear tracks), which in turn may lead to replay of similar experiences in the hippocampus. As the rats experienced more and more linear tracks over the six days of recordings, it is likely that the schema related to the task (running back and forth) based on an abstract context (linear tracks with varying sensory features) progressively evolve over that period. We did not attempt to analyse how the amount of experience (session number) may affect the hippocampal dynamics of representation stabilisation or remote replay rate. Another interesting research avenue would be to understand the link between schema retrieval and remote replay of specific experiences. In this study - with the limitation of not being able to decode experiences from previous days - we observed remote replay of temporally adjacent experiences. If a schema is retrieved in cortical areas, one could posit it would trigger the reactivation of the corresponding 'schema' or 'concept' cells in the hippocampus (Baraduc et al., 2019; Quiroga, 2012). However, as a consequence of their abstractness these cells will in theory be active in all contexts related to the schema, and therefore trigger the reactivation of any of these representations. From our study, we speculate that within a wake episode, the temporally adjacent experiences - with highly potentiated synapses - will be the representations more likely to be reactivated, and not those from previous days. This can not be tested without

being able to record the same cells over multiple days.

Causal manipulations of remote replay are needed to determine which of these functions it serves. If remote replays contributes to a greater generalisation between memories, targeted online disruption of these events, would lead to slower learning rates, equivalent to *de novo* learning rates, while remote replay enhancement - perhaps through the targeted stimulation of cortical traces associated with meaningful shared features - would improve learning rates.

If remote replay is required to prevent catastrophic interference, an online blockade of such events would reveal changes in hippocampal representations and inappropriate behaviour (retroactive interference) would emerge when the animal is put back in previously experienced contexts. Future work may also focus on rigid cells (Grosmark and Buzsáki, 2016): place cells that have been defined by their slower firing rate properties, broader place fields and putative involvement in generalisation mechanisms. For this thesis, we did not classify pyramidal cells as rigid or plastic, but an analysis to identify whether rigid cells are in fact cells that participate in previous contexts, and whether they tend to represent more-commonly encountered features would be a first step to identify neural correlates of generalisation. Tracking the activity of 'generalising' cells during SWS and REM may help resolve some of the debates about of the function of these sleep stages, as well as what a generalised representation looks like at a systems level.

6.2 Temporal Dynamics of Memory Triage

Stemming from the need to efficiently consolidate all the different contexts experienced between periods of sleep, memory triage is the process ensuring that the most relevant memory traces are preferentially consolidated and end up being better remembered. Salient features such as pain, reward or novelty have been shown to be 'tickets' for prioritised memory consolidation. Temporal proximity to sleep is also a deciding factor, with experiences closer to sleep ending up being better remembered. Replay of experiences is one of the mechanisms underlying memory consolidation, and the amount of replay for contexts associated with any of these

prioritisation tags has been shown to be higher than for other contexts during wake and sleep. Awake replay has been shown to be modulated by reward (or reward prediction) within environments (Ambrose et al., 2016; Bhattarai et al., 2020; Michon et al., 2019; Singer and Frank, 2009), in line with prioritised replay models (Mattar and Daw, 2018). Strikingly, varying reward between contexts did not lead to the same effect, with an absence of awake replay increase in high reward contexts. In line with another recent study (Roscow et al., 2019), our findings suggest that awake replay may only encode reward prediction errors within a context rather than reward magnitude.

To the best of our knowledge, no study has looked at the temporal consolidation dynamics of memory prioritisation during sleep. Our data shows that memory triage is not a uniform process, with each context being replayed at a constant rate throughout sleep according to its priority ranking. Instead, consolidation seems to occur sequentially, with the context at the top of the priority list being replayed preferentially for a set amount of time, then the second, and so on. Temporal proximity to sleep was the main priority factor in our experimental setup, with reward acting as a boosting effect. Changing the amount of time between contexts and rewards (quantity, MFB stimulation, cocaine...) would of course alter these results by re-ordering the prioritisation list accordingly to the salience and the decay in synaptic potentiation with wake time. The temporal dynamics of memory triage therefore have a cyclic component (time attributed to each memory) and an amplitude (relative proportion) component. The amplitude might be salience modulated while the cyclic frequency may be regulated by the alternation of SWS and REM bouts, and/or the 'memory capital' that needs to be consolidated (shorter cycles when more traces need to consolidated).

Our analysis could benefit from the construction of predictive models (GLMMs) to better assess the interactions between prioritising factors. However, to do so, recording from more animals is needed. Given more time, it would be interesting to investigate the prioritisation parameter space further: testing different levels of reward, varying the number and familiarity of the recorded environments, shortening

or extending the amount of time between the contexts. Inclusion of context-specific tasks as a means to assess memory performance would be yet another asset to build a detailed model of memory triage.

In addition to increasing the replay frequency of prioritised contexts, memory triage may also support building and storing more detailed representations of the experience, or prioritised elements within the representation. Developing recording bias-free methods to quantify the fidelity of representations during wake and sleep states is an important direction for future work.

Finally, the role of the cortex in memory triage is unknown. It is known that memory consolidation is dependent on bidirectional hippocampo-cortical interactions (Girardeau et al., 2009; Ji and Wilson, 2007; Maingret et al., 2016; Pavlides and Wilson, 1989; Peyrache et al., 2009; Wilson and McNaughton, 1994). While hippocampal traces are potentiated and tagged during wake states (Duszkiewicz et al., 2019; Frey and Morris, 1997; McNamara et al., 2014), so are cortical ones (Lesburguères et al., 2011), and therefore the cortex may also 'vote' for which memory will be prioritised in subsequent replay events. Likewise, the cortex may also provide feedback to the hippocampus to indicate which representation has been replayed enough, and it is time for the next context to be prioritised.

Appendix A

Appendix Chapter 5

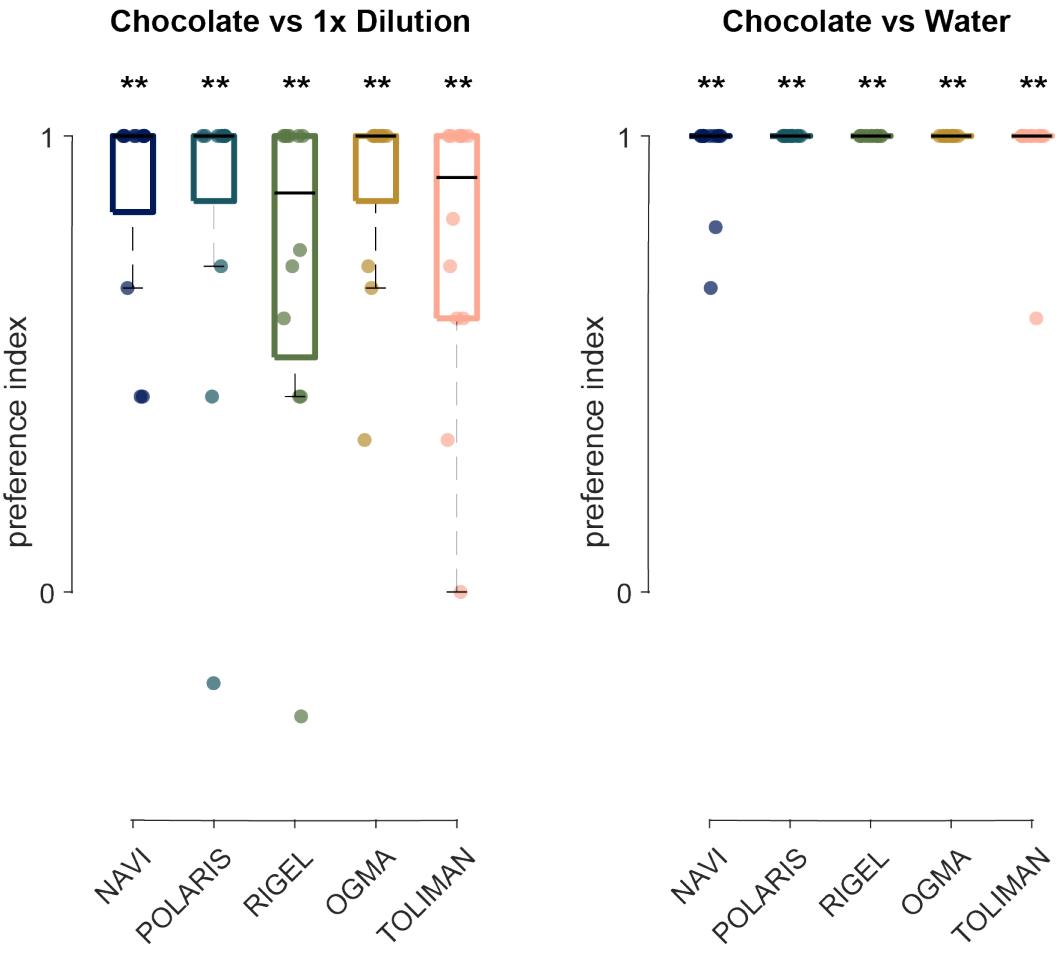

Figure A.1: Reward Preference: **LEFT** boxplot and individual trial data of the preference index for each rat. A value of 1 indicates a strong that the chocolate reward was exclusively consumed on that trial, and a value of -1 that the 1x dilution was exclusively consumed. p-values of the Wilcoxon signed rank test (*** indicates $p < 0.001$) **RIGHT** Similarly, preference index for chocolate over water

Test	Rat	Preference Index	signed rank	z value	p value
Chocolate vs 1x Dilution	NAVI	0.87	78	3.06	** **0.002**
	POLARIS	0.828	76.5	2.94	** **0.003**
	RIGEL	0.72	74	2.77	** **0.005**
	OGMA	0.89	78	3.08	** **0.002**
	TOLIMAN	0.75	66	2.95	** **0.003**
Chocolate vs Water	NAVI	0.95	78	3.08	** **0.002**
	POLARIS	1	78	3.08	** **0.002**
	RIGEL	1	78	3.07	** **0.002**
	OGMA	1	78	3.08	** **0.002**
	TOLIMAN	0.96	78	3.08	** **0.002**

Table A.1: Summary statistics for reward preference tests

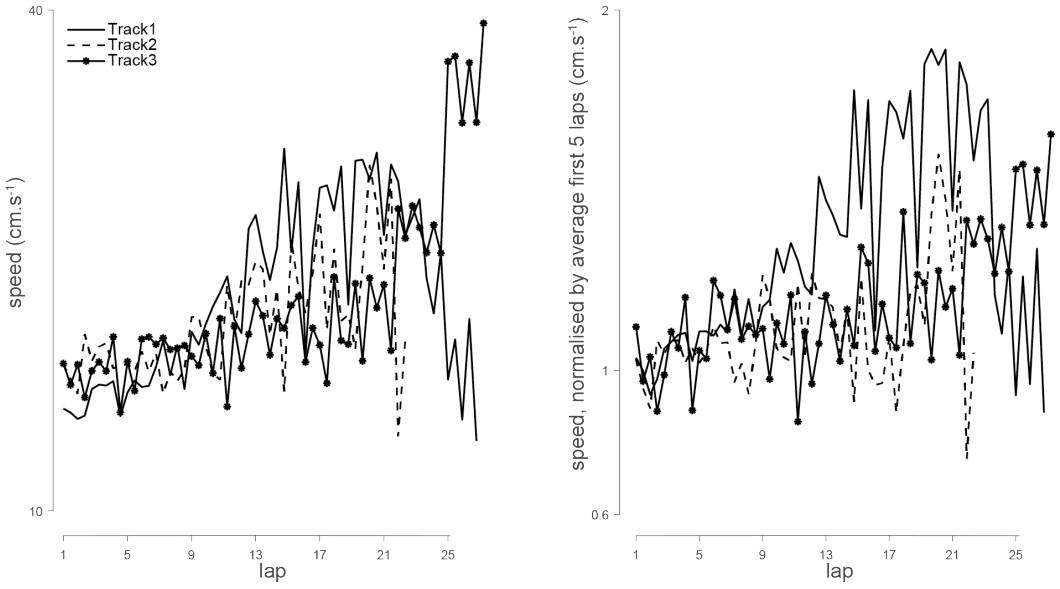

Figure A.2: Left: Median running speed per lap, averaged over all rats **Right:** Median running speed per lap, normalised by the mean running speed during the first 5 laps for each track, and averaged over all rats

	Est.	S.E.	z val.	p value
(Intercept)	2.58	0.06	38.85	*** < **0.001**
reward.L	0.19	0.04	4.68	*** < **0.001**

Contrast	Ratio	Lower CI	Upper CI	S.E.	z ratio	p value
HIGH/LOW	1.32	1.17	1.48	0.07	4.68	*** < **0.001**

Table A.2: Summary statistics for the mixed Poisson model: number of laps $\sim$ reward + (rat|session), back transformed to response scale

	Est.	S.E.	z val.	p value
(Intercept)	2.58	0.07	39.46	*** < **0.001**
reward.L	0.20	0.04	4.57	*** <**0.001**
recency.L	0.08	0.05	1.52	0.13
recency.Q	0.04	0.05	0.83	0.41
reward.L:recency.L	0.02	0.08	0.21	0.83
reward.L:recency.Q	0.19	0.08	2.39	* **0.02**

Contrast	Ratio	Lower CI	Upper CI	S.E.	z ratio	p value
HIGH T1/LOW T1	1.45	0.17	1.08	1.94	3.19	** **0.006**
HIGH T3/LOW T1	1.64	0.18	1.25	2.15	4.62	*** < **0.001**
HIGH T3/LOW T2	1.40	0.14	1.09	1.78	3.46	** **0.002**
HIGH T1/LOW T3	1.32	0.13	1.03	1.70	2.79	* **0.02**
HIGH T3/LOW T3	1.50	0.16	1.14	1.97	3.75	*** < **0.001**

Table A.3: Summary statistics for the mixed Poisson model: number of laps $\sim$ reward*recency + (rat|session), contrasts back transformed to response scale

	Est.	S.E.	z val.	p value
(Intercept)	2.61	0.06	45.56	*** < **0.001**
reward diff.L	0.19	0.07	2.78	** **0.006**
reward diff.Q	-0.01	0.08	-0.13	0.89
reward diff.C	-0.22	0.09	-2.38	* **0.017**

Contrast	Ratio	Lower CI	Upper CI	S.E.	z ratio	p value
(H-H)/(L-L)	1.47	1.07	2.02	0.20	2.88	* **0.01**
(H-H)/(H-L)	1.33	1.03	1.72	0.14	2.67	* **0.02**

Table A.4: Summary statistics for the mixed Poisson model: number of laps $\sim$ change in reward + (rat|session), back transformed to response scale

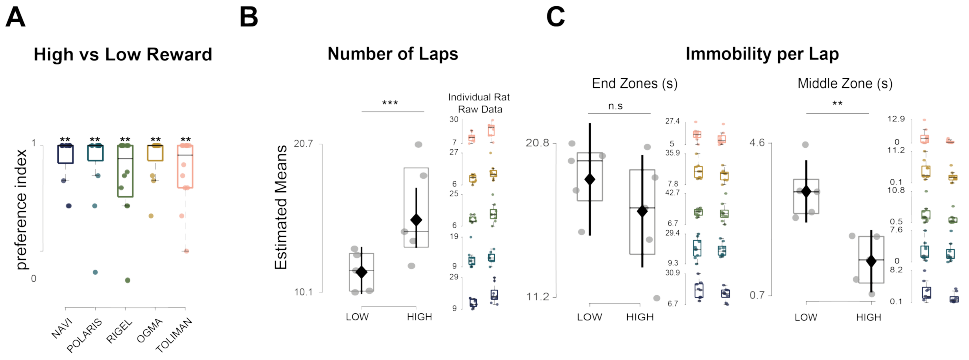

Figure A.3: **A**: boxplot and individual trial data of the preference index for each rat for pure chocolate vs its 1:1 dilution. **B-C**: Left plots: boxplot of the raw data, estimated means and their 95% confidence intervals for the number of laps for each rat (n=5) in each condition. Right plots: boxplot of the number of laps per environment across conditions, for each rat . **B**: output of the mixed poisson model number of laps $\sim$ reward + (rat|session). **C, left**: stopping time at the end zones **C, right**: stopping time in the middle of the track

	Est.	S.E.	t val.	d.f	p value
(Intercept)	12.28	0.40	30.90	3.99	*** $<$ **0.001**
reward.L	1.01	0.24	4.19	60.55	*** $<$ **0.001**
recency.L	0.62	0.29	2.17	52.95	* **0.034**
recency.Q	0.24	0.29	0.83	52.98	0.41
reward.L:recency.L	-0.02	0.46	-0.04	80.01	0.97
reward.L:recency.Q	1.22	0.45	2.69	79.95	** **0.009**

Contrast	Ratio	Lower CI	Upper CI	S.E.	d.f.	t ratio	p value
HIGH T1/LOW T1	2.15	0.50	3.80	0.64	77.85	3.35	** **0.006**
HIGH T3/LOW T1	3.01	1.45	4.58	0.60	63.34	4.99	*** $<$ **0.001**
HIGH T3/LOW T2	1.8	0.29	3.31	0.58	62.89	3.08	* **0.01**
HIGH T3/LOW T3	2.11	0.46	3.77	0.64	78.40	3.31	** **0.007**

Table A.5

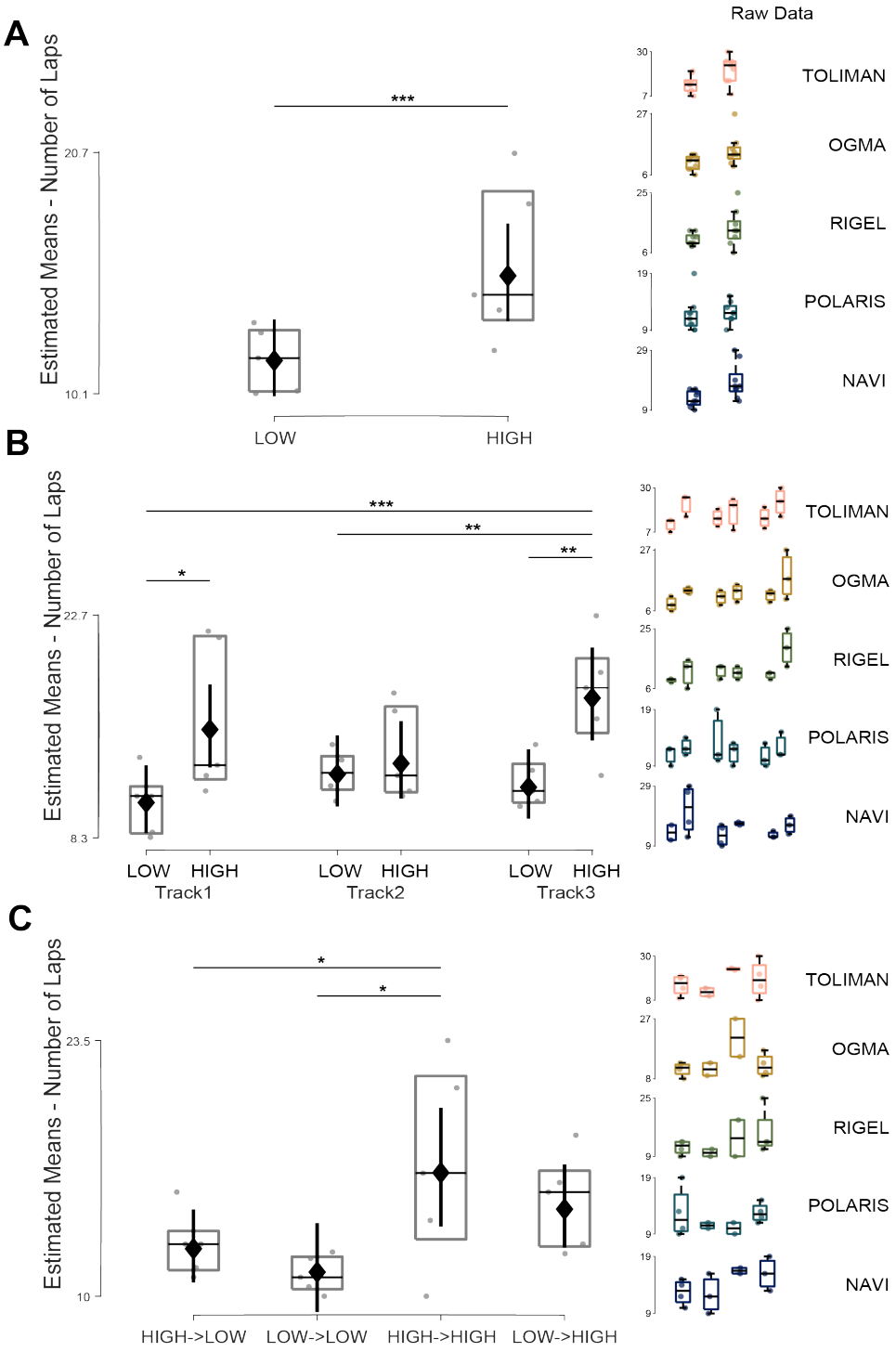

Figure A.4: Left plots: boxplot of the raw data, estimated means and their 95% confidence intervals for the number of laps for each rat (n=5) in each condition. Right plots: boxplot of the number of laps per environment across conditions, for each rat . **A**: output of the mixed poisson model number of laps $\sim$ reward + (rat|session). **B**: output of the mixed poisson model number of laps $\sim$ reward*recency + (rat|session). **C**: output of the mixed poisson model number of laps $\sim$ change in reward + (rat|session)

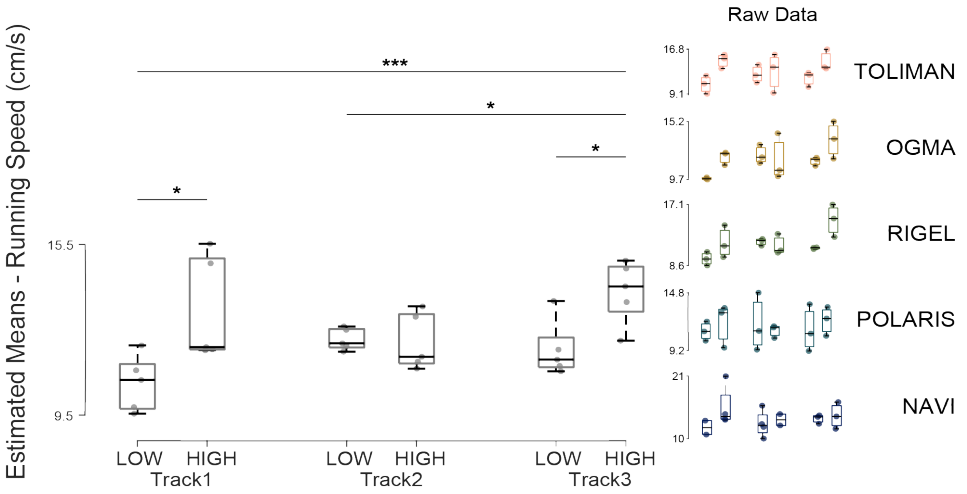

Figure A.5: Left plots: boxplot of the estimated means for running speed (v $>$ 5cm.s $^{-1}$) for each rat (n=5) for each condition following the mixed gaussian model running speed $\sim$ reward*recency + (rat|session) . Right plots: boxplot of the running speed per environment across conditions, for each rat.

