BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Dissertation

**THE TITLE OF THE DISSERTATION IN ALL**

**CAPITAL LETTERS BOLD AND CENTERED**

by

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B.A., Cornell University, 2014

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

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Approved by

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# DEDICATION

I would like to dedicate this work to my patient spouse Landry, my wonderful children Charlie and Phoenix, and my dog Armani.

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# ACKNOWLEDGMENTS

Sometimes, a dissertation or thesis will have an acknowledgments page. Here's where you thank the people who helped you write this work. Your advisor and committee, archivists and librarians, your best friends, your spouse, your study buddy.

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**THE TITLE OF THE DOCTORAL DISSERTATION**

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**AND CENTERED**

**WILLIAM MAU**

Boston University School of Medicine, 2019

Major Professor: Type the name of your first reader, Professor of ............ *(wrap around to this point if name and title are too long for one line)*

# ABSTRACT

The body of the abstract begins here and is typed double spaced. A doctoral dissertation abstract is limited to 350 words.

# PREFACE

It was a dark and stormy night; the rain fell in torrents — except at occasional intervals, when it was checked by a violent gust of wind which swept up the streets (for it is in London that our scene lies), rattling along the housetops, and fiercely agitating the scanty flame of the lamps that struggled against the darkness.

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# LIST OF ABBREVIATIONS

BU Boston University

ISO International Standards Organization

RCMP Royal Canadian Mounted Police

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# GLOSSARY

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# CHAPTER ONE

**The Hippocampal Formation, Amygdala, and Associative Memory**

One central function of a complex nervous system is to perceive stimuli from the external environment, perform internal computations, and output actions that ensure survival. To do so, the brain must have machinery to store and retrieve that information as well as its associated behaviors. For example, a street mouse needs to remember where in the city it might find food scraps and seek them at appropriate times of day. The ability for an organism to learn and recall relationships such as these is called associative memory. Although other types of learning and memory exist, in this thesis, I will focus solely on how associative and “episodic” memories are supported by structures in the temporal lobe. In particular, I will pay special attention to the hippocampal formation and the amygdalar complex.

## Historical considerations of the hippocampal formation and amygdalar complex in learning and memory

One of the earliest theorists of human memory function was a German scientist named Richard Semon. He was one of the first thinkers to put forth the idea that memory resided on a physical substrate rather than in the intangible psyche (Semon, 1921). Thus, he proposed the term “engram” as the physical manifestation of a memory trace, despite no apparent means for observing such an entity. Years later, the synaptic plasticity mechanisms endorsed by Donald Hebb (Hebb, 1949) provided the foundations for how an engram could form and exist, as a network of coactive neurons via potentiated connections. However, early attempts to localize the engram in the rat brain proved difficult (Lashley, 1950). A few years later, the neuropsychological patient H.M. attracted much attention after his medically mandated hippocampal resection left him with profound anterograde amnesia and temporally graded retrograde amnesia despite retention of most other intellectual faculties (Scoville and Milner, 1957). This serendipitous finding propelled the field into investigating the medial temporal lobe (MTL) as the brain’s center for episodic memory encoding.

The investigations surrounding H.M. and related patients’ memory deficits launched a search for an animal model of amnesia. It was eventually found that in nonhuman primates the MTL, but not the amygdala, was required for normal performance at a memory probe called the delayed non-match to sample task (Squire and Zola-Morgan, 1991). Instead, the amygdala is involved in “emotional” memory, such as that elicited by fear conditioning (Ledoux, 1995), and facial recognition of fear in humans (Adolphs et al., 1994). Thus, research on the amygdala has generally been focused on how it is involved in forming associations between environmental cues and aversive stimuli.

## Anatomical connections of the hippocampal formation

The anatomy of the MTL has been thoroughly studied throughout the years and extensive literature exists on its connectivity within itself and between other cortical and subcortical regions. In rodents, the MTL consists of the hippocampal formation, entorhinal cortex (EC), perirhinal cortex, and postrhinal cortex. The hippocampus is a laminated structure that can be further subdivided into the dentate gyrus (DG) and Cornu Ammonis (CA) fields, CA1, CA2, and CA3. The output region of the hippocampus is the subicular complex, which is comprised of the subiculum proper, presubiculum, and parasubiculum.

When referring to circuitry in the hippocampal formation, there are two canonical pathways originating from its primary input region, the EC. However, recent studies have uncovered novel connections that are just beginning to be investigated (Kitamura et al., 2014; Kohara et al., 2014; Rajasethupathy et al., 2015; Witter, 1993). The first canonical circuit is commonly referred to as the “trisynaptic loop”, where neurons from layer II of EC (ECII) project to granule cells in the DG, which in turn send axons called mossy fibers to pyramidal cells in CA3. CA3 Schaffer collaterals then synapse onto CA1, which finally sends projections to layer V/VI of EC (ECV/VI). The second circuit, the temporammonic pathway, is a monosynaptic pathway from layer III of EC (ECIII) that synapses directly onto CA1.

