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# Cooperate to compete — Identifying a potential role for hippocampal region CA2 in episodic memory formation

**Thesis submitted for the degree of Philosophiae Doctor**

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To my wife Rahel and our children Merlin, Karla and Lotta.

# Preface

This thesis is submitted in partial fulfillment of the requirements for the degree of *Philosophiae Doctor* at the University of Oslo. The research presented here has been conducted under the supervision of Professor Marianne Fyhn, Associate Professor Arvind Kumar, Associate Professor Trygve Solstad and Professor Jill Leutgeb. Financial support for this work came from the Simula-UCSD-University of Oslo Research and PhD training (SUURPh) program, an international collaboration in computational biology and medicine funded by the Norwegian Ministry of Education and Research.

The thesis is a collection of three articles, which together build a cohesive theory for a general role of hippocampal region CA2 in episodic memory processing. The preceding chapters aim at providing the reader with the necessary background to critically evaluate the claims of the thesis, to summarize and discuss the findings and to highlight emerging research directions.

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**Tristan Manfred Stöber**
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# Summary

The hippocampus has fascinated scientists for decades. Its crucial role in episodic memory, navigation and imagination has propelled an enormous research effort. While attention has focused on three of the four major regions, the dentate gyrus, CA3 and CA1, the relatively small region CA2 has been mostly ignored.

The recent discovery that CA2 is important for social recognition memory has fueled a drastic surge in interest. Without a functional CA2, rats and mice no longer discriminate between known and unknown conspecifics. Moreover, experimental data suggest that CA2 plays an important role in several non-social behaviors and in controlling hippocampal network dynamics. On a physiological level, recurrent interactions between CA3 and CA2 stand out due to their neuromodulatory-gated plasticity and strong mutual inhibition. However, we miss a cohesive theory that explains how these findings relate to each other and what computational role CA2 may play in the hippocampal circuit.

Synthesizing experimental data about its network architecture, synaptic plasticity, and interactions with neighboring regions, I try to outline the potential computations CA2 may perform. Based on this *from-structure-to-function* approach, I propose that at the computational level, CA2 interacts with CA3 to prioritize the reactivation of selected neuronal activity sequences based on contextual and behavioral states. In particular, neuromodulatory-gated plasticity and mutual inhibition may enable sequences in both regions to support each other while suppressing the reactivation of competing sequences. Such a function may be important because the reactivation of neural activity sequences determines which experiences become long term episodic memories.

The proposed computational role provides an explanation why CA2 is important in some but not all episodic memory tasks. For a given experience, the number of recruited pyramidal cells depends on the type and familiarity of the encoded information. For example, fewer cells represent locations of other animals and objects compared to the animal's own location. By modelling sequence competition and cooperation with discrete, pre-defined assemblies in a non-linear rate model, I demonstrate that sequences with small assemblies have difficulties to reactivate in the presence of strong competitors. However, when two co-active sequences with small assemblies pair, they can ensure their reactivation and suppress competing sequences. Thus, it is proposed that neuromodulatory-gated plasticity between CA3 and CA2 is required whenever a salient memory trace represented by few neurons needs to be reactivated.

In conclusion, considering CA2 as a sequence prioritization unit provides a cohesive interpretation of many unique functional properties, makes further steps towards incorporating CA2 into an overarching theory of hippocampal memory processing, and provides new experimental avenues to advance our

understanding of CA2 beyond social recognition memory.

# List of Papers

## Paper I

*CA2 beyond social memory: Evidence for a fundamental role in hippocampal information processing*
Lehr, A.B., Kumar, A., Tetzlaff, C. Hafting, T., Fyhn, M., Stöber, T.M.
Submitted for publication, under review

## Paper II

*Selective neuromodulation and mutual inhibition within the CA3–CA2 system can prioritize sequences for replay*
Stöber, T.M.*, Lehr, A.B.*, Hafting, T., Kumar, A., Fyhn, M.
Published in *Hippocampus* (2020), DOI: 10.1002/hipo.23256
* These authors contributed equally

## Paper III

*Competition and Cooperation of Assembly Sequences in Recurrent Neural Networks.*
Stöber, T.M., Lehr, A.B., Fyhn, M., Kumar, A.
In preparation

# Contents

# Chapter 1

# Introduction

It is difficult to imagine living without the hippocampus — not only because living becomes hard, but also the act of imagining itself becomes hard. Indeed, the hippocampus is crucial for making us who we are. Without it, the present would simply pass us by. We would lose the ability to memorize special moments, like the birth of a child or the funeral of a beloved uncle, rendering our autobiography blank[1]. Equally devastating, we would struggle to navigate through this complex world, more likely to get lost when walking through a city we do not know well[2–4]. Perhaps worse, we would find it very difficult to imagine how life would be without the hippocampus, because it is also essential for mentally exploring hypothetical scenarios and potential futures[5–7].

Because of its crucial role for cognition[i], the hippocampus has fascinated researchers for decades. An enormous research effort has provided us with rich anatomical and physiological data about the three major hippocampal regions, the *dentate gyrus* (DG), *cornus ammonis* region 3 (CA3) and 1 (CA1). However, despite the many insights on various levels, our understanding of how the hippocampus works is far from complete.

The incompleteness of our understanding becomes apparent when considering hippocampal region CA2. Sandwiched between CA3 and CA1, this anatomically distinct region was mainly considered a mere transition zone and therefore mostly ignored. This drastically changed after Hitti and Siegelbaum in 2014 unequivocally demonstrated that without a functional CA2, mice no longer distinguish between known and unknown animals. Since then, a number of follow-up studies have corroborated the importance of CA2 for social recognition memory, exploring the role of neuromodulation and plasticity[9–11], interactions with other hippocampal regions[12,13], underlying neuronal activity[14–16], and the relation to brain diseases such as schizophrenia[15,17]. To make the situation more complex, several findings indicate that CA2's role extends beyond social recognition memory. It has been implicated in memory for temporal order[18], habituation to novelty[19] and contextual fear memory[20].

By connecting the many, seemingly disparate anatomical, physiological and behavioral findings, this work develops a functional theory of hippocampal

[1]Scoville and Milner, 1957 [2]Teng and Squire, 1999 [3]Rosenbaum et al., 2000 [4]Maguire et al., 2006 [5]Hassabis et al., 2007 [6]Rosenbaum et al., 2009 [7]Andelman et al., 2010 [9]Smith et al., 2016 [10]Leroy et al., 2017 [11]Dominguez et al., 2019 [12]Meira et al., 2018 [13]Okuyama et al., 2016 [14]Alexander et al., 2016 [15]Donegan et al., 2020 [16]Oliva et al., 2020 [17]Piskorowski et al., 2016 [18]DeVito et al., 2009 [19]Boehringer et al., 2017 [20]Alexander et al., 2019

[i]Cognition is "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses" (Lexico, Oxford University Press, 2020).

region CA2. In particular, I argue that interactions between CA3 and CA2 can prioritize the reactivation of selected neural activity sequences. Such a function is important because hippocampal reactivation of neural activity defines which information will be stored as long-term memory[16,21–24].

To outline this theory, I present three scientific articles. Order and content follow the three levels of analysis proposed by David Marr[25]. The first article is an extensive literature review about CA2's role beyond social recognition memory. It helps us to identify computations CA2 may potentially perform. The second article describes on an algorithmic level how CA3 and CA2 could interact to preferentially reactivate certain neuromodulatory-cued experiences, while suppressing others. The third article demonstrates how the underlying competition and interaction of neural activity sequences can be implemented in recurrent neural networks.

## 1.1 Brain fundamentals

Everyone of us who had the chance to hold a real human brain in his or her own hands, may know this feeling of being both amazed and disappointed at the same time. With its consistency of mushroom and the appearance of a walnut, it is hard to imagine that such an object has been "the place where someone once felt, thought and loved" (Robert Winston[26]). It is not until you start using a microscope that you realize the breathtaking properties of this organ.

The brain consists of an intricate network of cells interacting with each other and the environment. In the brain, two major cell types are distinguished based on whether they can create electrical impulses or not: neurons and glia cells. While neurons are considered to be the main computational units, glia cells provide a variety of supportive and complementary functions, crucial for the development and proper functioning of the nervous system (for more information see[27–29]). In the following we will focus on neurons.

The cellular structure of neurons is optimized for receiving, integrating and transmitting information. A neuron typically consists of several separable structures, of which we will highlight the most important here: Its cell body, also called soma, the axon, dendrites and synapses. The cell body contains the nucleus and other cell organelles. Here, most proteins are created; building blocks, necessary for proper neuronal function. The axon, a long, cable-like protrusion of the soma, forms the output part of the neuron. It can extend over long distances, often connecting neurons across brain regions and throughout the spinal cord. In extreme cases, certain axons can be longer than one meter. Along their way, axons often branch, forming so called collaterals. At the end of each branch, axon terminals can form connections to other neurons at a structure called synapse. While the axon terminal forms the pre-synaptic site, the post-synaptic site of a synapse is typically located either directly on the soma,

[16]Oliva et al., 2020 [21]Girardeau et al., 2009 [22]Ego-Stengel and Wilson, 2010 [23]Jadhav et al., 2012 [24]Fernández-Ruiz et al., 2019 [25]Marr and Poggio, 1976 [26]Boswell, 2011 [27]Haydon, 2001 [28]Allen and Barres, 2009 [29]Fields et al., 2014

or on a dendrite of the receiving neuron. Dendrites are fine, heavily branched extensions of the cell body, receiving and integrating a large number of synaptic inputs. Some dendrites form even smaller protrusions, called synaptic spines, typically targeted by one excitatory synapse.

Neurons can create fast electrical pulses, so called action potentials. In their baseline state, neurons are typically negatively charged with respect to the outside medium. This is due to differing ion concentrations and a semipermeable cell membrane. Positively charged potassium ions ($K^+$), but not other negatively charged anions leave the cell along their concentration gradients, leaving excess negative charge inside the cell. To induce action potentials, the soma must be sufficiently depolarized. The resulting sequential opening of different voltage-gated ion-channels at the beginning of the axon allows sodium ions ($Na^+$) to enter the cell, resulting in a strong and rapid depolarization. The subsequent outflow of potassium ions restores the negative charge and transiently prevents additional spikes at this part of the axon during the so-called refractory period. This dynamical process creates a wave of depolarization travelling down the axon.

Action potentials allow to transmit information onto other neurons. When an action potential arrives at the pre-synaptic terminal, it induces a cascade of biochemical reactions, eventually resulting in the release of neurotransmitters into the small space between the pre- and the post-synaptic terminal. Neurotransmitters bind to receptors on the post-synaptic terminal, which directly or indirectly open ion channels. Depending on the type of channel, the influx of ions induces positive, also called excitatory, or negative, inhibitory, deflections of the membrane potential. Except for a few exceptions, a neuron releases the same neurotransmitter at all of its pre-synaptic terminals, a principle called *Dale's law*. Thus, based on the type of connections, neurons in the brain are classified as either excitatory or inhibitory.

In contrast to the temporally and spatially confined action of neurotransmitters, neuromodulatory substances often influence neural circuits in a complex and long-lasting fashion. Just imagine the profound changes in information processing and behavior of someone who has recently fallen in love. An intricate mixture of dopamine, oxytocin, vasopressin and other neurochemicals modify a variety of brain regions and induce changes in attachment, partner preference and motivation. Some of the biological underpinnings are changes in intrinsic firing properties and modifications of synaptic transmission, which together can strongly modify circuit function[30]. Neuromodulatory substances typically bind to G-protein coupled receptors and induce intracellular signalling cascades with multi-faceted effects. Thus, neuromodulation greatly diversifies the functional repertoire of neurons and circuits.

The brain can be structured in anatomically, physiologically and functionally distinct subregions. On the highest level, the brain can be divided into three major parts[31,32]. The cerebrum, the largest part, with its two hemispheres, is typically associated with sensory, motor and higher cognitive functions like

[30]Marder, 2012 [31]Hansen and Koeppen, 2002 [32]Kandel et al., 2000

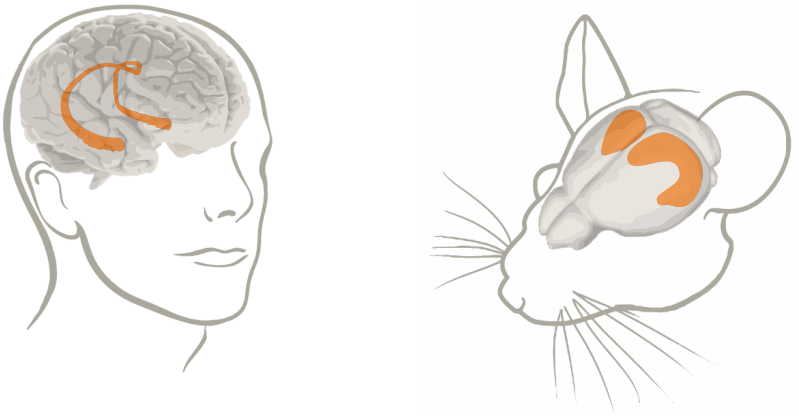

Figure 1.1: **The hippocampus in the human and the mouse brain.** Illustration of the hippocampus (orange) in a schematic of the human (left) and the mouse brain (right). Adapted with permission from[33].

acquiring knowledge, reasoning, speaking, hearing, seeing and fine motor control and planning. Below the cerebrum, at the back of our heads, lies the cerebellum, which is commonly associated with muscle coordination and maintaining posture and balance. Third, the brainstem, a relatively small part of the brain, connects cerebrum and cerebellum to the spinal cord. The brainstem regulates several key automatic functions like for example the beating of the heart.

The three main parts of the brain can be further subdivided in a plethora of regions. Given the specific scope of the thesis, I will focus primarily on the hippocampus in the cerebrum (Fig. 1.1). Few other regions will be specifically important later in this work: the entorhinal cortex, the main input and output region of the hippocampus, as well as the paraventricular and the supramammillary nuclei, both major sources of neuromodulation and involved in encoding novelty and stress.

## 1.2 Functions of the hippocampus

For decades, the hippocampus has fascinated scientists mainly for its crucial contributions to two seemingly separate functions: episodic memory and spatial navigation. In recent years, experimental evidence has mounted that the hippocampus is also contributing to imagining the future or hypothetical scenarios.

### 1.2.1 Episodic memory

The importance of the hippocampus for episodic long-term memory was primarily established by the seminal studies of patient H.M.[1]. To treat his severe epilepsy, large parts of both hippocampi and significant portions of the adjacent entorhinal cortex were removed[34]. After the surgery, H. M. was drastically impaired in forming memories of new experiences, a diagnosis called *anterograde amnesia*. For instance, if you were to introduce yourself to him, leave the room, and come back in again, he would not be able to recognize you[1].

Studies on H. M. led to the distinction of different memory types. Long-term memories can be grouped into two main categories[35]. Declarative memories are conscious recollections of facts and events, which can be explained to others. In contrast, unconsciously acquired memories, such as motor skills, are called non-declarative (for more info see[36]). Declarative memories are further divided into semantic and episodic memories[37]. While semantic memories represent facts about the world, episodic memories reflect conscious experiences, which can be described by the terms what or who, where and when. While H.M. was completely unable to form new episodic memories, he had reduced abilities to acquire new semantic memories[38]. These observations are consistent with findings from other individuals with bilateral hippocampal damage[39]. As for non-declarative memories, H.M. was able to learn new motor skills. However, his acquisition rate was slower compared to healthy control subjects[40].Thus, the hippocampus is crucial for episodic memory and it contributes to semantic and other non-declarative forms of learning.

Lacking both hippocampi, H.M. was not only unable to form new episodic memories, he also lost access to already existing memories with a temporal gradient, a diagnosis called *retrograde amnesia*. While early memories, for example from his childhood, were still intact, H.M. could not recall events up to 11 years before the operation[41]. Observations that the hippocampal lesions affect recent but not early memories, have led to proposals that episodic memories are first stored in the hippocampus and over time gradually transferred to the cortex for long term storage[42,43]. However, more recent studies on other patients with hippocampal lesions questioned the temporal gradient in retrograde amnesia. They provided evidence that there is no gradient when defining episodic memories more strictly[44] or that the temporal gradient is too long to match biologically realistic timelines for memory consolidation[45] While many details are still intensively debated[42,46,47], the crucial role of the hippocampus for episodic memory is now generally accepted.

[1]Scoville and Milner, 1957 [34]Annese et al., 2014 [35]Squire, 1992 [36]Schacter, 1987 [37]Tulving et al., 1972 [38]O'kane et al., 2004 [39]Vargha-Khadem et al., 1997 [40]Corkin, 1968 [41]Sagar et al., 1985 [42]Squire, 1992 [43]McClelland et al., 1995 [44]Cipolotti et al., 2001 [45]Steinvorth et al., 2005 [46]Nadel et al., 2000 [47]Lisman et al., 2017

### 1.2.2 Spatial navigation

Besides episodic memory, the hippocampus is known to be involved in spatial navigation. In a series of seminal experiments Edward Tolman trained rats to navigate in a complex spatial maze. By opening and closing doors in the maze, he showed that rats are able to deliberately take shortcuts, even though they had not experienced these paths before[48]. Thus, he concluded that rats must possess an internal *cognitive map* of the environment, allowing flexible navigation. The discovery of spatially tuned place cells[49,50] provided the basis for the theory that such a cognitive map is located in the hippocampus[51] (more about place cells in Sec. 1.5).

In the years to follow, the direct contribution of the hippocampus to spatial navigation was firmly established. For this purpose, animal behavior has been commonly tested in the water maze reference memory task[52]. Here, rats or mice are forced to swim in a pool of water to find a submerged escape platform. Because the water prevents the use of local cues, animals must rely on landmarks outside of the maze for navigation. By repeatedly placing the animal at random locations while keeping the position of the platform fixed, the learning performance can be quantified by the time to reach the platform. With this and similar versions of the task, it has been shown that hippocampal lesions severely impair spatial learning[53,54]. Given enough training, lesioned rats eventually do learn the platform location[55], indicating that extra-hippocampal structures are also able to form spatial representations. However, lesioned animals use inflexible navigation strategies, making it difficult to re-adapt their behavior when platform location changes[55,56].

Accumulating evidence suggests that the hippocampus is also important for spatial navigation in humans. For example, taxi drivers in London, who navigate the city on a daily basis, have a significantly increased posterior hippocampal volume compared to non-taxi drivers[57]. Correspondingly, a smaller volume of the right hippocampus is associated with impaired spatial navigation performance[58]. Relating to the sparing of remote episodic memories[41], patients with hippocampal lesions are able to recall the spatial layout of places they got to know before but not after the damage[2,3]. However, the hippocampus seems to facilitate navigation even on such remote spatial memories, especially when detailed spatial representations are required. For example, a taxi driver with hippocampal lesions was able to navigate along previously learned routes, but he got lost when he had to leave the main roads[4].

### 1.2.3 Imagining future or hypothetical scenarios

In recent years, evidence has been mounting that the hippocampus plays a critical role in imagining hypothetical or future scenarios. First evidence came from

[48]Tolman, 1948 [49]O'Keefe and Dostrovsky, 1971 [50]O'Keefe, 1976 [51]O'keefe and Nadel, 1978 [52]Morris, 1984 [53]Morris et al., 1982 [54]Sutherland et al., 1983 [55]Morris et al., 1990 [56]Eichenbaum et al., 1990 [57]Maguire et al., 2000 [58]Nedelska et al., 2012 [41]Sagar et al., 1985 [2]Teng and Squire, 1999 [3]Rosenbaum et al., 2000 [4]Maguire et al., 2006

observations that amnesic patients with damage to the hippocampus are impaired in imagining new experiences upon short verbal cues[5]. Imagined experiences lacked spatial coherence, consisting only of fragmented images, not embedded in a holistic representation of the environment. This matched observations from other patients, who were impaired in generating cohesive and detail-rich narratives of fictional events and well-known fairy tales[6], as well as in planning their personal future[7].

In addition, patients with hippocampal lesions day-dream only in the present. Studies on the self-generation of thoughts revealed that hippocampal damage does not reduce the time spent day-dreaming[59]. However, whereas healthy humans imagined vivid scenes from past, present and future, day-dreaming in patients with hippocampal damage was limited to the present and was mainly comprised of semantic knowledge[59].

## 1.3 Hippocampal anatomy

To understand how the hippocampus works, it is helpful to take a close look at its anatomy. The hippocampal formation comprises the hippocampus proper and associated regions. The hippocampus proper can be subdivided into three regions: CA1, CA2, and CA3, with CA the initials of *C*ornu *A*mmonis, an early name of the hippocampus[60]. Further, the hippocampal formation encompasses the dentate gyrus (DG), the entorhinal cortex (EC), and the pre- and parasubiculum. DG and EC are the main input structures to the CA regions.

The well-defined laminar organisation is a remarkable feature of all CA regions (Fig. 1.2). The somata of all excitatory neurons are located within a single two-dimensional layer, the so-called pyramidal cell layer. Dendrites of pyramidal cells branch below in the *stratum oriens* as well as above in the *stratum radiatum*, and the *stratum lacunosum-moleculare*. Within CA3, an additional layer, the *stratum lucidum*, can be identified.

### 1.3.1 Subdivision of the CA region based on pyramidal cells and their projection patterns

The different layers of the CA region correspond to distinct arrival sites of excitatory inputs. Projections from the entorhinal cortex arrive at distal pyramidal dendrites in the *stratum lacunosum-moleculare*. In contrast, recurrent or feed-forward projections within the CA region terminate at proximal dendrites in the *stratum radiatum* and *stratum oriens*. Mossy fibers, strong projections from granule cells of the dentate gyrus, are located in the *stratum lucidum* of CA3.

Anatomical properties and gene expression patterns delineate the boundaries between CA3, CA2 and CA1. The somata of pyramidal cells in CA3 and CA2 are larger and more loosely packed compared to CA1[61]. In contrast to CA3,

[5]Hassabis et al., 2007 [6]Rosenbaum et al., 2009 [7]Andelman et al., 2010 [59]Maguire and Hassabis, 2011 [60]Andersen et al., 2006 [61]Ramon and Cajal, 1893

pyramidal cells in CA2 do not possess large, complex excrescences on their apical dendrites[62]. This has led to the notion that CA2 may not receive mossy fiber input[62]. However, direct mossy fiber projections onto pyramidal cells in CA2 have recently been documented[63]. Distinct gene-expression profiles corroborate the anatomical subdivision of the CA regions[64–67]. Further, pyramidal cells between subregions differ in basic intrinsic properties, such as membrane capacitance, time constants and action potential thresholds[63,68].

Axons of pyramidal cells in CA3 and CA2 form various collaterals and arborize into all CA regions across the ipsilateral and contralateral hippocampus[69]. In contrast, CA1 shows much less internal branching and no projections to CA3[70] or CA2 have been observed[71]. Monosynaptic recurrent connections between excitatory neurons have been documented in all CA regions, with CA3 having a connection probability of 0.92%[72], CA2 1.4%[73] and CA1 0.6%[74]. It appears that CA3a (the part of CA3 closest to CA2) and CA2b form a particularly recurrent network. Excitatory recurrency is weakest in CA3c and strongest in CA3a[69,75,76]. CA2 pyramidal cells project mostly to CA3a[75,77]. In contrast to projections from CA3 to CA2, back-projections from CA2 to CA3 are thinner and sparser[75]. Further, CA2 recurrent connections are biased towards CA2b[73].

Excitatory projections from CA3 and CA2 differentially target deep and superficial CA1 pyramidal cells. Whereas projections from CA3 arrive mostly in the stratum radiatum of CA1, CA2 projections favor the stratum oriens[62,71,77,78]. In accordance, projections from CA2 pyramidal cells are biased towards deep CA1 pyramidal cells[63]. The soma of deep and superficial pyramidal cells are located towards the stratum oriens or stratum radiatum, respectively. CA3 pyramidal cells projected equally strong to both deep and superficial CA1 pyramidal cells[63]. Superficial and deep CA1 pyramidal cells have been shown to be two separate subgroups with unique gene-expression profiles[79], physiological characteristics[80] and extrahippocampal targets[81].

In addition to the proximo-distal axis from CA3 to CA1, the dorsal-ventral axis is an important dimension of hippocampal organization. In rodents, in which the hippocampus is roughly banana-shaped, the dorsal end is located at the top and the ventral at the bottom of the skull. Anatomical, physiological and gene-expression properties point to a functional separation between the dorsal/medial and the ventral poles of the hippocampus[82,83]. For example, pyramidal cells in dorsal CA2 send projections to both dorsal and ventral CA1. However, only projections to ventral CA1 appear to contribute to social recognition memory[12,13].