	Est.	S.E.	t val.	d.f.	p value
(Intercept)	17.57	1.29	13.57	4	*** $<$ **0.001**
reward.L	-1.41	0.87	-1.61	66.23	0.11

Contrast	Ratio	Lower CI	Upper CI	S.E.	d.f.	t ratio	p value
HIGH/LOW	-1.99	-4.48	0.48	1.24	66.31	-1.60	0.11

Table A.6: Summary statistics for the mixed Gaussian model: time spent $<$ 5cm.s^{-1} at end zones $\sim$ reward + (rat|session)

	Est.	S.E.	t val.	d.f.	p value
(Intercept)	2.47	0.26	9.34	88	*** $<$ **0.001**
reward.L	-1.26	0.37	-3.35	88	*** **0.001**

Contrast	Ratio	Lower CI	Upper CI	S.E.	d.f.	t ratio	p value
HIGH/LOW	-1.78	-2.83	-0.72	0.53	84	-3.35	** **0.001**

Table A.7: Summary statistics for the mixed Gaussian model: time spent $<$ 5cm.s^{-1} in middle zone $\sim$ reward + (rat)

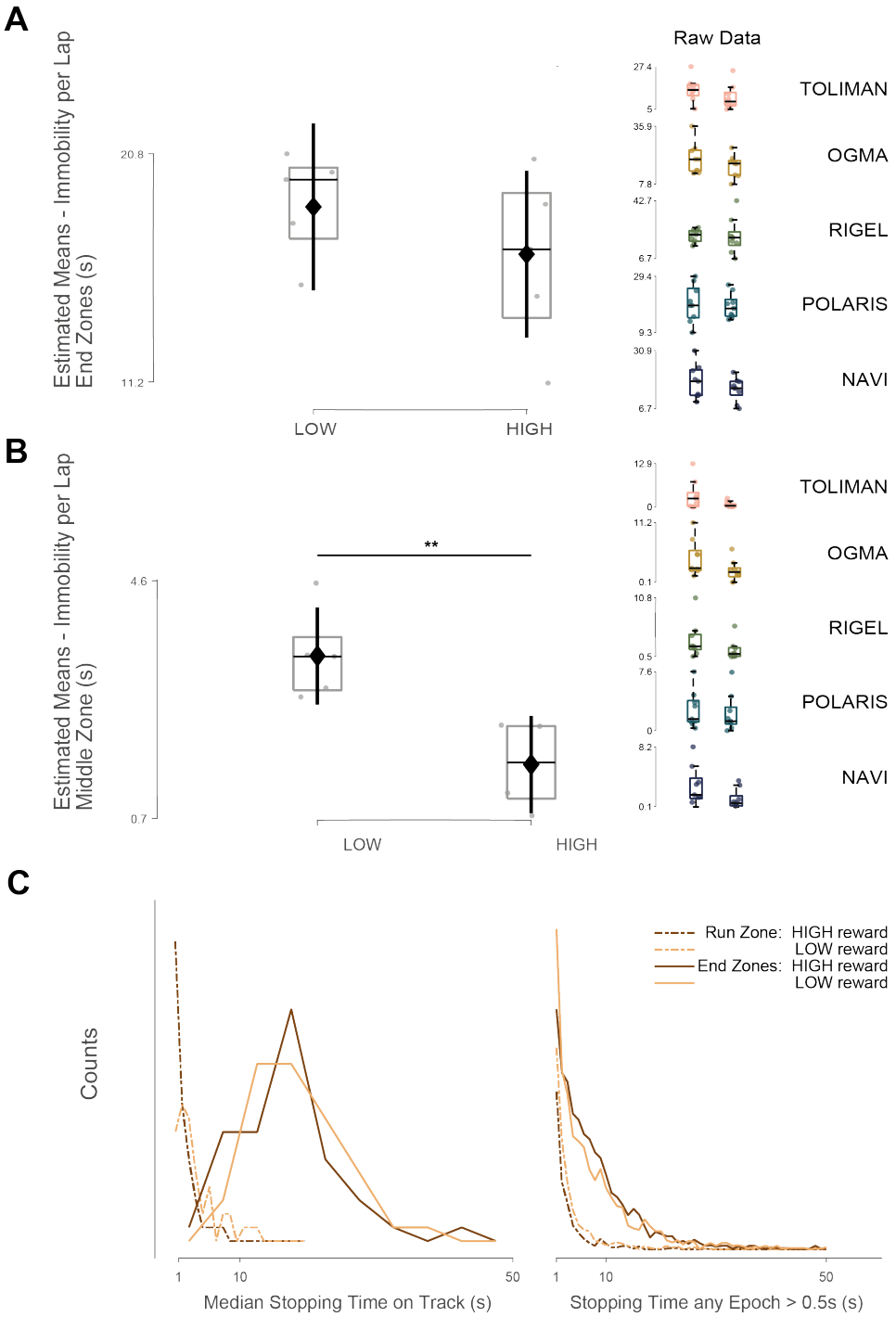

Figure A.6: Left plots: boxplot of the estimated means for time spent immobile (v $<$ 5cm.s $^{-1}$) for each rat (n=5) for each condition. Right plots: boxplot of the time spent immobile per lap across conditions, for each rat . **A**: output of the mixed gaussian model time spent immobile per lap at end zones $\sim$ reward + (rat|session). **B**: output of the mixed gaussian model time spent immobile per lap in middle zone $\sim$ reward + (1|rat). **C**, Left: Count distributions of median stopping time per lap. Right: Count distributions of stopping times ($>$ 0.5s) at end and middle zones, for LOW or HIGH reward

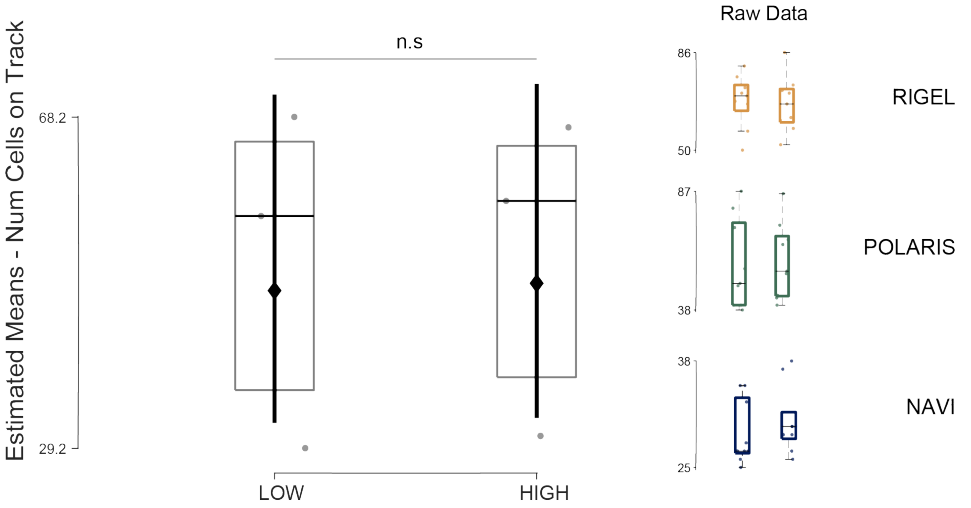

Figure A.7: Left plots: boxplot of the estimated means for the number of spatially modulated cells for each rat (n=3) for each condition following the mixed Poisson model: number of cells $\sim$ reward + (1|rat) . Right plots: boxplot of the number of cells per environment across conditions, for each rat.

	Est.	S.E.	z val.	p value
(Intercept)	3.87	0.20	19.36	*** $<$ **0.001**
reward.L	0.01	0.02	0.45	0.45

Contrast	Ratio	Lower CI	Upper CI	S.E.	z ratio	p value
HIGH/LOW	1.01	0.94	1.1	0.04	0.45	0.65

Table A.8: Summary statistics for the mixed Poisson model: number of cells on track $\sim$ reward + (rat|session)

	Est.	S.E.	z val.	p value
(Intercept)	4.14	0.01	287	*** $<$ **0.001**
reward.L	0.06	0.003	20.35	*** $<$ **0.001**

Contrast	Ratio	Lower CI	Upper CI	S.E.	z ratio	p value
HIGH/LOW	1.10	1.09	1.11	0.005	20.35	*** $<$ **0.001**

Table A.9: Summary statistics for the mixed Poisson model: Peak in field firing rate $\sim$ reward + (rat|session)

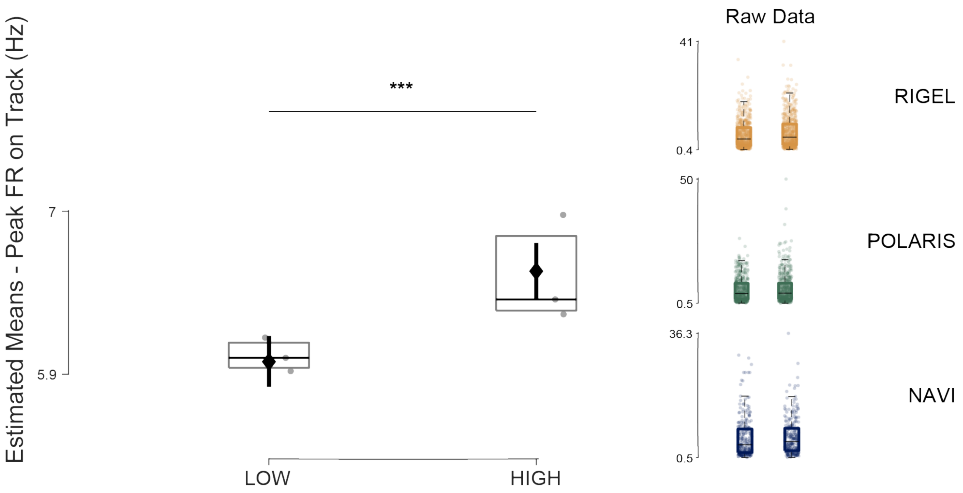

Figure A.8: Left plots: boxplot of the estimated means for the peak in field firing rate for each rat (n=3) for each condition following the mixed Poisson model: peak firing rate $\sim$ reward + (1|rat) . Right plots: boxplot of the peak firing rate per environment across conditions, for each rat.

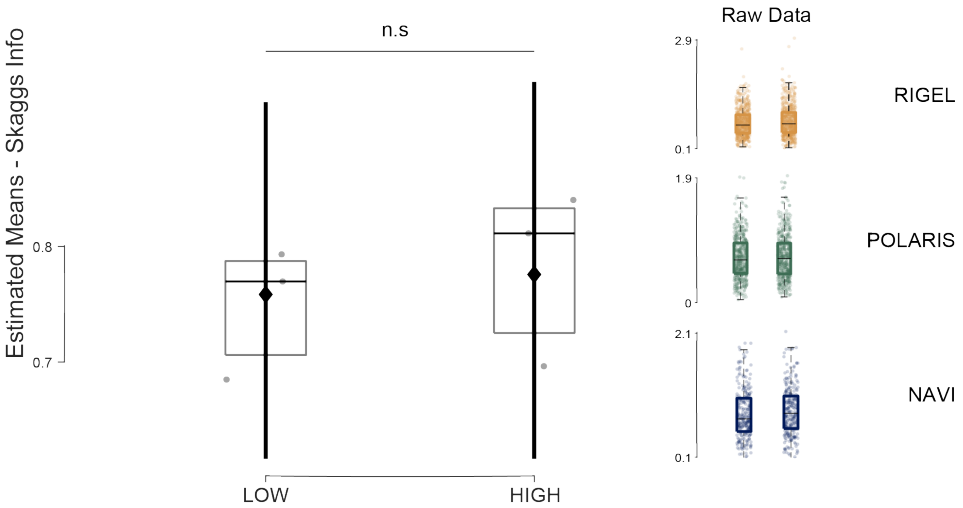

Figure A.9: Left plots: boxplot of the estimated means for the skaggs information of spatially modulated cells, for each rat (n=3) and condition following the mixed gaussian model: skaggs information $\sim$ reward + (1|rat) . Right plots: boxplot of skaggs information content of cells per environment across conditions, for each rat.

	Est.	S.E.	t val.	p value
(Intercept)	-0.27	0.04	-5.15	*** $<$ **0.001**
reward.L	0.015	0.013	1.18	0.23

Contrast	Ratio	Lower CI	Upper CI	S.E.	z ratio	p value
HIGH/LOW	1.02	0.98	1.06	0.019	1.18	0.23

Table A.10: Summary statistics for the mixed gaussian model: skaggs information $\sim$ reward + (rat|session), estimated effect on the log scale. contrasts back transformed to the response scale.

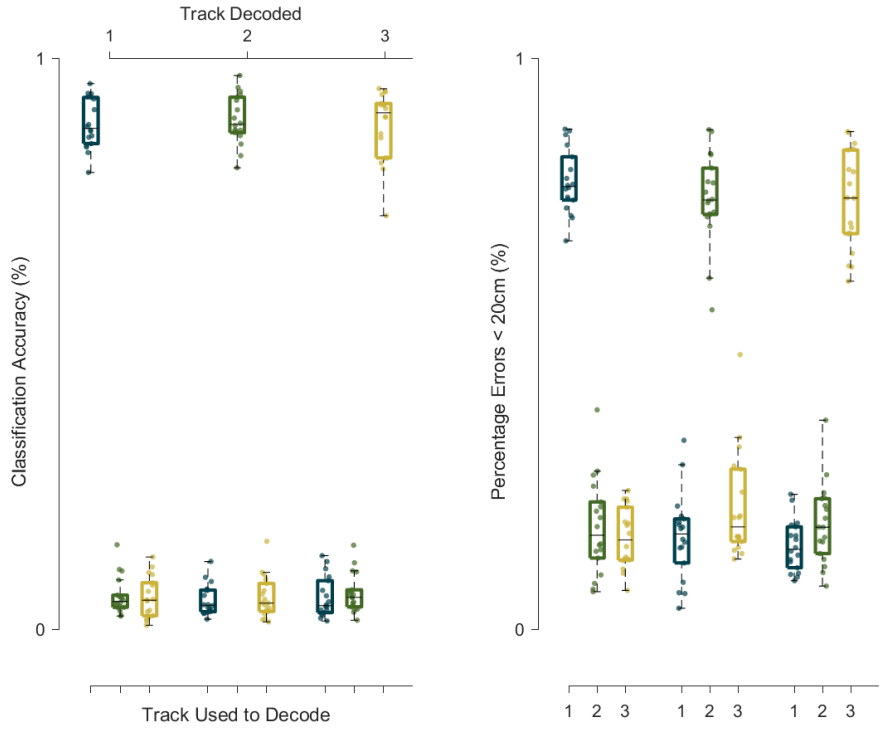

Figure A.10: Classification Accuracy and Decoding Error: **LEFT** Percentage of time bins during exploration ($v > 5cm.s^{-1}$) where the maximum decoded probability falls on the current track. For each track, ratemaps from all three environments were used in turn. A high classification accuracy when using the current track's ratemaps but a low classification accuracy when using those of other tracks indicates that the representations are distinct enough for us to attribute replay events (for example) to one particular environment over the others. **RIGHT** Percentage of time bins with a distance between the real and decoded positions smaller than 20cm. Again, the decoder does not have a mirror representation of the current track when using alternate tracks, as is shown by the higher number of bins with a small distance when using the current track's ratemaps.

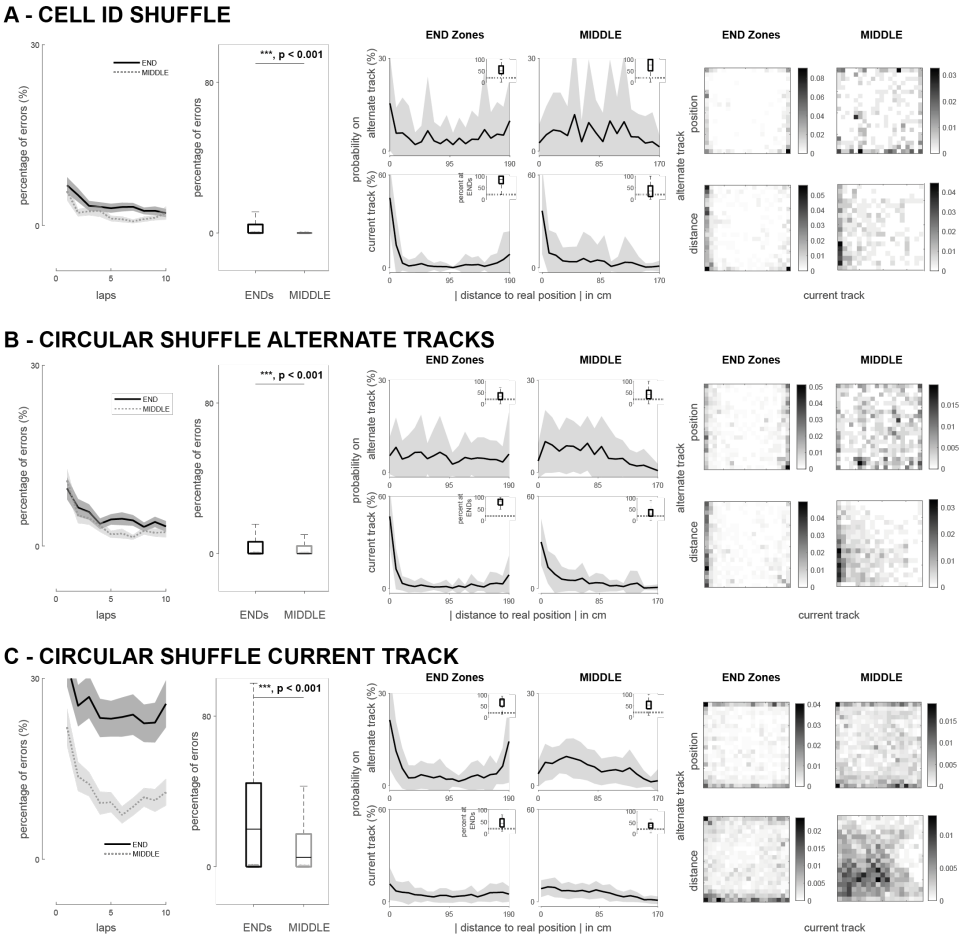

Figure A.11: Only a major disruption of the distribution of cells on the track remove teleportation to the end zones effects. For each panel, Left: percentage of errors for the middle and end zones as a function of the number of laps. Center: histogram of the absolute distance from decoded to real position in cm when there is a classification error, for the current and alternate tracks depending if the real position is in the end zones or middle zone. Right: probability matrix of decoded positions on the current track versus the alternate track (top) and for distance to real position (bottom)

A: Cell ID shuffle. The identity of the ratemap corresponding to each spatially tuned cell was randomly shuffled for each alternate track independently, keeping the current track intact

B: Circular ratemap shuffle. The ratemap of each spatially tuned cell was circularly randomly shifted for each alternate track independently, keeping the current track intact