### Dentate gyrus

The principal cell type of the DG is the granule cell, which is glutamatergic. These receive excitatory input from ECII, a projection often referred to as the perforant path. Granule cells are the only cell type in the DG that have axons leaving the DG to project to CA3, though contacts are also made onto DG mossy cells in the hilus. Until recently, it was thought that DG innervation halted at the CA3/CA2 border, but optogenetic studies have since found that granule cell mossy fibers also contact neurons in CA2 (Kohara et al., 2014). Another major cell type in the DG is the mossy cell, which is large and sends axons exclusively to the contralateral DG onto granule cells. The remaining cell types in the DG are a heterogeneous population of GABAergic interneurons that have various axonal ramification patterns onto distributed domains of postsynaptic granule and mossy cells.

The DG is known for its sparse activity and for being one of few brain regions that exhibit adult neurogenesis (Gonçalves et al., 2016; Jung and McNaughton, 1993). These features are thought to synergistically support “pattern separation”, or the neural orthogonalization of similar events (Leutgeb et al., 2007; Neunuebel and Knierim, 2014; Yassa and Stark, 2011). Recently, two-photon imaging experiments in the DG found evidence for a pattern separation mechanism supported by mossy cells and adult-born granule cells (Danielson et al., 2016a, 2017). In a general sense, information from cortical inputs may be parsed by the DG into discrete events to then be funneled into CA3 for additional processing.

### CA3

From the DG, mossy fibers synapse onto pyramidal cells of CA3, though there is also a direct EC-CA3 projection (van Strien et al., 2009) as well as inhibitory synapses from local interneurons. DG-CA3 mossy fiber boutons are uncharacteristically large and their contacts are known as “detonator synapses” for their ability to reliably discharge the postsynaptic cell in the absence of dendritic summation from other compartments (Henze et al., 2002). Thus, mossy fibers inputs from DG into CA3 have been hypothesized to serve as an unmitigated source of depolarization necessary for synaptic strengthening between DG and CA3 (McNaughton and Morris, 1987).

CA3 itself is widely acknowledged to have bountiful excitatory autoassociative connections originating from both ipsilateral and contralateral CA3 (via the hippocampal commissure). This feature is believed to support episodic memory through an autoassociative network possibly involving neuronal sequences (Levy, 1996; Rolls, 1996; Salz et al., 2016). The theory suggests that the highly recurrent connectivity of CA3 is conducive for establishing a synaptic matrix that would enable retrieval of a detailed representation given minimal input. Thus, a small cue could trigger the recall of a larger memory, a process called pattern completion (Rolls, 1996; Treves and Rolls, 1994). It has been recently discovered that CA3-CA3 synapses have unusually large plasticity windows which may support a specialized role of this circuit for associative recall (Mishra et al., 2016). Knierim and colleagues have shown that pattern completion occurs in CA3 (Lee et al., 2004; Neunuebel and Knierim, 2014), though more recent work from their lab suggests that this process is topologically heterogeneous along the transverse axis (Lee et al., 2015). Early modeling theories proposed that pattern completion could be mechanistically realized via cell sequences (Levy, 1996; Wallenstein et al., 1998). Indeed, a recent tour de force *in vitro* recording study showed that CA3 exhibited connectivity motifs that supported its role as a network of sequentially activated cells that could enable pattern completion (Guzman et al., 2016). Furthermore, work from our laboratory confirmed cell sequences in CA3 (Salz et al., 2016).

In addition to its recurrent outputs, CA3 also sends projections to CA2 and CA1. The CA3-CA2 projection’s functional implications have been almost entirely unexplored, but there has been more attention paid to the CA3-CA1 connection. The CA3 axons that innervate CA1 are called the Schaffer collaterals and are the primary inputs into the pyramidal cells of CA1.

### CA1

The principal cell in CA1 is the pyramidal neuron, which has been extensively studied by the neuroscience field. CA1 pyramidal cells receive input from CA3 Schaffer collaterals as well as ECIII (temporoammonic path) and local inhibitory interneurons. However, a recent study observed a subpopulation of clustered cells in ECII, termed “island” cells, that also sent projections to CA1, onto inhibitory interneurons that regulated ECIII excitatory input (Kitamura et al., 2014). Additional monosynaptic inputs come from the nucleus reuniens of the thalamus (Ito et al., 2015), CA2 (Hitti and Siegelbaum, 2014; Kohara et al., 2014), and anterior cingulate cortex (Rajasethupathy et al., 2015). Also prevalent is a reciprocal connection between basolateral amygdala (BLA) and ventral CA1 (Herry et al., 2008; Pikkarainen et al., 1999).

In contrast with CA3, CA1 pyramidal cells form very limited connections with themselves. Instead, CA1 is viewed as the primary output region of the hippocampus, with much of its information conveyed to extrahippocampal structures through the subiculum, with which it also has reciprocal connections (Amaral et al., 1991; Xu et al., 2016). Other notable output regions include ECV/VI, retrosplenial cortex (Wyss and Van Groen, 1992), medial prefrontal cortex (Jay and Witter, 1991; Kim and Cho, 2017), and the BLA (Kim and Cho, 2017; Kishi et al., 2006). CA1 pyramidal cells also contact local inhibitory neurons, which then synapse onto other CA1 pyramidal neurons.

