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

Tristan M. Stöber[1,2,3,◕,✉], Andrew B. Lehr[1,2,4,◕,✉], Torkel Hafting[2,5], Arvind Kumar[6], and Marianne Fyhn[2,7,✉]

[1]Department of Computational Physiology, Simula Research Laboratory, Norway
[2]Centre for Integrative Neuroplasticity, University of Oslo, Norway
[3]Department of Informatics, University of Oslo, Norway
[4]Department of Computational Neuroscience, University of Göttingen, Germany
[5]Institute of Basic Medical Sciences, University of Oslo, Norway
[6]Department of Computational Science and Technology, KTH Royal Institute of Technology, Sweden
[7]Department of Biosciences, University of Oslo, Norway
[◕]The first two authors contributed equally to this work.

[✉]Correspondence: tristan.stoeber@posteo.net, andrew.lehr@phys.uni-goettingen.de, marianne.fyhn@ibv.uio.no

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Contents

1 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 show 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.

2 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, 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 (Wersinger et al., 2002, 2004, 2007, 2008; DeVito et al., 2009; Young et al., 2006; Smith et al., 2016; Stevenson and Caldwell, 2014; Meira et al., 2018; Okuyama et al., 2016). However, experimental data also suggests that CA2 plays an important role in several non-social 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 (Oliva et al., 2016; Alexander et al., 2017), 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., 2017). 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. David Marr used the "from-structure-to-function" approach. Based on the anatomy, he suggested that CA3 may act as an auto-associative memory unit (Marr, 1971; Papp et al., 2007). Similarly, the dentate gyrus, at a computational level, is considered a pattern separator (Gluck and Rumelhart, 1990; Treves and Rolls, 1992; Leutgeb et al., 2007). 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.

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 et al., 1994), the dentate gyrus (Kohara et al., 2014) and entorhinal cortex layer II (Bartesaghi and Gessi, 2004; Chevaleyre and Siegelbaum, 2010). Like CA3, axons of CA2 pyramidal cells widely project along the proximodistal (subdivided into CA1, CA2a/b, and CA3a/b/c) as well as the septotemporal axes.

CA2 axons arborize within all CA regions (Li et al., 1994; Tamamaki et al., 1988), with some reaching into the dentate gyrus (Ishizuka et al., 1990). Pyramidal cells in dorsal CA2 have been shown to directly project to

the ventral hippocampus (Okuyama, 2017; Tamamaki et al., 1988; Meira et al., 2018). Thus despite its small size, CA2 can integrate information from and exert influence over a large portion of the hippocampus.

CA2, similar to CA3, has abundant recurrent excitatory connections. Within CA2, monosynaptic recurrent connections occur with a probability of 1.4% (Okamoto and Ikegaya, 2018), comparable to CA3 (1.75%, Miles and Wong, 1986) as opposed to more sparse recurrent connectivity of pyramidal cells in CA1 (0.6%, Deuchars and Thomson, 1996). Interestingly, this connectivity is heterogeneous, as recurrent connections are biased towards CA2b (Okamoto and Ikegaya, 2018).

Zooming in along the proximodistal axis, it appears that CA2b 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 and Siegelbaum, 2010; Kohara et al., 2014) and limited plasticity (Zhao et al., 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., 2015, 2019).

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 et al., 2009), dense perineuronal nets (Carstens et al., 2016), and plasticity limiting signalling pathways (Lee et al., 2010; Simons et al., 2012). 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 et al. (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 (Pagani et al., 2015; Dasgupta et al., 2017). In turn, precise timing of distal and proximal inputs, called input-timing-dependent plasticity (ITDP) (Leroy et al., 2017), and low-frequency stimulation can reduce feed-forward inhibition (Nasrallah et al., 2015). Interestingly, plasticity induced by vasopressin (Pagani et al., 2015), oxytocin (Pagani et al., 2015), substance P (Dasgupta et al., 2017), iLTD (Nasrallah et al., 2015, 2016) and ITDP (Leroy et al., 2017) share similar dynamics. Net excitation increases slowly and peaks after around 20 minutes, roughly doubling the excitatory drive.

While we have direct experimental evidence for plasticity inside CA3, we can only make assumptions about projections from CA2 to CA3 and within CA2. Excitatory synapses inside CA3 exhibit symmetric spike-timing-dependent plasticity (Mishra et al., 2016). 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). For that reason we assume that excitatory projections from CA2 to CA3 may express similar symmetric spike-timing-dependent plasticity as those inside CA3 (Mishra et al., 2016). 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.