C: Circular ratemap shuffle of the current track. The ratemap of each spatially tuned cell was circularly randomly shifted for the current track, keeping the alternate tracks intact

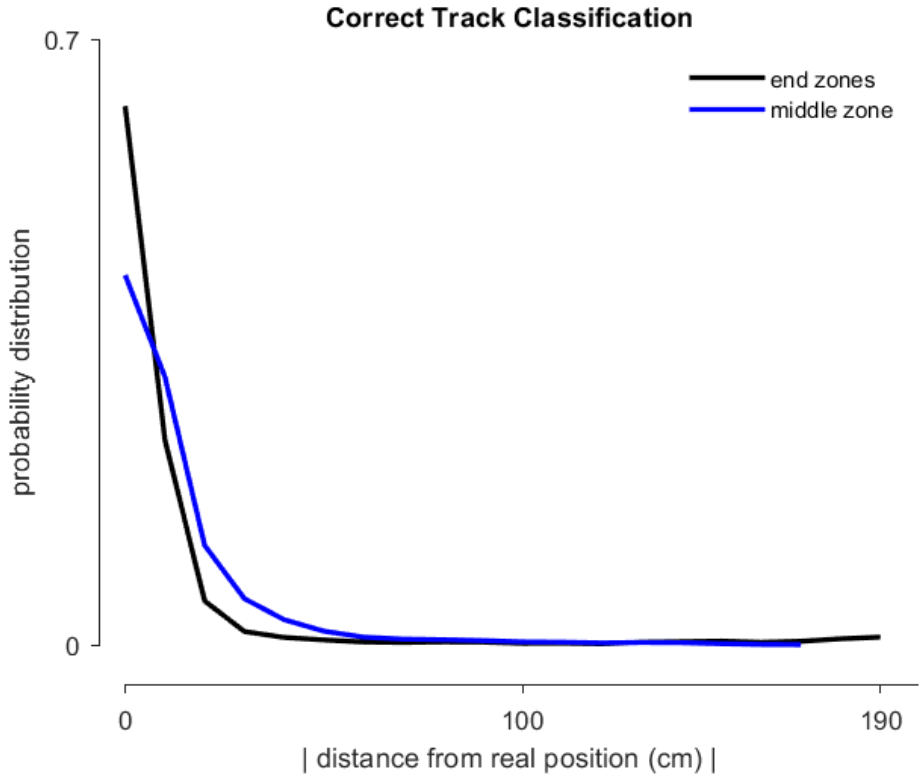

Figure A.12: Probability distributions of the absolute distance between real and decoded position when the track classification is accurate, for end zones and middle zone

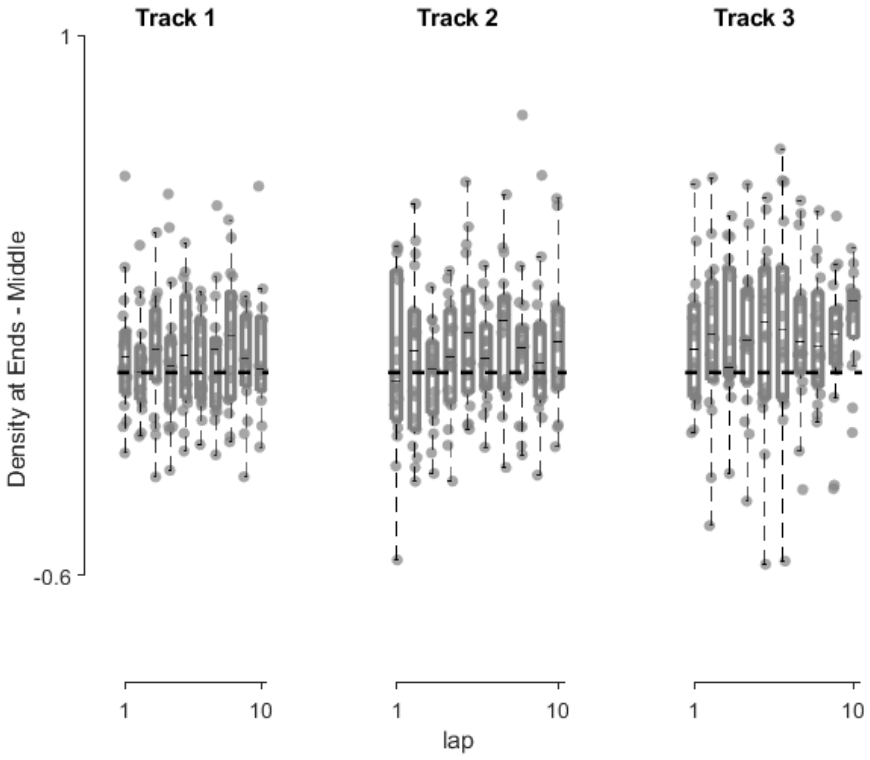

Figure A.13: Difference in percentage of cells per cm between the end zones and the middle zone. positive values indicate a higher density in the end zones.

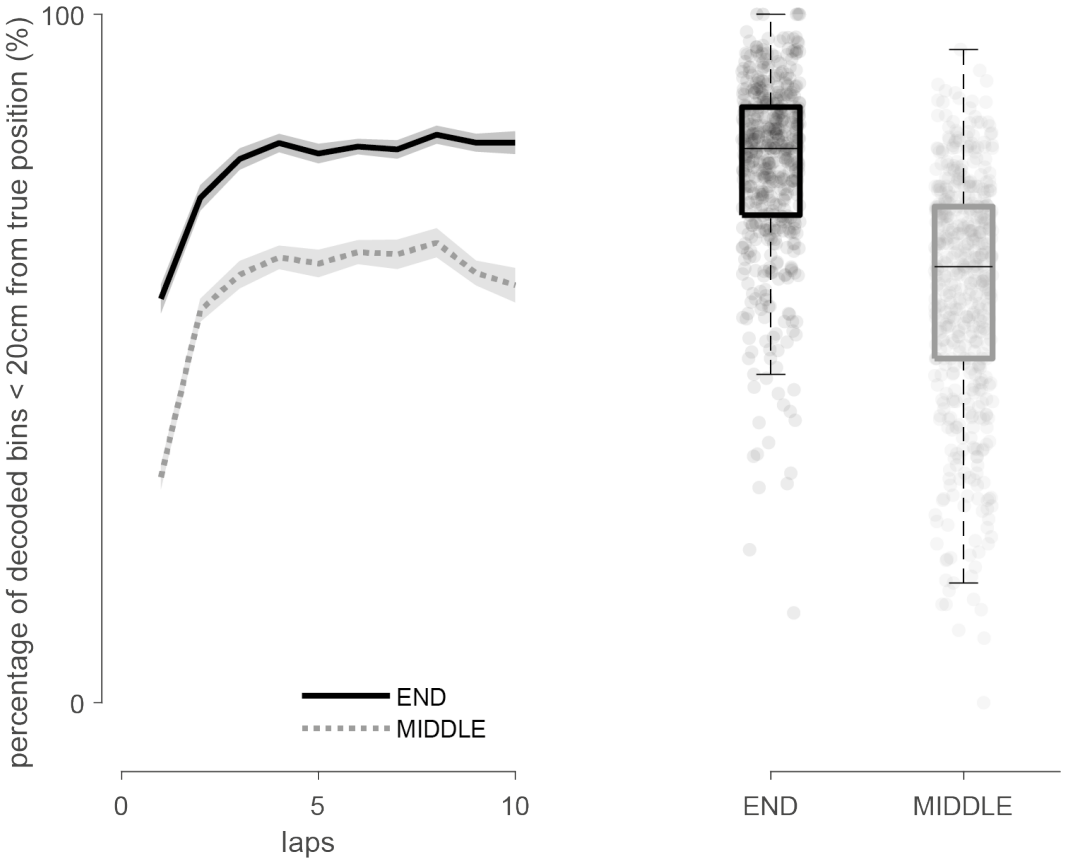

Figure A.14: Left: percentage of decoded bins within 20cm of the animal's true position as a function of the number of laps on a track, for end and middle zones. **Right:** boxplot and raw data to the left aggregated over the first 10 laps

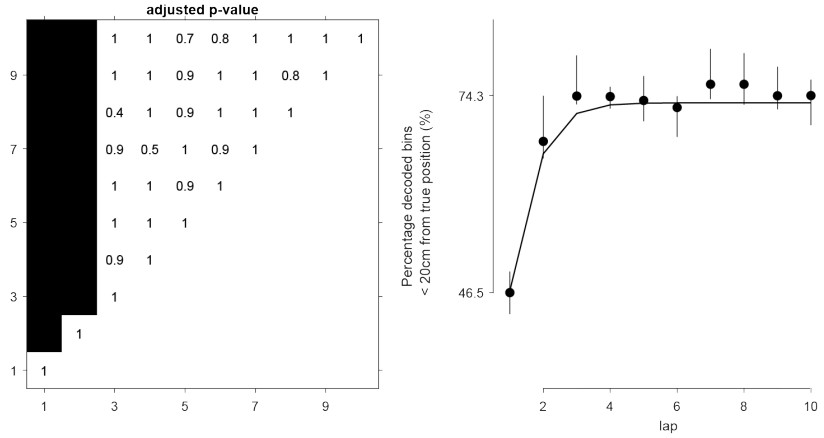

Figure A.15: Left: Holm-Sidak adjusted p-values for between lap differences in the percentage of small position errors, Friedman with post-hoc Conover tests Right: percentage of small position errors for each lap

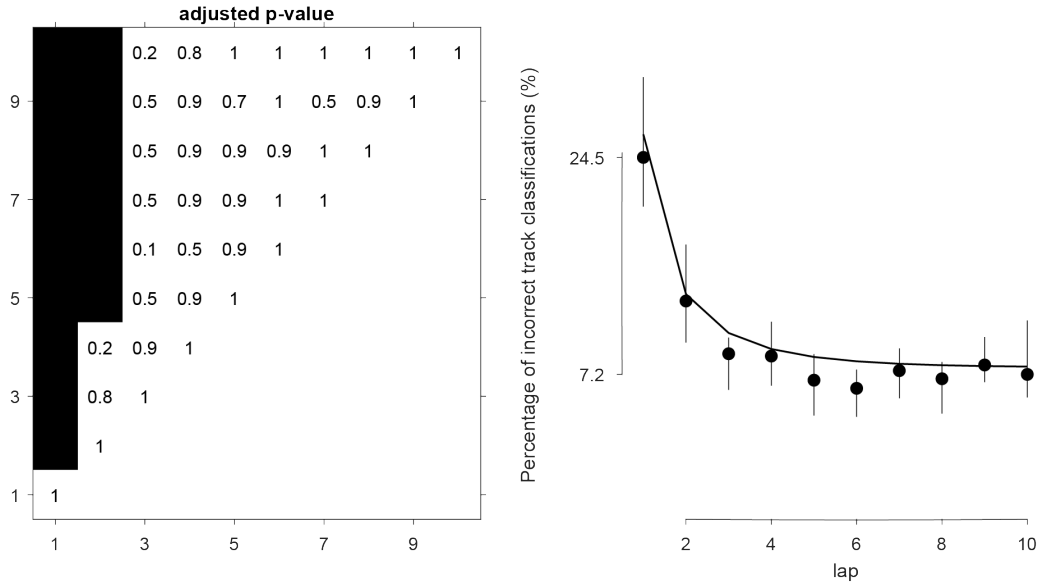

Figure A.16: Left: Holm-Sidak adjusted p-values for between lap differences in the percentage of track classification errors, Friedman with post-hoc Conover tests Right: percentage of track classification errors over laps

Appendix B

Appendix Chapter 6

Epoch	Comparison	z-score	p-value	tail
Sleep PRE	T2-T1	-1.04	0.29	two-tailed
	T3-T1	-0.21	0.82	two-tailed
	T3-T2	0.84	0.39	two-tailed
Track1	T3-T2	0.02	0.98	two-tailed
	T1-T2	6.23	<0.001	one-tailed
	T1-T3	3.26	<0.001	one-tailed
Rest1	T3-T2	0.02	0.98	two-tailed
	T1-T2	6.23	<0.001	one-tailed
	T1-T3	3.26	<0.001	one-tailed
Track2	**T1-T3**	2.24	0.012	one-tailed
	T2-T1	4.41	<0.001	one-tailed
	T2-T3	6.50	<0.001	one-tailed
Rest2	**T1-T3**	3.92	<0.001	one-tailed
	T2-T1	1.6	0.053	one-tailed
	T2-T3	5.61	<0.001	one-tailed
Track3	T2-T1	0.34	0.72	two-tailed
	T3-T1	6.14	<0.001	one-tailed
	T3-T2	5.64	<0.001	one-tailed
Rest3	T2-T1	1.52	0.12	two-tailed
	T3-T1	5.71	<0.001	one-tailed
	T3-T2	3.85	<0.001	one-tailed
sleep POST	T2-T1	-0.12	0.91	two-tailed
	T3-T1	3.27	<0.001	one-tailed
	T3-T2	3.37	<0.001	one-tailed

Table B.1: Summary statistics of recency effects for each epoch.

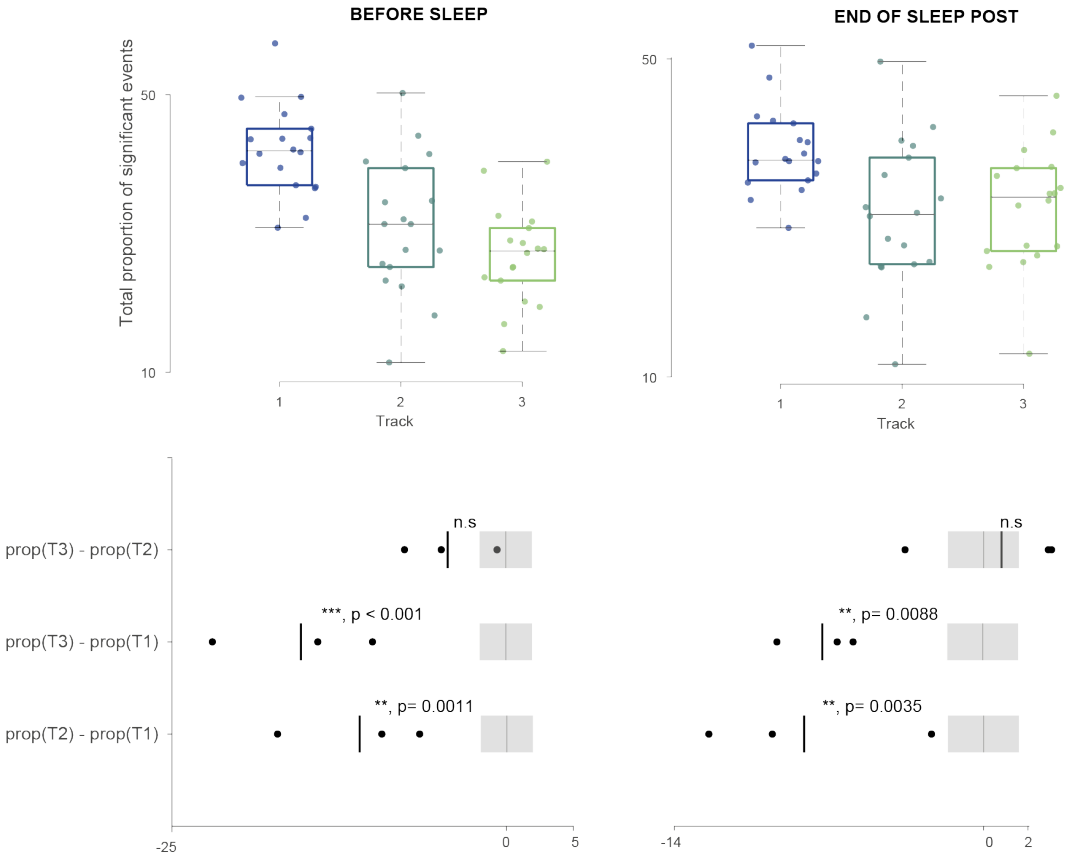

Figure B.1: **Top row:** Boxplot and session data of the proportion of replay events for each track calculated over all session until designated epoch
Bottom row: difference in proportions between track pairs. the black line indicates the observed difference, the grey rectangles are the mean and standard deviations of the bootstrapped label-shuffled distributions. Significance is denoted by an asterisk
Left: up to just before sleep, including Rest3, Right: at the end of the sleep period

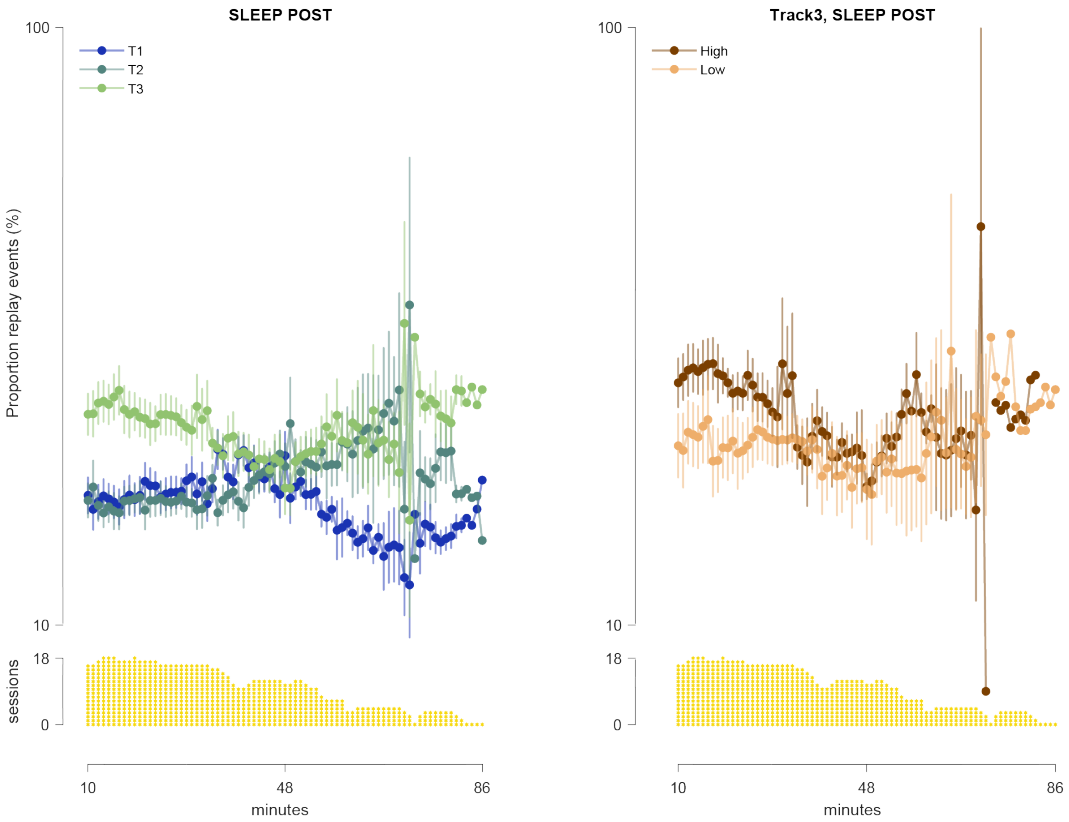

Figure B.2: Top: proportion of significant replay events during sleepPOST with a moving average of 20min and step size of 1min Left: grouped by recency, Right: Track3 grouped by reward.
Bottom: Number of sessions contributing to each time point

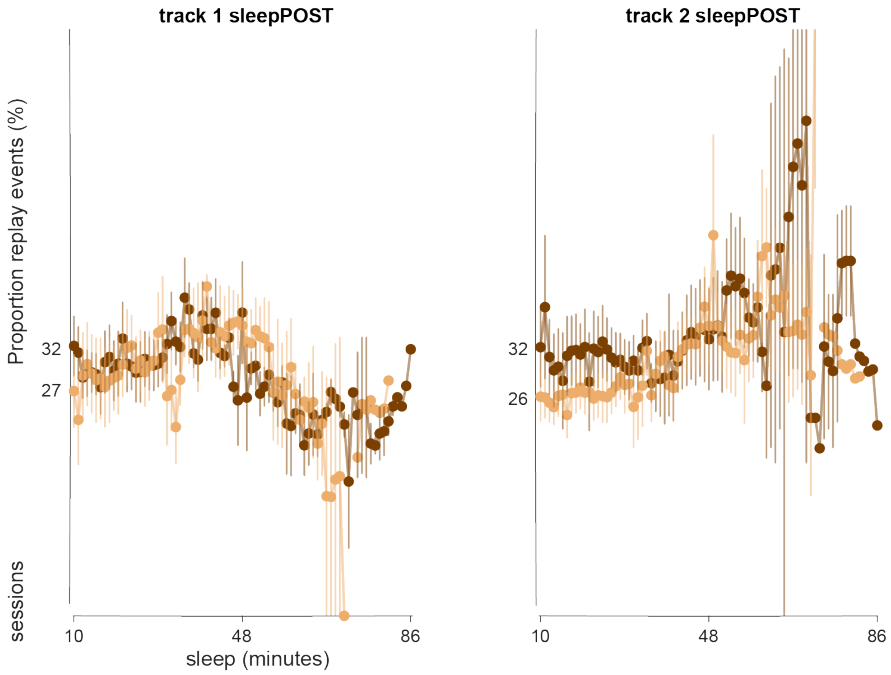

Figure B.3: proportion of significant replay events during sleepPOST with a moving average of 20min and step size of 1min Left: Track1, grouped by reward Right: Track2, grouped by reward.
The number of sessions is similar to B.2

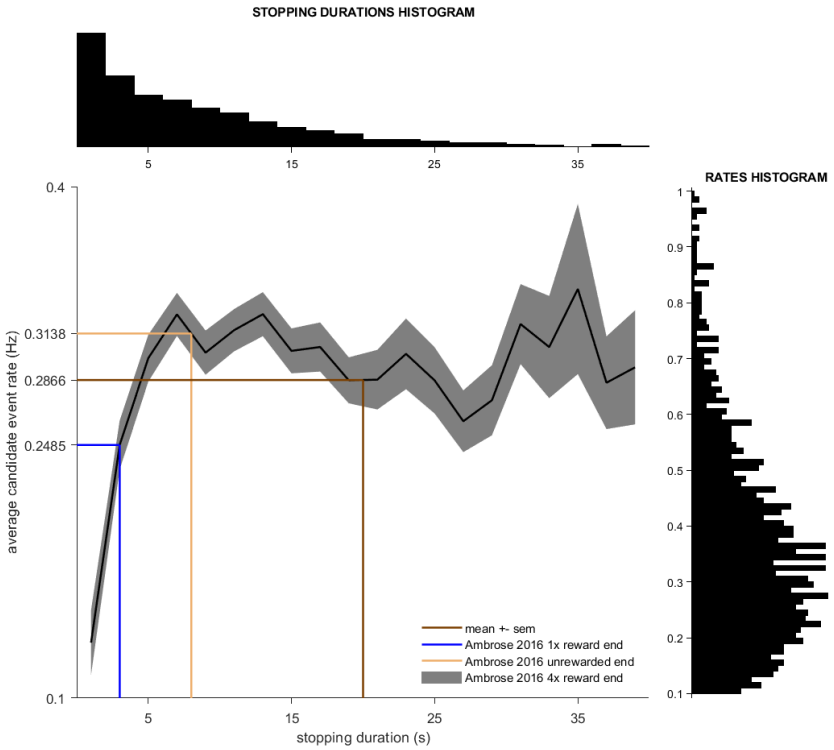

Figure B.4: main plot: average candidate event rate as a function of the stopping duration on the tracks (2s bins). Super-imposed, mean stopping times from Ambrose et al. (2016) for different reward conditions
Top: histogram of stopping durations (>1s). **Right:** histogram of candidate event rate per stopping epoch (>1s)

Bibliography

R. Alison Adcock, Arul Thangavel, Susan Whitfield-Gabrieli, Brian Knutson, and John D.E. Gabrieli. Reward-Motivated Learning: Mesolimbic Activation Precedes Memory Formation. *Neuron*, 50(3):507–517, 5 2006. ISSN 08966273. doi: 10.1016/j.neuron.2006.03.036.