The role of CA1 is under active research, and many functions have been ascribed to this highly-studied subregion. Its claim to fame is that it was the region where “place cells” were first discovered (O’Keefe and Dostrovsky, 1971). These are pyramidal neurons that exhibit spatial selectivity patterns, prompting early theories on the hippocampus as the locus of a “cognitive map” (O’Keefe and Nadel, 1978), although contemporary scholars now mostly agree that the hippocampus is involved in cognition beyond the spatial domain (Eichenbaum, 2004, 2017; Eichenbaum and Cohen, 2014; Smith and Bulkin, 2014; Squire, 1992).

CA1 seems suited for processing conjunctive inputs, possibly acting as an input comparator or coincidence detector for multiple sources of incoming information. Evidence for this theory comes from intracellular recordings that demonstrate CA1 neurons integrating inputs from CA3 (presumably containing internally stored information) and EC (presumably containing external sensory information) to drive firing (Bittner et al., 2015). Additionally, our lab has observed complex conjunctive responses in CA1 pyramidal cells to combinations of objects, locations, and contexts (Komorowski et al., 2009; McKenzie et al., 2014, 2016). However, this view is complicated by the fact that CA1 consists of multiple parallel processing streams within its radial axis (Danielson et al., 2016b; Soltesz and Losonczy, 2018). Another open question is the role of the temporal organization of CA1 pyramidal cell firing patterns in its mnemonic function (Buzsáki and Tingley, 2018; Eichenbaum, 2014).

### Subicular complex

The subicular complex is comprised of the subiculum, presubiculum (the dorsal aspect being called the postsubiculum), and parasubiculum. CA1 sends a dense, topographical projection to subiculum (Amaral et al., 1991), which then is relayed to ECV, mirroring the CA1-ECV projection. While it has long been thought that this intrahippocampal connection was unidirectional, there has been accumulating evidence that there is also a subiculum-CA1 backprojection (Berger et al., 1980; Sun et al., 2014; Xu et al., 2016). The subiculum also sends projections to the pre- and parasubiculum, subcortical regions such as the amygdala (Kishi et al., 2006), and numerous neocortical targets, one notable example being the retrosplenial cortex (Wyss and Van Groen, 1992).

The subiculum proper is regarded as one of the primary outputs of the hippocampal formation, but despite this important role, not much is known about its function. A recent study dissected the CA1-subiculum-EC circuit and suggested that the CA1-subiculum-ECV projection was involved in memory retrieval, whereas the CA1-ECV direct projection was essential for memory formation (Roy et al., 2017). On the other hand, there is a respectable amount of literature on the pre- and parasubiculum, most of which focus exclusively on its contributions to spatial navigation via head-direction cells, which were first discovered by Jeffrey Taube in these regions (Taube et al., 1990).

### CA2

CA2 is a small subregion that rests in between CA1 and CA3. It receives bilateral inputs from CA3 (Lorente de Nó, 1934), as well as newborn granule cells from DG (Kohara et al., 2014; Llorens-Martín et al., 2015). Extrahippocampal inputs also arise from subcortical areas such as the EC (Hitti and Siegelbaum, 2014), hypothalamus, medial septum, diagonal band of Broca, supramammillary nuclei, and median raphe nucleus (Cui et al., 2013). The primary output of CA2 is into CA1.

In part, due to the difficulty of reliably and accurately recording from the narrow band of cells in CA2, it has mostly been overlooked until recently. As a result, the function of CA2 is unclear and is currently being pursued from many different directions. One prominent theory suggests that CA2 is important for “social” memory (Dudek et al., 2016), an idea supported by high expression of a receptor for the “social” neuropeptide vasopressin in CA2 (Young et al., 2006) and the finding that CA2 lesions impact the ability to recognize familiar conspecifics (Hitti and Siegelbaum, 2014). Others propose a specialized role of CA2 in tracking changes in context and time due to its unusually high remapping rate (Mankin et al., 2015; Wintzer et al., 2014). Additional studies recently identified the role of CA2 in initiating oscillatory activity associated with an local field potential (LFP) complex called the sharp-wave (Kay et al., 2016; Oliva et al., 2016). The diversity of research in CA2 is apparent and the search for a common explanation for this diverse set of phenomena is currently ongoing.

### Medial septum

The medial septum provides GABAergic, cholinergic, and glutamatergic innervations onto the hippocampus and also receives GABAergic input from CA1 and CA3. In the rat, GABAergic cells exclusively synapse onto hippocampal GABAergic interneurons (Freund and Antal, 1988). However, recent optogenetic experiments in mice have found evidence for GABAergic and glutamatergic synapses onto both interneurons and pyramidal cells (Sun et al., 2014). Septal cholinergic projections also terminate onto CA1 pyramidal cells.

