Review article

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 in hippocampus-dependent memory processing. 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 has 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 an auto-associative storage and pattern completion site and CA1 as a novelty or mismatch detector (Hasselmo et al., 1996; Levy, 1989; Marr, 1971; McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; Treves and Rolls, 1994, 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 chronically silencing CA2 pyramidal cells in mice, 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 (Cymerblit-Sabba et al., 2020; Leroy et al., 2017; Meira et al., 2018; Okuyama et al., 2016; Oliva et al., 2020; Smith et al., 2016; Stevenson and Caldwell, 2014, all studies used adult male mice). 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 more general role in hippocampal-dependent memory processing, of which social memory may be just a special case.

In this targeted review, we focus on experimental findings and theoretical proposals that suggest a broader role for CA2. The article is organised as follows: First, in Section 2 we start by briefly reviewing the strategic position of CA2 within the hippocampus. For a more in depth treatment we refer readers to recent reviews (Benoy et al., 2018; Chevaleyre and Piskorowski, 2016; Dudek et al., 2016; Jones and McHugh, 2011; Middleton and McHugh, 2019; Okuyama, 2018; Tzakis and Holahan, 2019). Sections 3–8 each present a separate, self-contained argument for why CA2's role may go beyond social memory. In

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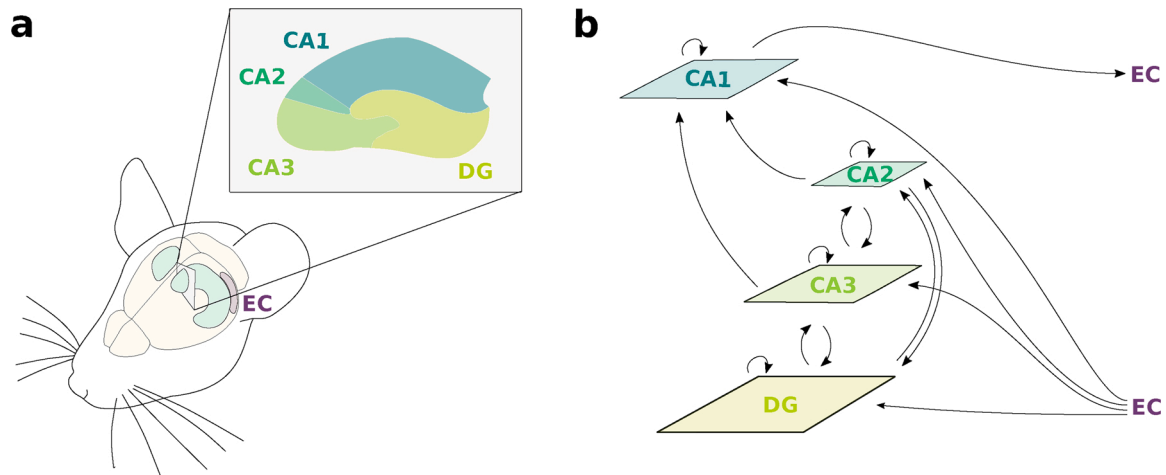
Fig. 1. CA2 is centrally located and well connected within the hippocampus. (a) Coronal section through the dorsal hippocampus of a rodent brain. The illustration shows the position of the hippocampus (green), the entorinal cortex (EC, purple), and magnified, the dentate gyrus (DG), CA3, CA2 and CA1. (b) CA2 has a central role in the hierarchy of recurrently connected hippocampal subnetworks. CA2 sends excitatory projections to all hippocampal regions and receives input from EC and all regions except CA1. Parts of (a) are redrawn from Flores et al. (2018). (For interpretation of color references, the reader is referred to the web version of this article.)

Section 9, we synthesize these different lines of argumentation and connect them with recent proposals that incorporate CA2 in our understanding of how the hippocampus works. Note that here, with an aim to draw overarching insights into the role of CA2, we blend experimental findings from rats, mice, and guinea pigs. It remains unclear to which degree reported properties of CA2 generalize across species.