Cristina M. Alberini. Transcription factors in long-term memory and synaptic plasticity, 1 2009. ISSN 00319333.

Alejandra Alonso, Jacqueline van der Meij, Dorothy Tse, and Lisa Genzel. Naïve to expert: Considering the role of previous knowledge in memory. *Brain and neuroscience advances*, 4:2398212820948686, 1 2020. ISSN 2398-2128. doi: 10.1177/2398212820948686. URL `http://www.ncbi.nlm.nih.gov/pubmed/32954007http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7479862`.

D. G. Amaral and M. P. Witter. The three-dimensional organization of the hippocampal formation: A review of anatomical data. *Neuroscience*, 31(3):571–591, 1989. ISSN 03064522. doi: 10.1016/0306-4522(89)90424-7.

R. Ellen Ambrose, Brad E. Pfeiffer, and David J. Foster. Reverse Replay of Hippocampal Place Cells Is Uniquely Modulated by Changing Reward. *Neuron*, 91 (5):1124–1136, 2016. ISSN 10974199. doi: 10.1016/j.neuron.2016.07.047. URL `http://dx.doi.org/10.1016/j.neuron.2016.07.047`.

M. V. Ambrosini and A. Giuditta. Learning and sleep: The sequential hypothesis, 12 2001. ISSN 10870792.

P. Andersen, T. V.P. Bliss, and K. K. Skrede. Lamellar organization of hippocampal excitatory pathways. *Experimental Brain Research*, 13(2):222–238, 8 1971. ISSN 00144819. doi: 10.1007/BF00234087.

Michael I. Anderson and Kathryn J. Jeffery. Heterogeneous modulation of place cell firing by changes in context. *Journal of Neuroscience*, 23(26):8827–8835, 10 2003. ISSN 02706474. doi: 10.1523/jneurosci.23-26-08827.2003.

Dmitriy Aronov, Rhino Nevers, and David W. Tank. Mapping of a non-spatial dimension by the hippocampal-entorhinal circuit. *Nature*, 543(7647):719–722, 3 2017. ISSN 14764687. doi: 10.1038/nature21692.

Marjan Alizadeh Asfestani, Valentin Brechtmann, João Santiago, Andreas Peter, Jan Born, and Gordon Benedikt Feld. Consolidation of reward memory during sleep does not require dopaminergic activation. *Journal of Cognitive Neuroscience*, 32(9):1688–1703, 9 2020. ISSN 15308898. doi: 10.1162/jocn{_}a{_}01585. URL https://www.mitpressjournals.org/doi/abs/10.1162/jocn_a_01585.

G. Aston-Jones and F. E. Bloom. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience*, 1(8):876–886, 8 1981. ISSN 02706474. doi: 10.1523/jneurosci.01-08-00876.1981.

Mercedes Atienza and Jose L. Cantero. Modulatory effects of emotion and sleep on recollection and familiarity. *Journal of Sleep Research*, 17(3):285–294, 9 2008. ISSN 09621105. doi: 10.1111/j.1365-2869.2008.00661.x.

Jaideep S. Bains, J. Mark Longacher, and Kevin J. Staley. Reciprocal interactions between CA3 network activity and strength of recurrent collateral synapses. *Nature Neuroscience*, 2(8):720–726, 1999. ISSN 10976256. doi: 10.1038/11184.

P. Baraduc, J.-R. Duhamel, and S. Wirth. Schema cells in the macaque hippocampus. *Science*, 363(6427):635–639, 2 2019. ISSN 0036-8075. doi: 10.1126/SCIENCE.AAV5404. URL https://science.sciencemag.org/content/363/6427/635https://science.sciencemag.org/content/363/6427/635.abstract.

Daniel N. Barry and Eleanor A. Maguire. Remote Memory and the Hippocampus: A Constructive Critique, 2 2019. ISSN 1879307X.

Susan J. Bartko, Boyer D. Winters, Rosemary A. Cowell, Lisa M. Saksida, and Timothy J. Bussey. Perirhinal cortex resolves feature ambiguity in configural object recognition and perceptual oddity tasks. *Learning and Memory*, 14(12): 821–832, 12 2007. ISSN 10720502. doi: 10.1101/lm.749207.

Frederic C. Bartlett and Walter Kintsch. *Remembering*. Cambridge University Press, 6 1995. ISBN 9780521483568. doi: 10.1017/CBO9780511759185. URL https://www.cambridge.org/core/product/identifier/9780511759185/type/book.

David I. Bass and Joseph R. Manns. Memory-Enhancing Amygdala Stimulation Elicits Gamma Synchrony in the Hippocampus. *Behavioral Neuroscience*, 129 (3):244–256, 6 2015. ISSN 19390084. doi: 10.1037/bne0000052.

Francesco P. Battaglia, Gary R. Sutherland, and Bruce L. McNaughton. Local sensory cues and place cell directionality: Additional evidence of prospective coding in the hippocampus. *Journal of Neuroscience*, 24(19):4541–4550, 5 2004. ISSN 02706474. doi: 10.1523/JNEUROSCI.4896-03.2004.

Oded Bein, Niv Reggev, and Anat Maril. Prior knowledge influences on hippocampus and medial prefrontal cortex interactions in subsequent memory. *Neuropsychologia*, 64:320–330, 11 2014. ISSN 18733514. doi: 10.1016/j.neuropsychologia.2014.09.046.

V Bellina, R Huber, M Rosanova, M Mariotti, and G Tononi. Cortical excitability

and sleep homeostasis in humans: a TMS/hd-EEG study O64. *Journal of Sleep*, 2008.

Daniel Bendor and Matthew A. Wilson. Biasing the content of hippocampal replay during sleep. *Nature Neuroscience*, 15(10):1439–1444, 10 2012. ISSN 10976256. doi: 10.1038/nn.3203.

Michael J. Beran, Charles R. Menzel, Audrey E. Parrish, Bonnie M. Perdue, Ken Sayers, J. David Smith, and David A. Washburn. Primate cognition: attention, episodic memory, prospective memory, self-control, and metacognition as examples of cognitive control in nonhuman primates, 9 2016. ISSN 19395086.

Ruud M.W.J. Berkers, Marieke van der Linden, Rafael F. de Almeida, Nils C.J. Müller, Leonore Bovy, Martin Dresler, Richard G.M. Morris, and Guillén Fernández. Transient medial prefrontal perturbation reduces false memory formation. *Cortex*, 88:42–52, 3 2017. ISSN 19738102. doi: 10.1016/j.cortex.2016.12.015.

Baburam Bhattarai, Jong Won Lee, and Min Whan Jung. Distinct effects of reward and navigation history on hippocampal forward and reverse replays. *Proceedings of the National Academy of Sciences*, 117(1): 689–697, 1 2020. ISSN 0027-8424. doi: 10.1073/PNAS.1912533117. URL `https://www.pnas.org/content/117/1/689https://www.pnas.org/content/117/1/689.abstract`.

E. L. Bienenstock, L. N. Cooper, and P. W. Munro. Theory for the development of neuron selectivity: Orientation specificity and binocular interaction in visual cortex. *Journal of Neuroscience*, 2(1):32–48, 1 1982. ISSN 02706474. doi: 10.1523/jneurosci.02-01-00032.1982.

Kenneth I. Blum and L. F. Abbott. A Model of Spatial Map Formation in the Hippocampus of the Rat. *Neural Computation*, 8(1):85–93, 1996. ISSN 08997667. doi: 10.1162/neco.1996.8.1.85.

Rafal Bogacz, Malcolm W. Brown, and Christophe Giraud-Carrier. Model of Familiarity Discrimination in the Perirhinal Cortex. *Journal of Computational Neuroscience 2001 10:1*, 10(1):5–23, 2001. ISSN 1573-6873. doi: 10.1023/A:1008925909305. URL https://link.springer.com/article/10.1023/A:1008925909305.

Annette Bohn and Dorthe Berntsen. Pleasantness bias in flashbulb memories: Positive and negative flashbulb memories of the fall of the Berlin Wall among East and West Germans. *Memory and Cognition*, 35(3):565–577, 2007. ISSN 0090502X. doi: 10.3758/BF03193295.

Bruno Bontempi, Catherine Laurent-Demir, Claude Destrade, and Robert Jaffard. Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature*, 400(6745):671–675, 8 1999. ISSN 00280836. doi: 10.1038/23270.

Romain Bourboulou, Geoffrey Marti, François Xavier Michon, Elissa El Feghaly, Morgane Nouguier, David Robbe, Julie Koenig, and Jerome Epsztein. Dynamic control of hippocampal spatial coding resolution by local visual cues. *eLife*, 8, 3 2019. ISSN 2050084X. doi: 10.7554/eLife.44487.

Leonore Bovy, Ruud M W J Berkers, Julia C M Pottkämper, Rathiga Varatheeswaran, Guillén Fernández, Indira Tendolkar, and Martin Dresler. Transcranial Magnetic Stimulation of the Medial Prefrontal Cortex Decreases Emotional Memory Schemas. *Cerebral Cortex*, 30(6):3608–3616, 5 2020. ISSN 1047-3211. doi: 10.1093/cercor/bhz329. URL https://academic.oup.com/cercor/article/30/6/3608/5699684.

Mark P. Brandon, Andrew R. Bogaard, Christopher P. Libby, Michael A. Connerney, Kishan Gupta, and Michael E. Hasselmo. Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science*, 332(6029):595–599, 4 2011. ISSN 00368075. doi: 10.1126/science.1201652.

Erin Kendall Braun, G. Elliott Wimmer, and Daphna Shohamy. Retroactive and

graded prioritization of memory by reward. *Nature communications*, 9(1):4886, 2018. ISSN 20411723. doi: 10.1038/s41467-018-07280-0. URL http://dx.doi.org/10.1038/s41467-018-07280-0.

M W Brown and Z I Bashir. Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 357(1424):1083, 8 2002. doi: 10.1098/RSTB.2002.1097. URL /pmc/articles/PMC1693011/?report=abstracthttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693011/.

Malcolm W. Brown and John P. Aggleton. Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience 2001 2:1*, 2(1):51–61, 2001. ISSN 1471-0048. doi: 10.1038/35049064. URL https://www.nature.com/articles/35049064.

Roger Brown and James Kulik. Flashbulb memories. *Cognition*, 5(1):73–99, 1 1977. ISSN 00100277. doi: 10.1016/0010-0277(77)90018-X.

Laure Buhry, Amir H. Azizi, and Sen Cheng. Reactivation, replay, and preplay: How it might all fit together, 2011. ISSN 16875443.

Neil Burgess, Eleanor A. Maguire, and John O'Keefe. The human hippocampus and spatial and episodic memory, 8 2002. ISSN 08966273.

Daniel Bushey, Giulio Tononi, and Chiara Cirelli. Sleep and synaptic homeostasis: Structural evidence in Drosophila. *Science*, 332(6037):1576–1581, 6 2011. ISSN 00368075. doi: 10.1126/science.1202839.

G. Buzsáki. Two-stage model of memory trace formation: A role for "noisy" brain states. *Neuroscience*, 31(3):551–570, 1 1989. ISSN 03064522. doi: 10.1016/0306-4522(89)90423-5.

G Buzsáki, D L Buhl, K D Harris, J Csicsvari, and A Morozov. HIPPOCAMPAL

NETWORK PATTERNS OF ACTIVITY IN THE MOUSE. Technical report, 2003.

György Buzsáki, Zsolt Horváth, Ronald Urioste, Jamille Hetke, and Kensall Wise. High-frequency network oscillation in the hippocampus. *Science*, 256(5059): 1025–1027, 5 1992. ISSN 00368075. doi: 10.1126/science.1589772.

Francesca Cacucci, Thomas J. Wills, Colin Lever, Karl Peter Giese, and John O'Keefe. Experience-dependent increase in CA1 place cell spatial information, but not spatial reproducibility, is dependent on the autophosphorylation of the α-isoform of the calcium/calmodulin-dependent protein kinase II. *Journal of Neuroscience*, 27(29):7854–7859, 7 2007. ISSN 02706474. doi: 10.1523/JNEUROSCI.1704-07.2007.

Larry Cahill and Michael T. Alkire. Epinephrine enhancement of human memory consolidation: Interaction with arousal at encoding. *Neurobiology of Learning and Memory*, 79(2):194–198, 3 2003. ISSN 10747427. doi: 10.1016/S1074-7427(02)00036-9.

Larry Cahill, Lukasz Gorski, and Kathryn Le. Enhanced human memory consolidation with post-learning stress: Interaction with the degree of arousal at encoding. *Learning and Memory*, 10(4):270–274, 7 2003. ISSN 10720502. doi: 10.1101/lm.62403.

Alyssa A. Carey, Youki Tanaka, and Matthijs A.A. van der Meer. Reward revaluation biases hippocampal replay content away from the preferred outcome. *Nature Neuroscience*, 22(9):1450–1459, 9 2019. ISSN 15461726. doi: 10.1038/s41593-019-0464-6.

R. McKell Carter. Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses. *Frontiers in Behavioral Neuroscience*, 3(AUG):21, 8 2009. ISSN 16625153. doi: 10.3389/neuro.08.021.2009. URL `http://journal.frontiersin.org/article/10.3389/neuro.08.021.2009/abstract`.

CDC. CDC - Data and Statistics - Sleep and Sleep Disorders. URL https://www.cdc.gov/sleep/data_statistics.html.

Sylvain Chauvette, Josée Seigneur, and Igor Timofeev. Sleep Oscillations in the Thalamocortical System Induce Long-Term Neuronal Plasticity. *Neuron*, 75(6): 1105–1113, 9 2012. ISSN 08966273. doi: 10.1016/j.neuron.2012.08.034.

Guifen Chen, Yi Lu, John A. King, Francesca Cacucci, and Neil Burgess. Differential influences of environment and self-motion on place and grid cell firing. *Nature Communications*, 10(1), 12 2019. ISSN 20411723. doi: 10.1038/s41467-019-08550-1.

Sen Cheng and Loren M. Frank. New Experiences Enhance Coordinated Neural Activity in the Hippocampus. *Neuron*, 57(2):303–313, 1 2008. ISSN 08966273. doi: 10.1016/j.neuron.2007.11.035.

Lisa Cipolotti, Tim Shallice, Dennis Chan, Nick Fox, Rachel Scahill, Gail Harrison, John Stevens, and Peter Rudge. Long-term retrograde amnesia... the crucial role of the hippocampus. *Neuropsychologia*, 39(2):151–172, 2 2001. ISSN 00283932. doi: 10.1016/S0028-3932(00)00103-2.

Chiara Cirelli, Reto Huber, Anupama Gopalakrishnan, Teresa L. Southard, and Giulio Tononi. Locus ceruleus control of slow-wave homeostasis. *Journal of Neuroscience*, 25(18):4503–4511, 5 2005. ISSN 02706474. doi: 10.1523/JNEUROSCI.4845-04.2005.

Robert E. Clark and Larry R. Squirea. Similarity in form and function of the hippocampus in rodents, monkeys, and humans. *Proceedings of the National Academy of Sciences of the United States of America*, 110(SUPPL2):10365–10370, 6 2013. ISSN 00278424. doi: 10.1073/pnas.1301225110.

Nicola S. Clayton and Anthony Dickinson. Episodic-like memory during cache recovery by scrub jays. *Nature*, 395(6699):272–274, 9 1998. ISSN 00280836. doi: 10.1038/26216.

Jeremy D Cohen, Mark Bolstad, and Albert K Lee. Experience-dependent shaping of hippocampal CA1 intracellular activity in novel and familiar environments. *eLife*, 2017. doi: 10.7554/eLife.23040.001.

Laura Lee Colgin, Edvard I. Moser, and May Britt Moser. Understanding memory through hippocampal remapping, 2008. ISSN 01662236.

Martin A Conway, Stephen J Anderson, Steen F Larsen, C M Donnelly, M A Mcdaniel, A G R Mcclelland, R E Rawles, and R H Logie. The formation of flashbulb memories. Technical Report 3, 1994.

Elisa Cooper, Andrea Greve, and Richard N. Henson. Little evidence for Fast Mapping (FM) in adults: A review and discussion. *Cognitive Neuroscience*, 10(4):196–209, 10 2019. ISSN 1758-8928. doi: 10.1080/17588928.2018.1542376. URL `https://www.tandfonline.com/doi/full/10.1080/17588928.2018.1542376`.

Marc N. Coutanche and Sharon L. Thompson-Schill. Fast mapping rapidly integrates information into existing memory networks. *Journal of Experimental Psychology: General*, 143(6):2296–2303, 2014. ISSN 00963445. doi: 10.1037/xge0000020.

Fabio C. Cruz, Eisuke Koya, Danielle H. Guez-Barber, Jennifer M. Bossert, Carl R. Lupica, Yavin Shaham, and Bruce T. Hope. New technologies for examining the role of neuronal ensembles in drug addiction and fear. *Nature Reviews Neuroscience*, 14(11):743–754, 11 2013. ISSN 1471003X. doi: 10.1038/nrn3597.

Tiziano D'Albis, Jorge Jaramillo, Henning Sprekeler, and Richard Kempter. Inheritance of hippocampal place fields through hebbian learning: Effects of theta modulation and phase precession on structure formation. *Neural Computation*, 27 (8):1624–1672, 8 2015. ISSN 1530888X. doi: 10.1162/NECO{_}a{_}00752.

Nathan B. Danielson, Jeffrey D. Zaremba, Patrick Kaifosh, John Bowler, Max Ladow, and Attila Losonczy. Sublayer-Specific Coding Dynamics during Spatial

Navigation and Learning in Hippocampal Area CA1. *Neuron*, 91(3):652–665, 8 2016. ISSN 10974199. doi: 10.1016/j.neuron.2016.06.020.

Thomas J Davidson, Fabian Kloosterman, and Matthew A Wilson. Hippocampal Replay of Extended Experience. *Neuron*, 63(4):497–507, 2009a. ISSN 08966273. doi: 10.1016/j.neuron.2009.07.027. URL https://ac.els-cdn.com/S0896627309005820/1-s2.0-S0896627309005820-main.pdf?_tid=f3d1caa6-073c-435f-aefa-f35c4799281b&acdnat=1525179487_4a163af336408ef96e0225e1406c65f3.