The medial septum is intimately involved in the generation of the theta rhythm in the hippocampus. Theta is often characterized by a continuous 4-12 Hz LFP oscillation in rodents, which is thought to be important for temporal organization of neural activity and coordination of synaptic modifications (Buzsáki, 2002; Hasselmo et al., 2002). An interesting phenomenon is also exhibited by hippocampal place cells, which spike at progressively earlier phases of theta at each theta cycle as the place field is traversed. “Phase precession” might provide an additional channel of information for spatial location based on spike-phase timing (O’Keefe and Recce, 1993; Skaggs et al., 1996). In addition, theta may play a role in arranging cell assemblies into temporally compressed sequences to inform previously visited versus upcoming locations (Colgin, 2013; Dragoi and Buzsáki, 2006; Foster and Wilson, 2007; Hasselmo, 2005; Lisman and Redish, 2009). Disrupting this theta rhythm has been shown to be detrimental to firing patterns in MTL structures (Brandon et al., 2011; Wang et al., 2015).

### Lateral entorhinal cortex

The EC can be regarded as the gateway to the hippocampus and the lateral entorhinal cortex (LEC) is a subdivision of the EC that is distinct from the medial entorhinal cortex (MEC) on the basis of cytoarchitecture and connectivity. As a general rule, the EC sends axons bound for hippocampal targets and receives neocortical input at layers I-III, while it receives hippocampal input and delivers neocortical ouputs at layers IV-VI. The LEC has reciprocal connections with the MEC, amygdala, perirhinal cortex, piriform cortex, subicular complex, and CA1, as well as afferents to DG (Burwell and Amaral, 1998; Kerr et al., 2007; Köhler, 1988; van Strien et al., 2009).

The function of the LEC is unclear, though some hypotheses proposed its role as a relay station for “what” information to be integrated with “where” information, originating from the MEC, at the hippocampal junction (Eichenbaum, 2016; Eichenbaum et al., 2012). This view is consistent with experimental findings of LEC showing sensitivity to objects (Deshmukh and Knierim, 2011; Deshmukh et al., 2012; Keene et al., 2016; Tsao et al., 2013). However, a recent study demonstrated that LEC might also support the associations of events across episodic timescales (Tsao et al., 2018). Due to the fact that its selectivity properties are hard to decipher, the LEC remains an active area of research.

### Medial entorhinal cortex

The medial entorhinal cortex (MEC), in contrast, receives most of its cortical inputs from the postrhinal and piriform cortex, but is also connected with the retrosplenial cortex, posterior parietal cortex, visual association areas, CA1, and DG (Burwell and Amaral, 1998; van Strien et al., 2009). Its connectivity to these regions has guided researchers towards studying the MEC as a spatial association structure and the supplier of “where” information to complement the “what” stream from LEC.

The MEC is perhaps most well-known for being the home of “grid cells”, which are (mostly pyramidal) neurons that fire in a hexagonal-lattice pattern tiling the environment (Hafting et al., 2005; Tang et al., 2014). Thus, many subsequent studies have focused on MEC contributions to spatial navigation, in particular on how it could create spatial firing fields in the hippocampus (Hasselmo, 2009; Rolls et al., 2006; Solstad et al., 2006). However, there have been multiple demonstrations that MEC is not required for hippocampal place cell formation (Hales et al., 2014; Kanter et al., 2017; Rueckemann et al., 2016; Schlesiger et al., 2015), leaving the field perplexed on its true function. Other efforts have focused on the temporal correlates of the MEC and downstream hippocampal spiking patterns. The MEC itself contains neurons that exhibit temporal firing fields during a delay (Heys and Dombeck, 2018; Kraus et al., 2015), and inhibiting MEC disrupts hippocampal sequences and temporal associative memory (Kitamura et al., 2014; Robinson et al., 2017; Schlesiger et al., 2015). A more recent hypothesis has suggested that the MEC might define a coordinate system of cognitive space for abstract associations, which would extrapolate the role of the MEC to beyond that of the spatial domain (Bellmund et al., 2018).

### Amygdala

The amygdala is an almond-shaped subcortical structure known to be involved in emotional learning and memory, and is studied most commonly in the context of fear conditioning (Ledoux, 1995). Approximately 80% of the cells are glutamatergic spiny projection neurons, with the remainder being GABAergic interneurons (McDonald, 1982, 1985; Rainnie et al., 2006). The amygdala’s basolateral nucleus is reciprocally connected with ventral CA1, subiculum, and medial prefrontal cortex (mPFC), as well as the central nucleus of the amygdala (McDonald, 1991; McDonald et al., 1996; Pitkänen et al., 2000). To contrast, the central amygdala sends inhibitory projections to the periaqueductal gray and the hypothalamus (Tovote et al., 2015).

Numerous mechanisms may be responsible for fear expression and extinction (decrease in fear expression), which involve amygdalar circuitry as well as interactions with other structures such as the medial prefrontal cortex and the ventral hippocampus. Locally, amygdalar microcircuitry is highly dependent on inhibitory and disinhibitory control of projection neurons via interneurons, which also modulate plasticity on their postsynaptic targets (Tovote et al., 2015; Trouche et al., 2013). Specific projection neurons in the amygdala drive fear expression, and perisomatic inhibition by parvalbumin (PV)-expressing interneurons are important for regulating which neurons are assigned this role (Davis et al., 2017; Grewe et al., 2017; Rashid et al., 2016; Yokose et al., 2017). Though strides have been made on understanding how single neurons in the amygdala support fear expression and anxiety, this region does not drive behavior in isolation.