2. CA2 is centrally located, well connected, and tightly regulated

Traditionally hippocampal computations have been associated with the main trisynaptic circuit connecting EC, DG, 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 (Fig. 1) and receives extensive neuromodulatory projections. From within the hippocampus, pyramidal cells in CA2 receive direct excitatory input from CA3 (Chevaleyre and Siegelbaum, 2010; Ishizuka et al., 1990; Kohara et al., 2014; Li et al., 1994; Tamamaki et al., 1988; Zhao et al., 2007). In addition, a portion of CA2 pyramidal cells also receive input from DG (Kohara et al., 2014; Llorens-Martín et al., 2015; Shinohara et al., 2012). From outside the hippocampus, CA2 pyramidal cells receive 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, diagonal band of Broca, the paraventricular nucleus, and the median raphe nucleus (Cui et al., 2013; Hitti and Siegelbaum, 2014; Leroy et al., 2018; Vertes and McKenna, 2000; Zhang and Hernandez, 2013).

CA2 sends excitatory output throughout the hippocampus and beyond. Pyramidal cells in CA2 form recurrent connections with other CA2 pyramidal cells (Okamoto and Ikegaya, 2019). Further, axons of CA2 pyramidal cells branch extensively in CA1 and CA3 (Hitti and Siegelbaum, 2014; Ishizuka et al., 1990; Kohara et al., 2014; Tamamaki et al., 1988), with projections innervating both the functionally distinct dorsal and ventral hippocampus (Meira et al., 2018; Okuyama et al., 2016). While projections from CA2 to CA1 are unidirectional, CA2 and CA3 are bidirectionally connected (Chevaleyre and Siegelbaum, 2010; Ishizuka et al., 1990; Tamamaki et al., 1988). CA2 and EC may also be bidirectionally connected, as a projection from CA2 back to the EC was observed with retrograde tracing (Rowland et al., 2013), however this was not confirmed with anterograde tracing (Cui et al., 2013; Hitti and Siegelbaum, 2014). 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, diagonal band of Broca, and supramammillary nucleus (Cui et al., 2013; Ishizuka et al., 1995; Leroy et al., 2018), forming reciprocal loops with each of these structures as well.

Perhaps most investigated are the reciprocal interactions between CA2 and CA3. Despite the existence of excitatory synapses in both directions, connections between CA3 and CA2 are dominated by bidirectional feed-forward inhibition (Boehringer et al., 2017; Chevaleyre and Siegelbaum, 2010; Kohara et al., 2014; Nasrallah et al., 2015). 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 Dominguez 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.

In conclusion, the described connectivity patterns stand in stark contrast with the traditional idea of a feedfoward circuit through the hippocampus. Instead, they point towards hippocampal circuitry as a hierarchy of recurrently connected networks, with CA2 taking a central role (see Fig. 1b).

3. CA2's interactions within the dorsal hippocampus are not required for social recognition memory

Dorsal CA2 (dCA2) sends direct excitatory projections throughout the whole hippocampus (Kohara et al., 2014; Meira et al., 2018; Okuyama et al., 2016). But inhibition of neural activity in dorsal CA3 (Chiang et al., 2018), or in dorsal CA1 (dCA1) (Okuyama et al., 2016; Oliva et al., 2020) does not have any measurable effect on social recognition/discrimination (Fig. 2a). 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 the projections from CA2 to dorsal CA1 and CA3?

Dorsal CA2 sends strong excitatory projections to dorsal CA1 (Chevaleyre and Siegelbaum, 2010). Optogenetically silencing these projections in mice destabilizes sequential firing patterns in CA1 and disrupts working memory (MacDonald and Tonegawa, 2021, see Section 6 for effect on network dynamics and Section 8 for behavior). And dorsal CA1 inputs from CA2/CA3a are necessary for novel object recognition memory but not for social recognition memory in mice (Raam et al., 2017). Anatomically, dorsal CA2 preferentially innervates dorsal CA1