Thomas J Davidson, Fabian Kloosterman, and Matthew A Wilson. Hippocampal Replay of Extended Experience. *Neuron*, 63(4):497–507, 2009b. ISSN 08966273. doi: 10.1016/j.neuron.2009.07.027. URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364032/pdf/nihms138690.pdf.

Licurgo De Almeida, Marco Idiart, and John E. Lisman. Memory retrieval time and memory capacity of the CA3 network: Role of gamma frequency oscillations. *Learning and Memory*, 14(11):795–806, 11 2007. ISSN 10720502. doi: 10.1101/lm.730207.

Mauricio R. Delgado, Rita L. Jou, and Elizabeth A. Phelps. Neural Systems Underlying Aversive Conditioning in Humans with Primary and Secondary Reinforcers. *Frontiers in Neuroscience*, 5(MAY):71, 5 2011. ISSN 1662-4548. doi: 10.3389/fnins.2011.00071. URL http://journal.frontiersin.org/article/10.3389/fnins.2011.00071/abstract.

Susanne Diekelmann and Jan Born. The memory function of sleep. *Nature Reviews Neuroscience*, 2010. ISSN 1471-003X. doi: 10.1038/nrn2762. URL http://www.nature.com/doifinder/10.1038/nrn2762.

George Dragoi and György Buzsáki. Temporal Encoding of Place Sequences by

Hippocampal Cell Assemblies. *Neuron*, 50(1):145–157, 4 2006. ISSN 08966273. doi: 10.1016/j.neuron.2006.02.023.

George Dragoi and Susumu Tonegawa. Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature*, 469(7330):397–401, 1 2011. ISSN 00280836. doi: 10.1038/nature09633.

George Dragoi and Susumu Tonegawa. Distinct preplay of multiple novel spatial experiences in the rat. *Proceedings of the National Academy of Sciences of the United States of America*, 110(22):9100–9105, 5 2013. ISSN 00278424. doi: 10.1073/pnas.1306031110.

Céline Drieu, Ralitsa Todorova, and Michaël Zugaro. Nested sequences of hippocampal assemblies during behavior support subsequent sleep replay. Technical report. URL `http://science.sciencemag.org/`.

Joseph E. Dunsmoor, Vinn D. Campese, Ahmet O. Ceceli, Joseph E. LeDoux, and Elizabeth A. Phelps. Outcome in place of an expected threat diminishes recovery of defensive responses. *Biological Psychiatry*, 78(3):203–209, 2015a. ISSN 18732402. doi: 10.1016/j.biopsych.2014.12.008.

Joseph E. Dunsmoor, Yael Niv, Nathaniel Daw, and Elizabeth A. Phelps. Rethinking Extinction. *Neuron*, 88(1):47–63, 2015b. ISSN 08966273. doi: 10.1016/j.neuron.2015.09.028. URL `http://linkinghub.elsevier.com/retrieve/pii/S089662731500817X`.

David Dupret, Joseph O'Neill, Barty Pleydell-Bouverie, and Jozsef Csicsvari. The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nature Neuroscience*, 13(8):995–1002, 8 2010. ISSN 10976256. doi: 10.1038/nn.2599.

Adrian J. Duszkiewicz, Colin G. McNamara, Tomonori Takeuchi, and Lisa Genzel. Novelty and Dopaminergic Modulation of Memory Persistence: A Tale of Two Systems, 2 2019. ISSN 1878108X.

Eleonore Duvelle, Roddy M Grieves, Vincent Hok, Bruno Poucet, Angelo Arleo, Kate J Jeffery, and Etienne Save. Insensitivity of Place Cells to the Value of Spatial Goals in a Two-Choice Flexible Navigation Task. 39(13):2522–2541, 2019.

Valérie Ego-Stengel and Matthew A. Wilson. Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus*, 20(1):NA–NA, 1 2009. ISSN 10509631. doi: 10.1002/hipo.20707. URL http://doi.wiley.com/10.1002/hipo.20707.

Howard Eichenbaum. Memory on time, 2013. ISSN 1879307X.

Howard Eichenbaum. Does the hippocampus preplay memories?, 11 2015. ISSN 15461726.

Nurhan Er. A new flashbulb memory model applied to the Marmara earthquake. *Applied Cognitive Psychology*, 17(5):503–517, 7 2003. ISSN 0888-4080. doi: 10.1002/acp.870. URL http://doi.wiley.com/10.1002/acp.870.

Jonathan P. Fadok, Tavis M.K. Dickerson, and Richard D. Palmiter. Dopamine is necessary for cue-dependent fear conditioning. *Journal of Neuroscience*, 29(36): 11089–11097, 9 2009. ISSN 02706474. doi: 10.1523/JNEUROSCI.1616-09.2009.

U. Farooq, Jeremie Sibille, K. Liu, and George Dragoi. Strengthened Temporal Coordination within Pre-existing Sequential Cell Assemblies Supports Trajectory Replay. *Neuron*, 103(4):719–733, 8 2019. ISSN 10974199. doi: 10.1016/j.neuron.2019.05.040.

Gordon B. Feld, Luciana Besedovsky, Kosuke Kaida, Thomas F. Münte, and Jan Born. Dopamine D2-like receptor activation wipes out preferential consolidation of high over low reward memories during human sleep. *Journal of cognitive neuroscience*, 26(10):2310–2320, 10 2014. ISSN 15308898. doi: 10.1162/jocn{_}a{_}00629. URL https://www.mitpressjournals.org/doi/abs/10.1162/jocn_a_00629.

Ting Feng, Delia Silva, and David J. Foster. Dissociation between the Experience-Dependent Development of Hippocampal Theta Sequences and Single-Trial Phase Precession. *Journal of Neuroscience*, 35(12):4890–4902, 3 2015. ISSN 0270-6474. doi: 10.1523/JNEUROSCI.2614-14.2015. URL `http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.2614-14.2015`.

A. A. Fenton, G. Csizmadia, and R. U. Muller. Conjoint control of hippocampal place cell firing by two visual stimuli: I. The effects of moving the stimuli on firing field positions. *Journal of General Physiology*, 116(2):191–209, 2000. ISSN 00221295. doi: 10.1085/jgp.116.2.191.

André A. Fenton and Robert U. Muller. Place cell discharge is extremely variable during individual passes of the rat through the firing field. *Proceedings of the National Academy of Sciences of the United States of America*, 95(6):3182–3187, 3 1998. ISSN 00278424. doi: 10.1073/pnas.95.6.3182.

André A. Fenton, Hsin Yi Kao, Samuel A. Neymotin, Andrey Olypher, Yevgeniy Vayntrub, William W. Lytton, and Nandor Ludvig. Unmasking the CA1 ensemble place code by exposures to small and large environments: More place cells and multiple, irregularly arranged, and expanded place fields in the larger space. *Journal of Neuroscience*, 28(44):11250–11262, 10 2008. ISSN 02706474. doi: 10.1523/JNEUROSCI.2862-08.2008.

Guillén Fernández and Richard G.M. Morris. Memory, Novelty and Prior Knowledge, 10 2018. ISSN 1878108X.

Graham Findlay, Giulio Tononi, and Chiara Cirelli. The evolving view of replay and its functions in wake and sleep. *SLEEP Advances*, 1(1), 1 2021. doi: 10.1093/sleepadvances/zpab002.

Christopher D. Fiorillo, Philippe N. Tobler, and Wolfram Schultz. Evidence that the delay-period activity of dopamine neurons corresponds to reward uncertainty rather than backpropagating TD errors, 6 2005. ISSN 17449081.

Stefan Fischer and Jan Born. Anticipated Reward Enhances Offline Learning During Sleep. *Journal of Experimental Psychology: Learning Memory and Cognition*, 35(6):1586–1593, 11 2009. ISSN 02787393. doi: 10.1037/a0017256.

David J. Foster. Replay Comes of Age. *Annual Review of Neuroscience*, 40:581–602, 7 2017. ISSN 15454126. doi: 10.1146/annurev-neuro-072116-031538.

David J. Foster and Matthew A. Wilson. Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature*, 440(7084):680–683, 3 2006. ISSN 14764687. doi: 10.1038/nature04587.

Loren M. Frank, Garrett B. Stanley, and Emery N. Brown. Journal of Neuroscience. *J. Neurosci.*, 17(17):6769–6782, 9 2004. ISSN 0270-6474. doi: 20026608.

Paul W. Frankland and Bruno Bontempi. The organization of recent and remote memories, 2 2005. ISSN 1471003X.

Paul W. Frankland, Cara O'Brien, Masuo Ohno, Alfredo Kirkwood, and Alcino J. Silva. α-CaMKII-dependent plasticity in the cortex is required for permanent memory. *Nature*, 411(6835):309–313, 5 2001. ISSN 00280836. doi: 10.1038/35077089.

Uwe Frey and Richard G.M. Morris. Synaptic tagging and long-term potentiation. *Nature*, 385(6616):533–536, 2 1997. ISSN 00280836. doi: 10.1038/385533a0.

Uwe Frey and Richard G.M. Morris. Synaptic tagging: Implications for late maintenance of hippocampal long- term potentiation. *Trends in Neurosciences*, 21(5):181–188, 5 1998. ISSN 01662236. doi: 10.1016/S0166-2236(97)01189-2.

Mark C. Fuhs and David S. Touretzky. Synaptic learning models of map separation in the hippocampus. *Neurocomputing*, 32-33:379–384, 6 2000. ISSN 09252312. doi: 10.1016/S0925-2312(00)00189-2.

Mark C. Fuhs, Shea R. VanRhoads, Amanda E. Casale, Bruce McNaughton, and David S. Touretzky. Influence of Path Integration Versus Environmen-

tal Orientation on Place Cell Remapping Between Visually Identical Environments. *Journal of Neurophysiology*, 94(4):2603–2616, 10 2005. ISSN 0022-3077. doi: 10.1152/jn.00132.2005. URL https://www.physiology.org/doi/10.1152/jn.00132.2005.

T Fujii, M Moscovitch, and L Nadel. Memory consolidation, retrograde amnesia, and the temporal lobe, 2000. URL https://psycnet.apa.org/record/2004-16990-010.

Marianne Fyhn, Sturla Molden, Stig Hollup, May Britt Moser, and Edvard I. Moser. Hippocampal Neurons Responding to First-Time Dislocation of a Target Object. *Neuron*, 35(3):555–566, 8 2002. ISSN 0896-6273. doi: 10.1016/S0896-6273(02)00784-5.

Steffen Gais and Jan Born. Declarative memory consolidation: Mechanisms acting during human sleep, 11 2004. ISSN 10720502.

Steffen Gais, Brian Lucas, and Jan Born. Sleep after learning aids memory recall. *Learning and Memory*, 13(3):259–262, 5 2006. ISSN 10720502. doi: 10.1101/lm.132106.

Jeffrey L. Gauthier and David W. Tank. A Dedicated Population for Reward Coding in the Hippocampus. *Neuron*, 99(1):179–193, 7 2018. ISSN 10974199. doi: 10.1016/j.neuron.2018.06.008.

Thomas Gener, Lorena Perez-Mendez, and Maria V. Sanchez-Vives. Tactile modulation of hippocampal place fields. *Hippocampus*, 23(12):1453–1462, 12 2013. ISSN 10509631. doi: 10.1002/hipo.22198.

Vanessa E. Ghosh and Asaf Gilboa. What is a memory schema? A historical perspective on current neuroscience literature, 1 2014. ISSN 00283932.

Paul E. Gilbert and Raymond P. Kesner. The amygdala but not the hippocampus is involved in pattern separation based on reward value. *Neurobiology of Learning*

and Memory, 77(3):338–353, 5 2002. ISSN 10747427. doi: 10.1006/nlme.2001.4033.

Paul E. Gilbert and Raymond P. Kesner. Recognition Memory for Complex Visual Discriminations Is Influenced by Stimulus Interference in Rodents with Perirhinal Cortex Damage. *Learning and Memory*, 10(6):525–530, 11 2003. ISSN 10720502. doi: 10.1101/lm.64503.

Giorgio F. Gilestro, Giulio Tononi, and Chiara Cirelli. Widespread changes in synaptic markers as a function of sleep and wakefulness in drosophila. *Science*, 324(5923):109–112, 4 2009. ISSN 00368075. doi: 10.1126/science.1166673.

Gabrielle Girardeau and Michaël Zugaro. Hippocampal ripples and memory consolidation. *Current Opinion in Neurobiology*, 21(3):452–459, 6 2011. ISSN 09594388. doi: 10.1016/j.conb.2011.02.005. URL `http://linkinghub.elsevier.com/retrieve/pii/S0959438811000316`.

Gabrielle Girardeau, Karim Benchenane, Sidney I. Wiener, György Buzsáki, and Michaël B. Zugaro. Selective suppression of hippocampal ripples impairs spatial memory. *Nature Neuroscience*, 12(10):1222–1223, 10 2009. ISSN 10976256. doi: 10.1038/nn.2384.

Antonio Giuditta, Maria Vittoria Ambrosini, Paola Montagnese, Paola Mandile, Mario Cotugno, Gigliola Grassi Zucconi, and Stefania Vescia. The sequential hypothesis of the function of sleep. *Behavioural Brain Research*, 69(1-2):157–166, 7 1995. ISSN 01664328. doi: 10.1016/0166-4328(95)00012-I.

April E. Gold and Raymond P. Kesner. The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. *Hippocampus*, 15(6):808–814, 1 2005. ISSN 1050-9631. doi: 10.1002/hipo.20103. URL `http://doi.wiley.com/10.1002/hipo.20103`.

Stephen N. Gomperts, Fabian Kloosterman, and Matthew A. Wilson. VTA neurons coordinate with the hippocampal reactivation of spatial experience. *eLife*, 4 (OCTOBER2015), 10 2015. ISSN 2050084X. doi: 10.7554/eLife.05360.001.

Jeffrey A. Gray and Neil McNaughton. The Neuropsychology of Anxiety: An enquiry into the function of the septo-hippocampal system. *The Neuropsychology of Anxiety: An enquiry into the function of the septo-hippocampal system*, pages 1–442, 1 1982. doi: 10.1093/ACPROF:OSO/9780198522713.001.0001.

Andres D. Grosmark and György Buzsáki. Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences. *Science*, 351(6280): 1440–1443, 3 2016. ISSN 10959203. doi: 10.1126/science.aad1935.

Andres D. Grosmark, Kenji Mizuseki, Eva Pastalkova, Kamran Diba, and György Buzsáki. REM Sleep Reorganizes Hippocampal Excitability. *Neuron*, 75(6): 1001–1007, 9 2012. ISSN 08966273. doi: 10.1016/j.neuron.2012.08.015.

Anoopum S. Gupta, Matthijs A.A. van der Meer, David S. Touretzky, and A. David Redish. Hippocampal Replay Is Not a Simple Function of Experience. *Neuron*, 65(5):695–705, 3 2010. ISSN 08966273. doi: 10.1016/j.neuron.2010.01.034.

Akash Guru, Changwoo Seo, Ryan Post, Durga Kullakanda, Julia Schaffer, and Melissa Warden. Ramping activity in midbrain dopamine neurons signifies the use of a cognitive map. *bioRxiv*, page 2020.05.21.108886, 5 2020. doi: 10.1101/2020.05.21.108886.

Torkel Hafting, Marianne Fyhn, Sturla Molden, May-Britt Moser, and Edvard I Moser. Microstructure of a spatial map in the entorhinal cortex. *Nature*, 436: 801–806, 2005. ISSN 0028-0836. doi: 10.1038/nature03721.

Jung-Soo Han, Michela Gallagher, and Peter Holland. Hippocampal lesions enhance configural learning by reducing proactive interference. *Hippocampus*, 8(2):138–146, 1 1998. ISSN 1050-9631. doi: 10.1002/(SICI)1098-1063(1998)8:2⟨138::AID-HIPO6⟩3.0.CO;2-H. URL https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1098-1063(1998)8:2<138::AID-HIPO6>3.0.CO;2-H.

Tom Hartley, N. Burgess, C. Lever, F. Cacucci, and J. O'Keefe. Modeling place fields in terms of the cortical inputs to the hippocam-

pus. *Hippocampus*, 10(4):369–379, 1 2000. ISSN 1050-9631. doi: 10.1002/1098-1063(2000)10:4⟨369::AID-HIPO3⟩3.0.CO;2-0. URL https://onlinelibrary.wiley.com/doi/10.1002/1098-1063(2000)10:4<369::AID-HIPO3>3.0.CO;2-0.

Michael E. Hasselmo and Howard Eichenbaum. Hippocampal mechanisms for the context-dependent retrieval of episodes. *Neural Networks*, 18(9):1172–1190, 11 2005. ISSN 08936080. doi: 10.1016/j.neunet.2005.08.007.

Mansuo L. Hayashi, Se Young Choi, B. S. Shankaranarayana Rao, Hae Yoon Jung, Hey Kyoung Lee, Dawei Zhang, Sumantra Chattarji, Alfredo Kirkwood, and Susumu Tonegawa. Altered cortical synaptic morphology and impaired memory consolidation in forebrain- specific dominant-negative PAK transgenic mice. *Neuron*, 42(5):773–787, 6 2004. ISSN 08966273. doi: 10.1016/j.neuron.2004.05.003.

D.O. Hebb. *The organization of behavior; a neuropsychological theory.* 1949.

RN Henson, S Cansino, JE Herron, WG Robb, and MD Rugg. A familiarity signal in human anterior medial temporal cortex? *Hippocampus*, 13(2):301–304, 2003. ISSN 1050-9631. doi: 10.1002/HIPO.10117. URL https://pubmed.ncbi.nlm.nih.gov/12699337/.

Jeffrey R. Hollerman and Wolfram Schultz. Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature Neuroscience*, 1(4):304–309, 1998. ISSN 10976256. doi: 10.1038/1124.

Stig A. Hollup, Sturla Molden, James G. Donnett, May Britt Moser, and Edvard I. Moser. Accumulation of hippocampal place fields at the goal location in an annular watermaze task. *Journal of Neuroscience*, 21(5):1635–1644, 3 2001. ISSN 02706474. doi: 10.1523/jneurosci.21-05-01635.2001.

J. J. Hopfield. Neural networks and physical systems with emergent collective computational abilities. *Proceedings of the National Academy of Sciences of*

the United States of America, 79(8):2554–2558, 4 1982. ISSN 00278424. doi: 10.1073/pnas.79.8.2554.

Mark W. Howe, Patrick L. Tierney, Stefan G. Sandberg, Paul E.M. Phillips, and Ann M. Graybiel. Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. *Nature*, 500(7464):575–579, 8 2013. ISSN 00280836. doi: 10.1038/nature12475.

Dan Hu and Abram Amsel. A simple test of the vicarious trial-and-error hypothesis of hippocampal function. *Proceedings of the National Academy of Sciences of the United States of America*, 92(12):5506–5509, 6 1995. ISSN 00278424. doi: 10.1073/pnas.92.12.5506.

Peter Hu, Melinda Stylos-Allan, and Matthew P. Walker. Sleep facilitates consolidation of emotional declarative memory. *Psychological Science*, 17(10):891–898, 10 2006. ISSN 09567976. doi: 10.1111/j.1467-9280.2006.01799.x.

John Huxter, Neil Burgess, and John O'Keefe. Independent rate and temporal coding in hippocampal pyramidal cells. *Nature 2003 425:6960*, 425(6960):828–832, 10 2003. ISSN 1476-4687. doi: 10.1038/nature02058. URL `https://www.nature.com/articles/nature02058`.

Hideyoshi Igata, Yuji Ikegaya, and Takuya Sasaki. Prioritized experience replays on a hippocampal predictive map for learning. *PNAS*, 2021. doi: https://doi.org/10.1073/pnas.2011266118.

Kinga Igloi, Giulia Gaggioni, Virginie Sterpenich, and Sophie Schwartz. A nap to recap or how reward regulates hippocampal-prefrontal memory networks during daytime sleep in humans. *eLife*, 4(OCTOBER2015), 10 2015. ISSN 2050084X. doi: 10.7554/eLife.07903.001.

Shantanu P. Jadhav, Caleb Kemere, P. Walter German, and Loren M. Frank. Awake hippocampal sharp-wave ripples support spatial memory. *Science*, 336(6087):1454–1458, 6 2012. ISSN 10959203. doi: 10.1126/science.1217230.

Yannick Jeantet and Yoon H. Cho. Evolution of hippocampal spatial representation over time in mice. *Neurobiology of Learning and Memory*, 98(4):354–360, 11 2012. ISSN 10959564. doi: 10.1016/j.nlm.2012.10.004.

John G. Jenkins and Karl M. Dallenbach. Obliviscence during Sleep and Waking. *The American Journal of Psychology*, 35(4):605, 10 1924. ISSN 00029556. doi: 10.2307/1414040.

Ole Jensen and John E. Lisman. Position reconstruction from an ensemble of hippocampal place cells: Contribution of theta phase coding. *Journal of Neurophysiology*, 83(5):2602–2609, 2000. ISSN 00223077. doi: 10.1152/jn.2000.83.5.2602.