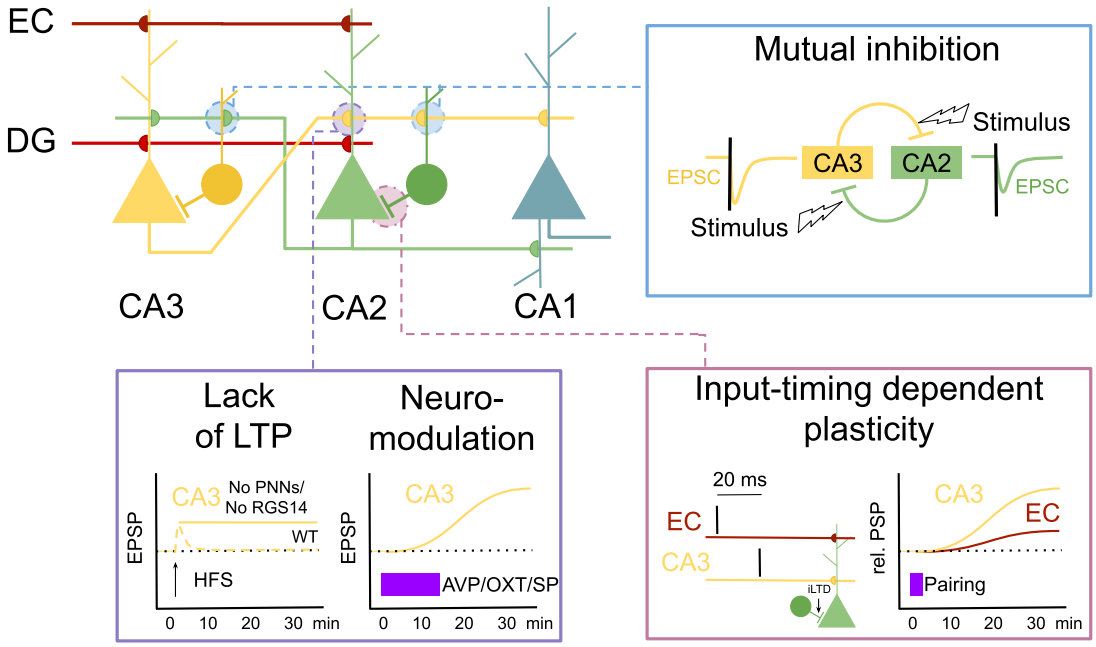

Figure 1: **Interactions between CA3 and CA2 are characterized by mutual inhibition and restricted plasticity** In contrast to hippocampal region CA1, pyramidal cells in CA3 and CA2 receive input from entorhinal cortex layer 2 (EC) and the dentate gyrus (DG). Interactions between both regions are strongly dominated by feed-forward inhibition, upper right box. Activating excitatory projections between CA3 and CA2 leads to a predominantly inhibitory response in the other region. Excitatory projections from CA3 to CA2 are characterized by a lack of activity-induced long term potentiation, lower left box. 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. Alternatively, the release of the neuromodulators vasopressin, oxytocin or substance P leads to potentiation of exitatory projections. If EC input precedes CA3 input by around 20 ms, input-timing-dependent plasticity leads to a reduction of feed-forward inhibition, lower right box. In consequence the relative strength of feed-forward excitation from CA3 to CA2 increases. Interestingly, also EC to CA2 projections are strengthened to some degree. Both potentiation of excitation or depotentiation of inhibition unfolds slowly, peaks around 30 minutes and results in roughly a doubling of the post-synaptic potential.

3 Flexible sequence prioritization is required for optimized memory consolidation

Both spatial and non-spatial tasks elicit temporal sequences of neuronal activation in the hippocampus, encoding consecutive aspects of a given experience (Pastalkova et al., 2008; MacDonald et al., 2011). 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 (Jadhav et al., 2012; Singer et al., 2013; Fernández-Ruiz et al., 2019; Dupret et al., 2010). In their natural state, animals encounter a host of events and stimuli. Because animals do not form long-term memory for all events and stimuli, there must be a mechanism to prioritize which sequences should be replayed.

Sequences representing different events/tasks likely deviate in the number of co-activated cells. For example, recent studies found that smaller cell assemblies represent position of other animals and objects compared to the animals own location (Omer et al., 2018; Danjo et al., 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 et al. (2017) provides an intuitive understanding on how assembly sizes affect sequence reactivation. For conceptual simplicity, assemblies are populations of pre-wired, recurrently connected excitatory and inhibitory neurons. During an experience, external input is thought to activate assemblies in a temporal order. Sequential activity leads to potentiation of feed-forward projections between subsequently activated assemblies (Fig. 2b). Given sufficient potentiation, cell assembly sequences reactivate either spontaneously or through external input.

Successful reactivation requires sufficient potentiation of feed-forward projections between assemblies. However, increasing assembly size allows for a drastic redution of the necessary potentiation, potentially allowing one-shot learning (Chenkov et al., 2017). Following the same argumentation, sequences with very small assemblies may not be able to potentiate feed-forward projections sufficiently to enable re-activation. To connect the concept of recurrently connected assembly sequences to a putative role of CA2, we first assume that two sequences compete inside CA3 for reactivation in short time windows during a consolidation period: A *strong* sequence with large assemblies and a *weak* sequence with small assemblies.

To understand sequence competition between assembly sequences, we extend the model proposed by Chenkov et al. (2017) (see Figure 2). In particular, we assume that each sequence exerts feed-forward inhibition onto subsequent assemblies of competing sequences (Figure 2:2). In such a setting, if two sequences s^0 and s^1 are activated at the same time, 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 which involves remembering the trajectory of another another animal or an inanimate object. In the latter case, there is strong evidence that assemblies are small compared to self-place cells (Omer et al., 2018; Danjo et al., 2018). But what if the experience of the weak sequence s^1 is much more relevant compared to the strong sequence s^0? In the scheme shown in Figure 2b, 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. Surprisingly, so far there has not been a suggestion about where such a mechanism may be implemented. 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.

4 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 will require more potentiation to sufficiently excite following assemblies. In addition, small assemblies recruit less feed-forward inhibition, making it more difficult to suppress the competing sequence. If s^1 were to boost its strength alone, it would have to strengthen feed-forward or recurrent projections between or inside its assemblies. This may be achieved via local release of neuromodulation or further cellular activity upon repeated exposures to the task. However, the amount of synaptic potentiation has physiological limits; and while local strengthening of a sequence may work if the difference to competing sequences is small, for large differences this strategy may become unfeasible.

Alternatively, one can make use of the observation that sequential activity is also present in CA2 (Mankin et al., 2015; Alexander et al., 2016; Lee et al., 2015). We call s^2 the CA2 sequence concurrently present with the CA3 sequence s^1. Because s^1 and s^2 were concurrently active, 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^* for the following reason. We assume that s^0 was not of particular importance, not associated with neuromodulatory release and hence not coupled to its respective CA2 sequence.