[62]Lorente de Nó, 1934 [63]Kohara et al., 2014 [64]Zhao et al., 2001 [65]Lein et al., 2004 [66]Lein et al., 2005 [67]Lein et al., 2007 [68]Chevaleyre and Siegelbaum, 2010 [69]Li et al., 1994 [70]Amaral et al., 1991 [71]Cui et al., 2013 [72]Guzman et al., 2016 [73]Okamoto and Ikegaya, 2019 [74]Deuchars and Thomson, 1996 [75]Ishizuka et al., 1990 [76]Abbott and Blum, 1996 [75]Ishizuka et al., 1990 [77]Tamamaki et al., 1988 [75]Ishizuka et al., 1990 [73]Okamoto and Ikegaya, 2019 [62]Lorente de Nó, 1934 [71]Cui et al., 2013 [77]Tamamaki et al., 1988 [78]Shinohara et al., 2012 [63]Kohara et al., 2014 [63]Kohara et al., 2014 [79]Dong et al., 2009 [80]Mizuseki et al., 2011 [81]Lee et al., 2014 [82]Fanselow and Dong, 2010 [83]Strange et al., 2014 [12]Meira et al., 2018 [13]Okuyama et al., 2016

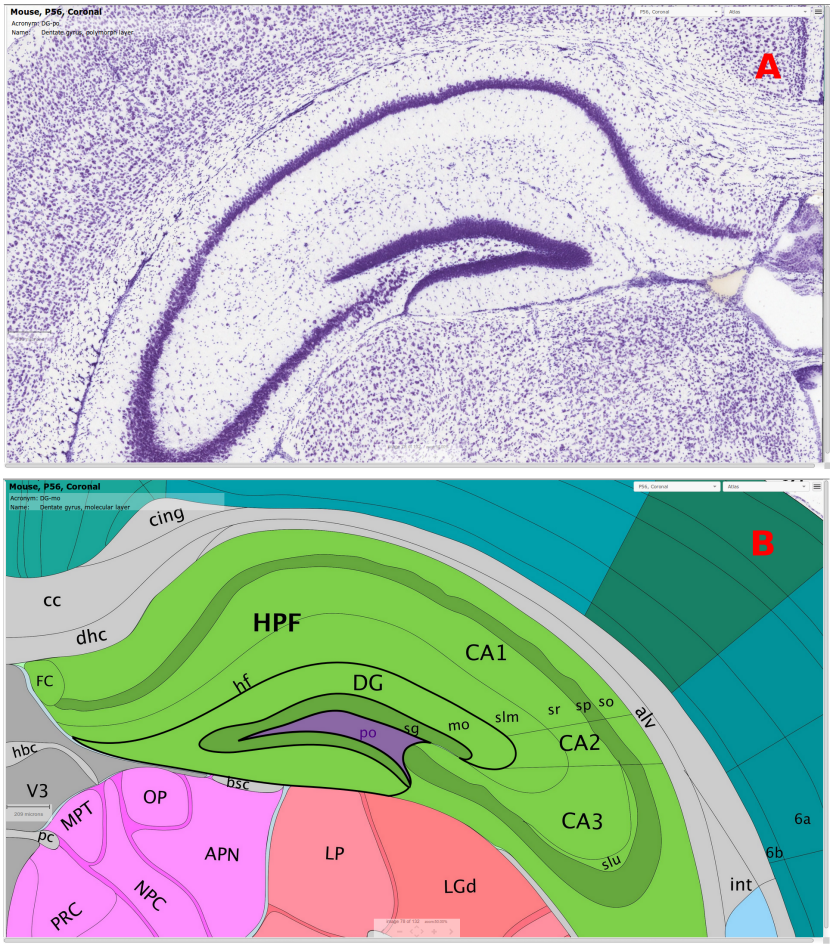


Figure 1.2: **Coronal section through the mouse hippocampus. A)** Nissl stained cell bodies of the hippocampus and surrounding tissue. **B)** Mirrored scheme of A), with hippocampal subdivisions and layers. Dentate Gyrus (DG), CA3, CA2, and CA1. Layers of the CA regions: stratum oriens (so), stratum pyramidale (sp), stratum radiatum (sr), stratum lacunosum-moleculare (slm), stratum lucidum (slu). Image A) and scheme B) are adopted from the Allen Mouse Brain Atlas[67,84].

### 1.3.2 Inhibitory interactions within the CA region

With at least 21 distinct cell types, the inhibitory interneurons of the hippocampus are diverse compared to the excitatory pyramidal cells[85]. It is estimated that between 7 and 11 percent of all cells in the hippocampus are interneurons[86,87]. Different subclasses of interneurons are distinguished by their morphology, target cells, or by the expression of specific calcium-binding proteins. The spatio-temporally coordinated activity of interneurons constitutes a rich and complex machinery, which supports distributed computations in the compartments of pyramidal cells. Often, firing of interneurons is tightly coupled to specific network synchronization states, like shape-wave ripples, theta- or gamma-waves. Despite being outnumbered by excitatory neurons, interneurons play a crucial role in controlling information processing.

Excitatory interactions between CA3 and CA2 are dominated by feed-forward inhibition (see Fig. 1 in **Paper** II, upper right box). Excitatory projections from CA3 to CA2 and vice versa activate interneurons which locally inhibit pyramidal cells, a process called *feed-forward inhibition*. When simultaneously stimulating many projections feed-forward inhibition exceeds feed-forward excitation, preventing the induction of spikes in pyramidal cells of the other region[63,68]. To allow spike transmission, excitation may be increased and feed-forward inhibition decreased. The CA3-CA2 recurrent system possesses specific mechanisms to do so, which we will discuss after introducing synaptic plasticity.

## 1.4 Plasticity and neuromodulation

Synaptic plasticity modifies the strength of synapses and allows to store information over extended periods of time. Here, synaptic strength is loosely defined as the average membrane potential deflection in the post-synaptic neuron upon arrival of an action potential at the pre-synaptic terminal. Synaptic plasticity is an umbrella term for numerous mechanisms with different timescales, ranging from milliseconds to years.

Short-term plasticity is due to transient changes in ion concentrations, the availability/depletion of neurotransmitters and the modification of existing synaptic proteins. In contrast, long term plasticity typically involves changes in gene expression, leading to protein synthesis and in certain cases to the growth of new synapses. Depending on whether a synapse becomes stronger or weaker, the phrases long term potentiation (LTP) and long term depression (LTD) are used. I will focus on long-term synaptic modifications.

Brief, high-frequency electrical stimulation can induce long lasting potentiation for hours, or even days. LTP was first discovered on projections from the entorhinal cortex to the dentate gyrus in anaesthesized rabbits[88,89]. Thereafter, LTP has been commonly studied in acute *in vitro* slices of the hippocampus,

[85]Freund and Buzsáki, 1996 [86]Woodson et al., 1989 [87]Aika et al., 1994 [63]Kohara et al., 2014 [68]Chevaleyre and Siegelbaum, 2010 [88]Lømo, 1966 [89]Bliss and Lømo, 1973

allowing to precisely record and stimulate individual fibers and neurons. After removing the brain from a deeply anaesthesized animal, a thin slice is placed in a recording chamber, perfused with a nutritious solution, oxygenated and held at a temperature similar to *in vivo* conditions. Recording and stimulation are performed by extra- or intracellular electrodes. Extracellular electrodes can be used to simultaneously activate multiple axons and to record field potentials. In contrast, intracellular electrodes allow to excite individual cells and to measure their membrane potentials. Further, by perfusing a slice with substances specifically blocking or activating different receptors, proteins or regulating genes, the cellular machinery underlying LTP has been studied in detail.

Three key properties of long term potentiation make it attractive for information storage. First, LTP can act as a *coincidence detector*. Potentiation only occurs if activity in pre- and post-synaptic neurons occur within a small time window[90]. In accordance with Hebb's theory of learning[91], this allows the formation of functionally connected cell assemblies. Second, LTP is *input specific*, meaning that of all the synapses connecting a neuron, only those are potentiated that have actually been activated. The ability to enhance only specific inputs is expected to be crucial to store individual pieces of information. Third, LTP allows to encode *associativity*. An input synapse, that is only weakly activated, may not be potentiated. However, if coinciding with strong stimulation at other synapses, also a weakly activated synapse can undergo potentiation. Strengthening jointly activated synapses allows to link different pieces of information, providing for example the cellular basis for classical Pavlovian conditioning[92].

### 1.4.1 Plasticity within and between CA3 and CA2

Unlike projections from CA3 to CA1, LTP at CA3 to CA2 projections is strictly limited (see Fig. 1 in **Paper** II, lower left box). CA2 pyramidal cells employ several mechanisms to block LTP at CA3 projections following classical high-frequency stimulation[93].

Perineuronal nets (PNNs), wrapping CA2 pyramidal cells, are one key factor to limit synaptic plasticity. PNNs are specialized extracellular matrix structures, composed of negatively charged chondroitin sulfated proteoglycans[94]. While typically associated with interneurons, PNNs in CA2 mostly enwrap pyramidal cells and co-localize with excitatory synapses[95,96]. Removing PNNs in young mice, unlocks LTP at CA3 to CA2 projections, increasing potentiation to levels seen in CA3 to CA1 projections[95]. While the causal mechanism of how PNNs in CA2 contribute to limited plasticity still requires clarification[11], it is clear that they are not the only factor. LTP could also be induced by raising extracellular calcium levels[97], blocking a specific receptor called RGS14[98], or by antagonizing either adenosine A1[99] or group III glutamate receptors[100]. Thus, it appears that

[90]Gustafsson et al., 1987 [91]Hebb, 1949 [92]Gruart et al., 2015 [93]Zhao et al., 2007 [94]Fawcett et al., 2019 [95]Carstens et al., 2016 [96]Lensjø et al., 2017 [95]Carstens et al., 2016 [11]Dominguez et al., 2019 [97]Simons et al., 2009 [98]Lee et al., 2010 [99]Simons et al., 2012 [100]Dasgupta et al., 2020

limited plasticity at CA3 to CA2 synapses is an important property actively implemented by a multitude of mechanisms.

Recurrent projections between CA3 pyramidal cells have been shown to express symmetric spike timing dependent plasticity[101]. Typically, in spike timing dependent plasticity, the pre-synaptic cell must spike before the post-synaptic cell for potentiation to occur[102,103]. Otherwise, the synapse is either depressed or maintains its synaptic strength. However, between pyramidal cells in CA3, the order is not important, as long as post-synaptic potentials and action potential generation happen close in time[101]. Unfortunately, we lack information about plasticity in excitatory recurrent projections inside CA2 as well as from CA2 to CA3. In both cases, synapses terminate in the stratum radiatum and stratum oriens[75,77]. Thus, it is to be expected that CA2's recurrent plasticity is equally blocked while projections to CA3 are plastic.

### 1.4.2 Neuromodulation in the CA3/CA2 system

CA2 is a hub for neuromodulation in the hippocampus. Most neuromodulatory substances activate second messenger pathways that lead to modifications of intrinsic properties and synaptic efficacy. Neuromodulation is a key component in regulating synaptic plasticity. Here, I focus on CA2 and four neuropeptides: vasopressin, oxytocin, substance P and enkephalin.While vasopressin, oxytocin, and substance P directly affect excitatory transmission, enkephalin is required for the expression of delta-opioid mediated long term depression of feed-forward inhibition within CA3 and from CA3 to CA2.

Vasopressin and oxytocin are two closely related peptides, that arrive via projections from the paraventricular and the supraoptic nucleus[104,105]. Both projections are present in all ventral hippocampus subregions. In the dorsal hippocampus, vasopressin fibers have been found almost exclusively in CA2[104]. This corresponds with the specific expression of the vasopressin receptor 1b in CA2[106]. The receptor for oxytocin is in the dorsal hippocampus primarily expressed in CA2 and adjacent CA3a[107]. Both vasopressin and oxytocin signalling in the hippocampus contribute to social recognition memory[9,108,109]. Further, vasopressin likely also plays a role in temporal sequence memory[18].

Substance P is released by projections from the supramammillary nucleus targeting specifically CA3a and CA2[110]. While the behavioral conditions of substance P release are not known yet, activity of the supramammillary nucleus is associated with stress, anxiety[111–113] and novelty[114].

Release of vasopressin, oxytocin, and substance P induce LTP on activated synapses with very similar dynamics (see Fig. 1 in **Paper** II, lower boxes). In all three cases, neuromodulator application leads to a slow onset potentiation

[101]Mishra et al., 2016 [102]Markram et al., 1997 [103]Dan and Poo, 2004 [101]Mishra et al., 2016 [75]Ishizuka et al., 1990 [77]Tamamaki et al., 1988 [104]Zhang and Hernandez, 2013 [105]Knobloch et al., 2012 [104]Zhang and Hernandez, 2013 [106]Young et al., 2006 [107]Ripamonti et al., 2017 [9]Smith et al., 2016 [108]Wersinger et al., 2002 [109]Lin et al., 2018 [18]DeVito et al., 2009 [110]Borhegyi and Leranth, 1997 [111]Choi et al., 2012 [112]Miyata et al., 1998 [113]Silveira et al., 1993 [114]Ito et al., 2009

that peaks after 20-30 minutes and roughly doubles the strength of excitatory synapses[115,116]. However, this mechanism only works if a test stimulus is repeatedly applied throughout the potentiation phase, indicating this mechanism is selectively strengthening activated synapses.

Interestingly, delta-opioid mediated input-timing dependent plasticity follows similar dynamics[10]. Despite acting via reducing feed-forward inhibition, net excitation approximately doubles 30 minutes after stimulation. Input-timing dependent plasticity depends on the correct timing between preceding cortical and trailing CA3 inputs and the presence of enkephalin[117]. Enkephalin has been found in pre-synaptic terminals of granule cell projections coming from the dentate gyrus and around parvalbumin positive interneurons located near CA2 pyramidal cell bodies. As with the previously mentioned neurotransmitters, input-timing dependent plasticity contributes to social recognition memory. Additionally, it has been shown that social interactions occlude input-timing dependent plasticity. In conclusion, the four mentioned neurotransmitter systems similarly increase excitatory projections from CA3 to CA2. Yet, the functional role of these modifications remains elusive.

Despite the similar effects on CA3 to CA2 projections, the four neuromodulatory systems strongly differ in their effects on the excitatory projections from entorhinal cortex to CA2. Release of vasopressin has been shown to selectively reduce the synaptic strengths of previously potentiated synapses[118]. In contrast, substance P release and input-timing dependent plasticity potentiate simultaneously activated EC projections. Further, substance P mediates interactions between CA3 and EC input. Weak tetanic stimulation of EC input alone leads to rapid, but transient potentation. However, if weak tetanic stimulation is paired with substance P release and CA3 input, it leads to long-lasting potentiation of EC synapes, a process called synaptic tagging and capture[116].

In summary, the four examples underline two key properties of neuromodulatory systems. First, neuromodulation rarely happens in isolation. Instead, a complex cocktail of vasopressin, oxytocin and enkephalin is necessary for successful formation of social recognition memory. Second, different neuromodulatory systems may converge on similar mechanisms. The two closely related substances vasopressin and oxytocin differ strongly from substance P both on the molecular level and in regards to the behavioral context of their release. Yet, all three systems have very similar effects on excitatory projections from CA3 to CA2. This indicates that different behavioral contexts may induce a similar mechanism in CA2.

[115]Pagani et al., 2015 [116]Dasgupta et al., 2017 [10]Leroy et al., 2017 [117]Basu et al., 2013 [118]Chafai et al., 2012 [116]Dasgupta et al., 2017

## 1.5 Neural correlates of episodic memory processing in the hippocampus

### 1.5.1 Encoding of space and other variables

The discovery of hippocampal place cells provided the long sought-after link between the concept of the cognitive map[48] and measurable neuronal activity. The development of *in-vivo* extracellular electrophysiological recordings[119,120] paved the way for the seminal discovery of place cells[49,50]. Place cells are spatially modulated cells, active in one or few parts of the environment. Whenever the animal traverses the region associated with a place field, the respective cell has an increased propensity to fire. Averaging over many traversals, the discharge probability in relation to space appears more or less gaussian, creating the so called place field. Different place cells are active at any given point in the relevant space. Thus, given a sufficient number of simultaneously recorded place cells, the position of the animal can be precisely decoded from the neuronal activity alone.

Distinct types of information are differently represented in the hippocampus. Two recent studies reported place cells which encode the allocentric position of other animals or objects[121,122]. While the populations of social-, object- and self-relating place cells partly overlap, they differ in certain key properties. Fewer cells encode social and object location and they have lower firing rates compared to self-place cells[121,122] [ii].

### 1.5.2 Rate remapping

Place cells dynamically respond to changes in the local environment. Thus, their coding properties go beyond the pure representation of physical location[50] For example, upscaling the size of the recording environment led to an expansion of place fields in some cells[126]. Other cells completely changed their spatial representation. Shifting from a circular to a rectangular recording environment,

[48]Tolman, 1948 [119]Ainsworth et al., 1969 [120]Wall et al., 1967 [49]O'Keefe and Dostrovsky, 1971 [50]O'Keefe, 1976 [121]Omer et al., 2018 [122]Danjo et al., 2018 [121]Omer et al., 2018 [122]Danjo et al., 2018 [50]O'Keefe, 1976 [126]Muller and Kubie, 1987

[ii]In CA1 and CA3 around 40 % to 70% of pyramidal cells are typically classified as self place cells, representing the animals own location in a given environment[121–123]. Around 30% of putative pyramidal cells are classified as time cells in both CA3 and CA1[123,124], yet their ratio depends strongly on the underlying statistical method[125]. In bats, 18% of all recorded cells in pyramidal layer of CA1 were found to significantly encode the position of a conspecific, while 69% of cells encoded self-position[121]. In rats, 13% of all place responsive units preferred the conspecific and 58% were self-place cells[122]. In addition, peak rates of social- and object-relating place cells in bats are considerably lower compared to self-place cells, 8 Hz versus 13 Hz[121]. Further, while firing rates of social- and self-relating place cells are modulated by the direction of movement, firing rates of object-relating place cells are similarly active in both directions[121]. In summary, evidence from CA1, and in the case of time cells also from CA3, suggest that hippocampal representations of time, other animals or objects are not as prominent compared to the animal's own location.

induced a complete rearrangement of the spatial map, a process called *global remapping*. In contrast, minor modifications, such as changing the wall color, do not induce a complete reorganisation of place fields[127]. Instead, place fields mostly retain their location, but up- or downscale firing rates, a process called *rate remapping*[127].

### 1.5.3 Oscillations of extracellular potentials

In rodents, at least three distinct rhythmic activity regimes can be classified: Theta and gamma oscillations as well as sharp wave ripples. Rhythmic activity is quantified by the power of different frequency bands in the local field potential (LFP). The LFP is the electric potential recorded outside of neurons, limited to frequencies below 500 Hz[128]. Deviations in the LFP are mostly induced by synchronized synaptic currents[128].

Theta rhythms cover a frequency band of 4–12 Hz and are observed during phases of active movement, exploration or rapid eye movement sleep[129–132].

Gamma rhythms are further subdivided in slow, 25–55 Hz, and fast gamma, 60–100 Hz[133–135]. Slow and fast gamma likely represent different pathways of information flow to CA1. While slow gamma is associated with input from CA3, fast gamma is entrained by inputs from the entorhinal cortex[136].

The third prominent hippocampal rhythm is referred to as sharp-wave ripples (SPWRs). In CA1, SPWRs are short, transient events, composed of a large low frequency deflection, called sharp wave, 0.01-3 Hz, and a superimposed high frequency oscillation, the ripple complex, 110-250 Hz. SPWRs are most frequently observed during waking immobility, consummatory behaviors and slow-wave sleep[137].

### 1.5.4 Neural activity sequences

Place cell sequences are organized on three different timescales, corresponding to behavior, theta oscillations and sharp-wave ripples (see Fig. 1.3). Moving in space implies the traversal of overlapping place fields. Intuitively, this creates a sequence of place cell activations reflecting the movement of the animal on the behavioral timescale.

#### 1.5.4.1 Theta sequences

Theta sequences are internally organized, time-compressed versions of behavioral sequences. While traversing an individual place field, several theta cycles may occur. Depending on whether the animal is at the beginning, center, or end of the field, the place cell tends to spike at progressively earlier phases of the cycle,

[127]Leutgeb et al., 2005 [127]Leutgeb et al., 2005 [128]Einevoll et al., 2013 [128]Einevoll et al., 2013 [129]Vanderwolf, 1969 [130]Ekstrom et al., 2005 [131]Pastalkova et al., 2008 [132]Wang et al., 2015 [133]Bragin et al., 1995 [134]Chrobak and Buzsáki, 1998 [135]Colgin et al., 2009 [136]Colgin, 2016 [137]Buzsáki, 2015

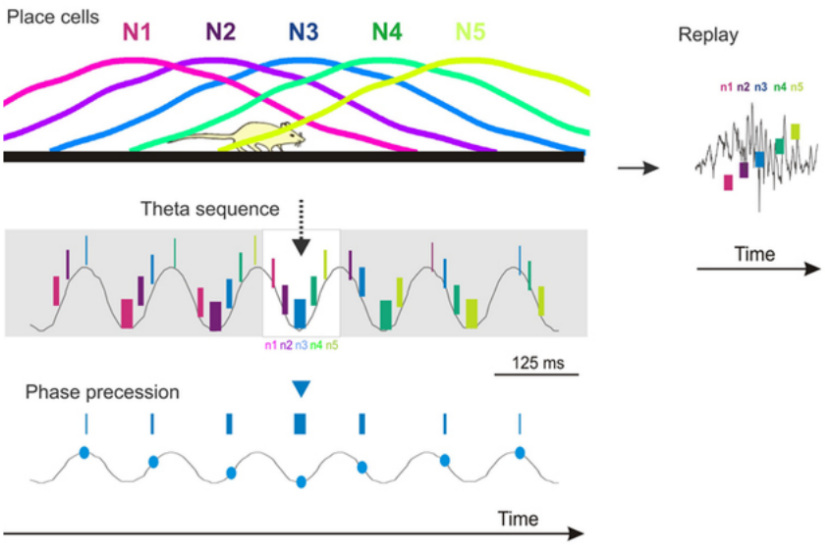


Figure 1.3: **Illustration of place cell activity, theta sequences, phase precession and replay in the hippocampus. Left**: Upper row, spiking activity of five place cells, with place fields N1-N5. Central row, order of place fields is reflected in time-compressed theta sequences, n1-n5. Lower row, while the animal traverses a given place field, here N3, the respective place cell tends to fire progressively earlier during each theta oscillation, a process called phase precession. **Right**: During sleep or awake rest, time-compressed sequential activity is reactivated during sharp wave ripples. Adapted from[138] under CC BY 3.0.

moving from the ascending late phase to the descending early phase of the cycle. This spike-theta-phase relationship is known as phase precession[139].

Theta sequences emerge by the coordinate activity of overlapping place cells. When multiple overlapping place cells are activated within one theta cycle, their activity is ordered according to the position of their place fields[140]. Thus theta sequences represent past, present and future locations in a time-compressed manner.

CA3 plays an important role in the formation of theta sequences. When blocking CA3 input to CA1, firing correlations of overlapping place cells in CA1 do no longer exceed chance levels during a theta cycle[141]. Thus, input from CA3 is crucial for the fine-scale coordination of firing activity in CA1. Interestingly, phase precession in CA1 is not abolished by blocking CA3 inputs.

Theta sequences may facilitate storing of experienced place cell sequences with synaptic plasticity. Neighboring place cells are activated close in time during theta sequences. The time scale of co-activation matches with spike

[139]O'Keefe and Recce, 1993 [140]Dragoi and Buzsáki, 2006 [141]Middleton and McHugh, 2016

timing dependent plasticity[103,142], making it plausible that synaptic plasticity between subsequently active place cell assemblies allows to store an experienced spatial trajectory. Additionally, symmetric spike timing dependent plasticity in CA3[101] may strengthen projections between neighboring place cell assemblies in forward and reverse order. Together, place cell activation during theta sequences may allow to encode information and thus provide the substrate for subsequent memory consolidation via forward and backward reactivation during sharp wave ripples.

#### 1.5.4.2 Neural activity sequences during sharp wave ripples

During sharp wave ripples, previous or anticipated place cell sequences are activated[143,144]. SPWRs are thought to arise from recurrent excitatory activity in the hippocampus[137,145]. Before or after a given experience, for example running back and forth on a familiar linear track, the corresponding sequence of place cells is frequently activated. This is also called replay. Sequence activation during SPWRs can be in forward or reverse order[143,144]. Before starting to run, forward replay dominates, while at a goal location backward replay is more frequent, potentially optimizing future decisions[146].

Besides planning[147], sequence reactivation during SPWRs is crucial for memory consolidation. Disrupting SPWRs after learning impairs both spatial[21–23] and social memory[16]. In contrast, artificial prolongation of SPWRs improves performance on a spatial navigation task[24]. Accordingly, SPWR occurrence increases after learning[148] and associated neural activity assemblies or sequences are activated more frequently[149–152].

Sharp wave ripples are accompanied by strong cellular activity. The probability for a neuron to spike during a SPWR is much higher compared to an equally long temporal window in slow-wave-sleep or active exploration[137,153]. Typically more than 10 percent of all cells are activated during a sharp wave ripple[153]. It remains to be tested whether multiple sequences are activated at the beginning of a ripple. If so, they may compete for reactivation via the recruitment of inhibition, contributing to the strong rise of inhibitory activity at the beginning of a ripple[154,155].