In addition to local circuitry, oscillatory dynamics between the amygdala and mPFC/ventral CA1 also influence fear-associated behavior. The amygdala exhibits a theta rhythm similar to that of the hippocampus, and hippocampal-amygdalar theta synchrony has been shown to be important for communication between these two regions and consequent freezing behavior (Herry et al., 2008; Seidenbecher et al., 2003). Theta entrainment between mPFC and amygdala is also predictive of discrimination between averse and safe environments (Likhtik et al., 2014), though there is an important distinction between two subregions of the mPFC, infralimbic (IL) and prelimbic cortex (PL) (Davis et al., 2017; Senn et al., 2014); PL is associated with high fear, whereas IL is recruited after extinction. The specifics behind these oscillatory interactions are still under active investigation.

## Hippocampal function

With the discovery of place cells in the 1970’s, early neuroscientists studying the hippocampus focused on its role as a “cognitive map” of the environment (O’Keefe and Dostrovsky, 1971; O’Keefe and Nadel, 1978). However, many have recognized its role in relational memory, not necessarily in the spatial domain (Buzsáki and Tingley, 2018; Cohen and Eichenbaum, 1993; Davachi and DuBrow, 2015; Eichenbaum, 2017; Eichenbaum and Cohen, 2014; Friston and Buzsáki, 2016; Howard and Eichenbaum, 2015; Morton et al., 2017; Ranganath and Hsieh, 2016; Smith and Bulkin, 2014). In the spatial navigation view, place cells identify spatial locations within an allocentric reference frame, overlaid on a Euclidean coordinate system provided by entorhinal grid cells (Hartley et al., 2014; Moser et al., 2008). However, this mechanism could be extrapolated and generalized to nonspatial features as well. Rather than representing strictly spatial location, neurons in the hippocampus could also model spatiotemporally-related events (Eichenbaum and Cohen, 2014). Indeed, memory researchers are approaching the hippocampus from multiple avenues of investigation. In general, theories converge on a flexible role of the hippocampus for discovering associations across time and space, enabling forecasting given sparse cues (Howard and Eichenbaum, 2015; Levy et al., 2005; Lisman and Redish, 2009). For the remainder of this chapter, I will broadly review these branches in the context of rodent neurophysiology and how they relate to associative memory.

### Place cells and allocentric spatial representation

Edward Tolman first proposed the idea of a “cognitive map” when he discovered that rats are able to use a global representation of a maze to navigate via shortcuts (Tolman, 1948). However, at the time, there was no indication that the brain was capable of producing any such representation. Decades later, hippocampal place cells were found to exhibit spatial selectivity in a fixed environment, thus providing Tolman with the neural substrate supporting his idea of a cognitive map (O’Keefe and Dostrovsky, 1971; O’Keefe and Nadel, 1978). Shortly after, it was confirmed that hippocampal cells display spatially-modulated activity in an open field (Muller et al., 1987a) and that those cells also track the position of distal cues in the environment (Muller et al., 1987b) establishing the hippocampus as a locus for processing spatial information.

Place cells are intimately involved in spatial memory. Place cells reliably fire in the same locations over repeated exposures to an environment over long periods of time (Thompson and Best, 1990; Ziv et al., 2013), demonstrating that they can store spatial information to form associations between places or between locations and events. Sequences of place cells are also reactivated during rapid eye movement sleep, perhaps supporting rehearsal of ensemble dynamics encoding spatial layouts (Louie and Wilson, 2001). Using large-scale recordings, the animal’s spatial position can be reliably inferred based on place cell ensemble activity (Wilson and McNaughton, 1993; Ziv et al., 2013). In a broader context, place fields form a coherent relational structure that persists across time (Kinsky et al., 2018), suggesting that real-world spatial relationships are mapped onto place cell ensembles. Spatial features in the environment can also be linked to other variables, such as reward. In one intriguing study, the authors paired offline place cell reactivations (during sleep) with rewarding stimulations in the medial forebrain bundle. This procedure induced a behavioral place preference for the location of the place cell’s firing field and established a causal role for place cells in spatial navigation (de Lavilléon et al., 2015).

Place cell populations in the hippocampus are also responsible for spatial planning. Place cell firing predicts errors in navigation (O’Keefe and Speakman, 1987) and place field locations predict goal-seeking behavior (Dupret et al., 2010; Keinath et al., 2017). During spatial navigation, temporally compressed place cell sequences depict future trajectories that are enacted shortly after the sequence (Pfeiffer and Foster, 2013; Wikenheiser and Redish, 2015). Place cell ensemble activations also correlate with mental exploration of space. Early in learning spatial decision tasks, rats will deliberate at the choice point, where they would pause and consider future possible routes (Redish, 2016). These “vicarious trial-and-error” (VTE) events are often associated with place cell activity that “sweeps” down possible paths (Johnson and Redish, 2007), suggesting that the hippocampus is exploring decision space and subsequently selecting beneficial routes.