To understand how two sequences can support each other consider the schematic of s^0, s^1, s^2 shown in Fig. 2. 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 (Fig. 2b), we can find conditions under which $s^1 + s^2$ can overcome s^0 and replay more frequently. This analysis suggests that a bidirectional increase in net excitation is necessary to join s^1 and s^2 (Stöber et al., in prep.). Bidirectional increase in net excitation allows each side to recruit feed-forward excitation that helps to excite their own next assembly. Further, because of mutual inhibition between the two networks, a bidirectional increase in net excitation will recruit inhibition on competing assemblies. If net excitation increases only in one direction, e.g. from s^2 to s^1, no beneficial cooperation arises between the two sequences. In this scenario, s^1 may receive some extra excitation at the start, but this in turn leads to additional feed-forward inhibition on s^2. In consequence, unidirectional increase in net excitation makes it more likely that s^2 disappears, prohibiting further help to s^1.

In summary, for the proposed sequence prioritization mechanism to be specific, we need a three-factor rule for synaptic potentiation in at least one direction. Plasticity must be absent, unless the following three conditions are met: 1) presynaptic activity, 2) a salience signal and 3) postsynaptic activity. Mutual inhibition between the two networks helps in suppressing competing sequences and ensures that only correctly paired sequences in both networks are reactivated.

5 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 (Kohara et al., 2014; Tamamaki et al., 1988; Ishizuka et al., 1995) 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 et al., 2010; Beyeler et al., 2013; Botcher et al., 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 (Zhao et al., 2007; Carstens et al., 2016; Lee et al., 2010). However, release of any of the neuromodulatory substances oxytocin, vasopressin or substance P in combination with presynaptic activity leads to selective potentiation of excitatory projections (Pagani et al., 2015; Dasgupta et al., 2017) There is no (Dasgupta et al., 2017; Pagani et al., 2015) or, in the the case of oxytocin (Pagani et al., 2015), very little effect on synapses that are silent during the release. Additionally, enkephalin-dependent input-timing dependent plasticity selectively reduces feed-forward inhibition (Leroy et al., 2017). This provides

a complementary mechanism for sequence interactions and suggests that effective coupling relies on both potentiation of excitation and reduction of inhibition. Interestingly, input-timing dependent plasticity does not require postsynaptic activation, only correctly timed input. This likely provides a way to recruit previously silent neurons into CA2 assemblies. 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. Input-timing-dependent plasticity depends on locally released enkephalin (Leroy et al., 2017). Vasopressin is released by projections from the paraventricular nucleus (Zhang and Hernandez, 2013; Smith et al., 2016; Swanson et al., 1978) and substance P from the supramammiliary nucleus (Cui et al., 2013; Borhegyi and Leranth, 1997). There is strong evidence that the release of vasopressin and substance P reflects experience of vital relevance to the animal. For example vasopressin is strongly released in the dorsal hippocampus during parturition (Landgraf et al., 1991). Social recognition memory is blocked by the application of vasopressin anti-serum immediately after an encounter (van Wimersma Greidanus and 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 non-spatial sequence memories (DeVito et al., 2009). While the release of substance P in the hippocampus has not been studied directly, the activity of its originating region, the supramamilliary nucleus, has been associated with enviromental novelty (Ito et al., 2009), forced immobilization (Choi et al., 2012) and cold exposure (Miyata et al., 1998). The latter two are stress situations that the animal likely wants to avoid in the future.

Unless specialized pre-wired connectivity exists within CA2 and from CA2 to CA3, the proposed sequence prioritization mechanism requires two more plastic projections in addition to conditional plasticity at CA3-CA2 synapses. First, feed-forward plasticity within the two subregions is required to link assemblies into sequences. While excitatory plasticity inside CA2 has not been studied yet, CA3 is known to express symmetric spike timing dependent plasticity (Mishra et al., 2016). Symmetric spike timing dependent plasticity may allow reactivation of assembly sequences in forward and backward directions. In case excitatory plasticity inside CA2 exists, independent assembly sequences may form. If not, sequence prioritization may still work, it just requires more potentiation between the paired sequences (compare Fig 2c). Second, plasticity between CA2 and CA3 should be bidirectional. Thus in addition to conditional plasticity from CA3 to CA2, CA2-CA3 synapses should also be plastic. No study has yet addressed plasticity of excitatory CA2 projections to CA3. Because they arrive at similar locations on CA3 pyramidal neurons as CA3 recurrent projections (Tamamaki et al., 1988; Ishizuka et al., 1990), we assume that they are equally plastic. Of interest, applying a δ-opioid receptor agonist reduces feed-forward inhibition on CA3 pyramidal cells. One may speculate that input-timing dependent plasticity may also act from CA2 to CA3.

6 Sequence prioritization provides new interpretations of experimental findings

We illustrate the sequence prioritization mechanisms in a very simplified scenario: With only three discretized and pre-wired 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 potentially even dynamically change over time. What we defined as the *strength* of a sequence is likely a continuum. A complex cocktail of neuromodulators is potentially 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 assume that sequence reactivation is not a binary variable, but rather a distribution over multiple sequences, modified by the sequence prioritization mechanism.

Experimental studies have shown that lesioning CA2 has little or no effect on several hippocampal-dependent

memory tasks, such as spatial navigation in a Morris water maze (Hitti and Siegelbaum, 2014). For a strong sequence, with many neurons participating at any given moment in time, potentiation inside CA3 may suffice for successful propagation and inhibition of other competing sequences. In this case, help from CA2 may not be necessary. Since position is represented by a large number of pyramidal cells in the hippocampus, the respective memory trace in the Morris water maze may constitute a very strong sequence that is sufficiently replayed without 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 and Siegelbaum, 2014). Our interpretation is that this could be a defect in prioritizing the respective behavioral sequences that facilitate consolidation of the new platform location.