During rest, replay disengages from the current task[156] and remote experiences can be reactivated[157]. Further, it has been shown that replay is dominated by pre-existing activity patterns[158]. In comparison, sequences representing a recent novel experience are only rarely reactivated during subsequent replay[158]. Further, it has been reported that existing neural activity

[103]Dan and Poo, 2004 [142]Isaac et al., 2009 [101]Mishra et al., 2016 [143]Foster and Wilson, 2006 [144]Diba and Buzsáki, 2007 [137]Buzsáki, 2015 [145]Oliva et al., 2016 [143]Foster and Wilson, 2006 [144]Diba and Buzsáki, 2007 [146]Mattar and Daw, 2018 [147]Pfeiffer and Foster, 2013 [21]Girardeau et al., 2009 [22]Ego-Stengel and Wilson, 2010 [23]Jadhav et al., 2012 [16]Oliva et al., 2020 [24]Fernández-Ruiz et al., 2019 [148]Eschenko et al., 2008 [149]O'Neill et al., 2008 [150]Cheng and Frank, 2008 [151]McNamara et al., 2014 [152]Michon et al., 2019 [137]Buzsáki, 2015 [153]Mizuseki and Buzsáki, 2013 [153]Mizuseki and Buzsáki, 2013 [154]Ellender et al., 2010 [155]Sasaki et al., 2014 [156]Ólafsdóttir et al., 2017 [157]Karlsson and Frank, 2009 [158]Gupta et al., 2010 [158]Gupta et al., 2010

sequences pre-define identity and order of place cells in an upcoming, novel experience[159,160]. However, this phenomenon, called preplay, is still heavily debated[161,162] and contradictory data has been presented[163].

## 1.6 Computational theories of hippocampal subregions

### 1.6.1 The standard framework of hippocampal information processing

Attributing distinct functional roles to each hippocampal subregion, one line of thinking dominates the field to such a degree that it has been referred to as the *standard model*[164] or *standard framework*[165] of hippocampal information processing.

The standard framework puts a special emphasis on CA3 and its plastic recurrent connections. Motivated by early anatomical studies that suggested recurrent excitatory projections in the CA regions[62,166], David Marr argued that the CA regions may act as an auto-associative network[167]. Such a network can store an activity pattern by synaptic modifications between co-active cells via Hebbian plasticity[91]. If a fraction of neurons in a stored pattern are activated at a later time point, the network can restore the full pattern[168]; a process called pattern completion. Because pyramidal cells in CA3 are more likely to form recurrent excitatory connections compared to CA1[75], the role of the auto-associative memory storage has been explicitly attributed to CA3[169] and its plastic[10,11,170,171] recurrent connections.

The main input structure to CA3, the dentate gyrus, is believed to perform pattern separation[167,172,173]. Pattern separation is important to avoid interference when a new memory is to be stored in an auto-associative network. If the overlap between a new and an existing pattern exceeds a critical value, the auto-associative network would instead restore the existing pattern. The dentate gyrus has a number of features that make it particularly suited to perform the role of a pattern separator. External input arrives at a very large number of granule cells[174], which interact primarily via lateral inhibition[175], and thus allow very sparse and orthogonal signal representations. Further, outgoing projections from granule cells to CA3 form few, but exceptionally strong synapses[176,177]. Finally, new granule cells are constantly created throughout lifetime[178], and their projections to CA3 are highly plastic[179], potentially further reducing memory interference[180–182].

[159]Dragoi and Tonegawa, 2011 [160]Dragoi and Tonegawa, 2014 [161]Foster, 2017 [162]Pfeiffer, 2020 [163]Silva et al., 2015 [164]Nadel and Moscovitch, 1997 [165]Cheng, 2013 [62]Lorente de Nó, 1934 [166]Ramon y Cajal, 1911 [167]Marr, 1971 [91]Hebb, 1949 [168]Hopfield, 1982 [75]Ishizuka et al., 1990 [169]Treves and Rolls, 1994 [10]Leroy et al., 2017 [11]Dominguez et al., 2019 [170]Debanne et al., 1998 [171]Pavlidis et al., 2000 [167]Marr, 1971 [172]McNaughton and Morris, 1987 [173]O'Reilly and McClelland, 1994 [174]Rapp and Gallagher, 1996 [175]Espinoza et al., 2018 [176]Jonas et al., 1993 [177]Henze et al., 1997 [178]Altman and Das, 1965 [179]Schmidt-Hieber et al., 2004 [180]Becker, 2005 [181]Wiskott et al., 2006 [182]Aimone et al., 2009

The CA1 region is believed to be a novelty or mismatch detector by comparing input from CA3 and the cortex[183–185]. CA1 is the only hippocampal subregion to receive direct excitatory input from layer III of the entorhinal cortex via the so-called temporo-ammonic pathway. In the standard framework it is postulated that CA1 may detect mismatches between the current sensory input, thought to be represented by cortical activity, and the retrieved pattern from CA3. In agreement with this prediction, novel experiences lead to increased activity in CA1[186–188].

Several experimental observations have been pointed out to challenge the standard framework in its core assumptions[165]. One key prediction of the standard framework is that CA3 is important both for pattern completion and rapid, single-trial memory storage. While animals with CA3 lesions or with blocked plasticity inside CA3 are indeed impaired in pattern completion, they are nevertheless able to successfully remember a spatial location when all training cues are available[189–191] Further, synaptic plasticity in CA3 is not required for single trial learning of either spatial locations[189] or contextual fear memory[192].

Lesioning or blocking plasticity in the dentate gyrus impairs pattern separation, but does not lead to memory interference. The importance of the dentate gyrus for pattern separation is supported by a variety of studies[193–196]. Following the standard framework, the primary purpose of DG-mediated pattern separation is to prevent memory interference in CA3. However, while animals with lesioned DG or inactivated NMDA receptors were impaired in learning associations similar to old ones, interference with pre-existing memories has not been observed[193,197].

### 1.6.2 The CRISP theory of hippocampal function in episodic memory

Recently, an alternative theory about how the hippocampus encodes memory has been put forward[165]. The CRISP theory, Context Reset by dentate gyrus, Intrinsic Sequences in CA3, and Pattern completion in cornu ammonis 1, is motivated by a number of experimental observations either unexplained by or in contradiction to the standard framework: 1) the lack of pattern separation in DG seems not to lead to catastrophic inference with previously stored patterns[193,197], 2) CA3 is not required for single trial learning[189,192], and 3) the observation of pre-configured sequential activity in the hippocampus[159,198].

CRISP attributes novel roles to CA3, CA1 and the dentate gyrus[165]. In CRISP, CA3 is proposed to provide pre-existing, intrinsic sequences. Plasticity at perforant path synapses, from layer II of the cortex to pyramidal cells in CA3,

[183]Levy, 1989 [184]Hasselmo et al., 1996 [185]Lisman and Otmakhova, 2001 [186]Nitz and McNaughton, 2004 [187]Csicsvari et al., 2007 [188]Karlsson and Frank, 2008 [165]Cheng, 2013 [189]Nakazawa et al., 2003 [190]Gold and Kesner, 2005 [191]Fellini et al., 2009 [189]Nakazawa et al., 2003 [192]Cravens et al., 2006 [193]Gilbert et al., 2001 [194]Clelland et al., 2009 [195]Creer et al., 2010 [196]Sahay et al., 2011 [193]Gilbert et al., 2001 [197]McHugh et al., 2007 [165]Cheng, 2013 [193]Gilbert et al., 2001 [197]McHugh et al., 2007 [189]Nakazawa et al., 2003 [192]Cravens et al., 2006 [159]Dragoi and Tonegawa, 2011 [198]Gupta et al., 2010 [165]Cheng, 2013

allows to map individual memory elements onto sequence states. At the same time, plasticity at Schaffer collaterals connects the current CA3 state to the CA1 output pattern. Pattern completion is proposed to happen in the reciprocal feed-forward connections between the entorhinal cortex and CA1, from EC layer III to CA1 and back to EC layer V. Whenever a distinct sequence in CA3 is required, either because a new experience needs to be stored, or a memory needs to be recalled, strong input from the DG is proposed to overcome on-going recurrent dynamics in CA3 and to start a different sequence.

The CRISP theory states that episodic and semantic memories differ not only in content but also in their neuronal representation: While episodic memories are represented by temporal sequences of neuronal activity, semantic memories are proposed to be encoded by static neuronal patterns. During systems consolidation, information is not simply transferred to the cortex. Instead, it is proposed that repeated reactivation allows the cortex to extract semantic from episodic memory. Thus, the main role of the hippocampus is proposed to lie in storing and retrieving neural activity sequences. Retrieval of any true episodic memory, also very remote ones, should therefore depend on the hippocampus.

The feed-forward learning in the CRISP framework has been criticized for its limited storage capacity, the role of the perforant path input, and limited pattern completion abilities. Based on the observation that there are fewer perforant path versus recurrent inputs per CA3 pyramidal cells, it has been argued that the storage capacity of the CA3 system would be drastically reduced if it were to rely on learning in feed-forward projections as proposed by the CRISP theory[199]. Further, it has been pointed out that perforant path input onto CA3 pyramidal cells may be too weak to drive action potential firing in the presence of strong recurrent interactions[199]. However, as recently shown, input-timing dependent plasticity allows the selective potentiation of EC inputs without postsynaptic activity in CA3[10]. Thus, pairing of EC and CA3 states and EC driven recall in CA3 may nevertheless be possible. Lastly, it has been argued that pattern completion may not be successful because feed-forward based pattern association in reciprocal CA1-EC interactions may not possess a basin of attraction[199].

## 1.7 The role of CA2

The recent surge in interest has been primarily motivated by CA2's involvement in social memory processing. Early indications for such a role came from studies on the vasopressin receptor 1b (Avpr1b).

Within the brain, Avpr1b is almost exclusively expressed in CA2[106] and deletion of the Avpr1b gene impairs social motivation, social recognition memory and aggressive behavior[18,108,200–202]. Further, hippocampal injections of vasopressin or oxytocin antagonist directly after social exposure impair[203]

[199]Rolls, 2013 [199]Rolls, 2013 [10]Leroy et al., 2017 [199]Rolls, 2013 [106]Young et al., 2006 [18]DeVito et al., 2009 [108]Wersinger et al., 2002 [200]Wersinger et al., 2004 [201]Wersinger et al., 2007 [202]Wersinger et al., 2008 [203]Wimersma Greidanus and Maigret, 1996

and optogenetic stimulation of PVN vasopressin terminals in CA2 during social exposure extends social recognition memory[9].

Moreover, bilateral CA2 lesions[204] or inactivation of CA2 pyramidal neurons[8] in adult mice abolishes social recognition memory while discrimination of non-social and social odors remains intact. Animals with CA2 pyramidal cell inactivation show normal sociability, while CA2-lesioned animals show reduced motivation for social interaction.

More recent studies have begun to elucidate the CA2-related circuitry involved in social memory. Dorsal CA2 sends direct excitatory projections to both ventral CA3 and ventral CA1[12,205]. Projections to ventral CA1 have been shown to be required for encoding social memory[12].

For other types of behavior and memory, the role of CA2 appears more complicated. Mice with inactivated CA2 pyramidal cells do not differ from controls in their locomotor activity, anxiety-like behavior, hippocampal-dependent contextual fear memory, or amygdala-dependent auditory fear memory[8]. However, chronically silencing CA2 pyramidal cells slows habituation to a novel context[19]. Transiently activating CA2 pyramidal cells leads to more freezing behavior in both cue and contextual (only females) fear conditioning[20]. In the Morris water maze a trend towards slower learning as well as slower reversal learning in CA2-silenced mice suggests a potential impairment in adapting navigational strategies[8].

Knocking out the Avpr1b receptor selectively impairs the ability to distinguish the temporal order of objects presented in the same spatial location[18]. Further, in a hippocampus-dependent[206] object-trace-odor task Avpr1b$^{-/-}$ animals are unable to recall object-odor pairs separated by a 10-second temporal delay[18]. These results suggest CA2 may be involved in more demanding hippocampus-dependent learning.

Given the role of CA2 in social behavior, one might expect to see neural correlates of social experience. Indeed, CA2 place cells remap upon encountering either a novel or a familiar conspecific[14]. But CA2 place cells don't just remap to social stimuli; a novel object placed into a familiar environment suffices to evoke a similar remapping[14].

CA2 activation patterns are sensitive to local content and less so to the global context[207–209]. When the spatial context remains the same, place cells in CA2 are less stable compared to those in CA1 and CA3[208,210]. With multiple unstable fields shifting location and firing rates over time, CA2 activity appears volatile[208].

Manipulations of CA2 affect hippocampal network dynamics. Acute CA2 inactivation changes the spatial distribution of place fields in CA3[19]. Chronic silencing of CA2 pyramidal cells shifts CA3 spike timing to a later phase of

[9]Smith et al., 2016 [204]Stevenson and Caldwell, 2014 [8]Hitti and Siegelbaum, 2014 [12]Meira et al., 2018 [205]Okuyama, 2017 [12]Meira et al., 2018 [8]Hitti and Siegelbaum, 2014 [19]Boehringer et al., 2017 [20]Alexander et al., 2019 [8]Hitti and Siegelbaum, 2014 [18]DeVito et al., 2009 [206]Kesner et al., 2005 [18]DeVito et al., 2009 [14]Alexander et al., 2016 [14]Alexander et al., 2016 [207]Wintzer et al., 2014 [208]Mankin et al., 2015 [209]Lee et al., 2015 [208]Mankin et al., 2015 [210]Lu et al., 2015 [208]Mankin et al., 2015 [19]Boehringer et al., 2017

the theta cycle[19]. Even more, animals with chronically silenced CA2 develop direction-specific place-triggered hyperexcitability events in CA3[19]

In summary, CA2 appears to play an important role in hippocampal memory processing. Characteristic for CA2 seems to be the focus on local information, a prominent role of neuromodulation and close interactions with neighboring CA3. However, neither the standard framework, nor the alternative CRISP model, provide a suggestion for what the computational role of CA2 may be.

[19]Boehringer et al., 2017 [19]Boehringer et al., 2017

Chapter 2

# Objectives

The overarching goal of this thesis is to develop a cohesive theory about the computational role of hippocampal region CA2 in general episodic memory processing. Each of the three presented articles makes a step in this direction.

**Paper I** reviews the existing hippocampal literature to identify a potential computational role of hippocampal region CA2.

**Paper II** describes how the CA3-CA2 circuit may perform a particular function: To prioritize the reactivation of selected memory sequences.

**Paper III** uses a computational model to demonstrate that sequence competition and cooperation can be implemented in recurrent neural networks.

# Chapter 3

# Summary of papers

Hippocampal region CA2 has received increased interest throughout the recent years. Various fields of research have provided fascinating insights, commonly underlining the uniqueness of CA2. Prominent examples are CA2's interactions with CA3 and CA1, the controlled plasticity on excitatory CA3 to CA2 projections, the convergence of neuromodulatory inputs, characteristic cell activation patterns, and a pivotal role for certain, but not all forms of hippocampal memory encoding. However, we miss a cohesive theory to explain how these findings relate to each other and what computational role CA2 may play in the hippocampal circuit. The three presented articles aim at bringing us closer to a functional understanding of CA2.

Order and content of the three articles correspond with David Marr's three levels on analysis[25]. To attribute a function to a brain region, it is helpful to separate between

1. The computational level - Identifying the problem to be solved.
2. The algorithmic level - Characterizing the required representations and processing of information.
3. The implementational level - Outlining how such an algorithm may be realized in the neural system.

The first article reviews existing literature to identify a potential computational role of CA2. The second article outlines this role, describing how prioritized memory reactivation could be performed by interactions between CA3 and CA2. The third article explores in a computational model how co-active sequences can compete and cooperate. It demonstrates that the proposed sequence prioritization mechanism can indeed be implemented in recurrent neural networks.

**Paper I** The first article, *CA2 beyond social memory: Evidence for a fundamental role in hippocampal information processing*, identifies six separate lines of evidence that support the assumption that CA2 is of general importance for episodic memory processing, extending beyond its well documented role in social recognition memory. In addition, the article tries to provide an exhaustive overview of existing proposals for CA2's role.

CA2's interactions within the dorsal hippocampus are not required for social recognition memory. Dorsal CA2 sends strong excitatory projections

[25] Marr and Poggio, 1976

throughout the whole hippocampus. However, silencing dorsal CA3[211] or dorsal CA1[13,16] did not result in a measurable impairment in social recognition memory. Thus, the role of these projections is yet to be determined.

Novel and potentially salient content in the animal's local environment affects CA2 activity. Introducing novel objects in the animal's environment leads to drastic changes in activity levels of CA2 pyramidal cells[14,207]. In contrast, modifying the global context has a relatively small effect on CA2 activity[208,212].

Neuromodulation in CA2 could mediate general saliency or novelty cues. Several distinct neuromodulatory systems converge on CA2, altering neuron excitability and gating synaptic transmission and plasticity. For example, the effects of vasopressin, oxytocin and substance P on CA3 to CA2 synapses are very similar. Upon release, net excitation increases slowly, peaking after around 20-30 minutes, roughly doubling the strength of activated synapses. Thus, despite different origins and likely different release profiles, they may employ a common mechanism. The role of this mechanism is yet to be defined.

CA2 acts as a potent regulator of hippocampal activity. It modulates place cells, spike timing, and communication between the dentate gyrus, CA3 and CA1 in dorsal hippocampus. For example, chronically silencing CA2 affects both DG to CA3 and CA3 to CA1 transmission and leads to location-specific hyperexcitability events[19]. In turn, transient silencing of CA2 leads to agglomeration of CA3 place fields in few spatial hotspots[19]. Further, CA2 activity positively regulates low gamma oscillations in the hippocampus and the prefrontal cortex[213] and, thus, is expected to influence CA3 to CA1 communication[135].

Activity in CA2 affects hippocampal sharp wave ripples, highly synchronous oscillation patterns implied in memory formation. Such ripples can locally emerge in CA2 and spread to CA3 and CA1[145]. In contrast to other hippocampal regions, CA2 has a large fraction of pyramidal cells that ramp up their activity before and are relative silent during a ripple[145,214]. Further, CA2 activity is associated with the frequency of ripple occurrence[213] and ripples initiated inside CA2 have been shown to be particularly important for social recognition memory[16].

CA2 is involved in hippocampal-dependent learning and memory. A direct role of CA2 has been demonstrated in two non-social hippocampal-dependent tasks: Habituation to a novel context[19] and fear conditioning[20]. In addition, indications for a general role are provided by other, less specific

[211]Chiang et al., 2018 [13]Okuyama et al., 2016 [16]Oliva et al., 2020 [14]Alexander et al., 2016 [207]Wintzer et al., 2014 [208]Mankin et al., 2015 [212]Lu et al., 2013 [19]Boehringer et al., 2017 [19]Boehringer et al., 2017 [213]Alexander et al., 2018 [135]Colgin et al., 2009 [145]Oliva et al., 2016 [145]Oliva et al., 2016 [214]Kay et al., 2016 [213]Alexander et al., 2018 [16]Oliva et al., 2020 [19]Boehringer et al., 2017 [20]Alexander et al., 2019

manipulations. Silencing CA3a/CA2 to CA1 projections hinders novel object recognition[215]. Animals without the CA2 specific vasopression receptor 1b are impaired remembering the temporal order of objects and odors[18]. Further, CA2's characteristic plasticity has been shown to affect hippocampal-dependent behavior. Unlocking CA3 to CA2 plasticity leads to enhanced object recognition memory and spatial learning[98], raising the question of why plasticity is limited in the first place.

The first article ends by summarizing existing proposals for CA2's functional role. CA2 has been suggested to act a) as a associator between separate memory traces[216], b) as a additional input structure to the dentate gyrus[68], c) to provide an alternative tri-synaptic pathway[63], d) to switch between memory- and sensory-based processing[217] and e) to encode time[208]. In our opinion, the existing proposals do not account for the bidirectional excitatory and inhibitory interactions between CA3 and CA2 and their characteristic neuromodulatory-gated plasticity.

**Paper II** The second article, *Selective neuromodulation and mutual inhibition within the CA3–CA2 system can prioritize sequences for replay*, argues that the reciprocal interactions between CA3 and CA2 allow for prioritized reactivation of neural activity sequences. During or immediately after a salient experience, neuromodulatory inputs to CA2 are expected to enable plasticity at CA3 to CA2 synapses. Under the yet to-be-tested assumption that synaptic plasticity also exists on reciprocal excitatory CA2 to CA3 projections, assembly sequences in CA3 and CA2 are proposed to pair and support each other's reactivation.

The concept of the cell assembly is a key component of this argumentation[91]. This term describes a set of cells, which together encode a specific piece of information. Place cells with similar place fields provide a prominent example. For conceptual simplicity, we assume that sequences are formed by subsequently active, discrete assemblies. However, a similar reasoning should extend to continuous sequences with overlapping assemblies[218].

Depending on the type of information, hippocampal representations differ in the number of recruited cells. Recent experimental findings show that pyramidal cells in the hippocampus encode location of other animals and objects in a similar way as the animal's own location[121,122]. However, in contrast to self-place cells, fewer cells are active at a given point in space. Transferring these observations to a conceptual level, different types of information are thus likely encoded by cell assemblies of different sizes.

Sequence interactions may be especially important for memory sequences encoded by small cell assemblies. As shown previously[218], successful reactivation of assembly sequences crucially depends on the number of cells

[215]Raam et al., 2017 [18]DeVito et al., 2009 [98]Lee et al., 2010 [216]Sekino and Shirao, 2006 [68]Chevaleyre and Siegelbaum, 2010 [63]Kohara et al., 2014 [217]Middleton and McHugh, 2019 [208]Mankin et al., 2015 [91]Hebb, 1949 [218]Chenkov et al., 2017 [121]Omer et al., 2018 [122]Danjo et al., 2018 [218]Chenkov et al., 2017

per assembly. Assuming that recurrent interactions inside an assembly are pre-configured, remain stable during learning, and have a fixed probability to form synapses onto other members of the assembly, the assembly size defines how many recurrent inputs a neuron in the assembly receives. With sufficient recurrent excitation, an incoming excitatory pulse can be amplified, creating excitatory input to the subsequent assembly. In contrast, if assembly size and thus recurrent excitation is small, amplification may be too weak to create a sufficiently strong pulse to activate the next assembly. Such a sequence cannot reactivate.

The situation for weak sequences, comprised of small assemblies, further aggravates when competing with stronger sequences via mutual inhibition. Here, weak sequences could additionally strengthen feed-forward or recurrent interactions. However, this may be limited by physiological constraints.

Alternatively, weak sequences may overcome their competitive disadvantage by pairing with other co-active sequences. We argue the CA3-CA2 system provides the necessary components for this process. Place cell sequences are active in both CA3 and CA2 for any given sensory experience[14,208–210]. Further, neuromodulation is released during potentially salient experiences[9,18,203]. Interestingly, many of the described neuromodulators have a similar effect: They increase net excitation from co-active CA3 to CA2 pyramidal cells, and reduce[10,115,219], or overcome[220], the otherwise predominant feed-forward inhibition[63,68]. A missing piece of information, and so far just an assumption, is that CA2 to CA3 synapses are also strengthened when assemblies are co-active. However, this seems plausible given that plasticity inside CA3 can be readily expressed[101].

For conceptual clarity, the article outlines only a highly simplified scenario for sequence interaction and competition. During encoding, assembly sequences are formed in both CA3 and CA2 for only two experiences. During consolidation, these two sequences are activated and compete for reactivation. The first experience is encoded by a strong sequence in CA3. Because pairing is not required, the co-active sequence in CA2 is ignored for the first experience. The second experience is encoded by two weak sequences, one in CA3 and one in CA2. Without the release of CA2-associated neuromodulation during encoding, the strong sequence in CA3 will dominate reactivation. However, upon release of neuromodulation and consequently unlocked plasticity at CA3 to CA2 projections, the weak sequences can pair and overcome the strong sequence.

The proposed mechanism may explain why CA2 is relevant in some but not all hippocampus dependent memory tasks and makes testable predictions

[14]Alexander et al., 2016 [208]Mankin et al., 2015 [209]Lee et al., 2015 [210]Lu et al., 2015 [9]Smith et al., 2016 [18]DeVito et al., 2009 [203]Wimersma Greidanus and Maigret, 1996 [10]Leroy et al., 2017 [115]Pagani et al., 2015 [219]Piskorowski and Chevaleyre, 2013 [220]Nasrallah et al., 2015 [63]Kohara et al., 2014 [68]Chevaleyre and Siegelbaum, 2010 [101]Mishra et al., 2016

for future experiments. CA2's contribution is believed to be significant if either sequences of interest inside CA3 are too weak to reactivate alone, or information in CA3 and CA2 needs to be combined. For example, during classical spatial navigation tasks, known to be independent of CA2[8], sequences reflecting the animal's own trajectory may be strong enough to reactivate independently. However, animals with a knockout of the vasopressin receptor 1b show impairments memorizing sequences of objects and odors[18]. We expect further impairments in complex environments, where multiple events of different importance happen close in time or where strategies need to be quickly re-adapted, as for example when platform location changes in the Morris water maze[8].

**Paper III** The third article, *Competition and Cooperation of Assembly Sequences in Recurrent Neural Networks*, demonstrates that the proposed pairing of co-active sequences to prioritize reactivation can be implemented in rate-based neural networks. In paper II, we argue that a) multiple sequences reflecting different sensory experiences compete for reactivation in the CA3/CA2 system, b) neuromodulation may pair simultaneously active sequences across CA3 and CA2 and c) this pairing may allow sequences comprised of fewer cells to successfully reactivate despite inhibition from stronger competitors. Modelling sequence interactions with discrete, pre-defined assemblies, we show that successful progression depends on sufficient recurrent projections to recover from competition, inhibitory interactions to avoid undesired co-activation, and increased feed-forward connections or mutual excitatory cooperation for sequences with small assemblies.