In spite of all the evidence showing the hippocampus is involved in spatial memory, the term “place cell” might be a misnomer. For example, during navigation, hippocampal units disambiguate prospective (and retrospective) turns when the rat is at a spatial location that is shared between different turns (Ferbinteanu and Shapiro, 2003; Wood et al., 2000). That is, despite the rat being in the same spatial location, hippocampal cells fire differently depending on the rat’s past and future trajectories. This finding refutes the idea that the hippocampus is devoted purely to storing spatial representations and instead suggests a broader role in spatiotemporal organization of experience (Buzsáki and Tingley, 2018; Howard and Eichenbaum, 2015).

### Theta sequences

Though the majority of the hippocampal literature in the past five decades has focused on spatial correlates, the function of hippocampal spikes may be more accurately described by their temporal organization. The first discussion of temporal relationships between hippocampal spikes originates from the initial observations of phase precession (O’Keefe and Recce, 1993). During active exploration, there is a prominent 4-12 Hz oscillation in the rodent hippocampus called the theta rhythm (Buzsáki, 2002; Hasselmo, 2005), which entrains hippocampal pyramidal cells. Because pyramidal cells burst at slightly higher frequencies than theta, this causes phase precession whereby spikes occur at progressively earlier phases of theta as the animal passes through a place field (O’Keefe and Recce, 1993). Phase precession has been hypothesized to serve a variety of functions, one of which is that high-resolution spatial location can be encoded in the theta phase information of pyramidal spikes (Skaggs et al., 1996). Also, because multiple place cells with overlapping fields are undergoing precession simultaneously, within a single theta cycle, place cells with fields early on the track will tend to fire before ones with fields later on the track. Consequently, place cell assemblies are organized into “theta sequences” that encode time-compressed, discrete units of traversals through multiple place fields (Dragoi and Buzsáki, 2006; Foster and Wilson, 2007; Jezek et al., 2011).

Theta sequences are the ordered firing patterns of a place cell population occurring within single theta cycles. While the mechanistic relationship between phase precession and theta sequences is still unclear, early theories suggested that the temporal compression of place cell sequences afforded by phase precession helps to give rise to theta sequences (Skaggs et al., 1996). Because they fit into single theta cycles, theta sequences are temporally compressed (into milliseconds) relative to behavioral-timescale (seconds) place cell sequences. This temporal compression enables a variety of physiological mechanisms. By condensing a sequence of place field traversals down to biophysical timescales, it falls under canonical temporal windows for plasticity and the strengthening of synaptic contacts (Bliss and Collingridge, 1993; Mehta et al., 2002). Under this framework, temporally coordinated place cells with adjacent fields can be bound together via Hebbian plasticity over learning (Leibold et al., 2008). Then, as a result, each sweep of the theta sequence can predict immediate future spatial locations ahead of the animal (Gupta et al., 2012). This requires learning, which is consistent with findings that theta sequences take a number of trials to fully mature (Feng et al., 2015; Mehta et al., 2002) despite phase precession being present on the very first trial (Schmidt et al., 2009). Additionally, under controlled circumstances where the rat is moving backwards in space, theta sequences appropriately flip to predict upcoming locations in reverse order (Cei et al., 2014). Finally as mentioned earlier, VTE events are accompanied by theta sequences with each sequence sweeping through possible future trajectories, enabling the rat to use learned knowledge about spatial layout to guide future decisions (Johnson and Redish, 2007).

Phase precession is also present during the formation and activity of cell assembly sequences outside of the spatial domain. During stationary running, where spatial input is fixed, cells with temporally-locked firing fields during the run still phase precess (Pastalkova et al., 2008). Inhibiting the theta pacemaker, the medial septum, disrupts these behavioral-timescale hippocampal sequences during stationary running, demonstrating that these sequences require theta modulation (Wang et al., 2015). CA1 neurons also form discrete theta sequences for distinct non-spatial events, such as odor-tone-reward pairings and jump events (Lenck-Santini et al., 2008; Terada et al., 2017). As these studies show, the theta oscillation and phase precession may be organizing structured information from the external environment through various modalities to inform upcoming behavior.

### Replay events

Sequences of hippocampal spikes are also played out during another LFP signature, the sharp wave (SPW). SPWs are large, transient deflections in the LFP that are often accompanied by a high frequency oscillation (110-200 Hz) called the ripple, and collectively this complex is often referred to as a sharp wave ripple (SPW-R). In contrast to the theta state which is present during rapid eye movement (REM) sleep, locomotion, rearing and sniffing, SPW-Rs occur primarily during slow-wave sleep (SWS), immobility, eating, and grooming (Buzsáki, 2015; Buzsáki et al., 1983, 1992; O’Keefe and Nadel, 1978) and co-occur with large, synchronous spiking events from single units.