Increased activity may compensate for fewer CA2 units. To have 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 the observation that CA2 place cells have multiple fields in a given arena and that each field is larger (Mankin et al., 2015; Lu et al., 2015). CA2 cells are also active across environments (Lee et al., 2015), further indicating participation of individual CA2 neurons in many different assemblies.

So far we have highlighted how a CA2 sequence may help prioritize a CA3 sequence. However, the proposed sequence prioritization is bidirectional. A CA3 sequence may equally support the reactivation of a CA2 sequence. Especially if plasticity within CA2 is blocked, support from a CA3 sequence is necessary for a novel CA2 sequence to be reactivated. Diverging place field properties (Mankin et al., 2015; Lu et al., 2015; Lee et al., 2015) indicate that CA3 and CA2 represent different information. With CA2/CA3a strongly responding to changes in local cues (Lee et al., 2015; Alexander et al., 2016) and CA3b/c more prone to global cues (Mankin et al., 2015; Lee et al., 2015), one can speculate that the pairing of assembly sequences embeds local information into a larger context. Both regions may then provide complementary information to downstream CA1.

Two recently described subpopulations of CA2 pyramidal cells, N units (Kay et al., 2016) and ramping cells (Oliva et al., 2016), fit nicely with our proposal of sequence prioritization. These two terms likely describe different aspects of the the same cell type. Ramping cells increase their firing rate before and are relatively silent during a sharp wave ripple event. N units are non-positively 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 and McHugh, 2019).

We expect that unconditionally unlocking plasticity of the CA3-CA2 synapse will increase the relative frequency of replays for less important experiences. This could for example be achieved by selectively preventing the expression of RGS14 (Lee et al., 2010) or removing perineuronal nets (Carstens et al., 2016) in or around CA2 pyramidal neurons, respectively. Moreover, with the prioritization mechanism shut off, stronger sequences, like those of place cell sequences for one's own location, would have an advantage over weaker sequences. Accordingly, RGS14$^{-/-}$ mice showed an increased learning rate in the Morris water maze (Lee et al., 2010). Interestingly, these mice also responded significantly stronger in a novel object recognition task. In both cases, animals were performing a single task in which an increase of unspecific replay could boost performance. However, we expect difficulties in complex environments. Especially when experiences with different relevance happen close in time, prioritizing sequences during replay is integral for optimizing performance. A potential experimental design may employ a modification of the non-spatial sequence memory task (Allen et al., 2014, 2016), in which different sequences have distinct reward values.

Artificially inducing net potentiation of the CA3-CA2 synapse by induction of ITDP or release of vasopressin, oxytocin or substance P, should prioritize replay of concurrently active CA2 and CA3 sequences. In contrast, deactivating CA2 during encoding, 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).

While the neuromodulators vasopressin, oxytocin and substance P seem to have very comparable effects on

excitatory CA3 to CA2 projections, differences become visible in the effect on cortical projections. Vasopressin transiently weakens excitatory cortical synapses, but only if they were previously potentiated, leaving them otherwise unchanged (Chafai et al., 2012). Substance P potentiates synapses which are active during the release and provides a synaptic tagging and capture mechanism (Dasgupta et al., 2017). If plasticity has been previously induced in CA3-CA2 projections, a weak stimulation is sufficient to establish long lasting potentiation of cortical synapses. The proposed CA3-CA2 sequence prioritization mechanism offers an intuitive interpretation for these differences. Upon vasopressin release, projections relating to preceding experiences are weakened and it becomes more difficult to reactivate their respective assembly sequences by external input. In contrast, substance P may facilitate external reactivation of the current sequence. In addition, the synaptic tagging and capture mechanism may provide a way to pair additional cortical patterns to previously established sequences.

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 seeems 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.

Experiment to test the role of CA2 in sequence prioritization

We outline an experiment to test our hypothesis that the interaction between CA2 and CA3 allows sequence prioritization. The key idea is to have two tasks in close succession followed by a rest period to measure memory reactivation. The tasks could for example entail running back and fourth on two different linear tracks (Diba and Buzsáki, 2007). The key aspect is that the reward differs between the two tasks. One task is strongly and the other weakly rewarded. In subsequent rest, we expect that memory reactivation in control animals is biased towards the strongly rewarded task. In contrast, major interference with CA3-CA2 interplay should reduce the difference in replay frequency between the strongly and the weakly rewarded task. Further, injection of the neuromodulatory substances vasopressin, oxytocin or substance P during the weakly rewarded task should increase its replay. We hypothesize that the following manipulations during encoding lead to similar qualitative effects: Lesioning or deactivating CA2, silencing excitatory projections or preventing excitatory plasticity between CA2 and CA3 in either one or both directions.

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 must either be plastic or are pre-wired such that a subset expresses net-excitation.
- Inducing net potentiation of the CA3-CA2 synapse prioritizes replay of concurrently active CA2 and CA3 sequences during later replay.
- 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 non-important information needs to be distinguished.