a CA2's interactions within the dorsal hippocampus are not required for social recognition memory
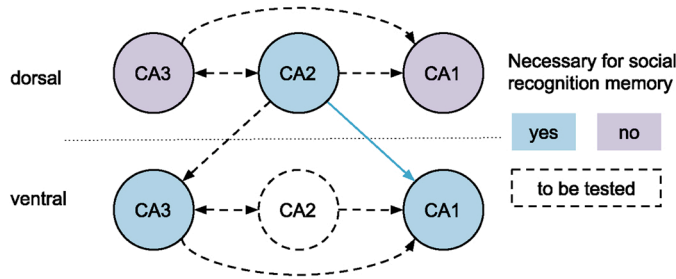
b Novel objects lead to global remapping in CA2
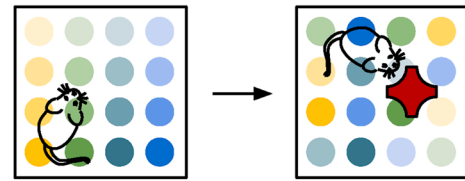
c CA2 receives diverse neuromodulatory input
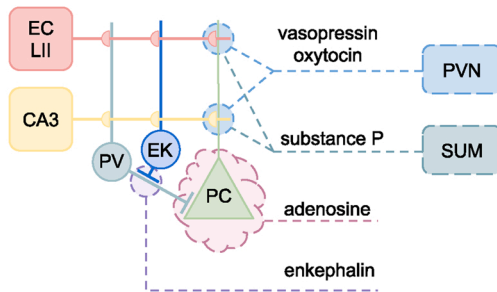
d CA2 deactivation leads to clustered place cells in CA3
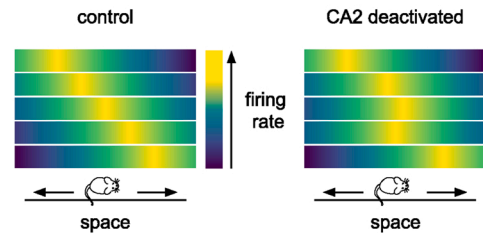
e Ramping units in CA2 increase activity before sharp wave ripples
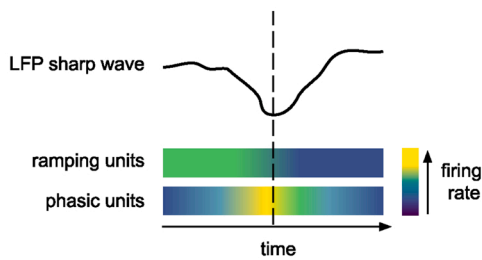
f Acute silencing of CA2 reduces ripple power and increases joint and out-of-ripple reactivation in CA1
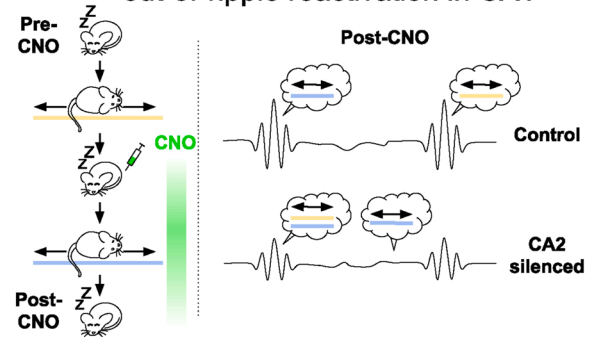
g Opto-inhibition of CA2 impairs spatial alternation and destabilizes episode sequences

h Chronic silencing of CA2 slows contextual habituation

(caption on next page)