Early observations of CA1 pyramidal cells dramatically increasing their firing rate during SPW-Rs attracted attention to this LFP signature and SWS (O’Keefe and Nadel, 1978). Owing to improvements in electrode array design, *in vivo* electrophysiologists were able to capture larger and larger populations of cells, allowing examination of complex spiking relationships between neurons. Pairs of place cells with overlapping fields are co-activated during SWS and these correlations persist post-sleep (Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994), implying a consolidation mechanism whereby co-active cells undergo synaptic modification. As ensemble analyses grew more sophisticated, a link was discovered between these co-activation events and SPW-Rs. CA1 pyramidal cells fired in fast (~20 ms), recurring sequences during SWS SPW-Rs that mirrored their activity during active wakefulness (Lee and Wilson, 2002; Nádasdy et al., 1999). These fast sequences during SPW-Rs were termed “replay” events in the sense that they repeatedly replayed previous experiences (usually place field traversals) in sequential order in the absence of external stimuli. Later, others found that these replay events occur also during awake SPW-Rs with the caveat that sometimes the sequence fires in reverse order, in which case the event is called “reverse replay” (Diba and Buzsáki, 2007; Foster and Wilson, 2006). Reverse replay is not to be confused with “preplay”, which is the phenomenon of hippocampal neurons firing in a preconfigured order, pre-experience, and later firing in a similar order within place cell sequences for future experiences (Dragoi and Tonegawa, 2011).

SPW-Rs also predict performance on memory tasks. Goal-directed replay events were strongly associated with memory performance (Dupret et al., 2010; Singer et al., 2013) and replay event reliably preceded avoidance maneuvers in a fear memory retrieval task (Wu et al., 2017). Though these findings provided strong correlational evidence for the role of SPW-Rs and replay events in memory, there had been a lack of a causational link. Using a closed-loop stimulation protocol, SPW-Rs were suppressed during sleep after learning a spatial navigation task, which interfered with memory performance the following day (Ego-Stengel and Wilson, 2009; Girardeau et al., 2009). Similar results were found when SPW-Rs during awake states were suppressed (Jadhav et al., 2012). Thus, SPW-Rs, and presumably the replay events that occur within them, are important for memory consolidation.

### Behavioral-timescale temporal sequences

While the previous sections discussed neural sequences occurring on the timescale of milliseconds, hippocampal cells also fire sequentially over a behavioral timescale (seconds). The diversity of timescales at which these sequences can be played out might reflect the flexibility of the brain’s computational prowess for retrieving information within a sequential context at a variety of requisite speeds (Buzsáki and Tingley, 2018; Friston and Buzsáki, 2016). At the behavioral timescale, CA1 pyramidal cells were found to reliably fire one after another over a 15 second delay (Pastalkova et al., 2008). In this experiment, rats ran on a fixed running wheel, thus eliminating optic flow and effectively “clamping space” (Czurkó et al., 1999). Yet, rather than place cells sensitive to the location of the running wheel continuously firing during running in place, different cells fired sequentially despite no apparent change in sensory cues. Thus, over a behavioral timescale, these cells collectively comprised a temporally-organized sequence initiated by the start of running.

The sequential activity of these cells also produced temporal fields such that each cell fired at specific time intervals, spanning the entire delay. This property earned them the moniker, “time cells”, as a reference to well-known “place cells” (Eichenbaum, 2013, 2014; Kraus et al., 2013; MacDonald et al., 2011). The difference, though, is that time cells fire in the absence of spatial cues (because the animal’s spatial location is fixed) at specific moments in a temporal delay. Therefore their activity is internally generated rather than externally driven. In an extreme case, mice running in complete darkness still exhibit sequentially active neurons, demonstrating their disengagement from sensory input apart from vestibular cues (Villette et al., 2015). The precise information content of behavioral-timescale hippocampal sequences is still under active study, but one possibility is that they represent the flow of time as a separate dimension parallel to space (Eichenbaum, 2013, 2014). However, others have proposed that spatial location should be regarded as a special instance of time and that neural sequences operate as syntactical units for representing temporal succession of events (Buzsáki and Llinás, 2017; Buzsáki and Tingley, 2018; Friston and Buzsáki, 2016; Liu et al., 2018). They argue that neural sequences over a delay period might simply be progression of network states that construct predictive models about the outside world (Friston and Buzsáki, 2016), namely the expectations of what would occur post-delay. Regardless, both views emphasize the importance of time as an organizing principle around which these sequences are built upon.

Especially considering the importance of the hippocampus in encoding associations between events separated by a temporal gap (Bangasser et al., 2006), time cells may be binding disparate events by sequentially firing over a delay (Eichenbaum, 2014; Levy, 1996; MacDonald et al., 2011; Wallenstein et al., 1998). These temporal relationships are likely stored via synaptic connections or delayed locking to an instantiating cue (Howard et al., 2014; Itskov et al., 2011; Levy, 1996; Rajan et al., 2016; Tiganj et al., 2015). But how do these temporal relationships develop? Importantly, behavioral timescale time cell sequences do not emerge *de novo* (though preplay of neural sequences during running in place have yet to be tested; Dragoi and Tonegawa, 2011). Rather, repeated experience and learning incrementally increases the number of neurons participating in the sequence (Gill et al., 2011; Modi et al., 2014; Taxidis et al., 2018). Increased network correlations are seen between cells that eventually enter the sequence, suggesting that plasticity contributes to stabilizing temporal (Modi et al., 2014), perhaps utilizing plasticity rules at the behavioral timescale (Bittner et al., 2017). Only after this information is stored in the network can particular contexts launch specific sequences, thus enabling precise prediction (Rajan et al., 2016).