Neural activity sequences are ubiquitous in the brain and underlie for example olfactory processing[221], encoding of birdsongs[222], episodic memory[50,223] and spatial navigation[224]. Reflecting their broad role, they unfold on a variety of timescales, in diverse brain regions and can be driven by sensory input or internal dynamics. Previous theoretical work has established how feed-forward and recurrent neural networks can form and reactivate neural activity sequences[218,225–228]. However, these studies either focused on individual sequences[218,225,227], or, if multiple sequences were present, competition was limited to specific points in space or time[226,228].

We model sequences with discrete, pre-configured assemblies, each consisting of a recurrently interacting excitatory and inhibitory population. Population activity is described by a non-linear rate equation with a sigmoidal activation function and self dampening[229]. Feed-forward inhibition dominates interactions between all assemblies. To form sequences, uni-lateral feed-forward projections between excitatory populations are

[8]Hitti and Siegelbaum, 2014 [18]DeVito et al., 2009 [8]Hitti and Siegelbaum, 2014 [221]Friedrich and Laurent, 2001 [222]Hahnloser et al., 2002 [50]O'Keefe, 1976 [223]Skaggs and McNaughton, 1996 [224]Johnson and Redish, 2007 [218]Chenkov et al., 2017 [225]Diesmann et al., 1999 [226]Kumar et al., 2008 [227]Fiete et al., 2010 [228]Spreizer et al., 2019 [218]Chenkov et al., 2017 [225]Diesmann et al., 1999 [226]Kumar et al., 2008 [228]Spreizer et al., 2019 [229]Wilson and Cowan, 1972

introduced. If sequences are cooperating, uni- or bi-directional projections between excitatory populations of co-active assemblies are added. Sequence formation/cooperation via adding excitatory to excitatory projections aims at approximating learning in biological networks, for which we expect that such connections are existing among most assemblies[72,74,75]. During encoding, when external input is thought to drive assembly activity, Hebbian plasticity may strengthen connections between assemblies activated close in time[163,218].

We start by showing that individual assembly sequences can successfully progress in such a non-linear rate model. We classify successful sequence progressing by three criteria: 1) All excitatory populations must be activated and exceed activity of other excitatory populations in the same sequence at least one point in time, 2) global activity must be sparse, and 3) peak activation times must maintain their predefined order. By scanning the parameter range of recurrent and feed-forward connection probabilities, we identify a parameter region with successful sequence progression. Outside this area, activities of excitatory populations either cease or saturate. The minimal requirements on connection strengths match with analytical predictions for assembly sequence progression in spiking neural networks[218].

To study a minimal case of sequence competition, we extend the non-linear rate model to two sequences. Four different scenarios are conceivable: a) Both sequences cease, b) first or c) second sequence wins, or d) both sequences successfully progress. By systematically varying assembly sizes in both sequences together with strengths of either recurrent, feed-forward or feed-forward inhibitory projections, we identify parameter ranges for each scenario. Without sufficient feed-forward excitation, activity cannot propagate and even strong sequences cease. Recurrent projections are required to recover from low activities. With low values of feed-forward inhibition, competition is weak, allowing both sequences to progress. Further, we show that a sequence with small assemblies may win against one with large assemblies by strengthening feed-forward projections. However, we show that the required amount of feed-forward excitation scales non-linearly with assembly size. Thus, for small assemblies, strengthening feed-forward projections may quickly reach physiological boundaries.

Alternatively, weak sequences can ensure their reactivation by cooperating with other sequences. We show that weak excitatory interactions between co-active assemblies of two sequences are sufficient to outcompete a strong sequence. However, we noticed that pairing slows the progression of interacting sequences, eventually leading to stalling activity in the first assembly. We propose three different strategies to increase the reduced progression speed: 1) stronger self-dampening of activation, 2) entrainment

[72]Guzman et al., 2016 [74]Deuchars and Thomson, 1996 [75]Ishizuka et al., 1990 [163]Silva et al., 2015 [218]Chenkov et al., 2017 [218]Chenkov et al., 2017

by oscillations or 3) pairing subsequently active assemblies across both regions.

Dynamics of single assembly sequence progression are comparable between the non-linear rate model and a previously published spiking neural network[218]. With only feed-forward connections, all assemblies are almost immediately activated, reminiscent of synfire chain explosions[225,230]. Too strong feed-forward and recurrent connections induce persistent activity which can compared to assembly bursting[218]. However, it remains to be tested whether sequence competition and cooperation express similar dynamics in a spiking neural network.

Based on the presented theoretical results, we conclude that the CA3/CA2 system should be able to prioritize sequences for offline reactivation, even when represented experiences are encoded by smaller assemblies.

[218]Chenkov et al., 2017 [225]Diesmann et al., 1999 [230]Tetzlaff et al., 2002 [218]Chenkov et al., 2017

# Chapter 4

# Discussion

Starting from an extensive literature review, this thesis identifies a potential role for hippocampal region CA2 in episodic memory processing: To mediate cooperation and competition between neural activity sequences in CA3 and CA2. Simulations of sequence interaction in recurrent neural networks demonstrate that such a function could in principle be implemented by the CA3/CA2 system.

## Sequence prioritization in the CA3-CA2 system is compatible with existing hippocampal theories

The core goal of this thesis is to integrate CA2 into the functional understanding of information processing within the hippocampal system. So far, CA2 has been ignored by both the large body of work forming the standard framework and by the alternative CRISP theory.

Embedding the proposed mechanism into the standard framework, CA3-CA2 interactions may combine different types of information and facilitate attractor reactivation. Classically, CA3 is thought to act like an auto-associator[169]. Whenever a large enough fraction of a previously stored pattern is presented, recurrent interactions in CA3 may reinstate the complete pattern via attractor dynamics. The proposed interactions between CA3 and CA2 may contribute to this process. When the encoding of a novel pattern is accompanied by the release of plasticity-inducing neuromodulation in CA2, currently active CA2 cells may become part of the attractor. Such a CA3-CA2 attractor may be appealing for two reasons: There are indication that CA3 and CA2 represent different types of information[208,209]. The joint attractor could combine both types. Further, having a larger attractor and increased inhibition on competitors may facilitate reactivation.

In the CRISP theory, CA2 may facilitate the reactivation of specific CA3 sequences. One core assumption of the CRISP theory is that CA3 provides activity sequences onto which episodic memories can be mapped and reactivated. Independent of whether these sequences are pre-existing or are formed during experience[161–163], this assumption matches well with CA3-CA2 mediated sequence prioritization.

## Parallel sequence prioritization in CA1

Optogenetic stimulation of dopaminergic projections from the ventral tegmental area to dorsal CA1 while mice are exploring a complicated maze increases

[169]Treves and Rolls, 1994 [208]Mankin et al., 2015 [209]Lee et al., 2015 [161]Foster, 2017 [162]Pfeiffer, 2020 [163]Silva et al., 2015

reactivation of current firing patterns and improves memory performance[151]. This matches with the observation that dopamine release facilitates synaptic potentiation inside CA1 after a novel experience[231]. Given that the actual level of recurrent excitatory projections inside CA1 is higher than initially expected[74,232,233], and that sharp wave ripples may also arise locally inside CA1[145], it seems plausible that sequence reactivation may be independently initiated in CA1. Alternatively, dopamine signalling could determine the response strength to sequences arriving from CA3 and CA2[234].

Further, sequence prioritization could be mediated by potentiated cortical synapses to the dentate gyrus or the CA regions[10,68,116,235]. Such a mechanism could either act in parallel or contribute to the proposed CA3-CA2 mechanism.

## Behavioral evidence for CA3-CA2 mediated sequence prioritization

Besides its contribution to social recognition memory[8,9,12], habituation to a novel context[19] and fear conditioning[20], CA2 likely contributes to novel object recognition[215] and memory for temporal order[18].

CA3-CA2 interactions are proposed to be important whenever multiple sequences in CA3 and CA2 compete for reactivation. Such situations may arise when an animal encounters multiple experiences with different relevance in close temporal succession. The selective reactivation of a weak, yet important, sequence is an obvious example. It remains to be tested whether the deficits in novel context habituation[19], fear conditioning[20], and memory for temporal order[18] are indeed the result of reduced reactivation specificity. Given strong cortical inputs[68], potential reactivation deficits must be separated from encoding deficits[12].

An interesting case arises also when two strong sequences compete. Animals with transiently silenced CA2 showed a characteristic trend towards slower relearning of new platform locations[8]. If not simply an artifact of small sample size, reactivation mediated by CA3-CA2 interactions would provide an explanation for the slower acquisition of the new platform location. Behavioral sequences that reflect the updated location are not sufficiently prioritized over those representing the previous location.

New, not yet peer-reviewed results directly support the proposed CA3-CA2 prioritization mechanism. Transiently silencing CA2 pyramidal cells between the exploration of two novel linear tracks reduces the temporal precision and specificity of subsequent reactivations[236]. Assemblies representing the first and second experience were more frequently co-activated during individual sharp

[151]McNamara et al., 2014 [231]Li et al., 2003 [74]Deuchars and Thomson, 1996 [232]Knowles and Schwartzkroin, 1981 [233]Yang et al., 2014 [145]Oliva et al., 2016 [234]Rosen et al., 2015 [10]Leroy et al., 2017 [68]Chevaleyre and Siegelbaum, 2010 [116]Dasgupta et al., 2017 [235]Nasrallah et al., 2016 [8]Hitti and Siegelbaum, 2014 [9]Smith et al., 2016 [12]Meira et al., 2018 [19]Boehringer et al., 2017 [20]Alexander et al., 2019 [215]Raam et al., 2017 [18]DeVito et al., 2009 [19]Boehringer et al., 2017 [20]Alexander et al., 2019 [18]DeVito et al., 2009 [68]Chevaleyre and Siegelbaum, 2010 [12]Meira et al., 2018 [8]Hitti and Siegelbaum, 2014 [236]He et al., 2020

wave ripples, suggesting reduced inhibition on competing assemblies. Further, the quality of replay is reduced. Reconstructed trajectories are shorter and more noisy. However, while these results demonstrate a clear role of hippocampal region CA2 in modulating reactivation of spatial sequences, a behavioral effect in the spatial domain is yet to be demonstrated.

## CA2 may hold back computational resources for flexible memory formation

Restricted, neuromodulatory-controlled plasticity is a key property of CA3 to CA2 synapses[93]. For this purpose, pyramidal cells in CA2 express the specific plasticity limiting protein RGS14[98]. RGS14 is almost exclusively expressed in CA2[98] and limits plasticity in dendritic spines, likely via attenuating calcium levels during plasticity induction[237]. Accordingly, following a global knockout of RGS14, long term potentiation can be readily induced at CA3 to CA2 synapses. Interestingly, these animals display increased learning rates in a spatial memory task and improved novel object recognition[98]. If generally unlocking plasticity at CA3 to CA2 synapses leads to improved learning, why has evolution converged on limiting plasticity instead?

Following the proposed theory, CA3-CA2 interactions allow prioritized replay of important over less important experiences. It is expected that generally unlocking plasticity at CA3 to CA2 synapses may lead to learning impairments when several experiences of different valence happen close in time. Thus, CA2 may be explicitly separated from the CA3 circuit to hold back computational resources for more flexible and specific memory formation.

## Assumptions and simplifications of the proposed theory

Given the fragmentary knowledge of the complex hippocampal circuit, the proposed role for CA2 rests on several strong assumptions and simplifications. One key assumption is that hippocampal region CA3 plays a decisive role in neural activity sequence reactivation. It has been argued that plastic recurrent connections inside CA3 allow the formation and reactivation of such sequences[161,162,165]. Accordingly, silencing CA3 abolishes theta sequences in CA1[141]. However, data is lacking to determine whether CA3 plays a similarly important role during reactivation and how this compares to other subregions[161].

Neuromodulatory-controlled sequence pairing is based on a three-factor learning rule. For selective pairing of co-active assemblies in CA3 and CA2, potentiation may only occur at synapses where the following three requirements are fulfilled in a small temporal window: Pre- and post-synatpic activity as well as neuromodulatory release. The necessity of pre-synaptic activity for potentiation is established for vasopressin[115] and substance P[116]. In contrast, oxytocin release

[93]Zhao et al., 2007 [98]Lee et al., 2010 [98]Lee et al., 2010 [237]Evans et al., 2018 [98]Lee et al., 2010 [161]Foster, 2017 [162]Pfeiffer, 2020 [165]Cheng, 2013 [141]Middleton and McHugh, 2016 [161]Foster, 2017 [115]Pagani et al., 2015 [116]Dasgupta et al., 2017

induces a minor potentiation without synaptic activity[115]. The dependence on postsynaptic activity has not been tested for any of these neuromodulators. Further, it remains to be shown whether these insights from slice experiments transfer to the *in vivo* situation.

## The proposed theory leaves certain CA2 properties unexplained

In contrast to previous proposals for the role of CA2[63,68,208,216,217], this work emphasizes the recurrent interactions between CA3 and CA2, accounting for the neuromodulatory-controlled plasticity of these projections.

However, this account does not yet specify a role for the recently described direct excitatory projections from the dentate gyrus to CA2[63] as well those in the opposite direction[75].

Further, release of oxytocin[238] and acetylcholine[239] has been shown to induce bursting behavior in CA2 pyramidal cells. While not explicitly addressed, it is conceivable that bursting behavior could facilitate plasticity underlying sequence formation and sequence pairing.

[115]Pagani et al., 2015 [63]Kohara et al., 2014 [68]Chevaleyre and Siegelbaum, 2010 [208]Mankin et al., 2015 [216]Sekino and Shirao, 2006 [217]Middleton and McHugh, 2019 [63]Kohara et al., 2014 [75]Ishizuka et al., 1990 [238]Tirko et al., 2018 [239]Robert et al., 2020

# Chapter 5

# Future perspective

The proposed role of CA2 creates novel avenues for both theoretical and experimental research.

## Sequence interactions in more biological plausible simulations

The primary aim of the simulation in the third article was to provide a proof of principle for sequence competition and cooperation in recurrent neural networks. To keep the model general and parsimonious we included only properties that appeared strictly necessary. On purpose we omitted key properties of biological neuronal networks, such as action potential generation, dendritic integration, oscillations, non-random wiring properties, plasticity and the diversity of interneurons. Further work should study how sequence interaction may be influenced by these factors.

Of particular interest would be to understand how multiple novel sequences can be learned in plastic networks and how joint reactivation may shape their interactions. During encoding of an episodic memory, the hippocampus seems to map information about an ongoing experience onto intrinsic neural activity sequences, either pre-existing[159] or formed during the process[163]. Thus, it is to be expected that certain physiological properties are particularly beneficial for this process. In a more elaborate simulation study one may elucidate which physiological properties contribute to sequence learning and sequence interaction. Prime candidates to explore are bi-directional wiring motifs[72], symmetric spike-timing-dependent plasticity[101], input-timing-dependent plasticity[10,117] and the input-timing-dependent formation of dendritic plateau potentials[240] and related formation of novel receptive fields[241]. To ensure stable activity dynamics, such plastic networks would also have to include homeostatic control mechanisms[242–244].

## Complex memory tasks may help to characterise the role of CA2

When studying episodic memory in mice or rodents, experiments typically involve stereotypic and isolated tasks in sterile environments to avoid confounding by uncontrolled variables and to simplify the readout. Such tasks are far from the natural behavior of rodents. Throughout its evolutionary history, the rodent brain has likely been required to memorize events in highly complex and changing environments. It is thus expected that current tasks capture only a small fraction of the cognitive repertoire of rodent brains.

[159]Dragoi and Tonegawa, 2011 [163]Silva et al., 2015 [72]Guzman et al., 2016 [101]Mishra et al., 2016 [10]Leroy et al., 2017 [117]Basu et al., 2013 [240]Bittner et al., 2015 [241]Bittner et al., 2017 [242]Vogels et al., 2011 [243]Zenke et al., 2015 [244]Turrigiano, 2011

Ongoing developments in analysing fine-grained behavior[245], long-term wireless recordings of large neuronal populations[246], high-resolution profiling of neuromodulation via optical imaging[247], and more complex behavioral tasks are likely to expand our understanding of the computations performed by the hippocampus and its subregions. This seems to be particularly true for hippocampal region CA2, as it is particularly involved in encoding local changes within the environment[14,207], regulated by many neuromodulators[10,18,116,248], and with widespread effects on hippocampal dynamics[19,20,145,213].

## Comparing CA2 across different species may provide functional indications

If CA2's primary contribution were indeed to mediate social aspects of episodic memory, one could expect marked differences between animals living in complex social relations versus those living solitarily. Different species within the family of African mole-rats, *Bathyergidae*, are prime candidates to test this assertion. While the cape mole rat, *Georychus capensis*, is strictly solitary, the highveld mole-rat, *Cryptomys hottentotus pretoriae*, lives in colonies with one breeding pair and up to 12 subordinates[249]. Further, the eusocial naked mole-rat, *Heterocephalus glaber*, lives in complex social groups of up to 100 animals with social hierarchies, division of labor and cooperative breeding[250]. A recent anatomical comparison found that social highveld and naked mole-rats have stronger neurogenesis in the hippocampus compared to the solitary cape mole rat[251]. However, CA2 has not been studied in these animals. While such comparative anatomical studies may provide valuable indications, one has to be cautious about potential confounders.

Nevertheless, the evolution of the hippocampal formation remains a highly interesting topic. Among mammals, it is commonly assumed that the anatomical organization and function of the hippocampal regions is highly conserved[252]. However, the origin of the hippocampus appears to lie much deeper in evolutionary history. Comparing gene expression patterns from turtles and lizards to mice confirms homologue structures for DG, CA3 and CA1, but not for CA2[253]. While only comparing three species, these findings indicate that CA2 evolved at a later point in evolutionary history compared to DG, CA3 and CA1.

Despites some exceptions, reptiles rarely express difficile social behavior[254]. Thus, one may speculate that CA2 may have primarily evolved to handle increased demands for memorizing social encounters in mammals. Since certain bird species also have rich social interactions and, thus, a need for social recognition[255,256], it would be interesting to search for a structural homologue to CA2 in the avian brain[257]. However, even if social interactions were the main

[245]Ziegler et al., 2020 [246]Barbera et al., 2019 [247]Ravotto et al., 2020 [14]Alexander et al., 2016 [207]Wintzer et al., 2014 [10]Leroy et al., 2017 [18]DeVito et al., 2009 [116]Dasgupta et al., 2017 [248]Ochiishi et al., 1999 [19]Boehringer et al., 2017 [20]Alexander et al., 2019 [145]Oliva et al., 2016 [213]Alexander et al., 2018 [249]Bennett and Faulkes, 2000 [250]Jarvis, 1981 [251]Amrein et al., 2014 [252]Manns and Eichenbaum, 2006 [253]Tosches et al., 2018 [254]Bull et al., 2017 [255]Schjelderup-Ebbe, 1935 [256]Boucherie et al., 2019 [257]Gupta et al., 2012

evolutionary driver behind the development of CA2, one would expect that such a powerful circuit gained relevance for other functions as well.

## CA2 may be a promising target to alleviate neurological disorders

Neurological changes in CA2 are associated with schizophrenia, epilepsy and multiple neurodegenerative diseases such as Lewy body dementia, Parkinson's disease, Alzheimer's disease and transmissible spongiform encephalopathies (for more details see[258]).

The development of schizophrenia in humans is frequently accompanied by deficits in social recognition[259] and distinct modifications in CA2: Altered gene expression patterns[260], morphological reorganization[261] and reduced density of parvalbumin positive interneurons[262,263]. Similar observations have been made in the *Df(16)A*$^{+/-}$ mouse model of the 22q11.2 microdeletion, a prominent schizophrenic risk factor[15,17]. Observations include a reduced density of parvalbumin positive cells, reduced feed-forward inhibition, less plasticity, altered CA2 properties, impaired social recognition memory[17] and reduced firing rates of pyramidal cells[15]. Interestingly, these alterations are caused by an increased membrane current through TREK-1 two-pore $K^+$ channels[15], preferentially expressed in CA2[264]. Blocking this current selectively inside CA2 restores firing properties of pyramidal cells and social recognition memory[15].

In medial temporal lobe epilepsy CA2 associated reorganizations likely contribute to hyperexcitability. Despite large effects on CA3 and CA1, cell loss in CA2 during epileptogenesis is relatively moderate[265]. The density of paralbumin-positive interneurons is reduced[266], with a strong decrease of inhibitory transmission in CA2[267,268]. In addition, in human patients, somata of CA2 pyramidal cells atypically receive excitatory synapes, likely originating from mossy fibers[267]. Sprouting of mossy fiber terminals into CA2 has also been observed in the kainate model of medial temporal lobe epilepsy[269] Supporting the hypothesis that reorganizations surrounding CA2 contribute to epileptic seizures, epileptiform bursts of activity have been shown to originate in or close to CA2 in hippocampal slices of rats[270] and humans[267].

Given the direct implication of CA2 in a variety of neurological diseases, a better understanding of its development, physiology, neuromodulation and interaction with neighboring regions will potentially provide new avenues to target these diseases.

[258]Chevaleyre and Piskorowski, 2016 [259]Penn et al., 2008 [260]Benes et al., 2008 [261]Narr et al., 2004 [262]Benes et al., 1998 [263]Zhang and Reynolds, 2002 [15]Donegan et al., 2020 [17]Piskorowski et al., 2016 [17]Piskorowski et al., 2016 [15]Donegan et al., 2020 [15]Donegan et al., 2020 [264]Talley et al., 2001 [15]Donegan et al., 2020 [265]Steve et al., 2014 [266]Andrioli et al., 2007 [267]Wittner et al., 2009 [268]Williamson and Spencer, 1994 [267]Wittner et al., 2009 [269]Häussler et al., 2015 [270]Knowles et al., 1987 [267]Wittner et al., 2009

## Understanding hippocampal information processing may help to design intelligent machines

Most modern-day approaches in artificial intelligence lack an internal causal model[271]. In other words, most current deep learning algorithms do not have an explicit mental representation of real world processes, including an understanding of objects, physical constraints and mental/motivational states of animals or humans. Instead, they approximate a non-trivial function in a high-dimensional space. Without doubt, deep learning approaches have led to enormous progress in fields such as image classification, reinforcement learning or natural language processing[272]. However, lacking true understanding, such algorithms fail in seemingly trivial edge cases. These shortcomings drastically hamper their employment in the real world, preventing for example a wide-adoption of fully-autonomous cars.

Automatically generated image captions vividly demonstrate what goes wrong without an internal causal model. For this purpose, images of unusual scenes were presented[271] to a pre-trained deep neural network[273]. A plane crashing on a street is described as "an airplane is parked on the tarmac at an airport", or people wading through a storm tide which is tearing down a house in the background as "a group of people standing on top of a beach". Thus, current algorithms perform well in recognizing objects, but fail at understanding their causal relationship[271].

In its general sense the cognitive map in the hippocampus is expected to represent relations between arbitrary objects. What is missing in the image caption example is an algorithm that can jump back and forth in time to determine the most likely sequence of events that have led to and will result from the presented scene. The hippocampus is known to play a crucial role in imagining hypothetical scenarios[5–7,274]. Here, we need its ability to move back and forth on a cognitive map; with the presented scene as the starting point. Thus, by understanding how the hippocampus and associated regions work, we hopefully gain insights to better design algorithms which efficiently learn from sequential experience and real world interaction to create an *in-silico* cognitive map[275].

To link this far-reaching thoughts back to the content of the thesis, it seems plausible that prioritized replay will play a major role in the efficient creation of *in-silico* cognitive maps. In the context of reinforcement learning, prioritized replay of important events has been demonstrated to improve the performance of Deep Q-Networks[276]. And vice versa, hippocampal replay and planning can be explained by optimizing which memory should be accessed to enable the most rewarding future decision[146].

[271]Lake et al., 2017 [272]Sejnowski, 2018 [271]Lake et al., 2017 [273]Karpathy and Fei-Fei, 2015 [271]Lake et al., 2017 [5]Hassabis et al., 2007 [6]Rosenbaum et al., 2009 [7]Andelman et al., 2010 [274]Hassabis et al., 2007 [275]Rikhye et al., 2020 [276]Schaul et al., 2015 [146]Mattar and Daw, 2018

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# Papers

Paper I

# CA2 beyond social memory: Evidence for a fundamental role in hippocampal information processing

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I

# CA2 beyond social memory: Evidence for a fundamental role in hippocampal information processing

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**Abstract**

Hippocampal region CA2 has received increased attention due to its importance in social recognition memory. While its specific function remains to be identified, there are indications that CA2 plays a major role in a variety of situations, widely extending beyond social memory. In this targeted review we highlight lines of research which have begun to converge on a more fundamental role for CA2. We discuss recent proposals that speak to the computations CA2 may perform within the hippocampal circuit.