Fig. 2. A multitude of experimental observations indicate 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 cro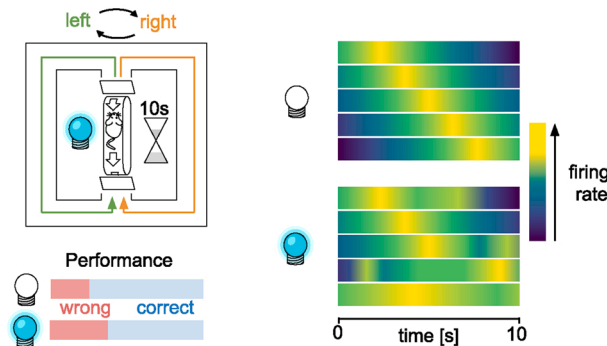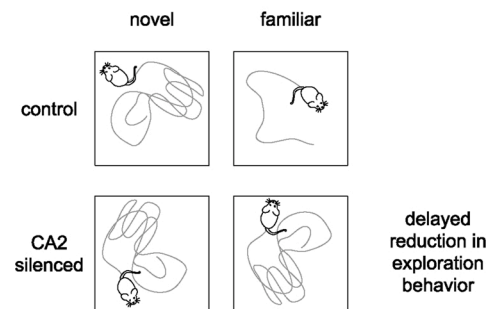ss. (c) Various neuromodulatory substances influence information transmission in CA2's excitatory, green triangle, and inhibitory neurons, round circles. Vasopressin, oxytocin and sustance P modify excitatory synapses from CA3 and EC LII, entorhinal cortex layer II, to pyramidal cells, PC. Adenosine 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) CA2 is silenced during the second of two novel linear tracks (left, yellow before and blue after CNO injection, green). Ripple power in CA1 is reduced in Post-CNO sleep session (right, indicated by smaller ripple fluctuations). Further, both experiences are more frequently reactivated during the same ripple event and reactivation outside of sharp wave ripples is increased. (g) Optogenetic inhibition of CA2 during the delay phase increases the percentage of wrong choices in a spatial alternation task (left). Sequential activity during treadmill running becomes more diffuse and deteriorates across the delay. (h) Chronic silencing of CA2 delays contextual habituation as measured by the length of the motion trajectory, gray, in an open field. (For interpretation of color references, the reader is referred to the web version of this article.)

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 oscillations (Fernandez-Ruiz et al., 2017; Navas-Olive et al., 2020; Schomburg et al., 2014) and sharp wave ripples (Mizuseki et al., 2011; Stark et al., 2014; Valero et al., 2015). How strong projections from dorsal CA2 affect animal behavior by modulating the activity of the functionally and physiologically distinct deep sublayer of dorsal CA1 remains to be elucidated. Genetic markers that distinguish deep from superficial CA1 pyramidal cells will pave the way for targeted interventions to ultimately shed light on the function of the CA2 → deep CA1 subcircuit (Cembrowski et al., 2016; Dobbins et al., 2018; Dong et al., 2009; Navas-Olive et al., 2020).

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), extra-hippocampal inputs (Stanfield and Cowan, 1984), place field properties (Lu et al., 2015), and greater gene expression overlap compared to other hippocampal regions (Lein et al., 2005; McCann et al., 2019; Ochiishi et al., 1999). Further, the two subregions seem to form a densely connected recurrent core. CA2 heavily innervates dorsal CA3a (closest to CA2b) (Ishizuka et al., 1990; Kohara et al., 2014; Mercer et al., 2007; Tamamaki et al., 1988), 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.

4. 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 (Fig. 2b). 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 one 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 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.

Thus, activity in CA2 remaps to novel objects, familiar and novel conspecifics, and follows the rotation of proximal cues. Moreover, CA2 place cells change their firing patterns across exposures to the same environment (Mankin et al., 2015). While a unified explanation is missing, these results have stimulated a number of hypotheses, which we outline in the following paragraphs.

Based on the observation that the spatial map in CA2 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 a downstream region were to read out CA2 remapping as a temporal code, decorrelation of the spatial map should depend on time alone, and not on sensory experiences. Alternatively, experience-induced decorrelation could be viewed as particular events being coded with higher temporal resolution, e.g. more change per unit time.