In support of the idea that time cell sequences predict upcoming events, neural trajectories diverge depending on the initial conditions, suggesting that specific external states trigger separate sequences for predicting different outcomes. Pastalkova et al. (2008) used a spatial alternation task where the rats were required to alternate between left and right turns every trial. They observed a different set of cells active prior to left turn trials compared to right turn trials, demonstrating that these neural sequences corresponded to behavior. In line with this framework, error trials evoked the “incorrect” neural sequence (Pastalkova et al., 2008). Relatedly, on delayed olfactory tasks, distinct odors activated different sequences (MacDonald et al., 2013; Taxidis et al., 2018; Terada et al., 2017) and on a goal seeking task, different behavioral contexts launched unique sequences (Gill et al., 2011).

Despite strong correlative evidence for time cell sequences being critical for memory across time, experiments attempting to establish a causal relationship are scarce due to the spatiotemporal intricacy of manipulation required. As such, hippocampal time cell sequences have not yet been perturbed nor simulated in a targeted manner, though other experiments have inhibited upstream structures, resulting in behavioral deficits and disrupted CA1 sequences. Muscimol inactivation of medial septum disrupts theta sequence generation, CA1 time cell sequences, and behavior in a delayed spatial alternation task (Wang et al., 2015). Additionally, optogenetic inhibition of MEC produces similar results (Robinson et al., 2017), perhaps unsurprisingly given that time cell sequences are also present in MEC (Kraus et al., 2015), which CA1 may be inheriting via the temporoammonic pathway. With the advent of holographically-guided optical stimulation (Rickgauer et al., 2014), precise spatiotemporally actuation and inhibition experiments are eagerly awaited to determine the behavioral contributions of hippocampal time cell sequences.

### Population “drift” and instability

Conventional thought presumes that the adult brain stores relatively stationary representations for later retrieval. Consequently, early experiments focused on the stability of hippocampal place cells in an environment over time (Kentros et al., 1998; Thompson and Best, 1990). However, others have found that hippocampal responses are surprisingly dynamic (Mankin et al., 2012, 2015), albeit using electrode recordings which are susceptible to physical drift through tissue. Recent advances in chronic imaging have enabled longitudinal tracking of functional activity and synaptic structure. Though not without their disadvantages, these techniques have overall enabled more robust methods of identification of neurons and synapses over long timescales. Chronic imaging experiments have produced some surprising results, namely that variance and instability are largely present in multiple brain structures, including the hippocampus (Chambers and Rumpel, 2017; Clopath et al., 2017). At the synaptic level, computational models based on *in vivo* imaging data have estimated complete CA1 dendritic spine turnover over a few weeks (Attardo et al., 2015). At the ensemble level, tuning fields are highly variable over days (Kinsky et al., 2018; Mau et al., 2018; Ziv et al., 2013) and there even appear to be differences in spatial stability profiles along the radial axis of the hippocampus (Danielson et al., 2016b).

Interestingly, these dynamics might support the formation of temporal associations. In a task involving repeated presentations of odors, hippocampal activity changed gradually over trials, and those dynamics were necessary for correct selection of an odor presented earlier in time (Manns et al., 2007). Notably, these results are consistent with the temporal context model, which predicts that the brain contains gradually shifting representations for encoding the evolution of temporal context (Howard et al., 2005). Even when presented with a fixed stimulus, the activity of hippocampal neurons “drifts” over time (Mankin et al., 2012; Mau et al., 2018; Rubin et al., 2015; Ziv et al., 2013), which may be a mechanism for organizing memory along a long timeline of experiences. Thus, differences in the ensemble activity from two separate time points could contain information about temporal proximity of those epochs. In support of this idea, neural ensemble overlap is significantly higher between events close in time compared to ones far apart in time (Cai et al., 2016; Mau et al., 2018; Rashid et al., 2016).

Population “drift” might also be useful for assembling neuronal ensembles and binding them to specific experiences. Because the population state is constantly shifting, new cells ramping up their excitability may be recruited to join the network for promoting learning and temporally linking memories via modification of synaptic connections (Lisman et al., 2018; Rogerson et al., 2014). Indeed, dendritic “hotspots” with high synaptic turnover have been found to be closely associated with learning (Frank et al., 2018). Circuit remodeling that occurs as a result of this process might selectively recruit neurons with particular firing rate characteristics (Buzsáki and Mizuseki, 2014; Grosmark and Buzsáki, 2016) to represent episodic experiences. It fits that cells expressing immediate-early genes in response to a novel context tend to have higher mean firing rates and better theta modulation (but surprisingly, less spatial precision; Tanaka et al., 2018). On the other hand, another study reported contradictory findings. In this study, neurons entering a replay ensemble after exposure to a novel context had low firing rates, high spatial specificity, and higher coactivation with ripples during sleep (Grosmark and Buzsáki, 2016). Evidently, much remains to be known about how cell excitability might contribute to its involvement in a neural ensemble representing a memory trace.

### “Engrams”

Sophisticated optogenetic and imaging studies have found that associative memories involve intricate networks of synchronously active neurons within and across brain regions (Choi et al., 2018; Ohkawa et al., 2015).

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# CHAPTER TWO

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# CHAPTER THREE

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# APPENDIX

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