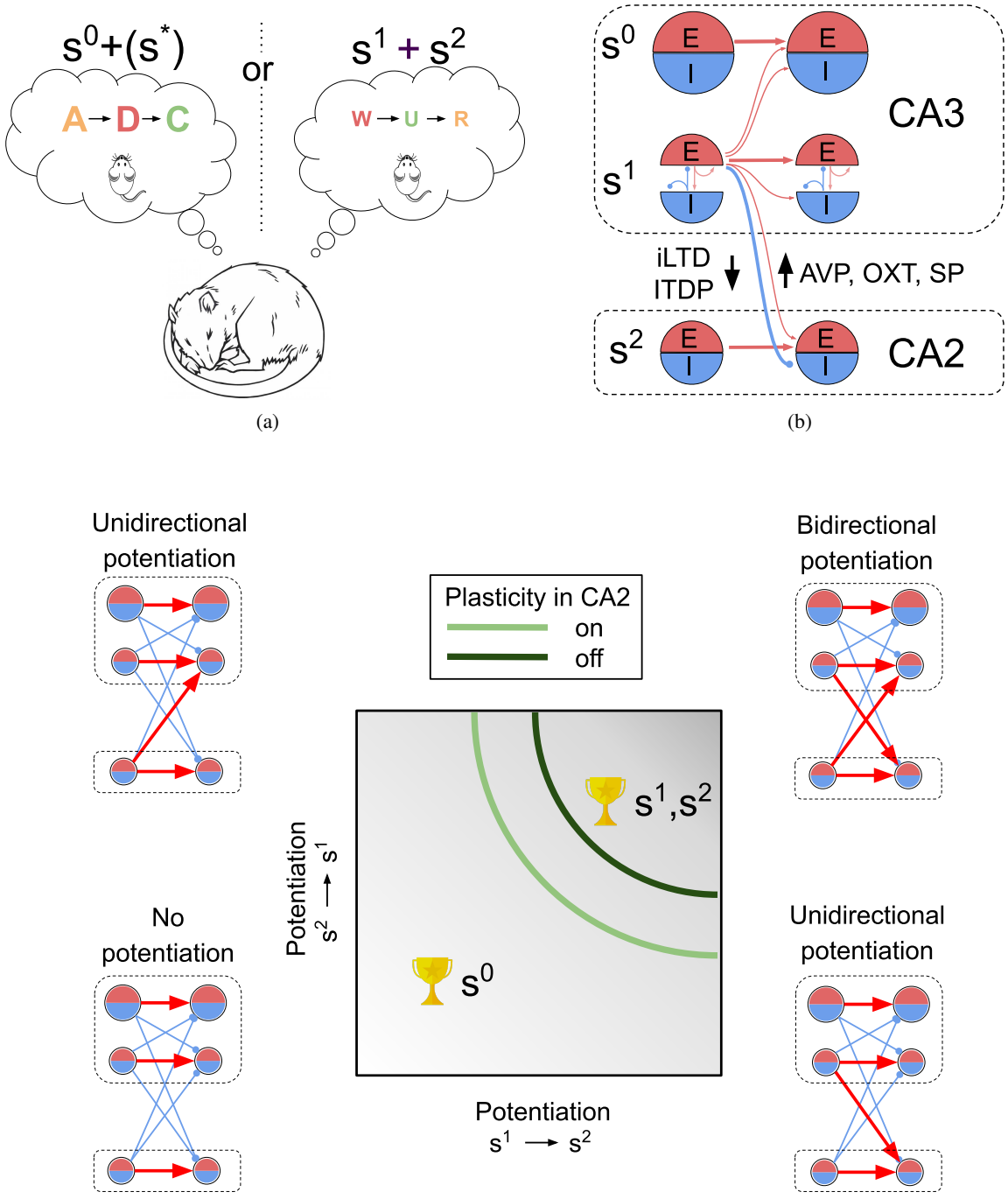

Figure 2: **Interactions between CA3 and CA2 can define which sequences are replayed. a)** An animal has two distinct experiences. First, the animal discovers a reward in a maze. The corresponding activity sequence in CA3 is s^0. Second, the animal observes a conspecific that presses a button to unlock another reward. The co-activated sequences s^1 in CA3 and s^2 in CA2 contain complementary information about the latter episode. In subsequent rest the animal prioritizes reactivation of sequences that correspond to important behavioral events. Credit for image of sleeping rat: Deepmind Ltd. *Caption continues on next page.*

Figure 2: **Continued caption b)** Conceptual framework of sequence prioritization via interactions between CA3 and CA2. Sequences are comprised of subsequently activated assemblies. Each assembly contains an excitatory (E) and an inhibitory (I) population. Sequence s^0 contains more neurons per assembly compared to s^1 and s^2. Because of its competitive advantage s^0 is considered strong, while s^1 and s^2 are weak. Inside an assembly, excitatory and inhibitory populations are recurrently connected. Assemblies inside and between sequences interact, but for simplicity projections are restricted to plastic feed-forward excitation (E to E) and feed-forward inhibition (E to I) of subsequent assemblies. For visual clarity we only highlight the complete projections for s_1. We assume that between assemblies of different sequences feed-forward inhibition exceeds feed-forward excitation. Between CA3 and CA2 feed-forward inhibition is particularly strong (thicker red arrow). During the animal's experience sequential activation of assemblies leads to potentiation of feed-forward excitation between subsequently activated assemblies, allowing replay during rest. Feedforward excitation from CA3 to CA2 is particularly restricted and only potentiated if activity coincides with the release of vasopressin (AVP), oxytocin (OXT) or substance P (SP). Feed-forward inhibition from CA3 to CA2 can be reduced via inhibitory long term depression (iLTD) or input-timing dependent plasticity (ITDP). **c)** Mutual potentiation is required for weak CA3 and CA2 sequences to win sequence competition during replay. In our conceptual framework the first assembly of each sequence is activated during a replay event. Feed-forward inhibition between assemblies leads to a winner take-all scenario. For clarity, blue lines indicate that a projection is dominated by feed-forward inhibition and red arrows indicate that feed-forward excitation dominates. Without preferential interactions between s_1 and s_2, lower left corner, the strong sequence s_0 manages to inhibit the other sequences. Unilateral potentiation between the weak sequences, upper left and lower right corner, is not sufficient because of increased feedback inhibition in the next time step. Only bidirectional potentiation, upper right corner, allows both weak sequences to support each others replay and to win over the strong sequence. Feed-forward potentiation between CA3 and CA2 can occur both via increased excitation because of neuromodulation or via weakening of inhibition. Without excitatory plasticity inside CA2, dark green line, more potentiation is required to ensure successful replay of both sequences.