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 (Middleton and McHugh, 2019; Wintzer et al., 2014). This is further supported by the observation that a subset (40 of 192 neurons, ~20%) of CA2 pyramidal cells increase their firing rate upon encountering a novel, but not a familiar, animal (Donegan et al., 2020, though firing rates for novel vs. familiar animals did not differ in Alexander et al., 2016). In addition, CA2 receives projections from novelty-signalling regions. CA2-projecting neurons in the supra-mammillary nucleus increase their firing for both social and contextual novelty (Chen et al., 2020). The ventral tegmental area (VTA), a major source of dopamine to the hippocampus, preferentially innervates CA2, compared to CA3 and CA1 (Han et al., 2020; Ntamati and Lüscher, 2016). However, its projections to CA2 are predominantly non-dopaminergic. While hypotheses have been proposed to explain the role of novelty-related release of dopamine from VTA into the hippocampus (Duszkiewicz et al., 2019; Lisman and Grace, 2005), the

function of non-dopaminergic VTA projections to CA2 awaits exploration.

It is also conceivable that CA2 activity reflects the importance of an experience to an animal. Consistent with this, CA2 neurons fire in bursts in response to oxytocinergic input (Tirko et al., 2018), presumably a 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. Therefore, future experimental studies should explicitly distinguish between novelty and saliency.

5. 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 (Fig. 2c).

5.1. 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 signalling are likely associated with CA2. A global knockout of the Avpr1b impairs social motivation, social recognition memory and aggressive behavior (DeVito et al., 2009; Wersinger et al., 2002, 2004, 2007, 2008). Accordingly, blocking vasopressin signalling 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 8: Manipulations of CA2 have measurable effects on hippocampal-dependent learning and memory).

At 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 latter 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.

5.2. Oxytocin

Oxytocinergic projections to the hippocampus originate from the paraventricular and supraoptic nucleus (Buijs, 1978; Knobloch et al., 2012). Such fibers are prominent in all regions of the ventral hippocampus, but 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 (Lin et al., 2017; Smith et al., 2016; Tirko et al., 2018).

While the role of hippocampal oxytocin signalling is firmly established in social recognition memory and stress responses, there is only indirect evidence for other behaviours. Injection of oxytocin antiserum in ventral, but not dorsal hippocampus (van Wimersma Greidanus and Maigret, 1996), as well as deletion of oxytocin receptors in dorsal CA2 and CA3a impaired social recognition memory (Lin and Hsu, 2018; Raam et al., 2017). 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 synapses (Pagani et al., 2015). Further, oxytocin receptor activation induced long term potentiation at EC → CA2 synapses, while receptor deletion impaired it (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 ripple-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).

5.3. 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 (Chen et al., 2020; Ito et al., 2009).

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, consistent with the synaptic tagging and capture hypothesis (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.

5.4. 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; Ohno and Watanabe, 1996; Zarrindast and Shafaghi, 1994). 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 3 h after training also shows no effect (Kopf et al., 1999). *In vitro* application of adenosine suppresses sharp wave ripples (Wu et al., 2009), events important for memory consolidation. And CA2 ripples in the first 2 h 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 (Caruana and Dudek, 2020; Muñoz and Solís, 2019). 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 (Muñoz and Solís, 2019; Simons et al., 2012). Muñoz and Solís (2019) showed that adenosine sensitivity of CA2 pyramidal cells 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 9: 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.

5.5. 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 (Blasco-Ibáñez et al., 1998; Fuentealba et al., 2008; Gall et al., 1981; Leroy et al., 2017; Sar et al., 1978). The

corresponding δ-opioid receptor is strongly expressed in CA2 (Duka et al., 1981), mainly in parvalbumin-positive (PV) interneurons (Erbs et al., 2012; Faget et al., 2012; Stumm et al., 2004).

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 δ-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 Chevaleyre, 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 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 signalling 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 the best of 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 feedforward 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).

5.6. Why the neuromodulatory cocktail?

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 min, 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

task and context is 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 (Lin et al., 2018; Raam et al., 2017), 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 aforementioned neuromodulators differ strongly when it comes to 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; Khan et al., 2000; Robert et al., 2020; Yohn et al., 2017). In addition to their release during important behavioral events, many neuromodulators that act on the hippocampus show circadian fluctuations (Deibel and McDonald, 2017; Hartsock and Spencer, 2020; Rawashdeh et al., 2018; Reppert et al., 1981; Snider et al., 2018). Given the neuromodulatory influence over CA2, and in particular over CA3 → CA2 transmission, CA2 may be a key place to look when studying the effect of hippocampal circadian rhythms on learning and memory (Lehr et al., 2021, for a link between hippocampal circadian rhythms and social recognition memory see Hasegawa et al., 2019).