# 1 Introduction

The hippocampus has fascinated neuroscientists and psychologists for decades given its crucial role in episodic memory and spatial navigation. Throughout this time, both experimental and theoretical research have focused on the three prominent subregions of the hippocampus: The dentate gyrus (DG) and cornu ammonis regions 3 (CA3) and 1 (CA1). The classical understanding of hippocampal information processing proposes that DG acts like a pattern separator, CA3 as a auto-associative storage and pattern completion site and CA1 as a novelty or mismatch detector (Marr, 1971; McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; Treves and Rolls, 1994; Levy, 1989; Hasselmo et al., 1996, but see Cheng, 2013).

Sandwiched between CA3 and CA1 is the relatively small subregion CA2. Until recently little work has been done to understand CA2's functional relevance. By specifically inactivating CA2 pyramidal cells, Hitti and Siegelbaum (2014) unequivocally demonstrated that CA2 plays a critical role in social recognition memory. Other hippocampus-dependent abilities, such as spatial or contextual fear memory appeared unaffected. Since then, a number of studies have corroborated that social recognition memory depends on CA2 (Stevenson and Caldwell, 2014; Smith et al., 2016; Leroy et al., 2017; Meira et al., 2018; Okuyama et al., 2016; Oliva et al., 2020; Cymerblit-Sabba et al., 2020). Thus, CA2 has emerged as a region primarily associated with the processing of social information.

But new findings about CA2 anatomy, physiology and the relationship between CA2 neural activity with behavior suggest that CA2 is playing a general role in memory processing of which social memory may be just a special case. In this targeted review we focus on experimental findings that suggest a broader role for CA2. To get started, we briefly summarize CA2's strategic position within the hippocampus (for review see Okuyama, 2018; Dudek et al., 2016; Jones and McHugh, 2011; Tzakis and Holahan, 2019; Benoy et al., 2018; Chevaleyre and Piskorowski, 2016; Middleton and McHugh, 2019). Each subsequent section presents a separate, self-contained argument for why CA2's role may go beyond social memory. Finally, we synthesize these different lines of argumentation and connect them with recent proposals that incorporate CA2 in our understanding of how the hippocampus works.

## 1.1 CA2 is centrally located, well connected, and tightly regulated

Traditionally hippocampal computations were associated with the main trisynaptic circuit from DG to CA3 and CA1. However, CA2 is strategically placed within the hippocampal network enabling it to play a central role in hippocampal information processing. CA2 is tightly connected with all hippocampal subregions and receives extensive neuromodulatory projections (Fig. 1). From within the hippocampus, CA2 receives direct excitatory input from the DG and CA3 (Kohara et al., 2014; Ishizuka et al., 1990; Tamamaki et al., 1988; Zhao et al., 2007; Chevaleyre and Siegelbaum, 2010). From outside the hippocampus, CA2 receives strong excitatory input from the entorhinal cortex (Bartesaghi and Gessi, 2004; Chevaleyre and Siegelbaum, 2010; Sun et al., 2014). Further, extrahippocampal projections arrive from the medial septum, the supramammillary nucleus, the paraventricular

and the median raphe nucleus (Cui et al., 2013; Hitti and Siegelbaum, 2014; Zhang and Hernandez, 2013; Vertes and McKenna, 2000; Leroy et al., 2018).

CA2 sends excitatory output throughout the hippocampus and beyond. Axons of CA2 pyramidal cells branch extensively in CA1 and CA3 (Tamamaki et al., 1988; Kohara et al., 2014; Ishizuka et al., 1990; Hitti and Siegelbaum, 2014), with projections innervating both the functionally distinct dorsal and ventral hippocampus (Meira et al., 2018; Okuyama et al., 2016). In addition, CA2 axons weakly innervate the hilus of the dentate gyrus (Ishizuka et al., 1995) and project out to the medial and lateral septum (Ishizuka et al., 1995; Cui et al., 2013; Leroy et al., 2018). Thus, in contrast to uni-directional CA2→CA1 projections, CA3 and CA2 are reciprocally connected (Ishizuka et al., 1990; Tamamaki et al., 1988; Chevaleyre and Siegelbaum, 2010). However, despite the existence of excitatory synapses in both directions, connections between CA3 and CA2 are dominated by bi-directional feed-forward inhibition (Chevaleyre and Siegelbaum, 2010; Nasrallah et al., 2015; Kohara et al., 2014; Boehringer et al., 2017). Remarkably, excitatory CA3→CA2 projections do not express classical long-term potentiation (LTP) (Zhao et al., 2007) because of dense perineuronal nets (Carstens et al., 2016, but see Domínguez et al. 2019); extensive calcium buffering (Simons et al., 2009); and plasticity limiting signalling pathways (Lee et al., 2010; Simons et al., 2012). To the best of our knowledge, plasticity of CA2→CA3 projections has not been reported yet.

# 2 CA2's interactions within the dorsal hippocampus are not required for social recognition memory

Dorsal CA2 sends direct excitatory projections throughout the whole hippocampus (Meira et al., 2018; Okuyama et al., 2016; Kohara et al., 2014). But inhibition of neural activity in dorsal CA3 (Chiang et al., 2018), or in dorsal CA1 (Okuyama et al., 2016; Oliva et al., 2020) does not have any measurable effect on social recognition/discrimination. Only dorsal CA2 projections to the ventral hippocampus appear to be required for social recognition memory (Meira et al., 2018). Naturally, the following question arises: What is the purpose of CA2's projections to dorsal CA1 and CA3?

CA2 sends strong excitatory projections to dorsal CA1 (Chevaleyre and Siegelbaum, 2010) which preferentially innervate pyramidal neurons adjacent to the stratum oriens in the so-called deep sublayer (Kohara et al., 2014). In comparison to superficial pyramidal cells, deep cells differ in several aspects. Deep cells (1) fire at higher rates and burst more (Mizuseki et al., 2011), (2) are more likely to form place cells (Mizuseki et al., 2011), which are less stable (Danielson et al., 2016), (3) respond more to goals/reward (Danielson et al., 2016), are more tied to landmarks (Geiller et al., 2017), and (5) are differentially modulated by theta (Schomburg et al., 2014; Fernandez-Ruiz et al., 2017; Navas-Olive et al., 2020) and sharp-wave ripples (Stark et al., 2014; Valero et al., 2015; Mizuseki et al., 2011). How strong projections from CA2 affect animal behavior by modulating the activity of the functionally and physiologically distinct deep sublayer of dorsal CA1 remains to be elucidated (for a potential link to novel object recognition memory, see Section 7).

It is remarkable that silencing dorsal CA3 had no significant effect on social recognition (Chiang et al., 2018). CA3a pyramidal neurons are strikingly similar both physiologically and functionally to their CA2 counterparts. They have comparable morphology (Tamamaki et al., 1988), gene expression patterns (Lein et al., 2005; Ochiishi et al., 1999), extra-hippocampal inputs (Stanfield and Cowan, 1984) and place field properties (Lu et al., 2015). Further, the two subregions seem to form a densely connected recurrent core. CA2 heavily innervates dorsal CA3a (closest to CA2b) (Ishizuka et al., 1990; Tamamaki et al., 1988; Kohara et al., 2014; Mercer et al., 2007), CA2's own recurrent connections project preferentially towards CA2b (Okamoto and Ikegaya, 2019) and recurrent projections are abundant in CA3a (Li et al., 1994). The role of the strong interactions between CA2 and CA3a remain elusive.

Taken together, CA2's strong excitatory projections to dorsal CA1 and its recurrent interactions with dorsal CA3 do not seem to be associated with its role in social recognition memory. Instead, their existence indicates that CA2 is likely to be involved in other, yet to be discovered, facets of hippocampal computation.

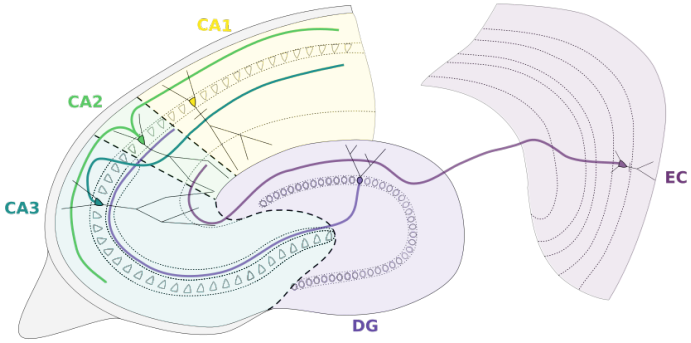


Figure 1: **CA2 is centrally located and well connected within the hippocampus.** CA2 receives strong direct excitatory input from CA3, the dentate gyrus (DG) and the entorhinal cortex (EC). Its main excitatory projections terminate in CA3 and CA1. Illustration of a coronal section through the dorsal rodent hippocampus and the neighbouring entorhinal cortex. Derived from NeuroSVG by Dr. Martin Pyka, used under CC BY 4.0

# 3 Novel and potentially salient content in the animal's local environment affects CA2 activity

Changes in close proximity to the animal induce strong responses in CA2, while modifying the global context has little impact. Using immediate early gene expression as a readout of neuronal activity, Wintzer et al. (2014) studied how CA2 population activity depends on small modifications of the environment. Introducing novel objects in an otherwise identical enclosure led to much bigger changes in the activity of CA2 ('global remapping') than in CA1 and CA3. This observation was further supported by single-unit recordings (Alexander et al., 2016). Curiously, introducing a familiar object did not result in remapping (Alexander et al., 2016). Further, global changes (e.g. the shape (Mankin et al., 2015) or the color (Lu et al., 2015) of the recording box) affected CA2 place fields to a lesser degree than CA3 or CA1. By rotating proximal cues in relation to distal landmarks, Lee et al. (2015) reported that CA2 place fields mainly maintain strong alignment to a local spatial reference frame.

Social interactions with both novel and familiar animals rearrange place maps in CA2, but not in CA1 (Alexander et al., 2016). In an experiment rats explored the same arena over four consecutive trials, with social interactions taking place in the second and third trials. Interestingly, not only introducing a familiar animal into an empty arena induced remapping (first vs second trial), but immediate re-exposure to the same animal also induced remapping (second vs third trial). When rats explored the empty arena after social exposure, the original place maps from before the social encounters were not re-expressed (first vs fourth trial). The effect on spatial maps was stronger than the small changes observed when animals were exposed to the same empty arena in four consecutive trials. It came as a surprise that encountering a familiar animal in a familiar arena had a lasting, but not repeatable, effect on CA2 activity. In contrast, in all cases rate maps in CA1 remained stable.

A unified explanation of the aforementioned experimental results is however still missing.

Based on the observation that CA2's spatial map gradually decorrelates upon repeated exposure to the same environment, Mankin et al. (2015) suggested that CA2 may provide a temporal code: The change in CA2's spatial map should correspond to the amount of time that has passed. However, this seems to be inconsistent with the strong remapping induced by local cues (Alexander et al., 2016). If CA2 remapping over time should be a temporal code, local cues would be able to speed up the clock.

Given that CA2 remaps to changes in the local environment, it has been suggested that downstream regions could use CA2 activity as a novelty signal (Wintzer et al., 2014; Middleton and McHugh, 2019). This is further supported by the observation that a large fraction of CA2 pyramidal cells increase their firing rate upon encountering a novel, but not a familiar, animal (Donegan et al., 2019). And CA2 receives projections from novelty-signalling regions. CA2-projecting neurons in the supramammillary nucleus increase their firing for both social and contextual novelty (Chen et al., 2020). Ventral tegmental area (VTA) preferentially innervates CA2, compared to CA3 and CA1. Though the projections are predominantly glutametergic and GABAergic (Han et al., 2020; Ntamati and Lüscher, 2016). While hypotheses exist regarding the role of novelty-related release of dopamine from VTA into hippocampus (Lisman and Grace, 2005; Duszkiewicz et al., 2019), the function of non-dopaminergic

VTA projections to CA2 awaits exploration.

It is also conceivable that CA2 activity reflects how important an experience was to an animal. For example, CA2 neurons fire in bursts in response to oxytocinergic input (Tirko et al., 2018), a hypothesized social salience signal (Shamay-Tsoory and Abu-Akel, 2016). Along the same lines, CA2 place cells remap during an encounter with a familiar animal (Alexander et al., 2016), a potentially salient but not novel experience. Further, CA2 firing is invariant to distant modifications e.g. a change of enclosure shape (Mankin et al., 2015) or the appearance of a familiar object without the possibility of direct interaction (Alexander et al., 2016), which most likely bear little saliency.

The aforementioned experiments suggest that CA2 is computing novelty or saliency, regardless of input modality or social relevance. Distinguishing between novelty and saliency in experimental design is particularly crucial if future studies should elucidate CA2's contribution.

# 4 Neuromodulation in CA2 could mediate more general saliency or novelty cues

A host of neuromodulatory systems converge on CA2 (for review, see Benoy et al., 2018). Neuromodulation can alter neuron excitability and modulate synaptic transmission by gating different types of synaptic plasticity. In the following we highlight the neurotransmitters acting in CA2 whose role reportedly or presumably goes beyond social recognition memory. We elucidate their effects on CA3-CA2 and EC-CA2 interactions and discuss potential roles in shaping the flow of information.

## Vasopressin

Vasopressinergic fibers have been found throughout the hippocampus. They originate primarily in the paraventricular and the supraoptic nucleus and extensively innervate the ventral hippocampus as well as dorsal CA2 (Zhang and Hernandez, 2013). Additional vasopressinergic projections to the ventral hippocampus arrive from the amygdala (Caffe et al., 1987). Beyond social memory, vasopressin injections into the hippocampus have been shown to increase memory retention during a passive avoidance task (Kovács et al., 1986). Correspondingly, injection of a vasopressin receptor antagonist impairs retention (Kovács et al., 1982). Further, hippocampal vasopressin injection increases cellular activity, measured by immediate-early gene expression, in all hippocampal subregions (Paban et al., 1999) and slows down theta rhythms (Urban, 1999).

To gain more directed insights into the role of CA2, we can look at the vasopressin receptor 1b (Avpr1b). Besides a weak expression in the paraventricular nucleus and the amygdala, Avpr1b is almost exclusively expressed in CA2 (Young et al., 2006). Therefore, learning deficits associated with disturbed Avpr1b signaling are likely associated with CA2. A global knockout of the Avpr1b impairs social motivation, social recognition memory and aggressive behavior (Wersinger et al., 2002, 2004, 2007, 2008; DeVito et al., 2009). Accordingly, blocking va-

sopressin signaling in the dorsal hippocampus impairs social recognition memory (van Wimersma Greidanus and Maigret, 1996), while exciting vasopressinergic projections to dorsal CA2 drastically extends memory duration (Smith et al., 2016). Beyond the effect on social memory, Avpr1b$^{-/-}$ mice were impaired on the *when* component of the *what-where-when* task and had difficulties associating an odor with an object presented with a temporal delay (DeVito et al., 2009). These results connect CA2 to hippocampal-dependent tasks with a social, temporal or sequential component (see Section 7: CA2's involvement in hippocampal-dependent learning and memory).

On the synaptic level, vasopressin increases feed forward excitation of CA3→CA2 synapses that were active during its release (Pagani et al., 2015). In contrast, cortical projections to CA2 are not affected by vasopressin release, unless they have been previously potentiated (Chafai et al., 2012). In the letter case, vasopressin transiently reduces the synaptic strength. Thus, at the circuit level a potential role for vasopressin could be to promote interactions between CA3 and CA2 while weakening cortical projections that relate to previous memory traces.

## Oxytocin

Oxytocinergic projections to the hippocampus originate from from the paraventricular and supraoptic nucleus (Buijs, 1978; Knobloch et al., 2012). Such fibers are prominent in all regions of the ventral hippocampus, dorsally they have only been found in CA2 (Knobloch et al., 2012). Correspondingly, the oxytocin receptor is expressed in all subregions (Yoshida et al., 2009), in the dorsal hippocampus prominently in CA2 and CA3a (Smith et al., 2016; Lin et al., 2017; Tirko et al., 2018).

While the role of hippocampal oxytocin signalling is firmly established in social recognition memory and stress reponses, there is only indirect evidence for other behaviours. Injection of oxytocin antiserum in ventral, but not dorsal (van Wimersma Greidanus and Maigret, 1996), as well as deletion of oxytocin receptors in dorsal CA2 and CA3a impaired social recognitiion memory (Raam et al., 2017; Lin and Hsu, 2018). Hippocampal microinjections of oxytocin after exposure to a predator scent reduced the risk for extreme stress responses and modified expression levels of glucocorticoid and mineralocorticoid receptors (Cohen et al., 2010).

Injection of oxytocin in the intracerebroventricular space reduced passive avoidance and decreased hippocampal theta peak frequency during REM sleep, with reverse effects of oxytocin antiserum (Bohus et al., 1978). A similar treatment also improved spatial learning in a radial maze, with no effect on anxiety, leading the authors to suggest a direct effect via the hippocampus (Tomizawa et al., 2003).

In-vitro studies showed that oxytocin signalling increases excitability, contributes to plasticity, and shapes spike timing in the hippocampus. Oxytocin receptor activation induces bursting behavior in CA2 pyramidal cells by depolarizing the resting membrane potential, effectively increasing the excitatory drive onto CA1 (Tirko et al., 2018). Comparable to vasopressin, oxytocin release leads to slowly developing long term potentiation at activated CA3→CA2 synapes (Pagani et al., 2015). Further, oxytocin receptor activation induced, while receptor deletion impaired long term potentiation at EC→CA2 synapses (Lin et al., 2018). On a network level, oxytocin receptor activation prominently reduced the occurrence of hippocampal wide sharp wave ripples, while at the same time

sharp-wave related precision of pyramidal spike timing increased (Maier et al., 2016).

In addition to its effect on pyramidal cells in CA2, oxytocin receptor activation depolarizes parvalbumin interneurons. A majority of parvalbumin positive interneurons in both CA1 and CA2 express oxytocin receptors (Tirko et al., 2018). In both regions, oxytocin receptor activation increases their excitability (Owen et al., 2013; Tirko et al., 2018). Because of its restrictive effects on burst duration and burst frequency in CA2 pyramidal neurons, increased excitability in interneurons is proposed to act as a balance mechanism (Tirko et al., 2018).

## Substance P

The supramammillary nucleus sends substance P expressing fibers specifically to CA3a and CA2 (Borhegyi and Leranth, 1997). To the best of our knowledge the behavioral conditions under which substance P is specifically released in the CA2-CA3a region are not yet known. Nevertheless, it has been established that activity in the supramammillary nucleus is driven by forced immobilization (Choi et al., 2012) and cold-exposure stress (Miyata et al., 1998) as well as anxiety (Silveira et al., 1993) and environmental novelty (Ito et al., 2009; Chen et al., 2020).

Like vasopressin, substance P release also increases feed-forward excitation of CA3 onto CA2. However, unlike vasopressin, substance P strengthens cortical synapses activated during the release (Dasgupta et al., 2017). Further, Dasgupta et al. (2017) showed that plasticity at cortical synapses is facilitated by substance P mediated potentiation of CA3 synapses, a mechanism called synaptic tagging and capture (Redondo and Morris, 2011). Weak tetanic stimulation of the EC→CA2 projection alone leads to rapid, but only transient potentiation. But if weak cortical stimulation occurs after substance P mediated potentiation of CA3 synapses, cortical synapses undergo long-term potentiation. Thus, substance P promotes both the interplay between CA3 and CA2, and it facilitates cortical projections that might reflect experiences during or after its release.

## Adenosine

Adenosine A1 receptors are expressed throughout the hippocampus, most strongly in CA2/CA3a (Ochiishi et al., 1999). Adenosine is released in an activity-dependent manner, accumulating in the hippocampus as a byproduct of ATP consumption (Wall and Dale, 2013). As hippocampal adenosine levels reach their peak, animals become less active and show more sleep-like behaviors (Huston et al., 1996).

Adenosine modulates hippocampus-dependent learning and memory, particularly during early memory consolidation and possibly memory encoding. Systemic administration of adenosine before or directly after training disrupts social recognition memory (Prediger and Takahashi, 2005) and other hippocampus-dependent memory (Normile and Barraco, 1991; Zarrindast and Shafaghi, 1994; Ohno and Watanabe, 1996). Adenosine receptor antagonist administered directly after training improves memory consolidation on hippocampal-dependent tasks (Angelucci et al., 2002; Kopf et al., 1999); however, when given before training may have a positive (Hauber and Bareiss, 2001) or no (Angelucci et al., 2002) effect, and when given three hours after training also shows no effect (Kopf et al., 1999). Interestingly, *in vitro* application of adenosine suppresses sharp wave ripples (Wu et al., 2009).

events important for memory consolidation. And CA2 ripples in the first two hours after a social encounter are crucial for later recall (Oliva et al., 2020).

At the circuit level, adenosine controls excitatory transmission in the hippocampus and its signalling is enhanced in CA2. Administration of an adenosine receptor agonist reduces the strength of excitatory transmission from DG→CA1 (Moore et al., 2003), CA3→CA1 (Moore et al., 2003; Muñoz and Solís, 2019) and CA3→CA2 (Muñoz and Solís, 2019; Caruana and Dudek, 2020). Adenosine receptors are particularly highly expressed in CA2 and CA3a subregions (Ochiishi et al., 1999) and antagonists induce much higher synaptic potentiation at CA3→CA2 synapses than at CA3→CA1 synapses (Simons et al., 2012; Muñoz and Solís, 2019). Muñoz and Solís (2019) showed that CA2's adenosine sensitivity stems from higher efficiency of the cAMP intracellular signalling cascade induced by postsynaptic A1R activation. Thus, excitatory synaptic transmission from CA3→CA2 is under adenosine's control.

It is conceivable that adenosine's effect on memory consolidation may stem from its modulation of CA2 ripple events and/or CA3→CA2 plasticity primarily during early consolidation. Stöber et al. (2020) proposed that potentiation of excitatory transmission between specific CA3 and CA2 subpopulations immediately after an experience is crucial in order to prioritize particularly important sequences of events for replay (see Section 8: A broader role for CA2). Indeed, by regulating CA3→CA2 potentiation, adenosine could gate this prioritization process, and by modulating ripple occurrence, adenosine is in a position to influence memory consolidation in general.

## Enkephalin

Enkephalin in the CA region has three different origins: Via mossy fibers from the DG, through projections of stellate cells in entorhinal cortex layer II or released from local interneurons targeting parvalbumin positive (PV) interneurons (Sar et al., 1978; Gall et al., 1981; Leroy et al., 2017; Blasco-Ibáñez et al., 1998; Fuentealba et al., 2008). The corresponding $\delta$-opioid receptor is strongly expressed in CA2 (Duka et al., 1981), mainly in parvalbumin-positive (PV) interneurons (Erbs et al., 2012; Stumm et al., 2004; Faget et al., 2012).

Enkephalin release induces inhibitory long term depression (iLTD) in CA2 and modifies information flow across the CA region. Because of strong feed-forward inhibition, even strong excitatory inputs from CA3 are not able to induce action potentials in CA2 pyramidal cells. However, release of $\delta$-opioid receptor agonists, mimicking enkephalin, persistently weakens this inhibition (Piskorowski and Chevaleyre, 2013), allowing excitatory transmission from CA3 to CA2 (Nasrallah et al., 2015). In consequence, increased activity of CA2 pyramidal cells provide additional excitatory input to deep pyramidal cells in CA1, effectively modifying CA3 to CA1 signal transmission (Nasrallah et al., 2019).

Enkephalin dependent iLTD can be induced by various stimulation protocols in *in-vitro* hippocampal slices without requiring the manual addition of enkephalin. iLTD can be robustly induced by stimulating excitatory CA3→CA2 projections with high- and low-frequency as well as theta burst stimulations (Piskorowski and Cheva-

leyre, 2013). Alternatively, iLTD can be also induced by the stimulation of cortical synapses, either with high-frequency stimulation (Nasrallah et al., 2016) or by precisely timing cortical and CA3 inputs, a process called input-timing dependent plasticity (Leroy et al., 2017). As a result of iLTD the amplitude of postsynaptic events in CA2 pyramidal cells upon upon CA3 inputs roughly doubles while cortical inputs are facilitated by around 30% (Leroy et al., 2017; Nasrallah et al., 2015, 2016). Notably, in the case of input-timing dependent plasticity, it has been shown that postsynaptic activity in CA2 pyramidal cells during induction is not required.

The diverse origins of enkephalin fibers and the plethora of ways to induce its release suggest that enkephalin signaling in CA2 is of general importance. However, while outside the hippocampus, enkephalin signalling is firmly associated with stress, anxiety and fear conditioning (reviewed by Henry et al., 2017), little is known about the behavioral conditions for enkephalin release in the CA region. To our knowledge, the functional relevance of enkephalin signalling in CA2 has only been directly shown for social recognition memory (Leroy et al., 2017). However, several indications exist that enkephalin in the CA region is also involved in stress responses. Immobilization stress leads to differential up/down-regulation of enkephalin subtypes (Li et al., 2018) and altered levels of enkephalin-degrading enzymes (Hernández et al., 2009). In the CA2/CA3a region specifically, immobilization stress reduces delta-opioid receptor phosphorylation in estrous females (Burstein et al., 2013).