7 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 able to generate and, in the presence of a salience cue, prioritize sequences for replay. We assign a role to limited plasticity, selective neuromodulation and input-timing-dependent plasticity at CA3-CA2 synapses.

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, 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, (Omer et al., 2018; Danjo et al., 2018) indicate that the hippocampus represents social information similar to other episodic memories (Buzsáki and 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. If not falsified, we expect that further details will be added with time. So far, it is not clear whether the different mechanisms of neuromodulation 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 (Raam et al., 2017; Lin et al., 2018) and ITDP (Leroy et al., 2017). In any case, the ITDP/enkephalin mechanism 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). It is therefore conceivable that ITDP is active in the baseline mode and the other neuromodulatory substances work on top of it.

8 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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References

Alexander, G., Brown, L., Farris, S., Lustberg, D., Pantazis, C., Gloss, B., Plummer, N., Riddick, N., Moy, S., Jensen, P., and Dudek, S. (2017). CA2 neuronal activity controls hippocampal oscillations and social behavior. *bioRxiv*, page 190504.

Alexander, G. M., Farris, S., Pirone, J. R., Zheng, C., Colgin, L. L., and Dudek, S. M. (2016). Social and novel contexts modify hippocampal CA2 representations of space. *Nature Communications*, 7.

Allen, T. A., Morris, A. M., Mattfeld, A. T., Stark, C. E., and Fortin, N. J. (2014). A sequence of events model of episodic memory shows parallels in rats and humans. *Hippocampus*, 24(10):1178–1188.

Allen, T. A., Salz, D. M., McKenzie, S., and Fortin, N. J. (2016). Nonspatial sequence coding in CA1 neurons. *The Journal of Neuroscience*, 36(5):1547–1563.

Bartesaghi, R. and Gessi, T. (2004). Parallel activation of field CA2 and dentate gyrus by synaptically elicited perforant path volleys. *Hippocampus*, 14(8):948–963.

Bazelot, M., Dinocourt, C., Cohen, I., and Miles, R. (2010). Unitary inhibitory field potentials in the CA3 region of rat hippocampus. *The Journal of Physiology*, 588(12):2077–2090.

Benoy, A., Dasgupta, A., and Sajikumar, S. (2018). Hippocampal area CA2: an emerging modulatory gateway in the hippocampal circuit. *Experimental Brain Research*, pages 1–13.

Beyeler, A., Retailleau, A., Molter, C., Mehidi, A., Szabadics, J., and Leinekugel, X. (2013). Recruitment of perisomatic inhibition during spontaneous hippocampal activity in vitro. *PLOS One*, 8(6):e66509.

Boehringer, R., Polygalov, D., Huang, A. J., Middleton, S. J., Robert, V., Wintzer, M. E., Piskorowski, R. A., Chevaleyre, V., and McHugh, T. J. (2017). Chronic loss of CA2 transmission leads to hippocampal hyperexcitability. *Neuron*, 94(3):642–655.

Borhegyi, Z. and Leranth, C. (1997). Substance P innervation of the rat hippocampal formation. *Journal of Comparative Neurology*, 384(1):41–58.

Botcher, N. A., Falck, J. E., Thomson, A. M., and Mercer, A. (2014). Distribution of interneurons in the CA2 region of the rat hippocampus. *Frontiers in Neuroanatomy*, 8.

Buzsáki, G. and Tingley, D. (2018). Space and time: the hippocampus as a sequence generator. *Trends in Cognitive Sciences*, 22(10):853–869.

Carstens, K. E., Phillips, M. L., Pozzo-Miller, L., Weinberg, R. J., and Dudek, S. M. (2016). Perineuronal nets suppress plasticity of excitatory synapses on CA2 pyramidal neurons. *The Journal of Neuroscience*, 36(23):6312–6320.

Chafai, M., Corbani, M., Guillon, G., and Desarménien, M. G. (2012). Vasopressin inhibits LTP in the CA2 mouse hippocampal area. *PLOS One*, 7(12):e49708.

Chenkov, N., Sprekeler, H., and Kempter, R. (2017). Memory replay in balanced recurrent networks. *PLOS Computational Biology*, 13(1):e1005359.

Chevaleyre, V. and Siegelbaum, S. A. (2010). Strong CA2 pyramidal neuron synapses define a powerful disynaptic cortico-hippocampal loop. *Neuron*, 66(4):560–572.

Choi, W. K., Wirtshafter, D., Park, H.-J., Lee, M.-S., Her, S., and Shim, I. (2012). The characteristics of supramammillary cells projecting to the hippocampus in stress response in the rat. *The Korean Journal of Physiology & Pharmacology*, 16(1):17–24.

Cui, Z., Gerfen, C. R., and Young, W. S. (2013). Hypothalamic and other connections with dorsal CA2 area of the mouse hippocampus. *Journal of Comparative Neurology*, 521(8):1844–1866.

Danjo, T., Toyoizumi, T., and Fujisawa, S. (2018). Spatial representations of self and other in the hippocampus. *Science*, 359(6372):213–218.

Dasgupta, A., Baby, N., Krishna, K., Hakim, M., Wong, Y. P., Behnisch, T., Soong, T. W., and Sajikumar, S. (2017). Substance P induces plasticity and synaptic tagging/capture in rat hippocampal area CA2. *Proceedings of the National Academy of Sciences*, 114(41):E8741–E8749.

Deuchars, J. and Thomson, A. (1996). CA1 pyramid-pyramid connections in rat hippocampus in vitro: dual intracellular recordings with biocytin filling. *Neuroscience*, 74(4):1009–1018.

DeVito, L. M., Konigsberg, R., Lykken, C., Sauvage, M., Young, W. S., and Eichenbaum, H. (2009). Vasopressin 1b receptor knock-out impairs memory for temporal order. *The Journal of neuroscience*, 29(9):2676–2683.