Daoyun Ji and Matthew A Wilson. Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature Neuroscience*, 10(1):100–107, 1 2007. ISSN 1097-6256. doi: 10.1038/nn1825. URL `http://www.nature.com/articles/nn1825`.

Mattias P Karlsson and Loren M Frank. Awake replay of remote experiences in the hippocampus. *Nature Neuroscience*, 12(7):913–918, 7 2009a. ISSN 1097-6256. doi: 10.1038/nn.2344. URL `http://www.nature.com/doifinder/10.1038/nn.2344`.

Mattias P Karlsson and Loren M Frank. Awake replay of remote experiences in the hippocampus. *Nature Neuroscience*, 12(7):913–918, 2009b. ISSN 1097-6256. doi: 10.1038/nn.2344. URL `http://www.nature.com/doifinder/10.1038/nn.2344`.

Kimberly A. Kempadoo, Eugene V. Mosharov, Se Joon Choi, David Sulzer, and Eric R. Kandel. Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. *Proceedings of the National Academy of Sciences of the United States of America*, 113(51):14835–14840, 12 2016. ISSN 10916490. doi: 10.1073/pnas.1616515114.

Pamela J. Kennedy and Matthew L. Shapiro. Motivational states activate distinct hippocampal representations to guide goal-directed behaviors. *Proceedings of the National Academy of Sciences of the United States of America*, 106(26):10805–10810, 6 2009. ISSN 00278424. doi: 10.1073/pnas.0903259106.

Steven W. Kennerley and Mark E. Walton. Decision making and reward in frontal cortex: Complementary evidence from neurophysiological and neuropsychological studies. *Behavioral Neuroscience*, 125(3):297–317, 6 2011. ISSN 07357044. doi: 10.1037/a0023575.

Clifford G. Kentros, Naveen T. Agnihotri, Samantha Streater, Robert D. Hawkins, and Eric R. Kandel. Increased attention to spatial context increases both place field stability and spatial memory. *Neuron*, 42(2):283–295, 4 2004. ISSN 08966273. doi: 10.1016/S0896-6273(04)00192-8.

Nathaniel R. Kinsky, David W. Sullivan, William Mau, Michael E. Hasselmo, and Howard B. Eichenbaum. Hippocampal Place Fields Maintain a Coherent and Flexible Map across Long Timescales. *Current Biology*, 28(22):3578–3588, 11 2018. ISSN 09609822. doi: 10.1016/j.cub.2018.09.037.

JJ Knierim, HS Kudrimoti, WE Skaggs, and BL McNaughton. The interaction between vestibular cues and visual landmark learning in spatial navigation. In T Ono, B McNaughton, S Molotchnikoff, E Rolls, and H. Nishijo, editors, *Perception, Memory, and Emotion*, pages 343–357. Pergamon Oxford, 1996.

Julie Koenig, Ashley N Linder, Jill K Leutgeb, and Stefan Leutgeb. The Spatial Periodicity of Grid Cells Is Not Sustained During Reduced Theta Oscillations. *New Series*, 332(6029):592–595, 2011. doi: 10.1126/science.l202333.

Krisztián A. Kovács, Joseph O■Neill, Philipp Schoenenberger, Markku Penttonen, Damaris K. Ranguel Guerrero, and Jozsef Csicsvari. Optogenetically Blocking Sharp Wave Ripple Events in Sleep Does Not Interfere with the Formation of Stable Spatial Representation in the CA1 Area of the Hippocampus. *PLOS ONE*, 11

(10):e0164675, 10 2016. ISSN 1932-6203. doi: 10.1371/journal.pone.0164675. URL https://dx.plos.org/10.1371/journal.pone.0164675.

Benjamin J. Kraus, Robert J. Robinson, John A. White, Howard Eichenbaum, and Michael E. Hasselmo. Hippocampal "Time Cells": Time versus Path Integration. *Neuron*, 78(6):1090–1101, 6 2013. ISSN 08966273. doi: 10.1016/j.neuron.2013.04.015.

Hemant S. Kudrimoti, Carol A. Barnes, and Bruce L. McNaughton. Reactivation of hippocampal cell assemblies: Effects of behavioral state, experience, and EEG dynamics. *Journal of Neuroscience*, 19(10):4090–4101, 5 1999. ISSN 02706474. doi: 10.1523/jneurosci.19-10-04090.1999.

D Kumaran and EA Maguire. Which computational mechanisms operate in the hippocampus during novelty detection? *Hippocampus*, 17(9):735–748, 2007. ISSN 1050-9631. doi: 10.1002/HIPO.20326. URL https://pubmed.ncbi.nlm.nih.gov/17598148/.

Dharshan Kumaran and Eleanor A. Maguire. An unexpected sequence of events: Mismatch detection in the human hippocampus. *PLoS Biology*, 4(12):2372–2382, 2006. doi: 10.1371/JOURNAL.PBIO.0040424.

Lia Kvavilashvili, Jennifer Mirani, Simone Schlagman, and Diana E. Kornbrot. Comparing flashbulb memories of September 11 and the death of Princess Diana: effects of time delays and nationality. *Applied Cognitive Psychology*, 17(9):1017–1031, 11 2003. ISSN 0888-4080. doi: 10.1002/acp.983. URL http://doi.wiley.com/10.1002/acp.983.

Lia Kvavilashvili, Jennifer Mirani, Simone Schlagman, James A.K. Erskine, and Diana E. Kornbrot. Effects of age on phenomenology and consistency of flashbulb memories of september 11 and a staged control event. *Psychology and Aging*, 25(2):391–404, 2010. ISSN 19391498. doi: 10.1037/a0017532.

Anthony Lanahan and Paul Worley. Immediate-early genes and synaptic function.

In *Neurobiology of Learning and Memory*, volume 70, pages 37–43. Academic Press Inc., 1998. doi: 10.1006/nlme.1998.3836.

Jean Michel Lassalle, Thierry Bataille, and Hélène Halley. Reversible inactivation of the hippocampal mossy fiber synapses in mice impairs spatial learning, but neither consolidation nor memory retrieval, in the Morris navigation task. *Neurobiology of Learning and Memory*, 73(3):243–257, 5 2000. ISSN 10747427. doi: 10.1006/nlme.1999.3931.

L. Matthew Law, David A. Bulkin, and David M. Smith. Slow stabilization of concurrently acquired hippocampal context representations. *Hippocampus*, 26 (12):1560–1569, 12 2016. ISSN 10509631. doi: 10.1002/hipo.22656. URL `http://doi.wiley.com/10.1002/hipo.22656`.

Albert K. Lee and Matthew A. Wilson. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*, 36(6):1183–1194, 2002. ISSN 08966273. doi: 10.1016/S0896-6273(02)01096-6.

Inah Lee and Raymond P. Kesner. Encoding versus retrieval of spatial memory: Double dissociation between the dentate gyrus and the perforant path inputs into CA3 in the dorsal hippocampus. *Hippocampus*, 14(1):66–76, 1 2004. ISSN 1050-9631. doi: 10.1002/hipo.10167. URL `http://doi.wiley.com/10.1002/hipo.10167`.

Edith Lesburguères, Oliviero L. Gobbo, Stéphanie Alaux-Cantin, Anne Hambucken, Pierre Trifilieff, and Bruno Bontempi. Early tagging of cortical networks is required for the formation of enduring associative memory. *Science*, 331(6019):924–928, 2 2011. ISSN 10959203. doi: 10.1126/science.1196164.

Jill K. Leutgeb, Stefan Leutgeb, Alessandro Treves, Retsina Meyer, Carol A. Barnes, Bruce L. McNaughton, May Britt Moser, and Edvard I. Moser. Progressive transformation of hippocampal neuronal representations in "morphed" environments. *Neuron*, 48(2):345–348, 2005. ISSN 08966273. doi: 10.1016/j.neuron.2005.09.007.

Jill K. Leutgeb, Stefan Leutgeb, May Britt Moser, and Edvard I. Moser. Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science*, 315(5814): 961–966, 2 2007. ISSN 00368075. doi: 10.1126/science.1135801.

Stefan Leutgeb, Jill K. Leutgeb, Alessandro Treves, May Britt Moser, and Edvard I. Moser. Distinct ensemble codes in hippocampal areas CA3 and CA1. *Science*, 305(5688):1295–1298, 8 2004. ISSN 00368075. doi: 10.1126/science.1100265.

Colin Lever, Tom Wills, Francesca Cacucci, Nell Burgess, and John O'Keefe. Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature*, 416(6876):90–94, 3 2002. ISSN 00280836. doi: 10.1038/416090a.

Colin Lever, Stephen Burton, Ali Jeewajee, John O'Keefe, and Neil Burgess. Boundary vector cells in the subiculum of the hippocampal formation. *Journal of Neuroscience*, 29(31):9771–9777, 8 2009. ISSN 02706474. doi: 10.1523/JNEUROSCI.1319-09.2009.

Shaomin Li, William K. Cullen, Roger Anwyl, and Michael J. Rowan. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nature Neuroscience*, 6(5):526–531, 5 2003. ISSN 10976256. doi: 10.1038/nn1049.

Wei Li, Lei Ma, Guang Yang, and Wen Biao Gan. REM sleep selectively prunes and maintains new synapses in development and learning. *Nature Neuroscience*, 20(3):427–437, 2 2017. ISSN 15461726. doi: 10.1038/nn.4479.

John E. Lisman and Anthony A. Grace. The Hippocampal-VTA Loop: Controlling the Entry of Information into Long-Term Memory. *Neuron*, 46(5):703–713, 6 2005. ISSN 0896-6273. doi: 10.1016/J.NEURON.2005.05.002.

Denise Li Juan Liu, Steven Graham, and Michael Zorawski. Enhanced selective memory consolidation following post-learning pleasant and aversive arousal. *Neurobiology of Learning and Memory*, 89(1):36–46, 1 2008. ISSN 10747427. doi: 10.1016/j.nlm.2007.09.001.

London Met. London, UK Metro Area Population 1950-2021 — MacroTrends. URL https://www.macrotrends.net/cities/22860/london/population.

Nicole M. Long, Hongmi Lee, and Brice A. Kuhl. Hippocampal Mismatch Signals Are Modulated by the Strength of Neural Predictions and Their Similarity to Outcomes. *The Journal of Neuroscience*, 36 (50):12677, 12 2016. doi: 10.1523/JNEUROSCI.1850-16.2016. URL /pmc/articles/PMC5157109//pmc/articles/PMC5157109/?report=abstracthttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC5157109/.

Ray Luo, Akira Uematsu, Adam Weitemier, Luca Aquili, Jenny Koivumaa, Thomas J. McHugh, and Joshua P. Johansen. A dopaminergic switch for fear to safety transitions. *Nature Communications*, 9(1):1–11, 12 2018. ISSN 20411723. doi: 10.1038/s41467-018-04784-7.

Christopher J. MacDonald, Stephen Carrow, Ryan Place, and Howard Eichenbaum. Distinct hippocampal time cell sequences represent odor memories in immobilized rats. *Journal of Neuroscience*, 33(36):14607–14616, 2013. ISSN 02706474. doi: 10.1523/JNEUROSCI.1537-13.2013.

Antoine D. Madar, Laura A. Ewell, and Mathew V. Jones. Pattern separation of spiketrains in hippocampal neurons. *Scientific Reports*, 9(1):1–20, 12 2019. ISSN 20452322. doi: 10.1038/s41598-019-41503-8.

Nicolas Maingret, Gabrielle Girardeau, Ralitsa Todorova, Marie Goutierre, and Michaël Zugaro. Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nature Neuroscience*, 19(7):959–964, 2016. ISSN 1097-6256. doi: 10.1038/nn.4304. URL http://www.nature.com/doifinder/10.1038/nn.4304.

Paola Mandile, Stefania Vescia, Paola Montagnese, Stefania Piscopo, Mario Cotugno, and Antonio Giuditta. Post-trial sleep sequences including transition sleep

are involved in avoidance learning of adult rats. *Behavioural Brain Research*, 112 (1-2):23–31, 7 2000. ISSN 01664328. doi: 10.1016/S0166-4328(00)00158-3.

Emily A. Mankin, Fraser T. Sparks, Begum Slayyeh, Robert J. Sutherland, Stefan Leutgeb, and Jill K. Leutgeb. Neuronal code for extended time in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, 109(47):19462–19467, 11 2012. ISSN 10916490. doi: 10.1073/pnas.1214107109.

Joseph R. Manns, Ramona O. Hopkins, and Larry R. Squire. Semantic memory and the human hippocampus. *Neuron*, 38(1):127–133, 2003. ISSN 08966273. doi: 10.1016/S0896-6273(03)00146-6.

JR Manns, MW Howard, and H Eichenbaum. Gradual changes in hippocampal activity support remembering the order of events. *Neuron*, 2007. URL https://www.sciencedirect.com/science/article/pii/S0896627307006435.

Pierre Maquet. The Role of Sleep in Learning and Memory. Technical Report 5544, 2001.

Stephen Maren, K Luan Phan, and Israel Liberzon. The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, 14(June):417–28, 2013. ISSN 1471-003X. doi: 10.1038/nrn3492. URL http://www.nature.com/doifinder/10.1038/nrn3492%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/23635870.

Etan J Markus, Yu-Lin Qin, Brian Leonard, William E Skaggs, Bruce L Mcnaughton, and Carol A Barnes1. Interactions between Location and Task Affect the Spatial and Directional Firing of Hippocampal Neurons. Technical Report 11, 1995.

D. Marr. A theory for cerebral neocortex. *Proceedings of the Royal Society of London. Series B. Biological Sciences*, 176(1043):161–234, 11

1970. ISSN 0080-4649. doi: 10.1098/rspb.1970.0040. URL https://royalsocietypublishing.org/doi/10.1098/rspb.1970.0040.

D. Marr. Simple memory: a theory for archicortex. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, 262(841):23–81, 7 1971. ISSN 0080-4622. doi: 10.1098/rstb.1971.0078. URL https://royalsocietypublishing.org/doi/10.1098/rstb.1971.0078.

Stephen J. Martin, Livia De Hoz, and Richard G M Morris. Retrograde amnesia: Neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. *Neuropsychologia*, 43 (4):609–624, 2005. ISSN 00283932. doi: 10.1016/j.neuropsychologia.2004.07.007.

Marcelo G. Mattar and Nathaniel D. Daw. Prioritized memory access explains planning and hippocampal replay. *Nature Neuroscience 2018 21:11*, 21(11): 1609–1617, 10 2018. ISSN 1546-1726. doi: 10.1038/s41593-018-0232-z. URL https://www.nature.com/articles/s41593-018-0232-z.

William Mau, David W. Sullivan, Nathaniel R. Kinsky, Michael E. Hasselmo, Marc W. Howard, and Howard Eichenbaum. The Same Hippocampal CA1 Population Simultaneously Codes Temporal Information over Multiple Timescales. *Current Biology*, 28(10):1499–1508, 5 2018. ISSN 09609822. doi: 10.1016/j.cub.2018.03.051.

Thibault Maviel, Thomas P. Durkin, Frédérique Menzaghi, and Bruno Bontempi. Sites of neocortical reorganization critical for remote spatial memory. *Science*, 305(5680):96–99, 7 2004. ISSN 00368075. doi: 10.1126/science.1098180.

James L Mcclelland, Bruce L Mcnaughton, and Randall C O'reilly. Why There Are Complementary Learning Systems in the Hippocampus and Neocortex: Insights From the Successes and Failures of Connectionist Models of Learning and Memory. Technical Report 3, 1995.

Sam McKenzie, Nick T.M. Robinson, Lauren Herrera, Jordana C. Churchill, and Howard Eichenbaum. Learning causes reorganization of neuronal firing patterns to represent related experiences within a hippocampal schema. *Journal of Neuroscience*, 33(25):10243–10256, 2013. ISSN 02706474. doi: 10.1523/JNEUROSCI.0879-13.2013.

Colin G. McNamara and David Dupret. Two sources of dopamine for the hippocampus, 7 2017. ISSN 1878108X.

Colin G. McNamara, Álvaro Tejero-Cantero, Stéphanie Trouche, Natalia Campo-Urriza, and David Dupret. Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nature Neuroscience*, 17(12):1658–1660, 1 2014. ISSN 15461726. doi: 10.1038/nn.3843.

B. L. McNaughton, C. A. Barnes, and J. O'Keefe. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Experimental Brain Research*, 52(1):41–49, 9 1983. ISSN 00144819. doi: 10.1007/BF00237147.

Jayme R. McReynolds, Kelly M. Anderson, Kyle M. Donowho, and Christa K. McIntyre. Noradrenergic actions in the basolateral complex of the amygdala modulate Arc expression in hippocampal synapses and consolidation of aversive and non-aversive memory. *Neurobiology of Learning and Memory*, 115:49–57, 11 2014. ISSN 10959564. doi: 10.1016/j.nlm.2014.08.016.

M. R. Mehta, A. K. Lee, and M. A. Wilson. Role of experience and oscillations in transforming a rate code into a temporal code. *Nature*, 417(6890):741–746, 6 2002. ISSN 00280836. doi: 10.1038/nature00807.

Mayank R. Mehta, Carol A. Barnes, and Bruce L. Mcnaughton. Experience-dependent, asymmetric expansion of hippocampal place fields. *Proceedings of the National Academy of Sciences of the United States of America*, 94(16):8918–8921, 8 1997. ISSN 00278424. doi: 10.1073/pnas.94.16.8918.

Frédéric Michon, Jyh Jang Sun, Chae Young Kim, Davide Ciliberti, and Fabian Kloosterman. Post-learning Hippocampal Replay Selectively Reinforces Spatial Memory for Highly Rewarded Locations. *Current Biology*, 2019. ISSN 09609822. doi: 10.1016/j.cub.2019.03.048.

Frédéric Michon, Esther Krul, Jyh Jang Sun, and Fabian Kloosterman. Single-trial dynamics of hippocampal spatial representations are modulated by reward value, 10 2020. ISSN 26928205.

Steven J. Middleton and Thomas J. McHugh. Silencing CA3 disrupts temporal coding in the CA1 ensemble. *Nature Neuroscience*, 19(7):945–951, 7 2016. ISSN 15461726. doi: 10.1038/nn.4311.

Mohammed R. Milad and Gregory J. Quirk. Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress. *Annual Review of Psychology*, 63(1):129–151, 1 2012. ISSN 0066-4308. doi: 10.1146/annurev.psych.121208.131631. URL `http://www.annualreviews.org/doi/abs/10.1146/annurev.psych.121208.131631`.

EK Miller, L Li, and R Desimone. Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 13(4):1460–1478, 1993. ISSN 0270-6474. doi: 10.1523/JNEUROSCI.13-04-01460.1993. URL `https://pubmed.ncbi.nlm.nih.gov/8463829/`.

Keiichiro Minatohara, Mika Akiyoshi, and Hiroyuki Okuno. Role of immediate-early genes in synaptic plasticity and neuronal ensembles underlying the memory trace. *Frontiers in Molecular Neuroscience*, 8(JAN2016):78, 1 2016. ISSN 16625099. doi: 10.3389/fnmol.2015.00078.

M. A. P. Moita. Putting Fear in Its Place: Remapping of Hippocampal Place Cells during Fear Conditioning. *Journal of Neuroscience*, 24 (31):7015–7023, 2004. ISSN 0270-6474. doi: 10.1523/JNEUROSCI.

5492-03.2004. URL http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.5492-03.2004.

Morris Moscovitch, Lynn Nadel, Gordon Winocur, Asaf Gilboa, and R. Shayna Rosenbaum. The cognitive neuroscience of remote episodic, semantic and spatial memory, 4 2006. ISSN 09594388.

Diptendu Mukherjee, Bogna Marta Ignatowska-Jankowska, Eyal Itskovits, Ben Jerry Gonzales, Hagit Turm, Liz Izakson, Doron Haritan, Noa Bleistein, Chen Cohen, Ido Amit, Tal Shay, Brad Grueter, Alon Zaslaver, and Ami Citri. Salient experiences are represented by unique transcriptional signatures in the mouse brain. *eLife*, 7, 2 2018. ISSN 2050084X. doi: 10.7554/eLife.31220.

R U Muller and J L Kubie. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 7(7):1951–68, 7 1987. ISSN 0270-6474. URL http://www.ncbi.nlm.nih.gov/pubmed/3612226.

Vishnu P. Murty, Kevin S. LaBar, and R. Alison Adcock. Threat of punishment motivates memory encoding via amygdala, not midbrain, interactions with the medial temporal lobe. *Journal of Neuroscience*, 32(26):8969–8976, 6 2012. ISSN 02706474. doi: 10.1523/JNEUROSCI.0094-12.2012.

Lynn Nadel. The Hippocampus and Context Revisited. In *Hippocampal place fields : relevance to learning and memory*, page 409. Oxford University Press, 2008. ISBN 9780198043454.

Lynn Nadel and Morris Moscovitch. Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology*, 7(2):217–227, 1997. ISSN 09594388. doi: 10.1016/S0959-4388(97)80010-4.