In summary, enkephalin dependent long-term depression of feed-forward inhibition in CA2 is a potent regulator of information flow in the whole hippocampus. Despite scarce data about the behavioral relevance, we interpret from its easy induction that iLTD is commonly available and thus potentially relevant in a variety of yet unknown situations. From the theoretical side, it has been suggested that the iLTD induction via input-timing dependent plasticity may allow pyramidal cells to recognize sequential input patterns (Ponulak, 2009).

## Why the neuromodulatory cocktail?

Interestingly, vasopressin, oxytocin (Pagani et al., 2015), substance P (Dasgupta et al., 2017), adenosine A1 receptor antagonists (Simons et al., 2012), and enkephalin-dependent inhibitory long-term depression (Piskorowski and Chevaleyre, 2013) affect the excitatory drive from CA3 to CA2 in very similar ways. Net excitation increases slowly, before it peaks after around 20 to 30 minutes, approximately doubling the initial synaptic currents. The shared effects suggest the aforementioned neuromodulators provide complementary ways to overcome strong feed-forward inhibition, enabling excitatory signal transmission from CA3 to CA2 (Nasrallah et al., 2015). It thus seems a plausible interpretation that this mechanism is of general nature and, depending on the situation, induced by a different combination of neuromodulators.

A comparison of recent experimental insights suggests that the interaction of several neuromodulators is needed for optimal memory performance. Long term social recognition memory is completely abolished upon deleting oxytocin receptors (Raam et al., 2017; Lin et al., 2018), but only partly affected by knocking out the vasopressin receptor 1b (Wersinger et al., 2002) or blocking iLTD (Leroy et al., 2017). So why does social recognition memory depend on multiple neuromodulators if they all have a comparable effect on CA3-CA2 interactions? The answer is likely twofold. First, while oxytocin, vasopressin and substance P directly strengthen

excitatory projections, iLTD reduces feed-forward inhibition. Long-term potentiation of excitatory projections and iLTD thus likely sum up and allow powerful excitation from CA3 to CA2. Second, the mentioned neuromodulators differ strongly on their effect on the entorhinal input to CA2. While oxytocin, substance P and iLTD strengthen concurrently active synapses, vasopressin only weakens previously potentiated synapses. So it could be that the right cocktail is necessary to gate optimal information flow from the cortex to the hippocampus during consolidation or retrieval.

Beyond the neuromodulatory inputs described here, CA2 receives projections from acetylcholine-releasing medial septum/diagonal band of Broca, serotonin-releasing medial raphe nucleus (Hensler, 2006), as well as dopamine-releasing locus coeruleus and ventral tegmental area (Takeuchi et al., 2016), and also expresses receptors for these neuromodulators (Benoy et al., 2018; Dale et al., 2016; Robert et al., 2020; Khan et al., 2000; Yohn et al., 2017). Future research will surely elucidate how synaptic transmission and neural excitability under the control of converging neuromodulatory inputs contributes to the computations CA2 performs.

# 5 CA2 modulates place cells, spike timing, and communication across the hippocampus

Chronic as well as acute inhibition of CA2 affects cellular activity in both CA3 and CA1 (Boehringer et al., 2017). In animals with chronic inhibition of CA2 pyramidal neurons spatial specificity of CA3 and CA1 place cells is reduced and timing of CA3 spikes with respect to the theta oscillation phase is altered (Boehringer et al., 2017). Further, when these animals ran along a linear track, epileptiform-like hyper-excitability events occurred at certain locations. The events were characterized by a surge in the broadband LFP power across all CA regions. Before the onset of these highly synchronous LFP events, CA3 and CA1 pyramidal cells increased their firing rates. Similar events also occurred during rest and were accompanied by a reduction in sharp-wave ripple occurrence. Acute inhibition of CA2 did not lead to such pronounced hyper-excitability events, however, a coordinated shift in place field locations was observed. The concentration of firing increased at particular locations on the track resembling "hotspots" of activity. Cells that shifted their field towards a hotspot increased, while those shifting away decreased their firing rate.

*In vitro* experiments further revealed that chronic inhibition of CA2 neurons can reduce CA3 to CA1 transmission and enhance recurrent excitation in CA3. Experiments confirmed that CA2 activation induces strong feed-forward inhibition in CA3 (Chevaleyre and Siegelbaum, 2010; Nasrallah et al., 2015; Kohara et al., 2014). The CA2 induced feed-forward inhibition does not only affect the CA3 recurrent activity and communication between CA3 and CA1, it also controls information flow from the dentate gyrus to CA3 (Boehringer et al., 2017).

Further evidence for CA2's influence on information transfer within and beyond the hippocampus stems from the observation that CA2 activity directly affects low gamma oscillations (30 to 55 Hz). These oscillations have been suggested to facilitate communication from CA3 to CA1 (Colgin et al., 2009). By transiently increasing

or decreasing CA2 activity, Alexander et al. (2018) demonstrated that CA2 positively modulates low- but not high-gamma oscillations recorded in CA1 during an open-field experiment without local stimuli. Interestingly, increasing CA2 activity also led to increased low-gamma power in the prefrontal cortex and enhanced low-gamma band coherence between the hippocampus and the prefrontal cortex. Further experiments revealed that silencing CA2 neurons using a chemogenetic approach has different effects on low gamma and fast gamma: while low gamma was reduced only during interaction with the social stimuli, fast gamma was reduced during both social and object stimuli interactions (Brown et al., 2020).

In conclusion, CA2's profound effects on place fields, spike timing, excitability and oscillations provide compelling evidence that CA2 is a potent regulator of network activity within and beyond the hippocampus. As such, taking the CA2 out of the circuit not only leads to electrophysiological changes, but also to changes in non-social behavior (see Section 7). As yet, little is known as to how CA2 exerts these effects nor how this relates to hippocampal dependent memory processing. Boehringer et al. (2017) suggested that the increased spatial concentration of neuronal activity and spatially localized hyperexcitability during CA2 inactivation implies sparsity of CA3's network activity is under CA2's control. The rearrangement of CA3 place field locations indicates that for the same trajectory through space, different CA3 cell assemblies become active. In consequence, it is conceivable that CA2 activity may directly influence the sequence of activated cells that represent a given experience.

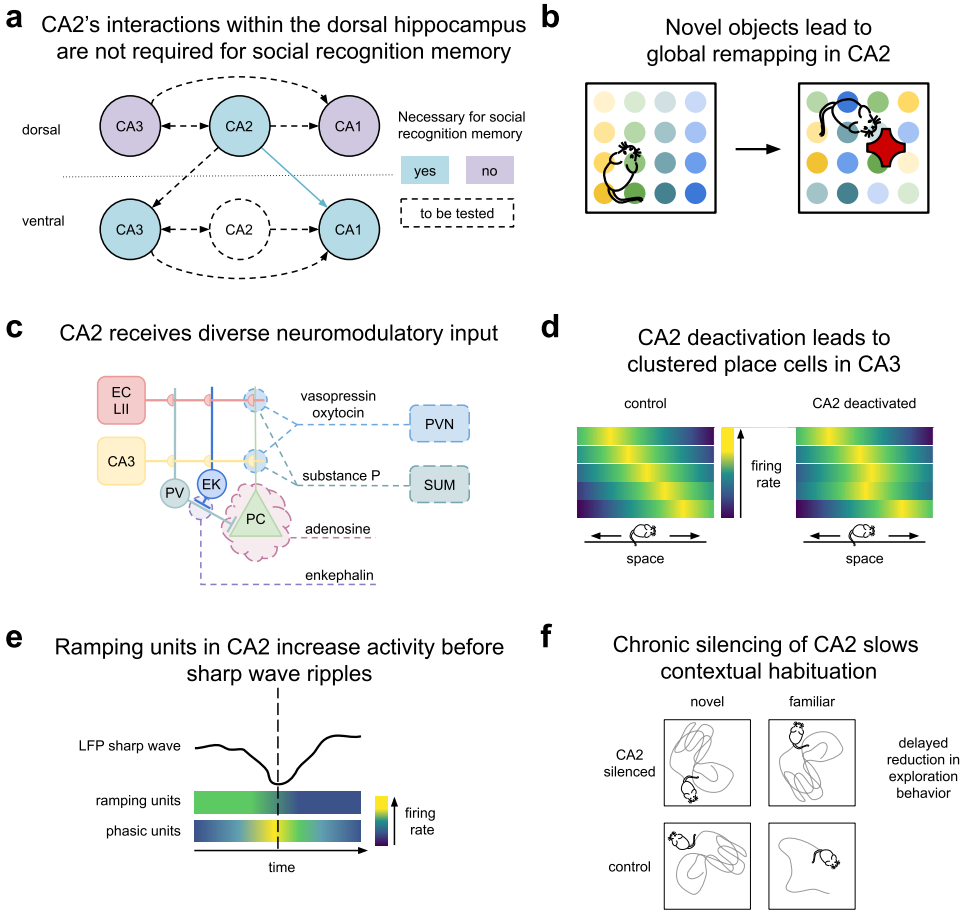


Figure 2: **A multitude of experimental observations advocate that CA2's role extends beyond social recognition memory.** **a)** CA2 sends strong excitatory projections to dorsal CA3 and CA1, both of which are not required for social recognition memory. The role of these projections remains elusive. **b)** The spatial map in CA2, represented by the colored dots, remaps when the animal encounters a novel inanimate object, red cross. **c)** Various neuromodulatory substances influence information transmission in CA2's excitatory, green triangle, and inhibitory neurons, round circles. Vasopressin, oxytocin and sustance P modify excitatory synapses from CA3 and EC LII, entorhinal cortex layer II, to pyramidal cells, PC. Adenosine receptors control excitatory transmission. Enkephalin-release by enkephalin-positive interneurons, EK, reduces feed-forward inhibition from parvalbumin-positive interneurons, PV. **d)** Transiently deactivating CA2 pyramidal cells leads to a spatial agglomeration of receptive fields in CA3 place cells. **e)** CA2 contains a large fraction of neurons that ramp up their firing before, and are suppressed during sharp wave ripples. **f)** Chronic silencing of CA2 delays contextual habituation as measured by the length of the motion trajectory, gray, in an open field.

# 6 CA2 influences hippocampal sharp wave ripples

Particularly compelling evidence supporting a more general role for hippocampal CA2 comes from its involvement in hippocampal sharp wave ripples (SWRs), highly synchronous oscillation patterns crucial for memory formation (Buzsáki, 2015). Early studies in guinea pigs had already established a link between CA2 and the initiation of so-called synchronized burst discharges (Wong and Traub, 1983; Miles et al., 1984; Wittner and Miles, 2007). Wong and Traub (1983) found that targeted application of potassium to a small patch of CA2 tissue sufficed to elicit these widespread and highly synchronous events.

Making use of implantable high-density electrodes, Oliva et al. (2016) studied the occurrence of ripple oscillations across all CA subregions in freely behaving animals. In contrast to the previous hypothesis that CA3 is the main generator of SWRs (Buzsáki, 2015), they found that local ripple oscillations can also emerge in CA2 before spreading to CA3 or CA1. Further they showed that a subset of CA2 pyramidal cells ramp up their activity immediately preceding sharp wave ripples. They hypothesized that these so-called *ramping units* may initiate SWRs. Likely representing the same subset, a separate study reported so-called *N units* that fired preferentially in certain states of immobility, such as awake rest and certain parts of non-REM sleep (Kay et al., 2016). SWRs occur frequently during these states (Buzsáki et al., 1983). Similarly to ramping units, N units decrease their activity during SWRs (Kay et al., 2016).

To directly test CA2's influence on SWRs, two recent studies selectively manipulated CA2 activity in behaving animals. Alexander et al. (2018) used a chemogenetic approach to manipulate CA2 pyramidal cells. Activating CA2 reduced and silencing CA2 increased SWR occurrence in CA1 30 to 60 minutes later. In contrast, repeated brief optogenetic silencing of CA2 pyramidal cells instead decreased ripple occurrence in CA1 (Oliva et al., 2020). A potential explanation for these diverging results is that longer periods of CA2 silencing may disinhibit CA3, which may then initiate more ripples (Oliva et al., 2016; Boehringer et al., 2017; Alexander et al., 2018; Oliva et al., 2020).

Further, Oliva et al. (2020) combined targeted SWR manipulation with a social recognition memory task to demonstrate that SWR events initiated in CA2 are important for non-spatial memory processing. Targeting CA2, they show that closed-loop interruption of SWR abolished social recognition memory, while artificial induction of ripples prolonged it. Artificial ripple induction in CA3 had no significant effect. It is important to note that while CA2 is involved in sharp wave ripples supporting social memory (Oliva et al., 2020), there is no evidence to suggest CA2 influences sharp wave ripples pertaining *only* to social memory. Further studies extending this protocol to other behavioral assays will reveal to which extent this effect may generalise.

While CA2's involvement in hippocampal SWR and related memory consolidation has been established, its computational role is not yet understood. Because of CA2's strong influence on CA3 and the presence of SWRs in CA1 despite silencing CA2, Boehringer et al. (2017) and Alexander et al. (2018) argued that SWRs are not generally initiated in CA2 (Oliva et al., 2016), but instead may sculpt CA3 output to CA1. In particular N units/ramping cells in CA2 are proposed to selectively bias which experience will become reactivated during an upcoming ripple

event (Middleton and McHugh, 2019; Stöber et al., 2020), with CA2 shifting hippocampal replay to more readily re-express salient experiences (Stöber et al., 2020). A first test of this hypothesis would simply require assessing whether patterns of activity in CA2 preceding a SWR can predict which assemblies are replayed.

# 7 CA2's involvement in hippocampal-dependent learning and memory

If CA2's role in hippocampal information processing extends beyond social memory, there should be measurable effects of CA2 manipulations on behaviour in hippocampal-dependent memory tasks. While so far data remain scarce, CA2 is indeed recruited, especially in tasks with a temporal/sequential component.

Studies selectively manipulating CA2 activity have identified subtle behavioral changes. Mice with inactivated CA2 pyramidal cells do not differ from controls in their locomotor activity, anxiety-like behavior, hippocampal-dependent contextual fear memory, or amygdala-dependent auditory fear memory (Hitti and Siegelbaum, 2014). However when CA2 pyramidal cells are chronically silenced, animals habituate to a novel context more slowly (Boehringer et al., 2017). Transiently activating CA2 pyramidal cells increases freezing in both cue and contextual (only females) fear conditioning (Alexander et al., 2019). While not CA2 specific, optogenetically silencing CA2 and CA3a projections to dorsal CA1 abolishes novel object recognition (Raam et al., 2017). In the Morris water maze, a task with complex cognitive demands that requires flexible representations, CA2 also seems to be recruited. A trend towards slower learning and in particular slower relearning of a hidden platform location in CA2-silenced mice suggests a potential impairment in more elaborate hippocampal-dependent spatial learning and perhaps in deviating from previous navigational sequences (Hitti and Siegelbaum, 2014).

Further behavioral effects have been demonstrated by selectively disrupting the vasopressin receptor, Avpr1b, which presumably selectively affects CA2 within the hippocampus (see Vasopressin). Avpr1b KOs show specific deficits in two memory tasks (DeVito et al., 2009), both of which are known to be hippocampus dependent (Kesner et al., 2005; DeVito and Eichenbaum, 2010). In the *what-where-when* memory task Avpr1b$^{-/-}$ mice were not able to distinguish the temporal order of objects presented in the same spatial location. In the *object-trace-odor* task animals were trained to associate an object with an odor presented after a delay of 10 seconds. In the training phase, Avpr1b$^{-/-}$ mice were able to learn the association between two object-odor pairs, but showed slower task acquisition. In the second phase, animals explored one of the objects and after the delay both odors were presented in the test box simultaneously. When faced with this choice, Avpr1b$^{-/-}$ mice completely failed to discriminate and even performed significantly below chance level. These results suggest that at the behavioral level, Avpr1b receptor expression in CA2 is involved in hippocampal-dependent memory with a temporal or sequential component.

Plasticity within CA2 has also been implicated in non-social hippocampal-dependent memory. Unlocking plasticity on CA3→CA2 excitatory projections by preventing the expression of plasticity-limiting factor RGS14 leads to enhanced object recognition memory and spatial learning in the water maze (Lee et al., 2010). As control, it was shown that RGS14 knock out mice performed normally on nonhippocampal-dependent behavioral tests.

Another link between plasticity and behavior in more complex environments stems from the observation that environmental enrichment leads to more extracellular matrix around pyramidal cells in CA2 (Carstens et al., 2016). Such structures, also called perineuronal nets, have been shown to block excitatory plasticity of CA3→CA2 during early postnatal development (Carstens et al., 2016) and to underlie inhibitory long term depression in late-adolesent and adult animals (Domínguez et al., 2019). Taken together, CA2 plasticity can affect behavior and behavior can affect CA2 plasticity.

While a clear pattern in the behavioral results is yet to emerge, one interpretation is that CA2 is involved in demanding hippocampal dependent tasks. Given the effects on more onerous spatial (Hitti and Siegelbaum, 2014; Lee et al., 2010) and non-spatial learning (DeVito et al., 2009) with a temporal or sequential component, future studies may aim to assess CA2 recruitment in complex episodic-like memory tasks.

# 8 A broader role for CA2

Experimental evidence indicating a role for CA2 beyond social memory is accumulating. However the nature of this broader role remains to be elucidated. What we do know is that CA2 integrates inputs from across the hippocampus and has strong influence over hippocampal network dynamics. Importantly this holds true for CA2's interactions with dorsal CA1 and CA3, regions not required for social recognition memory. However unlike neighbouring dorsal CA1 and CA3, it seems that CA2 responds more strongly to events, both social and non-social, in the animal's immediate environment. Moreover CA2 is a hub for neuromodulatory influence on the hippocampus and this neuromodulation unlocks plasticity at otherwise rigid CA3-CA2 synapses. Manipulations of CA2 affect CA1 and CA3 place cells, CA3 spike timing, as well as communication within the hippocampus and between the hippocampus and prefrontal cortex. In accordance with its role in hippocampal wide communication, CA2 plays an intricate role in hippocampal sharp wave ripples, which support the formation of episodic memory.

But what computational role may CA2 play? Here we summarize existing proposals for CA2's general contribution to memory processing These proposals can be grouped based on the emphasized circuit interactions (compare Fig. 3). The majority of recent proposals emphasizes CA2 and CA3 as parallel circuits. In our opinion, the existence of direct excitatory projections between pyramidal cells in CA2 and CA3 and the presumable importance of their neuromodulation suggests that CA3 and CA2 do more than inhibit one another.

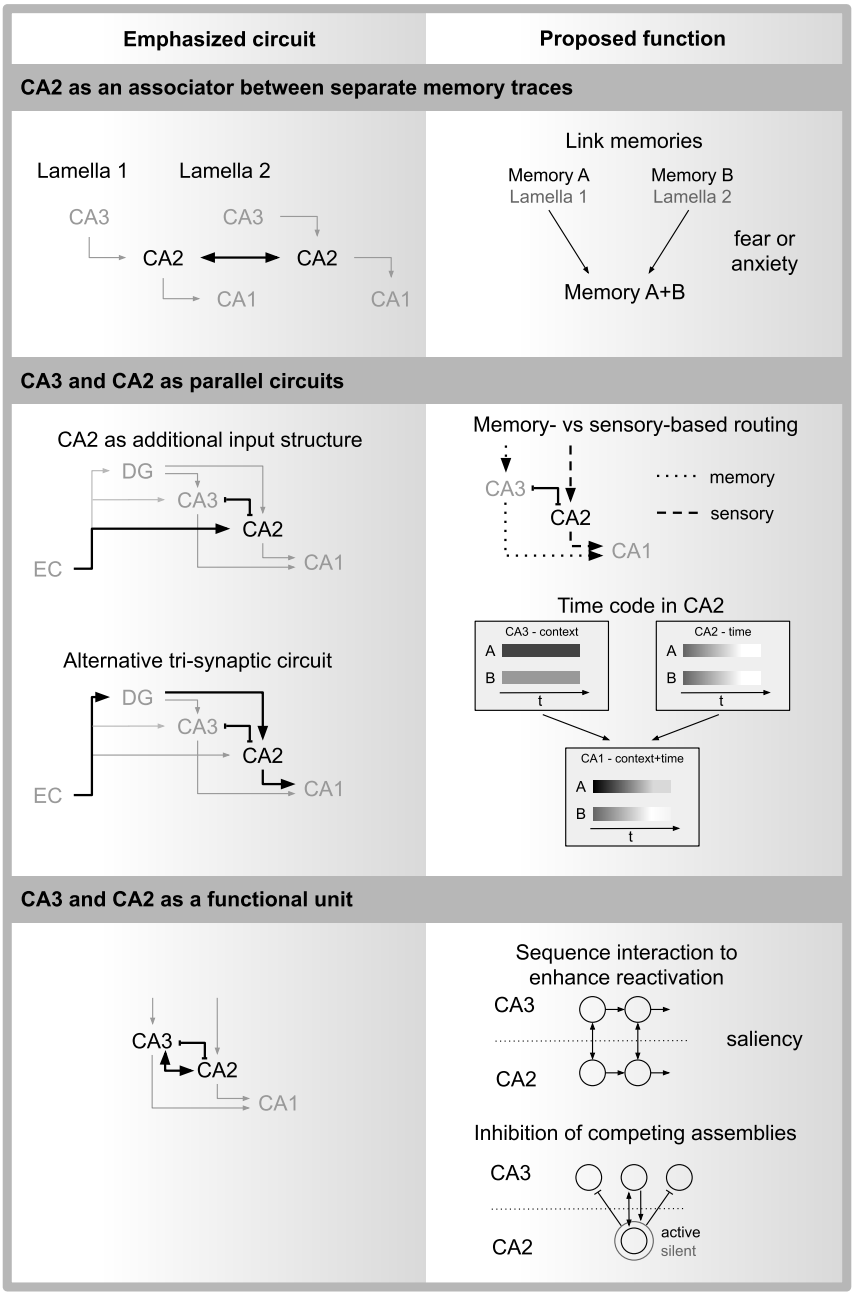


Figure 3: **Existing proposals for CA2's role in hippocampal memory processing.**

## 8.1 CA2 as an associator between separate memory traces

In a pioneering proposal it has been suggested that CA2 may act as an associator between simultaneously encoded memory traces across different hippocampal lamellae (Sekino and Shirao, 2006). This function is believed to depend on the supramammillary nucleus, activated by salient emotional states like fear and anxiety. Further, it is assumed that the contribution of CA2 is only possible during low adenosine levels, leading the authors to speculate that the CA2 mediated association may function only when the animal is awake.

While it remains unclear whether hippocampal lamellae with separate memory traces exist in the first place (Sloviter and Lømo, 2012), the proposal could be similarly transferred to the critical role of CA2 in bridging between dorsal and ventral hippocampus (Meira et al., 2018). In addition, the proposal anticipated a wealth of experimental findings linking the activity of CA2 to potentially salient experiences (see Section 4).

## 8.2 CA3 and CA2 as parallel circuits

**CA2 as a additional input structure.** Chevaleyre and Siegelbaum (2010) found that CA2 connects the entorhinal cortex to CA1 via a powerful disynaptic pathway: EC $\rightarrow$ CA2 $\rightarrow$ CA1. Feed-forward inhibition from CA3 to CA2 is suggested to ensure separation between the di- and the classical trisynaptic pathway: EC $\rightarrow$ DG $\rightarrow$ CA3 $\rightarrow$ CA1. Kohara et al. (2014) added that excitatory projections from CA2 to CA3 induce dominating inhibition and proposed that the two regions compete to route the flow of information through the hippocampus.

**The alternative trisynaptic pathway.** Dentate gyrus mossy fibers taper into CA2 (Gaarskjaer, 1986; Lein et al., 2005; Mercer et al., 2007) and provide direct excitatory input to CA2 pyramidal cells (Kohara et al., 2014). Thus, besides the disynaptic pathway, CA2 participates in an alternative trisynaptic pathway from EC $\rightarrow$ DG $\rightarrow$ CA2 $\rightarrow$ CA1 (Kohara et al., 2014), leaving out CA3. Interestingly, mossy fibers arriving in dorsal CA2 bend and longitudinally extend in the direction of the ventral hippocampus.

Further experiments led to the discovery that dorsal CA2 and in particular the dCA2 $\rightarrow$ vCA1 $\rightarrow$ NAc circuit are crucial for social recognition memory (Hitti and Siegelbaum, 2014; Okuyama et al., 2016; Okuyama, 2018; Meira et al., 2018). Given that EC $\rightarrow$ DG projections are also indispensable for social memory (Leung et al., 2018) it is tempting to hypothesize that the EC $\rightarrow$ DG pathway also recruits the dCA2 $\rightarrow$ vCA1 $\rightarrow$ NAc circuit, with CA2 bridging the gap between the dorsal dentate gyrus and ventral CA1. These results suggest that the dCA2 $\rightarrow$ vCA1 $\rightarrow$ NAc pathway and perhaps the alternative trisynaptic circuit support the learning and remembering of socially relevant information. However the interpretation that parallel trisynaptic circuits compete via mutual inhibition between CA2-CA3 leaves some questions unanswered. For example, if the two trisynaptic pathways are carrying complementary information then why should they compete via mutual inhibition instead of integrating their information in downstream CA1?