6. CA2 modulates place cells, spike timing, and communication across the hippocampus

Chronic as well as acute silencing of CA2 pyramidal cells affects cellular activity in both CA3 and CA1 (Boehringer et al., 2017). In mice with chronically silenced synaptic transmission specific to CA2 pyramidal neurons via expression of the tetanus neurotoxin light chain, spatial specificity of CA3 and CA1 place cells was reduced and timing of CA3 spikes with respect to the theta oscillation phase was 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 DREADD-mediated inhibition of CA2 did not lead to such pronounced hyper-excitability events, however, a coordinated shift in place field locations was observed (Fig. 2d). 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.

Another study showed that acute optogenetic inhibition of dCA2 → dCA1 projections affects the sequential organisation of CA1 firing patterns (MacDonald and Tonegawa, 2021). Mice were trained to alternate between the left and right arms of a figure eight maze, returning to the center arm before each left/right decision to run on a treadmill for a 10s delay period (see Section 8 for effects on performance). If dorsal CA2 inputs to dorsal CA1 were silenced during track running, the arrangement of CA1 place fields on the track changed for

around 15% of place cells. Therefore, with inputs from CA2 silenced, the same path along the track elicited a modified sequence of CA1 place cell activity. Firing rates, spatial information, sparsity, and firing stability of CA1 place cells remained unaffected. During the delay period, while the animal was not moving through space, silencing dCA2 → dCA1 projections produced stronger effects (MacDonald and Tonegawa, 2021). Out-of-field firing rates increased and firing became more diffuse in time. Information content and firing stability both decreased. Moreover, trial-specific sequences of activity in CA1, previously observed during a mnemonic delay in a similar task (Pastalkova et al., 2008), were more severely disrupted by inhibiting inputs from dorsal CA2 during the delay (48% of cells) than was observed for place cell sequences (Fig. 2g).

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; Kohara et al., 2014; Nasrallah et al., 2015). 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. 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 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, 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 8). 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 (Boehringer et al., 2017) and CA1 (MacDonald and Tonegawa, 2021) place fields indicates that for the same trajectory through space, different cell assemblies become active. The disruption of both spatial and non-spatial sequential firing patterns in CA1 when CA2 inputs are silenced (MacDonald and Tonegawa, 2021) suggests control over both sensory-driven and internally-generated sequence progression in the hippocampus.

7. 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 (Miles et al., 1984; Wittner and Miles, 2007; Wong and Traub, 1983). 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 (Fig. 2e). 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 its influence on SWRs, recent studies have 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 min 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 (Alexander et al., 2018; Boehringer et al., 2017; Oliva et al., 2016, 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.

In a recent study, He et al. (2020) chemogenetically silenced the activity of CA2 pyramidal cells during the second of two novel spatial experiences. The authors observed a variety of effects on sharp wave ripples and reactivation during a subsequent sleep session (see Fig. 2f). In particular, replays were of poorer quality under CA2 inactivation and ripple power in CA1 was reduced. The distribution of reactivation events was shifted towards the second experience, where CA2 had been inactive. Both experiences were more frequently reactivated together during the same sharp wave ripple. These findings implicate CA2 in the selection and reliable progression of sequences during replay.

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). Instead CA2 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.

8. Manipulations of CA2 have measurable effects on 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 in non-social memory tasks. Most studies selectively manipulating CA2 have only identified subtle behavioral changes. In a few cases, especially in non-social tasks with a temporal/sequential component, CA2 has been shown to play an indispensable role.

Mice with chronically silenced CA2 pyramidal cells did 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, in another study, chronically silenced animals habituated to a novel context more slowly (Fig. 2h) (Boehringer et al., 2017). Transiently activating CA2 pyramidal cells with DREADDs increased 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).