Kazu Nakazawa. Dentate Mossy Cell and Pattern Separation, 2 2017. ISSN 10974199.

Kazu Nakazawa, Michael C. Quirk, Raymond A. Chitwood, Masahiko Watanabe, Mark F. Yeckel, Linus D. Sun, Akira Kato, Candice A. Carr, Daniel Johnston, Matthew A. Wilson, and Susumu Tonegawa. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science*, 297(5579):211–218, 7 2002. ISSN 00368075. doi: 10.1126/science.1071795.

Ulric Neisser, Eugene Winograd, Erik T. Bergman, Charles A. Schreiber, Stephen E. Palmer, and Mary Susan Weldon. Remembering the Earthquake: Direct Experience vs. Hearing the News. *Memory*, 4(4):337–358, 1996. ISSN 09658211. doi: 10.1080/096582196388898.

Joshua P. Neunuebel and James J. Knierim. CA3 retrieves coherent representations from degraded input: Direct evidence for CA3 pattern completion and dentate gyrus pattern separation. *Neuron*, 81(2):416–427, 1 2014. ISSN 08966273. doi: 10.1016/j.neuron.2013.11.017.

Darren Newtson. Attribution and the unit of perception of ongoing behavior. *Journal of Personality and Social Psychology*, 28(1):28–38, 10 1973. ISSN 00223514. doi: 10.1037/h0035584.

Darren Newtson, Gretchen A. Engquist, and Joyce Bois. The objective basis of behavior units. *Journal of Personality and Social Psychology*, 35(12):847–862, 1977. ISSN 00223514. doi: 10.1037/0022-3514.35.12.847.

Masaki Nishida, Jori Pearsall, Randy L. Buckner, and Matthew P. Walker. REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex*, 19(5):1158–1166, 5 2009. ISSN 10473211. doi: 10.1093/cercor/bhn155.

Kenneth A. Norman and Randall C. O'Reilly. Modeling Hippocampal and Neocortical Contributions to Recognition Memory: A Complementary-Learning-Systems Approach. *Psychological Review*, 110(4):611–646, 10 2003. ISSN 0033295X. doi: 10.1037/0033-295X.110.4.611.

J. O'Keefe and D. H. Conway. Hippocampal place units in the freely moving rat: Why they fire where they fire. *Experimental Brain Research*, 31(4):573–590, 4 1978. ISSN 00144819. doi: 10.1007/BF00239813.

J. O'Keefe and J. Dostrovsky. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, 34(1):171–175, 1971. ISSN 00068993. doi: 10.1016/0006-8993(71)90358-1.

J. O'Keefe and A. Speakman. Single unit activity in the rat hippocampus during a spatial memory task. *Experimental Brain Research*, 68(1):1–27, 9 1987. ISSN 00144819. doi: 10.1007/BF00255230.

John O'Keefe. Place units in the hippocampus of the freely moving rat. *Experimental Neurology*, 51(1):78–109, 1976. ISSN 10902430. doi: 10.1016/0014-4886(76)90055-8.

John O'Keefe and Neil Burgess. Geometric determinants of the place fields of hippocampal neurons. *Nature*, 381(6581):425–428, 5 1996. ISSN 0028-0836. doi: 10.1038/381425a0. URL `http://www.nature.com/doifinder/10.1038/381425a0`.

John O'Keefe and Lynn Nadel. *The Hippocampus as a Cognitive Map*. Clarendon Press, 1978.

John O'Keefe and Michael L. Recce. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus*, 3(3):317–330, 1993. ISSN 10981063. doi: 10.1002/hipo.450030307.

Hiroyuki Okuno. Regulation and function of immediate-early genes in the brain: Beyond neuronal activity markers, 3 2011. ISSN 01680102.

Freyja H. Ólafsdóttir, Caswell Barry, Aman B. Saleem, Demis Hassabis, and Hugo J. Spiers. Hippocampal place cells construct reward related sequences through unexplored space. *eLife*, 4(JUNE2015), 6 2015. ISSN 2050084X. doi: 10.7554/eLife.06063.

H. Freyja Ólafsdóttir, Francis Carpenter, and Caswell Barry. Task Demands Predict a Dynamic Switch in the Content of Awake Hippocampal Replay. *Neuron*, 96(4): 925–935, 11 2017. ISSN 10974199. doi: 10.1016/j.neuron.2017.09.035.

H. Freyja Ólafsdóttir, Daniel Bush, and Caswell Barry. The Role of Hippocampal Replay in Memory and Planning, 1 2018. ISSN 09609822.

Joseph O'Neill, Timothy J. Senior, Kevin Allen, John R. Huxter, and Jozsef Csicsvari. Reactivation of experience-dependent cell assembly patterns in the hippocampus. *Nature Neuroscience*, 11(2):209–215, 2008. ISSN 10976256. doi: 10.1038/nn2037.

Javiera P. Oyarzún, Pau A. Packard, Ruth de Diego-Balaguer, and Lluis Fuentemilla. Motivated encoding selectively promotes memory for future inconsequential semantically-related events. *Neurobiology of Learning and Memory*, 133:1–6, 9 2016. ISSN 10959564. doi: 10.1016/j.nlm.2016.05.005.

Eva Pastalkova, Vladimir Itskov, Asohan Amarasingham, and György Buzsáki. Internally generated cell assembly sequences in the rat hippocampus. *Science*, 321 (5894):1322–1327, 9 2008. ISSN 00368075. doi: 10.1126/science.1159775.

G. T.W. Patrick and J. Allen Gilbert. Studies from the psychological laboratory of the University of Iowa: On the effects of loss of sleep. *Psychological Review*, 3 (5):469–483, 9 1896. ISSN 0033295X. doi: 10.1037/h0075739.

Anna R. Patten, Suk Yu Yau, Christine J. Fontaine, Alicia Meconi, Ryan C. Wortman, and Brian R. Christie. The Benefits of Exercise on Structural and Functional Plasticity in the Rodent Hippocampus of Different Disease Models. *Brain Plasticity*, 1(1):97–127, 2 2016. ISSN 22136304. doi: 10.3233/bpl-150016.

C Pavlides and J Wilson. Influences of Hippocampal Place Cell Firing in the Awake STate on the Activity of These Cells during Subsequent Sleep Episodes. (August):1–12, 1989.

Paul Pavlidis, Johanna Montgomery, and Daniel V. Madison. Presynaptic protein kinase activity supports long-term potentiation at synapses between individual hippocampal neurons. *Journal of Neuroscience*, 20(12):4497–4505, 6 2000. ISSN 02706474. doi: 10.1523/jneurosci.20-12-04497.2000.

Jessica D. Payne, Robert Stickgold, Kelley Swanberg, and Elizabeth A. Kensinger. Sleep preferentially enhances memory for emotional components of scenes. *Psychological Science*, 19(8):781–788, 8 2008. ISSN 09567976. doi: 10.1111/j.1467-9280.2008.02157.x.

Jessica D. Payne, Matthew A. Tucker, Jeffrey M. Ellenbogen, Erin J. Wamsley, Matthew P. Walker, Daniel L. Schacter, and Robert Stickgold. Memory for Semantically Related and Unrelated Declarative Information: The Benefit of Sleep, the Cost of Wake. *PLoS ONE*, 7(3):e33079, 3 2012. ISSN 1932-6203. doi: 10.1371/journal.pone.0033079. URL https://dx.plos.org/10.1371/journal.pone.0033079.

Rony Paz, Hagar Gelbard-Sagiv, Roy Mukamel, Michal Harel, Rafael Malach, and Itzhak Fried. A neural substrate in the human hippocampus for linking successive events. *Proceedings of the National Academy of Sciences of the United States of America*, 107(13):6046–6051, 3 2010. ISSN 00278424. doi: 10.1073/pnas.0910834107.

Adrien Peyrache, Mehdi Khamassi, Karim Benchenane, Sidney I Wiener, and Francesco P Battaglia. Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. *Nature Publishing Group*, 12, 2009. doi: 10.1038/nn.2337.

Marie A. Pezze and Joram Feldon. Mesolimbic dopaminergic pathways in fear conditioning, 12 2004. ISSN 03010082.

Brad E. Pfeiffer. The content of hippocampal "replay". *Hippocampus*, 30(1):6–18, 1 2020. ISSN 1050-9631. doi: 10.1002/hipo.22824. URL https://onlinelibrary.wiley.com/doi/abs/10.1002/hipo.22824.

Phillips 5th annual global survery. Philips releases 5th annual global sleep survey data - News — Philips. URL https://www.philips.com/a-w/about/news/archive/standard/news/press/2020/20200302-philips-sleep-survey-shows-only-half-of-people-worldwide-html.

Gina R Poe. Sleep Is for Forgetting. 37(3):464–473, 2017. ISSN 0270-6474. doi: 10.1523/JNEUROSCI.0820-16.2017.

B. Poucet and V. Hok. Remembering goal locations, 10 2017. ISSN 23521546.

Bruno Poucet, Etienne Save, and Pierre Pascal Lenck-Santini. Sensory and memory properties of hippocampal place cells, 2000. ISSN 03341763.

Gregory J. Quirk, Robert U. Muller, and John L. Kubie. The firing of hippocampal place cells in the dark depends on the rat's recent experience. *Journal of Neuroscience*, 10(6):2008–2017, 6 1990. ISSN 02706474. doi: 10.1523/jneurosci.10-06-02008.1990.

Rodrigo Quian Quiroga. Concept cells: the building blocks of declarative memory functions. *Nature Reviews Neuroscience 2012 13:8*, 13(8):587–597, 7 2012. ISSN 1471-0048. doi: 10.1038/nrn3251. URL https://www.nature.com/articles/nrn3251.

Caroline R. Raby and Nicola S. Clayton. Episodic-Like Memory in Food-Caching Birds. In *Encyclopedia of the Sciences of Learning*, pages 1159–1162. Springer US, 2012. doi: 10.1007/978-1-4419-1428-6{_}743.

Jr Ranck. Head direction cells in the deep cell layer of dorsal presubiculum in freely moving rats. In *Soc Neurosci*, 1984.

Charan Ranganath and Liang Tien Hsieh. The hippocampus: A special place for time. *Annals of the New York Academy of Sciences*, 1369(1):93–110, 4 2016. ISSN 17496632. doi: 10.1111/nyas.13043.

Björn Rasch and Jan Born. About sleep's role in memory. *Physiological Reviews*, 93(2):681–766, 2013. ISSN 00319333. doi: 10.1152/physrev.00032.2012.

G Rauchs, B Desgranges, J Foret, and F Eustache. The relationships between memory systems and sleep stages. *Journal of Sleep Research*, 14(2):123–140, 6 2005. ISSN 0962-1105. doi: 10.1111/j.1365-2869.2005.00450.x. URL http://doi.wiley.com/10.1111/j.1365-2869.2005.00450.x.

Géraldine Rauchs, Dorothée Feyers, Brigitte Landeau, Christine Bastin, André Luxen, Pierre Maquet, and Fabienne Collette. Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. *Journal of Neuroscience*, 31(7):2563–2568, 2 2011. ISSN 02706474. doi: 10.1523/JNEUROSCI.3972-10.2011.

Pascal Ravassard, Ashley Kees, Bernard Willers, David Ho, Daniel Aharoni, Jesse Cushman, Zahra M. Aghajan, and Mayank R. Mehta. Multisensory control of hippocampal spatiotemporal selectivity. *Science*, 340(6138):1342–1346, 6 2013. ISSN 10959203. doi: 10.1126/science.1232655.

A. David Redish and David S. Touretzky. The Role of the Hippocampus in Solving the Morris Water Maze. *Neural Computation*, 10(1):73–111, 1 1998. ISSN 08997667. doi: 10.1162/089976698300017908.

Roger L. Redondo and Richard G.M. Morris. Making memories last: The synaptic tagging and capture hypothesis, 1 2011. ISSN 1471003X.

Nancy L. Rempel-Clower, Stuart M. Zola, Larry R. Squire, and David G. Amaral. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *Journal of Neuroscience*, 16(16):5233–5255, 8 1996. ISSN 02706474. doi: 10.1523/jneurosci.16-16-05233.1996.

Charles E Ribak, Seress 1 Laszlo, and David G Amaral. The development, ultrastructure and synaptic connections of the mossy cells of the dentate gyrus. Technical report, 1985.

Sidarta Ribeiro, Damien Gervasoni, Ernesto S Soares, Yi Zhou, Shih-Chieh Lin, Janaina Pantoja, Michael Lavine, and Miguel A. L Nicolelis. Long-Lasting Novelty-Induced Neuronal Reverberation during Slow-Wave Sleep in Multiple Forebrain Areas. *PLoS Biology*, 2(1):e24, 1 2004. ISSN 1545-7885. doi: 10.1371/journal.pbio.0020024. URL `https://dx.plos.org/10.1371/journal.pbio.0020024`.

David Robbe and György Buzsáki. Alteration of theta timescale dynamics of hippocampal place cells by a cannabinoid is associated with memory impairment. *Journal of Neuroscience*, 29(40):12597–12605, 10 2009. ISSN 02706474. doi: 10.1523/JNEUROSCI.2407-09.2009.

Henry L. Roediger and Kathleen B. McDermott. Creating False Memories: Remembering Words Not Presented in Lists. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 21(4):803–814, 1995. ISSN 02787393. doi: 10.1037/0278-7393.21.4.803.

Emma L. Roscow, Matthew W. Jones, and Nathan F. Lepora. Behavioural and computational evidence for memory consolidation biased by reward-prediction errors. *bioRxiv*, page 716290, 7 2019. doi: 10.1101/716290. URL `https://www.biorxiv.org/content/10.1101/716290v1https://www.biorxiv.org/content/10.1101/716290v1.abstract`.

R. Shayna Rosenbaum, Sandra Priselac, Stefan Köhler, Sandra E. Black, Fuqiang Gao, Lynn Nadel, and Morris Moscovitch. Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neuroscience*, 3(10): 1044–1048, 10 2000. ISSN 10976256. doi: 10.1038/79867.

G Rothschild, E Eban, and L M Frank. A cortical-hippocampal-cortical loop of information processing during memory consolidation. *Nat Neurosci*, 20(February 2017), 2017.

Lisa Roux, Bo Hu, Ronny Eichler, Eran Stark, and György Buzsáki. Sharp wave rip-

ples during learning stabilize the hippocampal spatial map. *Nature Neuroscience*, 2017. ISSN 1097-6256. doi: 10.1038/nn.4543.

Amar Sahay, Donald A. Wilson, and René Hen. Pattern Separation: A Common Function for New Neurons in Hippocampus and Olfactory Bulb, 5 2011. ISSN 08966273.

Beatrice Salvetti, Richard G.M. Morris, and Szu Han Wang. The role of rewarding and novel events in facilitating memory persistence in a separate spatial memory task. *Learning and Memory*, 21(2):61–72, 2 2014. ISSN 10720502. doi: 10.1101/lm.032177.113.

Honi Sanders, Matthew A Wilson, and Samuel J Gershman. Hippocampal remapping as hidden state inference. *eLife*, 9, 6 2020. ISSN 2050-084X. doi: 10.7554/eLife.51140. URL `https://elifesciences.org/articles/51140`.

Susan J. Sara. Sleep to Remember. *The Neuroscientist*, 12(5):410–424, 2017. ISSN 1073-8584. doi: 10.1177/1073858406292647. URL `http://nro.sagepub.com/cgi/doi/10.1177/1073858406292647`.

Masaaki Sato, Kotaro Mizuta, Tanvir Islam, Masako Kawano, Yukiko Sekine, Takashi Takekawa, Daniel Gomez-Dominguez, Alexander Schmidt, Fred Wolf, Karam Kim, Hiroshi Yamakawa, Masamichi Ohkura, Min Goo Lee, Tomoki Fukai, Junichi Nakai, and Yasunori Hayashi. Distinct Mechanisms of Over-Representation of Landmarks and Rewards in the Hippocampus. *Cell Reports*, 32(1):107864, 7 2020. ISSN 22111247. doi: 10.1016/j.celrep.2020.107864.

Etienne Save, Arnaud Cressant, Catherine Thinus-Blanc, and Bruno Poucet. Spatial firing of hippocampal place cells in blind rats. *Journal of Neuroscience*, 18(5):1818–1826, 3 1998. ISSN 02706474. doi: 10.1523/jneurosci.18-05-01818.1998.

Etienne Save, Ludek Nerad, and Bruno Poucet. Contribution of multiple sensory information to place field stability in hippocampal place cells. *Hippocampus*, 10(1):64–76, 2000. ISSN 10509631. doi: 10.1002/(SICI)1098-1063(2000)10:1⟨64::AID-HIPO7⟩3.0.CO;2-Y.

Anna C. Schapiro, Elizabeth A. McDevitt, Timothy T. Rogers, Sara C. Mednick, and Kenneth A. Norman. Human hippocampal replay during rest prioritizes weakly learned information and predicts memory performance. *Nature Communications*, 9(1):1–11, 12 2018. ISSN 20411723. doi: 10.1038/s41467-018-06213-1.

R. Schmidt. Über Wiedererkennen und rückwirkende Hemmung" Neuauswertung einer Arbeit von Rosa Heine, 1914, 1987. URL `https://psycnet.apa.org/record/1989-72697-001`.

Nicolas W. Schuck and Yael Niv. Sequential replay of nonspatial task states in the human hippocampus. *Science*, 364(6447), 6 2019. ISSN 10959203. doi: 10.1126/science.aaw5181.

Nicolas W. Schuck, Ming Bo Cai, Robert C. Wilson, and Yael Niv. Human Orbitofrontal Cortex Represents a Cognitive Map of State Space. *Neuron*, 91(6): 1402–1412, 9 2016. ISSN 10974199. doi: 10.1016/j.neuron.2016.08.019.

Peter J. Schuette, Fernando M.C.V. Reis, Sandra Maesta-Pereira, Meghmik Chakerian, Anita Torossian, Garrett J. Blair, Weisheng Wang, Hugh T. Blair, Michael S. Fanselow, Jonathan C. Kao, and Avishek Adhikari. Long-term characterization of hippocampal remapping during contextual fear acquisition and extinction. *Journal of Neuroscience*, 40(43):8329–8342, 10 2020. ISSN 15292401. doi: 10.1523/JNEUROSCI.1022-20.2020.

W. Schultz, P. Dayan, and P. R. Montague. A neural substrate of prediction and reward. *Science*, 275(5306):1593–1599, 1997. ISSN 00368075. doi: 10.1126/science.275.5306.1593.

Wolfram Schultz. Behavioral dopamine signals, 5 2007. ISSN 01662236.

W B Scoville and B Milner. Loss of recentmemory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, 20(1):11–21, 1957. ISSN 0022-3050. doi: 10.1136/jnnp.20.1.11. URL `http://jnnp.bmj.com/cgi/doi/10.1136/jnnp.20.1.11`.

Matthew L. Shapiro, Heikki Tanila, and Howard Eichenbaum. Cues that hippocampal place cells encode: Dynamic and hierarchical representation of local and distal stimuli. *Hippocampus*, 7(6):624–642, 1 1997. ISSN 1050-9631. doi: 10.1002/(SICI)1098-1063(1997)7:6⟨624::AID-HIPO5⟩3.0.CO;2-E. URL https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1098-1063(1997)7:6<624::AID-HIPO5>3.0.CO;2-E.

ML Shapiro. *Hippocampal function and interference*. 1984. URL https://books.google.com/books?hl=en&lr=&id=4gdHL81eaQgC&oi=fnd&pg=PA87&ots=mVUUx3GJFG&sig=mzj5DrhIVo5vj69UBN34FYGus3Y.

Patricia E. Sharp, Hugh T. Blair, David Etkin, and Douglas B. Tzanetos. Influences of vestibular and visual motion information on the spatial firing patterns of hippocampal place cells. *Journal of Neuroscience*, 15(1 I):173–189, 1995. ISSN 02706474. doi: 10.1523/jneurosci.15-01-00173.1995.

Justin D. Shin, Wenbo Tang, and Shantanu P. Jadhav. Dynamics of Awake Hippocampal-Prefrontal Replay for Spatial Learning and Memory-Guided Decision Making. *Neuron*, 10 2019. ISSN 08966273. doi: 10.1016/j.neuron.2019.09.012. URL https://linkinghub.elsevier.com/retrieve/pii/S0896627319307858.

Delia Silva, Ting Feng, and David J Foster. Trajectory events across hippocampal place cells require previous experience. *Nature Neuroscience*, 18(12):1772–1779, 2015. ISSN 1097-6256. doi: 10.1038/nn.4151. URL http://www.nature.com/doifinder/10.1038/nn.4151.

Annabelle C. Singer and Loren M. Frank. Rewarded Outcomes Enhance Reactivation of Experience in the Hippocampus. *Neuron*, 64(6):910–921, 2009. ISSN 08966273. doi: 10.1016/j.neuron.2009.11.016. URL http://dx.doi.org/10.1016/j.neuron.2009.11.016.

William E Skaggs, Bruce L Mcnaughton, Katalin M Gothard, and Etan J Markus.

An Information-Theoretic Approach to Deciphering the Hippocampal Code. *Proceedings of the 5th International Conference on Neural Information Processing System*, 1994.