**Competition between memory and sensory based representations** Perhaps CA2 and CA3 mutually inhibit one another because they perform complementary but mutually exclusive tasks. For example it has been suggested that CA3 may convey information from memory and CA2 may transmit sensory based information on to CA1 (Wintzer et al., 2014; Middleton and McHugh, 2019). Middleton and McHugh (2019) consider whether CA2's increased firing rates and involvement in sharp wave ripples during the awake state may indicate a tendency towards CA2 driven sensory-based representations while awake versus CA3 driven memory-based representations during sleep. This switch may be modulated by adenosine, building up during neuronal activity and shutting CA2 down in subsequent sleep (as suggested by Sekino and Shirao, 2006), allowing CA3 to control sleep-based replay content (Middleton and McHugh, 2019). In accordance with the hypothesis that CA2 and CA3 inhibit one another to perform complementary but functionally disjunct tasks, this proposal provides mutually exclusive state-dependent roles for CA2 and CA3. It is worth noting, however, that the hippocampus likely needs to quickly and flexibly switch back and forth between sensory based and memory based processing. It is conceivable that an interplay between neuromodulators that up- and down-regulate the level of excitation in CA2 (e.g. oxytocin, acetylcholine vs adenosine) could facilitate such rapid switching. At the same time, if CA2 and CA3 were occupying these roles one would expect large fluctuations in firing rates as one region becomes active in turn inhibiting the other. And silencing CA2 or CA3 should then have differential effects on sensory or memory based processing.

**Complementary circuits for space and time** Another hypothesis is that complementary information from CA2 and CA3 is instead integrated in CA1. Mankin et al. (2015) proposed that CA2 codes for time and CA3 for spatial context and that these inputs converge on CA1 resulting in a spatio-temporal code. However this interpretation seems unlikely, considering potential disturbances of the temporal coding in CA2 by strong modifications of the spatial map upon encountering animals or novel objects (Alexander et al., 2016), as outlined in Section 3. Thus it remains unclear whether variability in CA2 place cell firing over time is a coding scheme or a byproduct of another process.

## 8.3 CA3 and CA2 as a functional unit

The mentioned proposals for a functional role of CA2 do not account for the following three key properties of the CA3-CA2 system: 1) bidirectional excitatory interactions between pyramdial cells of both regions, 2) limited plasticity of excitatory CA3→CA2 projections, and 3) the presumable importance of both increasing excitation and decreasing feed-forward inhibition of CA3→CA2 projections mediated by neuromodulation. While the contribution of reciprocal excitatory projections to memory formation has not been directly tested yet, several experiments suggest that their modulation is crucial for memory processing (refer to Section 4).

Dominating global inhibition does not preclude cooperation. One understandable motivation behind the parallel circuit and competition proposals is that interactions between CA3 and CA2 are mutually dominated by feed-forward inhibition. However, the observation of dominating inhibition has been the consequence of simultaneously activating a whole fiber bundle targeting the other region (Kohara et al., 2014; Chevaleyre and Siegelbaum,

2010). It remains to be tested whether inhibition surpasses excitation in all target cells if only individual neurons are activated. It would not come as a surprise if pyramidal cells have an inhomogenous projection pattern, leading to net-inhibition in most, but exciting a few pyramidal cells in the other region. But even if feed-forward inhibition were to dominate excitatory projections, it can be overcome. Enkepahlin-mediated long-term depression of inhibition has been shown to enable direct excitatory transmission between pyramidal cells in CA3 and CA2 (Nasrallah et al., 2015, 2019). Thus, the functional role of direct excitatory projections, accompanied by strong feed-forward inhibition and limited plasticity, deserves exploration.

**Prioritization of important experiences for replay** Together, the hardware described above may support a unique function in the CA3-CA2 recurrent system. Stöber et al. (2020) propose that excitatory and inhibitory interactions between CA2 and CA3 enable prioritized reactivation during consolidation. They outline how neuromodulator release during an important experience can lead to increased excitation between co-active groups of pyramidal neurons in the two regions. Increased activity of linked cell assemblies is expected to recruit more inhibition on competing assemblies thereby suppressing their reactivation. Taken together, bidirectional interactions between CA2 and CA3 may boost the reactivation of selected assembly sequences.

Further, Stöber et al. (2020) attribute a role to the observation that iLTD-mediated input timing dependent plasticity does not require postsynaptic activation (Leroy et al., 2017). If a CA2 neuron receives precisely timed CA3 and EC input, then feed-forward inhibition from CA3 onto this neuron is weakened. This is true regardless whether these inputs led to spiking activity or not. On future presentation of the same CA3 input pattern this CA2 cell will be more excitable, adding further global inhibition onto CA3. From all cells that received matching EC and CA3 input, some will have spiked. This activity may allow them to potentiate their excitatory projections to co-active CA3 neurons and thus pinch through the layer of global inhibition. Thus, input timing dependent plasticity may raise the threshold over which only paired CA2-CA3 assemblies interact, ensuring sparse activity patterns.

The suggestion that CA2 selects activity sequences corresponding to important experiences and prioritizes them for replay makes use of well described physiological properties as building blocks for a general computational role. It remains to be seen whether bidirectional excitatory interactions, limited plasticity of excitatory CA3→CA2 projections, and neuromodulatory influence over excitation and feed-forward inhibition can indeed fulfill the functions proposed by Stöber et al. (2020).

# 9 Outlook

It is becoming increasingly clear that CA2 is well positioned to broadly influence hippocampal dynamics, indicating that it plays a fundamental role in hippocampal computation. In particular, there is evidence for CA2's involvement in the following network level functions: (a) generating low gamma oscillations and modulating communication from CA3→CA1 as well as between hippocampus and prefrontal cortex, (b) influencing CA1 and

CA3 place cells as well as CA3 spike timing, (c) and modulating hippocampal sharp wave ripple occurrence and replay content. It seems unlikely that these effects are exclusively confined to social interactions.

However as yet a clear picture of the functional implications of CA2's control on hippocampal network dynamics remains elusive. Habituation to novelty (Boehringer et al., 2017), learning temporal sequences (DeVito et al., 2009), and flexible deviation from past learned behaviors (e.g. relearning on water maze, Hitti and Siegelbaum, 2014) seem to depend on CA2. And CA2 activity correlates with novel (Donegan et al., 2019; Alexander et al., 2016; Wintzer et al., 2014) and salient (Alexander et al., 2016; Tirko et al., 2018) events in an animal's local environment. Such events are commonly associated with neuromodulatory release. Accordingly, CA2 receives and is strongly influenced by a variety of neuromodulatory inputs, affecting information flow from EC and CA3 and relevant for a variety of learned behaviors.

Connecting CA2's fundamental network level effects with neuromodulator release and behavior remains a challenge for future research. Specialized and restricted plasticity at CA3→CA2 synapses under the control of a myriad of neuromodulatory systems indicates that CA2 may detect the saliency or novelty of an experience and rewire accordingly. Given that CA3→CA2 excitatory projections are sensitive to neuromodulation and both regions clearly play a role in sharp wave ripple generation, it would be logical to hypothesize that neuromodulator-induced changes in CA2-CA3 interactions allow saliency/novelty information to influence sharp wave ripple occurrence and potentially even content. It is conceivable that CA2's modulation of intrahippocampal and hippocampal-cortical communication gate which content passes through the hippocampus and back into cortex during memory consolidation. A definitive answer to these questions would narrow the scope of the search for CA2's functional role in the hippocampal circuit.

Key questions to be addressed experimentally

We expect that the following lines of research will be particularly beneficial to unravel the functional role of hippocampal region CA2.

- Several basic questions remain on the level of cell physiology, such as whether projections within CA2 and from CA2 to CA3 are plastic, how do neuromodulatory substances interact when co-released, and are N and P units a consequence of physiological heterogeneity in pyramidal cells?
- CA2's proposed functional roles (Middleton and McHugh, 2019; Nasrallah et al., 2019; Stöber et al., 2020) may be tested in more complex behavioral paradigms enabled by recent advances in wireless, long term recordings of neuronal activity (Barbera et al., 2019) as well as the automated, fine-grained analysis of animal behavior (von Ziegler et al., 2020).
- Release of the various neuromodulatory substances need to be characterized in naturalistic behaviors, for example by optical imaging of neuromodulation (Ravotto et al., 2020).
- The functional contribution of several key projections to and from CA2 are yet to be characterized. In the dorsal hippocampus, these are input projections from DG, CA3 and medial entorhinal cortex, as well as output projections to CA3 and CA1. The cell specificity of CA2-CA3 feed-forward inhibition still needs to be determined: Is this inhibition patchy and thus allows targeted interaction between cell assemblies, or does inhibition act on all cells with similar strength, speaking rather for global inhibition between CA3 and CA2?

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Paper II

# Selective neuromodulation and mutual inhibition within the CA3–CA2 system can prioritize sequences for replay

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WILEY

COMMENTARY

# Selective neuromodulation and mutual inhibition within the CA3–CA2 system can prioritize sequences for replay

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## Abstract

To make optimal use of previous experiences, important neural activity sequences must be prioritized during hippocampal replay. Integrating insights about the interplay between CA3 and CA2, we propose a conceptual framework that allows the two regions to control which sequences are reactivated. We suggest that neuromodulatory-gated plasticity and mutual inhibition enable discrete assembly sequences in both regions to support each other while suppressing competing sequences. This perspective provides a coherent interpretation for a variety of seemingly disconnected functional properties of CA2 and paves the way for a more general understanding of CA2.

**KEYWORDS**

CA2, CA3, consolidation, hippocampus, sequence prioritization

## 1 | INTRODUCTION

To understand the crucial role of the hippocampus for episodic memory, most research has focused on the dentate gyrus (DG) as well as on cornu ammonis subfields 1 and 3 (CA1/CA3). For the most part,

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hippocampal region CA2 has been considered a transition zone and ignored in the conceptual understanding of the hippocampus. However, in recent years hippocampal region CA2 has received increased attention. Several experimental studies established that CA2 and its distinct neuromodulation are crucial for social recognition memory (DeVito et al., 2009; Meira et al., 2018; Okuyama, Kitamura, Roy, Itohara, & Tonegawa, 2016; Smith, Avram, Cymerblit-Sabba, Song, & Young, 2016; Stevenson & Caldwell, 2014; Wersinger et al., 2004; Wersinger, Caldwell, Christiansen, & Young, 2007; Wersinger, Ginns, O'carroll, Lolait, & Young Iii, 2002; Wersinger, Temple, Caldwell, & Young 3rd, 2008; Young, Li, Wersinger, & Palkovits, 2006). Moreover, experimental data suggest that CA2 plays an important role in several nonsocial behaviors and in controlling hippocampal network dynamics. For example, it appears that CA2 may be involved in temporal sequence memory (DeVito et al., 2009), sharp wave ripples (Alexander et al., 2018; Oliva, Fernández-Ruiz, Buzsáki, & Berényi, 2016a), CA3 spike timing and place field arrangement (Boehringer et al., 2017), as well as generation of low-gamma oscillations and low-gamma coherence between hippocampus and prefrontal cortex (Alexander et al., 2018). From influencing network dynamics to supporting learning and memory, CA2's role appears diverse. How can we understand such diverse functions of an otherwise small subregion of the hippocampus?

To elucidate CA2's functional role we need to understand the computations it can potentially perform. Such an approach has a long history when studying the function of hippocampal subregions. Based on David Marr's "from-structure-to-function" approach, it has been suggested that CA3 may act as an auto-associative memory unit (Marr, 1971; Papp, Witter, & Treves, 2007; Rolls, Treves, & Rolls, 1998). Similarly, the DG, at a computational level, is considered a pattern separator (Gluck & Rumelhart, 1990; Leutgeb, Leutgeb, Moser, & Moser, 2007; Treves & Rolls, 1992). Despite their simplicity, such abstractions of CA3 and DG have provided a powerful conceptual framework to design new experiments exploring the functions of the hippocampus. In this article, we synthesize experimental data about the network architecture and synaptic plasticity in CA2. We propose that at the computational level, CA2 interacts with CA3 to prioritize selected neuronal activity sequences for replay based on contextual and behavioral states. This computational abstraction helps us understand how CA2 can have an important role in a multitude of behaviors beyond social memory. Finally, based on this framework we propose new experiments that can expose the contribution of CA2 in prioritizing neuronal activity sequences.

## 2 | INPUT AND RECURRENT CONNECTIVITY OF CA2

In order to elucidate CA2's function it is helpful to zoom out and look at its position within the hippocampus (see Figure 1, upper left panel). CA2 receives direct excitatory input from CA3 (Li, Somogyi, Ylinen, &

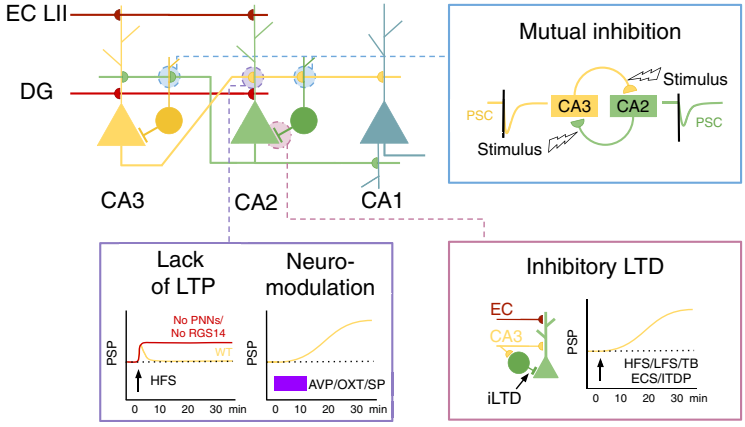


**FIGURE 1** Interactions between CA3 and CA2 are characterized by mutual inhibition and restricted plasticity. *Wiring diagram, upper left*: In contrast to hippocampal region CA1, pyramidal cells in CA3 and CA2 receive input from entorhinal cortex layer II (ECL II) and the dentate gyrus (DG). *Upper right box*: Interactions between both regions are strongly dominated by feed-forward inhibition. Activating excitatory projections between CA3 and CA2 leads to a predominantly inhibitory response in the other region. Postsynaptic current (PSC). *Lower left box*: Excitatory projections from CA3 to CA2 are characterized by a lack of activity-induced long-term potentiation (yellow line). Long-term potentiation can be artificially unlocked by selectively blocking the expression of CA2 specific receptors like RGS14 or the removal of perineuronal nets, PNNs (red line). Alternatively, the release of the neuromodulators vasopressin, oxytocin or substance P leads to potentiation of exitatory projections (yellow line). Postsynaptic potential (PSP). *Lower right box*: Further, excitatory drive from CA3 to CA2 can be increased by reducing feed-forward inhibition via inhibitory long term depression (iLTD). iLTD can be induced by stimulating CA3 inputs with high (HFS), low frequency stimulation (LFS) or theta bursts (TB). Further, stimulating EC inputs (ECS) or precise timing of EC and CA3 inputs (ITDP), also leads to iLTD. In consequence the relative strength of feed-forward excitation from CA3 to CA2 increases. *Note*: Both potentiation of excitation and iLTD unfold slowly, peak after around 30 minutes and result in roughly a doubling of the postsynaptic potential [Color figure can be viewed at wileyonlinelibrary.com]

Buzsaki, 1994), the DG (Kohara et al., 2014) and entorhinal cortex Layer II (Bartesaghi & Gessi, 2004; Chevaleyre & Siegelbaum, 2010; Kohara et al., 2014). Like CA3, axons of CA2 pyramidal cells widely project along the proximodistal (subdivided into CA1, CA2, and CA3a/b/c) as well as the septotemporal axes. CA2 axons arborize within all CA regions (Li et al., 1994; Tamamaki, Abe, & Nojyo, 1988), with some reaching into the DG (Ishizuka, Weber, & Amaral, 1990). Pyramidal cells in dorsal CA2 have been shown to directly project to the ventral hippocampus (Meira et al., 2018; Okuyama, 2018; Tamamaki et al., 1988). Thus despite its small size, CA2 can integrate information from and exert influence over a large portion of the hippocampus.

Pyramidal cells in CA2 are recurrently connected. Within CA2, monosynaptic excitatory connections occur with a probability of around 1.4%; seven identified connections in 502 tested pyramidal cell pairs (Okamoto & Ikegaya, 2019). Recurrent excitatory connection probability in CA3 is 0.92% (Guzman, Schlögl, Frotscher, & Jonas, 2016) and in CA1 0.6% (Deuchars & Thomson, 1996). Thus, experimental data suggest that recurrent excitatory connectivity in CA2 is more similar to CA3 (1.4 vs. 0.92%) than CA1 (1.4 vs. 0.6%). Interestingly, recurrent connections between pyramdidal cells inside CA2 appear to be spatially biased. Six out of the seven confirmed recurrent projections were oriented towards CA3 (Okamoto & Ikegaya, 2019).

Zooming in along the proximodistal axis, it appears that CA2 and CA3a form a bidirectionally coupled network. Ishizuka et al. (1990) observed that axons of CA3 pyramidal cells branch more extensively in CA3a/b compared to CA3c. CA2 pyramidal cells project mostly to CA3a (Ishizuka et al., 1990; Tamamaki et al., 1988). In contrast to projections from CA3 to CA2, back-projections from CA2 to CA3 are thinner and sparser (Ishizuka et al., 1990). Further, the recurrent interactions between CA3 and CA2 are strictly controlled by high levels of feed-forward inhibition (Chevaleyre & Siegelbaum, 2010; Kohara et al., 2014) and limited plasticity (Zhao, Choi, Obrietan, & Dudek, 2007). Therefore, recurrent inhibition between CA2 and CA3 prohibit most spike propagation unless feed-forward excitation is either potentiated or inhibition reduced (Nasrallah et al., 2019; Nasrallah, Piskorowski, & Chevaleyre, 2015).

## 3 | NEUROMODULATION AND SYNAPTIC PLASTICITY IN CA2

Excitatory projections from CA3 to CA2 do not express classical long-term potentiation (LTP; Zhao et al., 2007). This is due to strong calcium buffering (Simons, Escobedo, Yasuda, & Dudek, 2009), plasticity limiting signalling pathways (Lee et al., 2010; Simons, Caruana, Zhao, & Dudek, 2012), and dense perineuronal nets (Carstens, Phillips, Pozzo-Miller, Weinberg, & Dudek, 2016, but see Domínguez et al., 2019). Various neuromodulatory inputs specifically converge on CA2 and modulate strictly controlled net excitation from CA3 (see Figure 1, lower two panels, for more details see Benoy, Dasgupta, and Sajikumar (2018)). It has been shown that plasticity of CA3 excitatory feed-forward projections can be unlocked by the release of vasopressin, oxytocin and substance P in combination with synaptic activity (Dasgupta et al., 2017; Pagani et al., 2015). In turn, net excitation from CA3 to CA2 can also be increased by long term depression of feed-forward inhibition (iLTD) (Piskorowski & Chevaleyre, 2013; Nasrallah et al., 2015, 2019; Nasrallah, Piskorowski, & Chevaleyre, 2016). iLTD is mediated by enkephalin, which acts via delta-opioid receptors (Piskorowski & Chevaleyre, 2013). Multiple stimulation protocols at proximal (CA3) inputs allow iLTD induction, such as theta bursts and low or high frequency stimulation (Piskorowski & Chevaleyre, 2013). Further, iLTD can be induced by stimulating distal (cortical) inputs (Nasrallah et al., 2016) or by precisely timing distal and proximal inputs, called input-timing-dependent plasticity (ITDP) (Leroy, Brann, Meira, & Siegelbaum, 2017). Interestingly, plasticity induced by vasopressin, oxytocin, substance P, and enkephalin share similar dynamics. Net excitation increases slowly and peaks after around 30 minutes, roughly doubling the excitatory drive. [Correction added on 7 September, 2020, after first online publication: the duration in the previous sentence was changed from 20 to 30 minutes.]

While we have direct experimental evidence for plasticity inside CA3, we can only make assumptions about plasticity at projections from CA2 to CA3 and within CA2. Inside CA3, excitatory synapses exhibit symmetric spike-timing-dependent plasticity (Mishra, Kim, Guzman, & Jonas, 2016) without requiring additional neuromodulation. Comparable to CA3 → CA2 projections, feed-forward inhibition inside CA3 can be reduced by enkephalin-mediated iLTD (Domínguez et al., 2019; Leroy et al., 2017). To our knowledge no study has yet addressed plasticity of excitatory projections inside CA2 and from CA2 to CA3. However, it is known that axons from both regions arrive at similar locations as their recurrent counterparts (Ishizuka et al., 1990; Tamamaki et al., 1988). Therefore we assume that CA2 → CA3 projections are plastic. Net excitation may increase because of both potentiation of direct excitatory projections and iLTD at inhibitory feed-forward projections. In contrast, due to the mentioned plasticity-limiting factors, recurrent excitatory projections inside CA2 likely do not express Hebbian-type long-term plasticity in their baseline mode.

## 4 | FLEXIBLE SEQUENCE PRIORITIZATION IS REQUIRED FOR OPTIMIZED MEMORY CONSOLIDATION

Both spatial and nonspatial tasks elicit temporal sequences of neuronal activation in the hippocampus, encoding consecutive aspects of a given experience (MacDonald, Lepage, Eden, & Eichenbaum, 2011; Pastalkova, Itskov, Amarasingham, & Buzsáki, 2008). Sequences play out on the behavioral, theta and sharp wave ripple timescale and may reflect either previous and current experiences or future expectations (Carey, Tanaka, & van Der Meer, 2019; Diba & Buzsáki, 2007; Foster & Wilson, 2007; Gupta, Van Der Meer, Touretzky, & Redish, 2010; O'Keefe, 1976; Olafsdottir, Barry, Saleem, Hassabis, & Spiers, 2015; Singer, Carr, Karlsson, & Frank, 2013; Wu, Haggerty, Kemere, & Ji, 2017). We refer to co-activated cells as neuronal assemblies and to their respective sequences as assembly sequences. After an event, assembly sequences need to be reactivated to consolidate the respective experiences for long-term storage (Dupret,

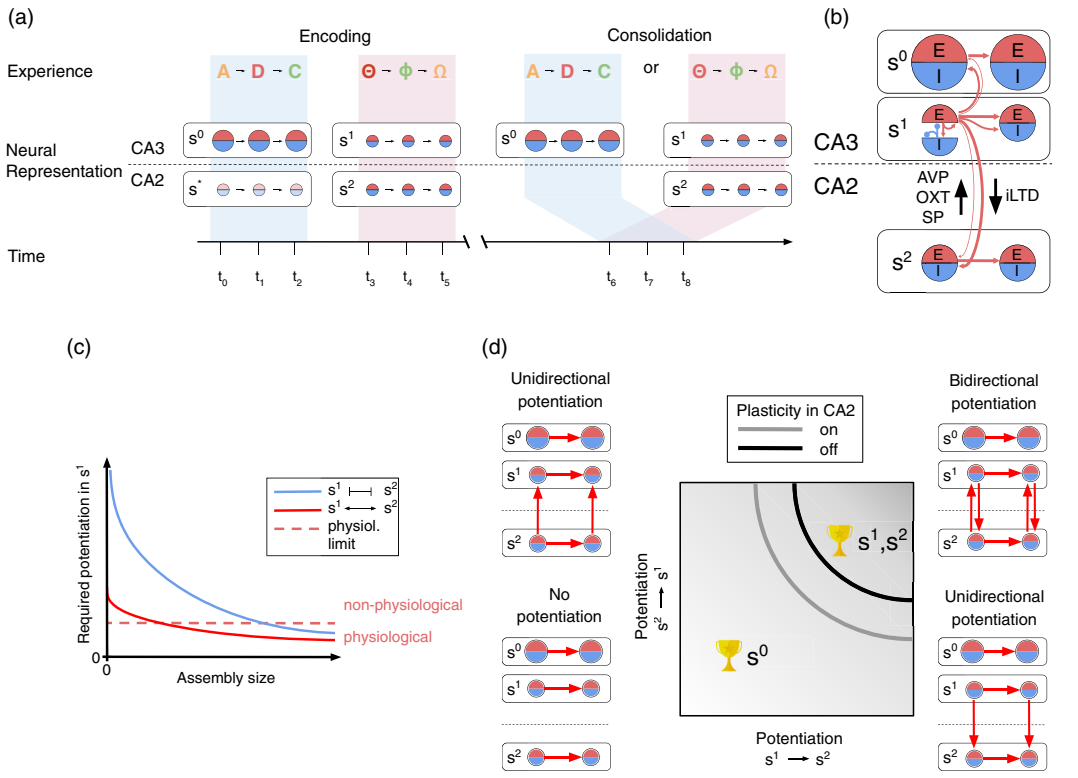


**FIGURE 2** Interactions between CA3 and CA2 can define which sequences are replayed during consolidation. *(a)* Simplified scenario, two successive experiences elicit neural assembly sequences in CA3 and CA2 during encoding. During subsequent memory consolidation, the first assemblies of each sequence are simultaneously activated. Competition between assemblies leads to winner-take-all dynamics. First experience, A → D → C, is represented by the *strong* CA3 sequence $s^0$. Sequential activity in CA2, $s^*$, is not paired and ignored. Second experience Θ → Φ → Ω is encoded as *weak* sequences in CA3 and CA2, $s^1$ and $s^2$. *(b)* Sequences are comprised of subsequently activated assemblies consisting of recurrently connected excitatory (E) and inhibitory (I) neurons. Assemblies in *strong* sequence $s^0$ have more neurons (larger circles). Except for feed-forward excitation in all sequences, we show exemplary projections only for the first assembly of $s_1$. Feed-forward inhibition between CA3 and CA2 assemblies is particularly strong. For CA3 → CA2 projections, excitation can be conditionally increased by the release of vasopressin (AVP), oxytocin (OXT) and substance P (SP); while inhibition can be decreased by inhibitory long term depression (iLTD). *(c)* Dependence of required feed-forward potentiation on assembly size. We schematically illustrate the amount of required potentiation of feed-forward weights in $s^1$ without (blue line, $s^1 \dashv s^2$), and with mutual excitatory interactions with $s^2$ (red line, $s^1 \leftrightarrow s^2$). *(d)* The graph in the middle shows how varying levels of potentiation between weak sequences $s^1$ and $s^2$ determine the outcome of the competition (indicated by the trophy). Without preferential interactions between $s^1$ and $s^2$, lower left corner, the strong sequence $s^0$ manages to inhibit $s^1$ and $s^2$. Unilateral potentiation between the weak sequences, upper left and lower right corner, is not sufficient to overcome the strong sequence. Only bidirectional potentiation, upper right corner, allows both weak sequences to support each others replay and to win over the strong sequence (gray line). If projections inside CA2 are not plastic, stronger sequence interactions can compensate for lack of feed-forward excitation (black line). For visual clarity, we show only projections with net excitation (red arrows) [Color figure can be viewed at wileyonlinelibrary.com]

O'Neill, Pleydell-Bouverie, & Csicsvari, 2010; Fernández-Ruiz et al., 2019; Jadhav, Kemere, German, & Frank, 2012; Singer et al., 2013). In their natural state, animals encounter a host of events and stimuli. Because animals do not form long-term memories of all events and stimuli, there must be mechanisms to prioritize which sequences should be replayed (Figure 2a).