Recent findings have clearly shown that inhibiting dorsal CA2 inputs to dorsal CA1 impairs hippocampal-dependent memory (MacDonald and Tonegawa, 2021). In a version of the *delayed spatial alternation* task, mice ran on a figure-eight shaped maze with a treadmill in the central alleyway. They were rewarded if on each trial they alternated between choosing the left and right alleyways, in between always returning to the treadmill in the center for a 10 s delay period. The task required the animals to maintain trial-specific information across this short delay. Optogenetically silencing dCA2 → dCA1 inputs during the 10 s delay disrupted performance (Fig. 2g). However, silencing dCA2 → dCA1 inputs as the animal traversed the left or right alleyways did not.

Further behavioral effects have been demonstrated by selectively disrupting the vasopressin receptor, Avpr1b, which presumably selectively affects CA2 within the hippocampus (see Section 5.1: Vasopressin). Avpr1b KOs show specific deficits in two memory tasks (DeVito et al., 2009), both of which are known to be hippocampus dependent (DeVito and Eichenbaum, 2010; Kesner et al., 2005). 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 across hours. In the *object-trace-odor* task animals were trained to associate an object with an odor presented after a delay of 10 s. 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 led to enhanced object recognition memory and spatial learning in the water maze (Lee et al., 2010). Further, global deletion of mineralocorticoid receptors, within the hippocampus preferentially expressed in CA2, enabled plasticity at CA3 → CA2 excitatory projections; and CA2-specific deletion of mineralocorticoid receptors increased the behavioral response to novel objects (McCann et al., 2019). 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-adolescent and adult animals (Dominguez et al., 2019). Taken together, CA2 plasticity can affect behavior and behavior can affect CA2 plasticity.

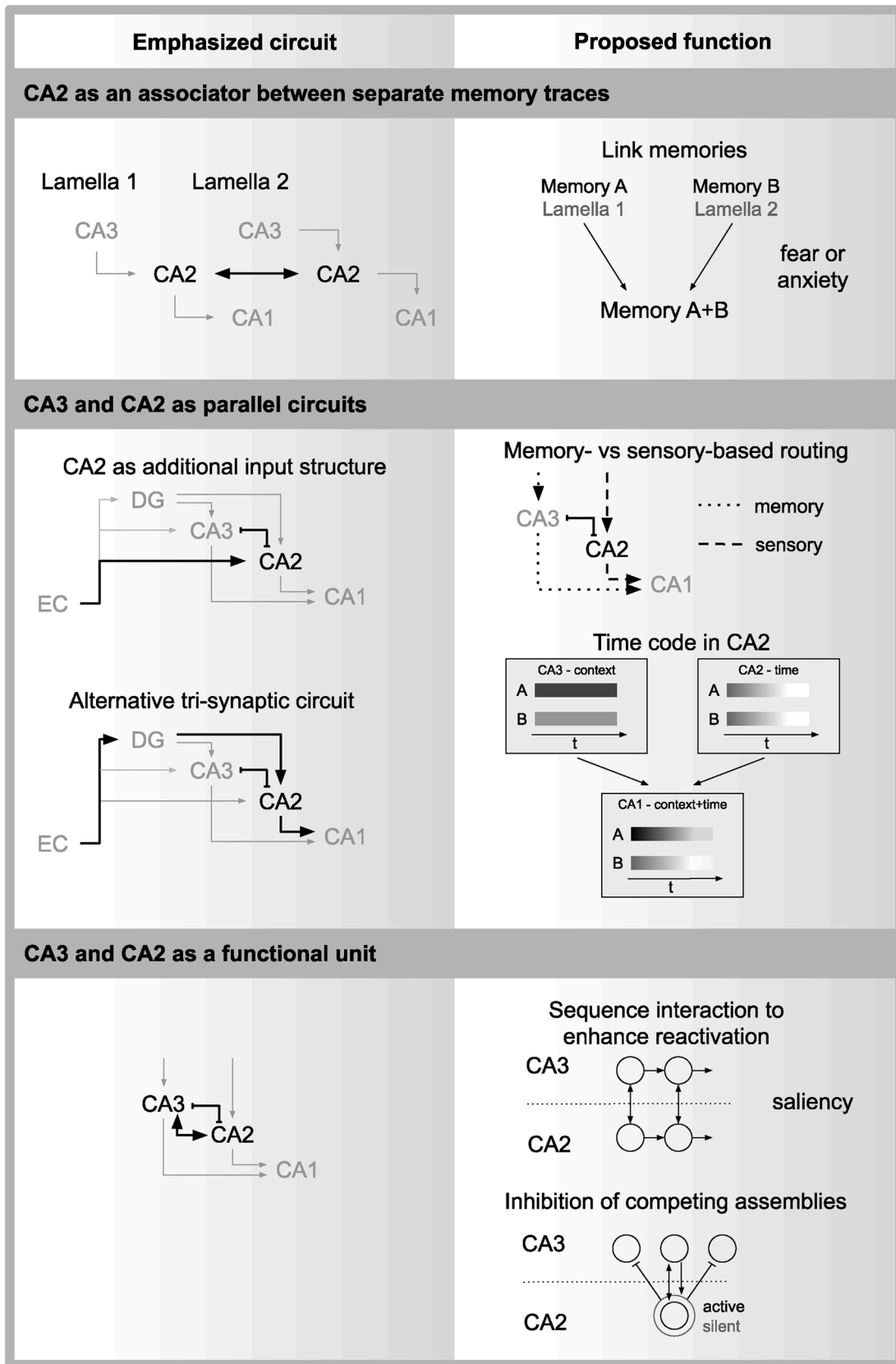While a clear pattern in the behavioral results is yet to emerge, one