Diba, K. and Buzsáki, G. (2007). Forward and reverse hippocampal place-cell sequences during ripples. *Nature Neuroscience*, 10(10):1241.

Dupret, D., O'Neill, J., Pleydell-Bouverie, B., and Csicsvari, J. (2010). The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nature Neuroscience*, 13(8):995–1002.

Fernández-Ruiz, A., Oliva, A., de Oliveira, E. F., Rocha-Almeida, F., Tingley, D., and Buzsáki, G. (2019). Long-duration hippocampal sharp wave ripples improve memory. *Science*, 364(6445):1082–1086.

Gluck, M. A. and Rumelhart, D. E. (1990). *Neuroscience and Connectionist Theory*, volume 1. Psychology Press.

Hitti, F. L. and Siegelbaum, S. A. (2014). The hippocampal CA2 region is essential for social memory. *Nature*, 508(7494):88–92.

Ishizuka, N., Cowan, W. M., and Amaral, D. G. (1995). A quantitative analysis of the dendritic organization of pyramidal cells in the rat hippocampus. *Journal of Comparative Neurology*, 362(1):17–45.

Ishizuka, N., Weber, J., and Amaral, D. G. (1990). Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. *Journal of Comparative Neurology*, 295(4):580–623.

Ito, M., Shirao, T., Doya, K., and Sekino, Y. (2009). Three-dimensional distribution of fos-positive neurons in the supramammillary nucleus of the rat exposed to novel environment. *Neuroscience Research*, 64(4):397–402.

Jadhav, S. P., Kemere, C., German, P. W., and Frank, L. M. (2012). Awake hippocampal sharp-wave ripples support spatial memory. *Science*, 336(6087):1454–1458.

Kay, K., Sosa, M., Chung, J. E., Karlsson, M. P., Larkin, M. C., and Frank, L. M. (2016). A hippocampal network for spatial coding during immobility and sleep. *Nature*, 531(7593):185.

Kohara, K., Pignatelli, M., Rivest, A. J., Jung, H.-Y., Kitamura, T., Suh, J., Frank, D., Kajikawa, K., Mise, N., Obata, Y., et al. (2014). Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits. *Nature Neuroscience*, 17(2):269–279.

Landgraf, R., Neumann, I., and Pittman, Q. J. (1991). Septal and hippocampal release of vasopressin and oxytocin during late pregnancy and parturition in the rat. *Neuroendocrinology*, 54(4):378–383.

Lee, H., Wang, C., Deshmukh, S., and Knierim, J. (2015). Neural population evidence of functional heterogeneity along the CA3 transverse axis: Pattern completion versus pattern separation. *Neuron*, 87(5):1093 – 1105.

Lee, S. E., Simons, S. B., Heldt, S. A., Zhao, M., Schroeder, J. P., Vellano, C. P., Cowan, D. P., Ramineni, S., Yates, C. K., Feng, Y., et al. (2010). Rgs14 is a natural suppressor of both synaptic plasticity in CA2 neurons and hippocampal-based learning and memory. *Proceedings of the National Academy of Sciences*, 107(39):16994–16998.

Leroy, F., Brann, D. H., Meira, T., and Siegelbaum, S. A. (2017). Input-timing-dependent plasticity in the hippocampal CA2 region and its potential role in social memory. *Neuron*, 95(5):1089–1102.

Leutgeb, J. K., Leutgeb, S., Moser, M.-B., and Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science*, 315(5814):961–966.

Li, X.-G., Somogyi, P., Ylinen, A., and Buzsaki, G. (1994). The hippocampal CA3 network: an in vivo intracellular labeling study. *Journal of Comparative Neurology*, 339(2):181–208.

Lin, Y.-T., Hsieh, T.-Y., Tsai, T.-C., Chen, C.-C., Huang, C.-C., and Hsu, K.-S. (2018). Conditional deletion of hippocampal CA2/CA3a oxytocin receptors impairs the persistence of long-term social recognition memory in mice. *Journal of Neuroscience*, 38(5):1218–1231.

Lu, L., Igarashi, K. M., Witter, M. P., Moser, E. I., and Moser, M.-B. (2015). Topography of place maps along the CA3-to-CA2 axis of the hippocampus. *Neuron*, 87(5):1078–1092.

MacDonald, C. J., Lepage, K. Q., Eden, U. T., and Eichenbaum, H. (2011). Hippocampal "time cells" bridge the gap in memory for discontiguous events. *Neuron*, 71(4):737–749.

Mankin, E. A., Diehl, G. W., Sparks, F. T., Leutgeb, S., and Leutgeb, J. K. (2015). Hippocampal CA2 activity patterns change over time to a larger extent than between spatial contexts. *Neuron*, pages 190–201.

Marr, D. (1971). Simple memory: a theory for archicortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 262:23–81.

Meira, T., Leroy, F., Buss, E. W., Oliva, A., Park, J., and Siegelbaum, S. A. (2018). A hippocampal circuit linking dorsal CA2 to ventral CA1 critical for social memory dynamics. *Nature Communications*, 9(1):4163.

Middleton, S. J. and McHugh, T. J. (2019). CA2: A highly connected intrahippocampal relay. *Annual Review of Neuroscience*, 43:2020.

Miles, R. and Wong, R. (1986). Excitatory synaptic interactions between CA3 neurones in the guinea-pig hippocampus. *The Journal of Physiology*, 373:397.

Mishra, R. K., Kim, S., Guzman, S. J., and Jonas, P. (2016). Symmetric spike timing-dependent plasticity at CA3-CA3 synapses optimizes storage and recall in autoassociative networks. *Nature Communications*, 7.

Miyata, S., Ishiyama, M., Shibata, M., Nakashima, T., and Kiyohara, T. (1998). Infant cold exposure changes fos expression to acute cold stimulation in adult hypothalamic brain regions. *Neuroscience Research*, 31(3):219–225.