William E. Skaggs, Bruce L. McNaughton, Matthew A. Wilson, and Carol A. Barnes. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus*, 6(2):149–172, 1 1996. ISSN 1050-9631. doi: 10.1002/(SICI)1098-1063(1996)6:2⟨149::AID-HIPO6⟩3.0.CO;2-K. URL https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1098-1063(1996)6:2<149::AID-HIPO6>3.0.CO;2-K.

Sleep Council. First Ever Great British Bedtime Report Launched - The Sleep Council Press Release. URL https://sleepcouncil.org.uk/latest-news/first-ever-great-british-bedtime-report-launched/.

C. Smith. Sleep states and memory processes in humans: Procedural versus declarative memory systems, 2001. ISSN 10870792.

David M. Smith and Sheri J.Y. Mizumori. Hippocampal place cells, context, and episodic memory. *Hippocampus*, 16(9):716–729, 9 2006. ISSN 1050-9631. doi: 10.1002/hipo.20208. URL http://doi.wiley.com/10.1002/hipo.20208.

E N Sokolov. Higher Nervous Functions: The Orienting Reflex. *http://dx.doi.org/10.1146/annurev.ph.25.030163.002553*, 25:545–580, 11 2003. doi: 10.1146/ANNUREV.PH.25.030163.002553. URL https://www.annualreviews.org/doi/abs/10.1146/annurev.ph.25.030163.002553.

Nicole K. Speer and Jeffrey M. Zacks. Temporal changes as event boundaries: Processing and memory consequences of narrative time shifts. *Journal of Memory and Language*, 53(1):125–140, 7 2005. ISSN 0749596X. doi: 10.1016/j.jml.2005.02.009.

Nicole K. Speer, Jeffrey M. Zacks, and Jeremy R. Reynolds. Human brain activity time-locked to narrative event boundaries: Research article. *Psychological Science*, 18(5):449–455, 5 2007. ISSN 09567976. doi: 10.1111/j.1467-9280.2007.01920.x.

Hugo J. Spiers, Eleanor A. Maguire, and Neil Burgess. Hippocampal amnesia, 2001. ISSN 13554794.

R. (Robert) Stickgold and Matthew P. Walker. *The neuroscience of sleep*. Academic Press/Elsevier, 2009. ISBN 9780123757227.

Robert Stickgold. Sleep-dependent memory consolidation, 10 2005. ISSN 14764687.

Robert Stickgold and Matthew P. Walker. Sleep-dependent memory triage: Evolving generalization through selective processing, 2 2013. ISSN 10976256.

Bryan A. Strange, Menno P. Witter, Ed S. Lein, and Edvard I. Moser. Functional organization of the hippocampal longitudinal axis, 10 2014. ISSN 14710048.

Robert J. Sutherland, Justin Q. Lee, Robert J. McDonald, and Hugo Lehmann. Has multiple trace theory been refuted? *Hippocampus*, 30(8):842–850, 8 2020. ISSN 1050-9631. doi: 10.1002/hipo.23162. URL `https://onlinelibrary.wiley.com/doi/abs/10.1002/hipo.23162`.

Khena M. Swallow, Jeffrey M. Zacks, and Richard A. Abrams. Event Boundaries in Perception Affect Memory Encoding and Updating. *Journal of Experimental Psychology: General*, 138(2):236–257, 5 2009. ISSN 00963445. doi: 10.1037/a0015631.

Tomonori Takeuchi, Adrian J. Duszkiewicz, Alex Sonneborn, Patrick A. Spooner, Miwako Yamasaki, Masahiko Watanabe, Caroline C. Smith, Guillén Fernández, Karl Deisseroth, Robert W. Greene, and Richard G.M. Morris. Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature*, 537(7620):357–362, 2016. ISSN 14764687. doi: 10.1038/nature19325.

Lucia M. Talamini, Ingrid L.C. Nieuwenhuis, Atsuko Takashima, and Ole Jensen. Sleep directly following learning benefits consolidation of spatial associative memory. *Learning and Memory*, 15(4):233–237, 4 2008. ISSN 10720502. doi: 10.1101/lm.771608.

J. S. Taube, R. U. Muller, and J. B. Ranck. Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *Journal of Neuroscience*, 10(2):420–435, 2 1990. ISSN 02706474. doi: 10.1523/jneurosci.10-02-00420.1990.

Rita Morais Tavares, Avi Mendelsohn, Yael Grossman, Christian Hamilton Williams, Matthew Shapiro, Yaacov Trope, and Daniela Schiller. A Map for Social Navigation in the Human Brain. *Neuron*, 87(1):231–243, 7 2015. ISSN 10974199. doi: 10.1016/j.neuron.2015.06.011.

Panagiota Theodoni, Bernat Rovira, Yingxue Wang, and Alex Roxin. Theta-modulation drives the emergence of connectivity patterns underlying replay in a network model of place cells. *eLife*, 7, 10 2018. ISSN 2050084X. doi: 10.7554/eLife.37388.

L. T. Thompson and P. J. Best. Long-term stability of the place-field activity of single units recorded from the dorsal hippocampus of freely behaving rats. *Brain Research*, 509(2):299–308, 2 1990. ISSN 00068993. doi: 10.1016/0006-8993(90)90555-P.

E. C. Tolman and C. H. Honzik. Introduction and removal of reward, and maze performance in rats. - PsycNET. *University of California Publications in Psychology*, 1930. URL `https://psycnet.apa.org/record/1931-02280-001`.

Edward C Tolman. Cognitive Maps in Rats and Men. Technical report, 1948.

Giulio Tononi and Chiara Cirelli. Sleep and synaptic homeostasis: A hypothesis, 2003. ISSN 03619230.

Giulio Tononi and Chiara Cirelli. Sleep function and synaptic homeostasis, 2 2006. ISSN 10870792.

Alessandro Treves and Edmund T. Rolls. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus*, 2(2):189–199, 1992. ISSN 10981063. doi: 10.1002/hipo.450020209.

Alessandro Treves and Edmund T. Rolls. Computational analysis of the role of the hippocampus in memory. *Hippocampus*, 4(3):374–391, 6 1994. ISSN 1050-9631. doi: 10.1002/hipo.450040319. URL `http://doi.wiley.com/10.1002/hipo.450040319`.

Dorothy Tse, Rosamund F. Langston, Masaki Kakeyama, Ingrid Bethus, Patrick A. Spooner, Emma R. Wood, Menno P. Witter, and Richard G.M. Morris. Schemas and memory consolidation. *Science*, 316(5821):76–82, 4 2007. ISSN 00368075. doi: 10.1126/science.1135935.

Dorothy Tse, Tomonori Takeuchi, Masaki Kakeyama, Yasushi Kajii, Hiroyuki Okuno, Chiharu Tohyama, Haruhiko Bito, and Richard G.M. Morris. Schema-dependent gene activation and memory encoding in neocortex. *Science*, 333 (6044):891–895, 8 2011. ISSN 00368075. doi: 10.1126/science.1205274.

Endel Tulving. Episodic and Semantic Memory. *Organization of memory/Eds E. Tulving, W. Donaldson*, 1972.

Gray Umbach, Pranish Kantak, Joshua Jacobs, Michael Kahana, Brad E. Pfeiffer, Michael Sperling, and Bradley Lega. Time cells in the human hippocampus and entorhinal cortex support episodic memory. *Proceedings of the National Academy of Sciences of the United States of America*, 117(45):28463–28474, 11 2020. ISSN 10916490. doi: 10.1073/pnas.2013250117.

Gido M. van de Ven, Stéphanie Trouche, Colin G. McNamara, Kevin Allen, and David Dupret. Hippocampal Offline Reactivation Consolidates Recently Formed Cell Assembly Patterns during Sharp Wave-Ripples. *Neuron*, 92(5):968–974, 12 2016. ISSN 10974199. doi: 10.1016/j.neuron.2016.10.020.

Matthijs van der Meer, Alyssa Carey, and Youki Tanaka. Optimizing for generalization in the decoding of internally generated activity in the hippocampus. *Optimizing for generalization in the decoding of internally generated activity in the hippocampus*, page 066670, 1 2016. ISSN 1098-1063. doi: 10.1101/066670.

Marlieke T.R. Van Kesteren, Mark Rijpkema, Dirk J. Ruiter, and Guillén Fernández. Retrieval of associative information congruent with prior knowledge is related to increased medial prefrontal activity and connectivity. *Journal of Neuroscience*, 30(47):15888–15894, 11 2010. ISSN 02706474. doi: 10.1523/JNEUROSCI.2674-10.2010.

Marlieke T.R. Van Kesteren, Dirk J. Ruiter, Guillén Fernández, and Richard N. Henson. How schema and novelty augment memory formation, 4 2012. ISSN 01662236.

Marlieke T.R. Van Kesteren, Sarah F. Beul, Atsuko Takashima, Richard N. Henson, Dirk J. Ruiter, and Guillén Fernández. Differential roles for medial prefrontal and medial temporal cortices in schema-dependent encoding: From congruent to incongruent. *Neuropsychologia*, 51(12):2352–2359, 10 2013. ISSN 00283932. doi: 10.1016/j.neuropsychologia.2013.05.027.

Marlieke T.R. Van Kesteren, Mark Rijpkema, Dirk J. Ruiter, Richard G.M. Morris, and Guillén Fernández. Building on prior knowledge: schema-dependent encoding processes relate to academic performance. *Journal of cognitive neuroscience*, 26(10):2250–2261, 10 2014. ISSN 15308898. doi: 10.1162/jocn{_}a{_}00630.

E. B. Van Ormer. Sleep and retention. *Psychological Bulletin*, 30(6):415–439, 6 1933. ISSN 00332909. doi: 10.1037/h0071478.

Stefania Vescia, Paola Mandile, Paola Montagnese, Fabio Romano, Gabriella Cataldo, Mario Cotugno, and Antonio Giuditta. Baseline transition sleep and associated sleep episodes are related to the learning ability of rats. *Physiol-*

ogy and Behavior, 60(6):1513–1525, 12 1996. ISSN 00319384. doi: 10.1016/S0031-9384(96)00302-2.

Indre V. Viskontas, Mary Pat McAndrews, and Morris Moscovitch. Memory for famous people in patients with unilateral temporal lobe epilepsy and excisions. *Neuropsychology*, 16(4):472–480, 2002. ISSN 08944105. doi: 10.1037/0894-4105.16.4.472.

Vladyslav V. Vyazovskiy, Umberto Olcese, Yaniv M. Lazimy, Ugo Faraguna, Steve K. Esser, Justin C. Williams, Chiara Cirelli, and Giulio Tononi. Cortical Firing and Sleep Homeostasis. *Neuron*, 63(6):865–878, 9 2009. ISSN 08966273. doi: 10.1016/j.neuron.2009.08.024.

Ullrich Wagner, Steffen Gais, and Jan Born. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning and Memory*, 8(2):112–119, 3 2001. ISSN 10720502. doi: 10.1101/lm.36801.

Matthew P. Walker and Robert Stickgold. Sleep-dependent learning and memory consolidation, 9 2004. ISSN 08966273.

Stefan Walter and Beat Meier. How important is importance for prospective memory? A review. *Frontiers in Psychology*, 5(JUN):657, 6 2014. ISSN 1664-1078. doi: 10.3389/fpsyg.2014.00657. URL `http://journal.frontiersin.org/article/10.3389/fpsyg.2014.00657/abstract`.

Jinhui Wang, Xindi Wang, Mingrui Xia, Xuhong Liao, Alan Evans, and Yong He. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. *Frontiers in Human Neuroscience*, 9(June):1–16, 2015. ISSN 1662-5161. doi: 10.3389/fnhum.2015.00386. URL `http://www.frontiersin.org/Journal/Abstract.aspx?s=537&name=human_neuroscience&ART_DOI=10.3389/fnhum.2015.00386%5Cnhttp://journal.frontiersin.org/article/10.3389/fnhum.2015.00386/pdf`.

M. E. Wang, E. G. Wann, R. K. Yuan, M. M. Ramos Alvarez, S. M. Stead, and I. A. Muzzio. Long-Term Stabilization of Place Cell Remapping Produced by a Fearful Experience. *Journal of Neuroscience*, 32(45):15802–15814, 2012. ISSN 0270-6474. doi: 10.1523/JNEUROSCI.0480-12.2012. URL `http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.0480-12.2012`.

Szu Han Wang, Roger L. Redondo, and Richard G.M. Morris. Relevance of synaptic tagging and capture to the persistence of long-term potentiation and everyday spatial memory. *Proceedings of the National Academy of Sciences of the United States of America*, 107(45):19537–19542, 11 2010. ISSN 10916490. doi: 10.1073/pnas.1008638107.

Xiao Jing Wang. Synaptic reverberation underlying mnemonic persistent activity, 8 2001. ISSN 01662236.

Michael J. Watkins and Endel Tulving. Episodic memory: When recognition fails. *Journal of Experimental Psychology: General*, 104(1):5–29, 3 1975. ISSN 00963445. doi: 10.1037/0096-3445.104.1.5.

Robyn Westmacott, Sandra E. Black, Morris Freedman, and Morris Moscovitch. The contribution of autobiographical significance to semantic memory: Evidence from Alzheimer's disease, semantic dementia, and amnesia. *Neuropsychologia*, 42(1):25–48, 1 2004. ISSN 00283932. doi: 10.1016/S0028-3932(03)00147-7.

Carin Whitney, Walter Huber, Juliane Klann, Susanne Weis, Sören Krach, and Tilo Kircher. Neural correlates of narrative shifts during auditory story comprehension. *NeuroImage*, 47(1):360–366, 8 2009. ISSN 10538119. doi: 10.1016/j.neuroimage.2009.04.037.

Tom J. Wills, Colin Lever, Francesca Cacucci, Neil Burgess, and John O'Keefe. Attractor dynamics in the hippocampal representation of the local environment. *Science*, 308(5723):873–876, 5 2005. ISSN 00368075. doi: 10.1126/science.1108905.

Donald A. Wilson. Pattern separation and completion in olfaction. In *Annals of the New York Academy of Sciences*, volume 1170, pages 306–312. Blackwell Publishing Inc., 2009. ISBN 9781573317382. doi: 10.1111/j.1749-6632.2009.04017.x.

M. Wilson and B. McNaughton. Reactivation of hippocampal ensemble memories during sleep. *Science*, 265(5172):676–679, 1994. ISSN 0036-8075. doi: 10.1126/science.8036517. URL http://www.sciencemag.org/cgi/doi/10.1126/science.8036517.

Robert C. Wilson, Yuji K. Takahashi, Geoffrey Schoenbaum, and Yael Niv. Orbitofrontal cortex as a cognitive map of task space. *Neuron*, 81(2):267–279, 1 2014. ISSN 10974199. doi: 10.1016/j.neuron.2013.11.005.

Sarah Witkowski, Eitan Schechtman, and Ken A. Paller. Examining sleep's role in memory generalization and specificity through the lens of targeted memory reactivation. *Current Opinion in Behavioral Sciences*, 33:86–91, 2020. ISSN 23521546. doi: 10.1016/j.cobeha.2020.01.007. URL https://doi.org/10.1016/j.cobeha.2020.01.007.

Menno P. Witter, Floris G. Wouterlood, Pieterke A. Naber, and Theo Van Haeften. Anatomical organization of the parahippocampal-hippocampal network. In *Annals of the New York Academy of Sciences*, volume 911, pages 1–24. New York Academy of Sciences, 2000. doi: 10.1111/j.1749-6632.2000.tb06716.x.

Bianca C. Wittmann, Nico Bunzeck, Raymond J. Dolan, and Emrah Düzel. Anticipation of novelty recruits reward system and hippocampus while promoting recollection. *NeuroImage*, 38(1):194–202, 10 2007. ISSN 10538119. doi: 10.1016/j.neuroimage.2007.06.038.

Emma R. Wood, Paul A. Dudchenko, R. Jonathan Robitsek, and Howard Eichenbaum. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron*, 27(3):623–633, 9 2000. ISSN 08966273. doi: 10.1016/S0896-6273(00)00071-4.

Chun-ting Wu, Daniel Haggerty, Caleb Kemere, and Daoyun Ji. Hippocampal awake replay in fear memory retrieval. *Nature Neuroscience*, (April 2016), 2017. ISSN 1097-6256. doi: 10.1038/nn.4507. URL http://dx.doi.org/10.1038/nn.4507.

J. Z. Xiang and M. W. Brown. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology*, 37(4-5):657–676, 4 1998. ISSN 0028-3908. doi: 10.1016/S0028-3908(98)00030-6.

Miwako Yamasaki and Tomonori Takeuchi. Locus Coeruleus and Dopamine-Dependent Memory Consolidation, 2017. ISSN 16875443.

Michael A. Yassa and Craig E.L. Stark. Pattern separation in the hippocampus, 10 2011. ISSN 01662236.

X. Yu, J. J. Knierim, I. Lee, and H. Z. Shouval. Simulating place field dynamics using spike timing-dependent plasticity. *Neurocomputing*, 69(10-12):1253–1259, 5 2006. ISSN 09252312. doi: 10.1016/j.neucom.2005.12.087.

Jeffrey M. Zacks. The brain■s cutting-room floor: segmentation of narrative cinema. *Frontiers in Human Neuroscience*, 4:168, 10 2010. ISSN 16625161. doi: 10.3389/fnhum.2010.00168. URL http://journal.frontiersin.org/article/10.3389/fnhum.2010.00168/abstract.

Jeffrey M. Zacks, Todd S. Braver, Margaret A. Sheridan, David I. Donaldson, Abraham Z. Snyder, John M. Ollinger, Randy L. Buckner, and Marcus E. Raichle. Human brain activity time-locked to perceptual event boundaries. *Nature Neuroscience*, 4(6):651–655, 2001. ISSN 10976256. doi: 10.1038/88486.

Jeffrey M. Zacks, Khena M. Swallow, Jean M. Vettel, and Mark P. McAvoy. Visual motion and the neural correlates of event perception. *Brain Research*, 1076(1): 150–162, 3 2006. ISSN 00068993. doi: 10.1016/j.brainres.2005.12.122.

Jingwei Zhang, Tian Liu, Ajay Gupta, Pascal Spincemaille, Thanh D Nguyen, and Yi Wang. Quantitative mapping of cerebral metabolic rate of oxygen (CMRO2

) using quantitative susceptibility mapping (QSM). *Magnetic resonance in medicine*, 74(4):945–52, 2015. ISSN 1522-2594. doi: 10.1002/mrm.25463. URL http://www.ncbi.nlm.nih.gov/pubmed/25263499.

Kechen Zhang, Iris Ginzburg, Bruce L Mcnaughton, and Terrence J Sejnowski. Interpreting Neuronal Population Activity by Reconstruction: Unified Framework With Application to Hippocampal Place Cells. *J. Neurophysiol. Zemel et al*, 79: 1017–1044, 1998. URL http://www.physiology.org/doi/pdf/10.1152/jn.1998.79.2.1017.

W. N. Zhang, H. H.J. Pothuizen, J. Feldon, and J. N.P. Rawlins. Dissociation of function within the hippocampus: Effects of dorsal, ventral and complete excitotoxic hippocampal lesions on spatial navigation. *Neuroscience*, 127(2):289–300, 1 2004. ISSN 03064522. doi: 10.1016/j.neuroscience.2004.05.007.

Wenyi Zhou and Jonathon D. Crystal. Evidence for remembering when events occurred in a rodent model of episodic memory. *Proceedings of the National Academy of Sciences of the United States of America*, 106(23):9525–9529, 6 2009. ISSN 00278424. doi: 10.1073/pnas.0904360106.

XO Zhu and MW Brown. Changes in neuronal activity related to the repetition and relative familiarity of visual stimuli in rhinal and adjacent cortex of the anaesthetised rat. *Brain research*, 689(1):101–110, 8 1995. ISSN 0006-8993. doi: 10.1016/0006-8993(95)00550-A. URL https://pubmed.ncbi.nlm.nih.gov/8528693/.

Yaniv Ziv, Laurie D. Burns, Eric D. Cocker, Elizabeth O. Hamel, Kunal K. Ghosh, Lacey J. Kitch, Abbas El Gamal, and Mark J. Schnitzer. Long-term dynamics of CA1 hippocampal place codes. *Nature Neuroscience*, 16(3):264–266, 3 2013. ISSN 10976256. doi: 10.1038/nn.3329.

S. Zola-Morgan, L. R. Squire, and D. G. Amaral. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion

limited to field CA1 of the hippocampus. *Journal of Neuroscience*, 6(10):2950–2967, 1986. ISSN 02706474. doi: 10.1523/jneurosci.06-10-02950.1986.

S M Zola-Morgan and L R Squire. The primate hippocampal formation: evidence for a time-limited role in memory storage. *Science*, 250:288–290, 1990. ISSN 0036-8075. URL `http://www.ncbi.nlm.nih.gov/pubmed/2218534`.

Stuart Zola-Morgan, Larry R. Squire, and Seth J. Ramus. Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. *Hippocampus*, 4(4):483–495, 1994. ISSN 10981063. doi: 10.1002/hipo.450040410.