Sequences representing different events/tasks likely deviate in the number of co-activated cells. In CA1, the position of other animals or inanimate objects is represented by smaller cell assemblies compared to an animal's own location (Danjo, Toyoizumi, & Fujisawa, 2018; Omer, Maimon, Las, & Ulanovsky, 2018). In addition, peak firing rates are lower for social compared to self place cells (Omer et al., 2018). Lower levels of activity may make it harder for an assembly to recruit further neurons and limit the amount of plasticity that can be induced during encoding.

A recent model by Chenkov, Sprekeler, and Kempter (2017) provides an intuitive understanding on how assembly sizes affect reactivation of individual sequences. For conceptual simplicity, assemblies

are discrete populations of prewired, recurrently connected excitatory and inhibitory neurons. During an experience, external input is thought to activate assemblies in a temporal order, with co-activity leading to potentiation of feed-forward projections between subsequently activated assemblies. The necessary amount of feed-forward potentiation for successful reactivation depends nonlinearly on assembly sizes (Chenkov et al., 2017). A sequence of large assemblies requires little potentiation. In contrast, the amount of potentiation required for sequences with small assemblies may become unphysiologically large (Figure 2c).

To understand sequence competition between multiple assembly sequences, we extend the model proposed by Chenkov et al. (2017). In its simplest form, competition between multiple sequences can be studied by considering only two sequences competing for reactivation in one network, here CA3. A *strong* sequence with large assemblies and a *weak* sequence with small assemblies. In particular, we assume that each sequence exerts feed-forward inhibition onto assemblies of competing sequences. In such a setting, if two sequences $s^0$ and $s^1$ are activated at the same time, for example by external input, the weaker sequence $s^1$ will disappear because the stronger sequence $s^0$ will recruit more inhibition onto the weaker sequence.

Each sequence, $s^0$ or $s^1$, is thought to represent an experience in one of two tasks, performed in close succession. For instance, $s^0$ may correspond to a classical spatial navigation task, for which we know that assemblies are relatively large, whereas $s^1$ may correspond to a task with small assemblies, like remembering the trajectory of another animal or an inanimate object. But, what if the experience of the weak sequence $s^1$ is much more relevant compared to the strong sequence $s^0$? Left as such, during subsequent consolidation, the strong sequence $s^0$ will be reactivated much more frequently than the weak sequence $s^1$.

How could the hippocampal circuit prioritize specific sequences despite different strengths? Such a prioritization of neuronal activity sequences is obviously important to form appropriate memories and an accurate model of the environment. Thus, we argue that there is a need for a sequence prioritization unit either within the hippocampus or in an upstream region. We propose that CA2 plays a role in strengthening sequences, increasing their chance to be replayed and thereby can perform the role of a sequence prioritization unit.

The framework we put forward is agnostic to content and timescale of sequences. To be prioritized during later reactivation, we only require that sequences, whatever they represent, are present during a neuromodulatory controlled pairing process. Therefore, we presuppose that CA2/CA3 have the necessary circuitry to generate sequences and focus on sequence competition and prioritization.

## 5 | SEQUENCES IN CA2 AND CA3 MAY MUTUALLY SUPPORT EACH OTHER'S REACTIVATION

In our sequence competition scenario, the weak sequence $s^1$ struggles for two reasons. Small assemblies require more feed-forward potentiation to sufficiently excite following assemblies. In addition, they recruit less feed-forward inhibition, making it more difficult to suppress competing sequences. In this situation, one can make use of the observation that sequential activity is also present in CA2 (Alexander et al., 2016; Lee, Wang, Deshmukh, & Knierim, 2015; Mankin, Diehl, Sparks, Leutgeb, & Leutgeb, 2015). Let $s^2$ be the CA2 sequence concurrently present with CA3 sequence $s^1$. Because assemblies in $s^1$ and $s^2$ are simultaneously active during encoding, and assuming coincidental neuromodulator release, they can team up and support each other via reciprocal potentiation. For the strong CA3 sequence $s^0$, we ignore the concurrently active CA2 sequence $s^*$ because we assume it was not associated with neuromodulatory release and hence not paired.

To understand how two sequences can support each other consider the schematic of $s^0$, $s^1$, $s^2$ shown in Figure 2b. Extending the computational model of sequence replay proposed by Chenkov et al. (2017) we can show that by increasing net excitation between $s^1$ and $s^2$, we can find conditions under which $s^1 + s^2$ will overcome $s^0$ and replay more frequently (Figure 2c,d). This analysis suggests that a bidirectional increase in net excitation between $s^1$ and $s^2$ is necessary (Stöber et al., in prep.). It allows each side to benefit from additional feedback excitation while increasing inhibition on competing assemblies. Instead, if net excitation increases only in one direction, for example, from $s^2$ to $s^1$, increased feedback inhibition makes sequence reactivation more difficult.

Bidirectional excitatory interactions can compensate for the presumed lack of plasticity inside CA2. It remains unresolved whether recurrent CA2 projections are plastic. If not, assemblies may not be able to potentiate feed-forward projections, hindering the formation of assembly sequences inside CA2. By linking CA2 assemblies through CA3, reliable reactivation of CA2 sequences may nevertheless be possible. Increased net potentiation between CA2 and CA3 could compensate for the lack of feed-forward excitation in CA2 (Figure 2d, gray vs. black line).

In summary, the proposed sequence prioritization mechanism is based on a three-factor rule for synaptic potentiation, in at least one direction. Plasticity unfolds when three conditions are met: (a) pre-, and (b) postsynaptic activity, as well as (c) a salience signal. Mutual inhibition between the two networks helps suppress competing sequences and ensures that only correctly paired sequences in both networks are reactivated.

## 6 | CA3-CA2 INTERACTIONS MAY IMPLEMENT SEQUENCE PRIORITIZATION

Based on anatomical and physiological studies, we argue that the CA3–CA2 system is well suited to implement sequence prioritization via pairing of co-active sequences. Dense recurrent excitatory projections (Ishizuka, Cowan, & Amaral, 1995; Kohara et al., 2014; Tamamaki et al., 1988) likely allow arbitrary cell assemblies to be linked within and across the two regions. Local inhibition within each region may create a winner-take-all scenario (Bazelot, Dinocourt,

Cohen, & Miles, 2010; Beyeler et al., 2013; Botcher, Falck, Thomson, & Mercer, 2014). Strong reciprocal inhibition provides additional means for suppressing competing sequences.

Neuromodulatory-gated plasticity can selectively strengthen projections from CA3 to CA2. Under baseline conditions excitatory plasticity is strongly restricted (Carstens et al., 2016; Lee et al., 2010; Zhao et al., 2007). However, release of any of the neuromodulatory substances oxytocin, vasopressin or substance P in combination with presynaptic activity leads to selective potentiation of activated excitatory synapses (Dasgupta et al., 2017; Pagani et al., 2015). In the case of vasopressin (Pagani et al., 2015) and substance P (Dasgupta et al., 2017) there is no effect, and in the case of oxytocin (Pagani et al., 2015), very little effect on synapses that are silent during the release. Furthermore, enkephalin-dependent iLTD selectively reduces feed-forward inhibition (Piskorowski & Chevaleyre, 2013). iLTD may provide a complementary mechanism for sequence interactions and suggests that effective coupling relies on both potentiation of excitation and reduction of inhibition. In all cases, synaptic potentiation develops slowly. The slow onset may be important to avoid interference with encoding.

Neuromodulation in CA2 may act as salience cue. Neuromodulation-gated plasticity in CA2 can arrive both from internal and external projections. iLTD depends on locally released enkephalin (Leroy et al., 2017). Vasopressin arrives via projections from the paraventricular nucleus (Smith et al., 2016; Swanson, Wyss, & Cowan, 1978; Zhang & Hernandez, 2013) and substance P from the supramammiliary nucleus (Borhegyi & Leranth, 1997; Cui, Gerfen, & Young, 2013). There is strong evidence that the release of vasopressin and substance P reflects experience of vital relevance to the animal. For example vasopressin is released in the dorsal hippocampus during parturition (Landgraf, Neumann, & Pittman, 1991). Social recognition memory is blocked by the application of vasopressin anti-serum immediately after an encounter (van Wimersma Greidanus & Maigret, 1996) and artificial release of vasopressin boosts the duration of social recognition memory (Smith et al., 2016). Further, vasopressin signaling is required for processing nonspatial sequence memories (DeVito et al., 2009). While the release of substance P in the hippocampus has not been directly studied, the activity of its originating region, the supramamilliary nucleus, has been associated with environmental novelty (Ito, Shirao, Doya, & Sekino, 2009), forced immobilization (Choi et al., 2012) and cold exposure (Miyata, Ishiyama, Shibata, Nakashima, & Kiyohara, 1998). The latter two are stress situations that the animal likely wants to avoid in the future.

## 7 | SEQUENCE PRIORITIZATION PROVIDES NEW INTERPRETATIONS OF EXPERIMENTAL FINDINGS

We illustrate the sequence prioritization mechanisms in a very simplified scenario: With only three discretized and prewired assembly sequences. A strong, uncoupled assembly sequence in CA3 competes with two weak and mutually supportive sequences in CA3 and CA2. Only the latter two sequences receive neuromodulation and we ignore plasticity inside assemblies. All sequences are reactivated at the same time and only one sequence group can win, while the other is suppressed. In reality, the situation is obviously much more complicated. While awake, an animal is constantly experiencing, likely leading to a multitude of assembly sequences being activated in short time windows. And assembly sequences are not discrete but continuous. Assembly sizes may vary and even dynamically change over time. A complex cocktail of neuromodulators may be constantly present. During rest, internal dynamics may strongly influence network activity and reactivation may arise both spontaneously and upon external input. For those reasons, we expect that sequence reactivation is not a binary variable, but rather a probability distribution with multiple sequences, biased by the proposed sequence prioritization mechanism.

For a strong sequence, with many neurons participating at any given moment in time, potentiation of feed-forward synapses may suffice for successful propagation and inhibition of other competing sequences. In this case, help from CA2 may not be necessary. It has been shown that lesioning CA2 has no significant effect on spatial navigation in the Morris water maze (Hitti & Siegelbaum, 2014). Since position is represented by a large number of pyramidal cells in the hippocampus, the respective memory traces may constitute strong sequences that do not require additional support. Yet, an interesting case arises when two such strong sequences compete. In the Morris water maze example, animals with CA2 lesions trended towards slower relearning of a new platform location (Hitti & Siegelbaum, 2014). In our interpretation, behavioral sequences that reflect the new platform location are not sufficiently prioritized. Sequences reflecting the old location are still present during replay, slowing down the acquisition of the new location.

Increased activity in CA2 may compensate for fewer cells. To have significant effect on CA3, a CA2 sequence must recruit sufficient neuronal activity. CA2 may compensate for its disadvantage in size by letting cells participate in multiple cell assemblies. This argument is supported by CA2 place cells having multiple fields and being active across different environments (Lee et al., 2015; Lu, Igarashi, Witter, Moser, & Moser, 2015; Mankin et al., 2015). The large spatial extent of CA2 place fields (Mankin et al., 2015; Oliva, Fernández-Ruiz, Buzsáki, & Berényi, 2016b) may help bias the transition between CA3 assemblies.

Bidirectional sequence pairing allows combining diverse information in CA3 and CA2. Diverging place field properties (Lee et al., 2015; Lu et al., 2015; Mankin et al., 2015) indicate that CA3 and CA2 represent different information. In contrast to stable CA3 place fields, the CA2 population vector completely decorrelates on a timescale of hours (Mankin et al., 2015). With CA2/CA3a strongly responding to changes in local cues (Alexander et al., 2016; Lee et al., 2015; Wintzer, Boehringer, Polygalov, & McHugh, 2014) and CA3b/c more prone to global cues (Lee et al., 2015; Mankin et al., 2015), one can speculate that the pairing of assembly sequences embeds variable local information into a stable global context. Both regions may then provide complementary information to downstream CA1.

In a related proposal, McHugh and colleagues suggest that a new CA2 subpopulation is recruited whenever sensory-based EC input differs sufficiently from memory-based CA3 input (Middleton & McHugh, 2019; Wintzer et al., 2014). Such a situation would be of

putative importance to the animal, and may therefore induce neuromodulator release. Within our framework, this would result in pairing of co-active CA2 and CA3 sequences and thus prioritization for replay. A new set of CA2 cells, and hence novel CA2 assembly sequences, would confer the additional benefit that the pairing not only prioritizes the salient experience for later replay, but also provides a unique index for the episode.

Two recently described subpopulations of CA2 pyramidal cells, N units (Kay et al., 2016) and ramping cells (Oliva et al., 2016a), fit nicely with our proposal of sequence prioritization. Despite some differences that require further clarification, it seems likely that these two terms are different descriptions of the same cell type. Ramping cells increase their firing rate before and are relatively silent during a sharp wave ripple event. N units are nonpositively modulated by sharp wave ripples, fire preferentially during immobility and are spatially selective. These properties may allow N units or ramping cells to bias sequence reactivation during sharp wave ripples by activating the first assemblies of a particular sequence. With more inhibition on other sequences and increased activation of subsequent assemblies, successful propagation of the selected sequence during the upcoming sharp wave ripple becomes more likely. As a consequence we expect that N units/ramping cells are co-activated in stable subgroups and that their activation predicts the replay of specific sequences (Middleton & McHugh, 2019).

We expect that unconditionally unlocking plasticity of the CA3 → CA2 synapse will lead to general pairing of sequences in CA3 and CA2. Under such conditions, selective prioritization of important, yet weak sequences becomes difficult, because strong sequences may dominate even more. Unlocking plasticity can for example be achieved by selectively preventing the expression of plasticity limiting gene RGS14 (Lee et al., 2010). Consistent with our prediction, RGS14$^{-/-}$ mice showed an increased learning rate in the Morris water maze and stronger responses in a novel object recognition task (Lee et al., 2010). However, we expect difficulties when multiple experiences with different relevance happen close in time. In such cases, prioritizing sequences during replay is integral for optimizing performance.

Artificially inducing net potentiation of the CA3 → CA2 synapse by releasing vasopressin, oxytocin, substance P and/or induction of iLTD should prioritize replay of concurrently active CA2 and CA3 sequences. In contrast, deactivating CA2 during encoding or consolidation or preventing plasticity should disrupt prioritization. This can be tested for example in the object-trace-odor task. We expect that silencing CA2 will lead to a similar lack of temporal sequence memory as globally knocking out the Avpr1b receptor (DeVito et al., 2009).

Diverse actions of neuromodulation on cortical synapses (e.g., from EC LII, Chevaleyre & Siegelbaum, 2010; Kohara et al., 2014) onto CA2 pyramidal cells can be interpreted in the light of sequence prioritization. In our simplified scenario, sequences are activated by external cortical synapses of equal strength. However, by modulating cortical synapses, one can influence the activity at the start of each sequence, thus providing an additional mechanism of sequence prioritization. For example, substance P potentiates cortical synapses active during its release (Dasgupta et al., 2017) and therefore may facilitate reactivation of the current experience. In contrast, vasopressin may hinder the reactivation of preceding experiences by selectively weakening previously potentiated synapses (Chafai, Corbani, Guillon, & Desarménien, 2012).

Input-timing dependent plasticity weakens feed-forward inhibition between CA3 and CA2 and strengthens cortical projections (Leroy et al., 2017). As with substance P, stronger cortical projections may facilitate externally triggered reactivation. Whether ITDP is synapse specific and whether it allows linking individual cell assemblies remains to be resolved. In contrast to ITDP in CA1, ITDP in CA2 does not require postsynaptic activity. Further, ITDP seems to recruit at least two mediating interneuron subgroups (Leroy et al., 2017). Hence, we assume that ITDP is not specific and expect it to allow the recruitment of previously silent pyramidal cells during reactivation. Cells that were silent during encoding, but received matching cortical and CA3 input, will receive more net excitation during subsequent reactivation. Those cells likely recruit further inhibition in CA3, potentially blocking other competing sequences.

Alternative sequence prioritization mechanisms may exist besides the proposed CA3/CA2 sequence pairing. McNamara, Tejero-Cantero, Trouche, Campo-Urriza, and Dupret (2014) found that activating dopaminergic fibers in dorsal CA1 further increases the reinstatement of spatial firing patterns after exploring a novel environment. Thus, the study shows that spatial sequences can be prioritized locally in CA1. Since the link between dopamine release and increased reactivation remains elusive, at least two interpretations are possible. On the one hand, the dopamine-based mechanism could facilitate prioritization of local sequences inside CA1. Alternatively, since CA1 receives CA3 and CA2 input, dopamine signalling may determine the response strength to sequences arriving from the CA3/CA2 system (Rosen, Cheung, & Siegelbaum, 2015). In the latter case, the dopamine-based mechanism would be additional to the CA3-CA2 prioritization. Further investigations are warranted.

### 7.1 | Experiment to test the role of CA2 in sequence prioritization

We outline one experiment to confirm or falsify our proposal that interactions between CA2 and CA3 allow one form of general sequence prioritization. The key is to have two tasks in close succession followed by a rest period to measure memory reactivation. In a very simple form, the tasks may entail running back and fourth on two different linear tracks (Diba & Buzsáki, 2007). To avoid prioritization by other mechanisms outside of CA2 (McNamara et al., 2014), one could optogenetically excite neuromodulatory fibers exclusively inside CA2 in only one of the two tasks (Smith et al., 2016). These may be fibers releasing vasopressin, oxytocin or substance P. In subsequent rest, we expect that memory reactivation is biased towards the task during which CA2 mediated neuromodulation was released.

### 7.2 | Predictions

- CA2 plays a general role in episodic memory tasks, extending beyond social recognition memory.

- Interplay between CA3 and CA2 selects which information is passed on to downstream CA1.
- Excitatory projections from CA2 to CA3 pyramidal cells are either plastic or prewired such that a subset expresses net-excitation.
- Inducing net potentiation at CA3-CA2 synapses prioritizes reactivation of concurrently active CA2 and CA3 sequences during later replay. [Correction added on 7 September, 2020, after first online publication: "replay" was changed to "reactivation" in this sentence.]
- Deactivating CA2 during encoding or consolidation, preventing or unconditionally unlocking plasticity should disrupt prioritization. In turn, selective release of neuromodulatory substances increases reactivation of concurrently activated sequences.
- Lack of sequence prioritization leads to behavioral deficits in complex environments, where important and nonimportant information needs to be distinguished.

## 8 | DISCUSSION

Investigations of CA2's functional role have only taken up pace in recent years. To our knowledge, our framework is the first attempt to build an overarching theory for CA2, integrating many of the fragmented anatomical and physiological insights. We propose that the recurrent CA3–CA2 system is, in the presence of a salience cue, able to prioritize sequences for replay. We assign a role to limited plasticity, selective neuromodulation and inhibitory plasticity at CA3–CA2 synapses.

The proposed framework is built on several strong assumptions. For example, we assumed that a *three-factor* learning rule underlies selective pairing of co-active assemblies, meaning that potentiation depends on pre- and postsynaptic activity as well as on neuromodulatory release. The influence of postsynaptic activity is yet to be tested for three of the mentioned neuromodulatory substances: vasopressin, oxytocin, and substance P (Dasgupta et al., 2017; Pagani et al., 2015). However, in case postsynaptic activity is not required, it is still conceivable that silent subpopulations in CA2 could be unidirectionally recruited by CA3 (see Leroy et al., 2017; Nasrallah et al., 2015), with bidirectional pairing taking place in a second step. Further, it is not known whether the insights from slice physiology transfer to the in vivo situation and under which behavioral conditions neuromodulatory substances are released. For conceptual simplicity, we assumed that assemblies are nonoverlapping and preconfigured. However, neither of these two properties are hard requirements. Similar dynamics underlie sequences with overlapping assemblies (Chenkov et al., 2017) and assembly formation and pairing could occur simultaneously.

Recent studies addressing CA2's relevance for memory have focused on social recognition memory. Recognition could simply rely on familiarity alone and thus may not depend on episodic memory (Brown & Aggleton, 2001; Patai et al., 2015), making it independent of the mechanism we propose. However, our framework may also apply to social recognition memory for two reasons. First, episodic memories of another animal should strengthen its recognition. To our knowledge this has not been explicitly tested yet. Second, recently discovered place cells for others, with phase precession solely as a function of the other's location (Danjo et al., 2018; Omer et al., 2018), indicate that the hippocampus represents social information similar to other episodic memories (Buzsáki & Tingley, 2018). For this reason we argue that mechanisms for prioritizing sequences for replay, also social sequences, should be of general nature.

We describe only the core mechanism of sequence prioritization. For conceptual simplicity we consider only two sets of sequences representing two distinct experiences, but a similar *winner-take-all* mechanisms ought to work for more than two sets of sequences, given enough recurrent excitation to recover from initial feed-forward inhibition. So far, it is not clear whether the different neuromodulators act together and what specific role they play. Experimental evidence suggests they complement each other. For example, social recognition memory depends on vasopressin (Wersinger et al., 2002), oxytocin (Lin et al., 2018; Raam, McAvoy, Besnard, Veenema, & Sahay, 2017) and enkephalin (Leroy et al., 2017). In any case, enkephalin-mediated iLTD appears to be a special case. It is the only mechanism for which a) the neuromodulator releasing cells are in close proximity and b) it is not necessary to add enkephalin to the acute slice experiments to unlock plasticity (Leroy et al., 2017; Piskorowski & Chevaleyre, 2013). It is therefore conceivable that iLTD is active in the baseline mode and the other neuromodulatory substances work on top of it.

Separating sequence generation (within CA2 and CA3) from sequence control/prioritization (CA2 ↔ CA3 projections) confers a number of advantages. As mentioned above, beyond prioritization, pairing of CA2 and CA3 assembly sequences could provide a unique index for novel/salient episodes and embed local information into global contexts. In addition, it could also tease apart overlapping CA3 sequences. For example, if two CA3 sequences with overlapping assemblies (e.g., A → B → C vs. A → C→ D) receive input to the first assembly (A), the sequence with the strongest feed-forward projections and largest assemblies will win out, the other being suppressed. In this case, it comes down to the relative strength of projections from A → B vs. A → C. However, if the CA3 sequences are paired with two different CA2 sequences (U → V → W and X → Y→ Z, respectively) then activation of assembly A in CA3 and either U or X from the paired CA2 sequence determines how replay will progress. Given that CA2 activity reorganizes after changes in local cues (Alexander et al., 2016; Lee et al., 2015; Wintzer et al., 2014) and decorrelates on a timescale of hours (Mankin et al., 2015), new CA2 sequences could be readily made available to pair with, and hence prioritize, stable CA3 sequences. These pairings could then influence replay and thus memory consolidation primarily in the first hours after an experience, after which the recruited neurons in CA2 may be flexibly reused to form new CA2-CA3 pairings.

## 9 | CONCLUSION

We propose that the hippocampus prioritizes important neural activity sequences, increasing the probability of their subsequent replay. We have formulated a conceptual framework that allows the CA3–

CA2 system to control which sequences are reactivated. Namely, neuromodulatory-gated plasticity and mutual inhibition enable sequences in both regions to support each other while suppressing competing sequences. In conclusion, considering CA2 as a sequence prioritization unit provides a cohesive interpretation of its unique functional properties and makes the first steps towards incorporating CA2 into an overarching theory of hippocampal memory processing.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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