Nasrallah, K., Piskorowski, R. A., and Chevaleyre, V. (2015). Inhibitory plasticity permits the recruitment of CA2 pyramidal neurons by CA3. *eneuro*, 2(4):ENEURO–0049.

Nasrallah, K., Piskorowski, R. A., and Chevaleyre, V. (2016). Bi-directional interplay between proximal and distal inputs to CA2 pyramidal neurons. *Neurobiology of Learning and Memory*.

Nasrallah, K., Therreau, L., Robert, V., Huang, A. J., McHugh, T. J., Piskorowski, R. A., and Chevaleyre, V. (2019). Routing hippocampal information flow through parvalbumin interneuron plasticity in area CA2. *Cell reports*, 27(1):86–98.

Okamoto, K. and Ikegaya, Y. (2018). Hippocampal CA2-CA2 excitatory synapses. In *Federation of European Neuroscience Societies - Forum*.

Okuyama, T. (2017). Social memory engram in the hippocampus. *Neuroscience Research*.

Okuyama, T., Kitamura, T., Roy, D. S., Itohara, S., and Tonegawa, S. (2016). Ventral CA1 neurons store social memory. *Science*, 353(6307):1536–1541.

Oliva, A., Fernández-Ruiz, A., Buzsáki, G., and Berényi, A. (2016). Role of hippocampal CA2 region in triggering sharp-wave ripples. *Neuron*.

Omer, D. B., Maimon, S. R., Las, L., and Ulanovsky, N. (2018). Social place-cells in the bat hippocampus. *Science*, 359(6372):218–224.

Pagani, J. H., Zhao, M., Cui, Z., Avram, S. W., Caruana, D. A., Dudek, S. M., and Young, W. (2015). Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. *Molecular Psychiatry*, 20(4):490–499.

Papp, G., Witter, M. P., and Treves, A. (2007). The CA3 network as a memory store for spatial representations. *Learning & memory*, 14(11):732–744.

Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsáki, G. (2008). Internally generated cell assembly sequences in the rat hippocampus. *Science*, 321(5894):1322–1327.

Raam, T., McAvoy, K. M., Besnard, A., Veenema, A., and Sahay, A. (2017). Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. *Nature Communications*, 8(1):2001.

Simons, S. B., Caruana, D. A., Zhao, M., and Dudek, S. M. (2012). Caffeine-induced synaptic potentiation in hippocampal CA2 neurons. *Nature Neuroscience*, 15(1):23.

Simons, S. B., Escobedo, Y., Yasuda, R., and Dudek, S. M. (2009). Regional differences in hippocampal calcium handling provide a cellular mechanism for limiting plasticity. *Proceedings of the National Academy of Sciences*, 106(33):14080–14084.

Singer, A. C., Carr, M. F., Karlsson, M. P., and Frank, L. M. (2013). Hippocampal swr activity predicts correct decisions during the initial learning of an alternation task. *Neuron*, 77(6):1163–1173.

Smith, A., Avram, S. W., Cymerblit-Sabba, A., Song, J., and Young, W. (2016). Targeted activation of the hippocampal CA2 area strongly enhances social memory. *Molecular Psychiatry*.

Stevenson, E. L. and Caldwell, H. K. (2014). Lesions to the CA2 region of the hippocampus impair social memory in mice. *European Journal of Neuroscience*, 40(9):3294–3301.

Swanson, L., Wyss, J., and Cowan, W. (1978). An autoradiographic study of the organization of intrahippocampal association pathways in the rat. *Journal of Comparative Neurology*, 181(4):681–715.

Tamamaki, N., Abe, K., and Nojyo, Y. (1988). Three-dimensional analysis of the whole axonal arbors originating from single CA2 pyramidal neurons in the rat hippocampus with the aid of a computer graphic technique. *Brain Research*, 452(1):255–272.

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

van Wimersma Greidanus, T. B. and Maigret, C. (1996). The role of limbic vasopressin and oxytocin in social recognition. *Brain Research*, 713(1):153–159.

Wersinger, S., Ginns, E. I., O'carroll, A., Lolait, S., and Young Iii, W. (2002). Vasopressin v1b receptor knockout reduces aggressive behavior in male mice. *Molecular Psychiatry*, 7(9):975–984.

Wersinger, S. R., Caldwell, H. K., Christiansen, M., and Young, W. S. (2007). Disruption of the vasopressin 1b receptor gene impairs the attack component of aggressive behavior in mice. *Genes, Brain and Behavior*, 6(7):653–660.

Wersinger, S. R., Kelliher, K. R., Zufall, F., Lolait, S. J., O'Carroll, A.-M., and Young, W. S. (2004). Social motivation is reduced in vasopressin 1b receptor null mice despite normal performance in an olfactory discrimination task. *Hormones and Behavior*, 46(5):638–645.

Wersinger, S. R., Temple, J. L., Caldwell, H. K., and Young 3rd, W. S. (2008). Disruption of the vasopressin 1b receptor gene impairs the attack component of aggressive behavior in mice. *Endocrinology*, 149(1):116–121.

Young, W. S., Li, J., Wersinger, S. R., and Palkovits, M. (2006). The vasopressin 1b receptor is prominent in the hippocampal area CA2 where it is unaffected by restraint stress or adrenalectomy. *Neuroscience*, 143(4):1031–1039.

Zhang, L. and Hernandez, V. (2013). Synaptic innervation to rat hippocampus by vasopressin-immuno-positive fibres from the hypothalamic supraoptic and paraventricular nuclei. *Neuroscience*, 228:139–162.

Zhao, M., Choi, Y.-S., Obrietan, K., and Dudek, S. M. (2007). Synaptic plasticity (and the lack thereof) in hippocampal CA2 neurons. *The Journal of Neuroscience*, 27(44):12025–12032.