Fig. 3. Existing proposals for CA2's role in hippocampal memory processing.

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; MacDonald and Tonegawa, 2021) 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. It will be important to differentiate between working memory (e.g. *object-trace-odor*, DeVito et al., 2009; e.g. *delayed spatial alternation*, MacDonald and Tonegawa, 2021), short term memory (e.g. *what-where-when*, DeVito et al., 2009) and long term memory (e.g. *water task*, Hitti and Siegelbaum, 2014; Lee et al., 2010), and to pinpoint whether CA2 is necessary/sufficient or only influencing aspects of the task. Study design should be able to detect whether effects stem from encoding, consolidation, recall, or perhaps other processes, like planning or signalling novelty/saliency.

9. 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. 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 place cells, spike timing, sequential organisation of firing, 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.

9.1. CA2 as an associator between separate memory traces

In a pioneering proposal, Sekino and Shirao (2006) suggested that CA2 may act as an associator between simultaneously encoded memory traces across different hippocampal lamellae. They suggest this function depends 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 5).

9.2. CA3 and CA2 as parallel circuits

9.2.1. CA2 as an additional input structure

Chevaleyre and Siegelbaum (2010) found that CA2 connects the entorhinal cortex to CA1 via a powerful disynaptic pathway:

EC → CA2 → CA1. Feed-forward inhibition from CA3 to CA2 is suggested to ensure separation between the di- and the classical trisynaptic pathway: EC → DG → CA3 → 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.

9.2.2. 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 a large portion of pyramidal cells in CA2 (Kohara et al., 2014). Thus, besides the disynaptic pathway, CA2 participates in an alternative trisynaptic pathway from EC → DG → CA2 → 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 → vCA1 → NAc circuit are crucial for social recognition memory (Hitti and Siegelbaum, 2014; Meira et al., 2018; Okuyama, 2018; Okuyama et al., 2016). Given that EC → DG projections are also indispensable for social memory (Leung et al., 2018), it is tempting to hypothesize that the EC → DG pathway also recruits the dCA2 → vCA1 → NAc circuit, with CA2 bridging the gap between the dorsal dentate gyrus and ventral CA1. These results suggest that the dCA2 → vCA1 → 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?

9.2.3. 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 (Middleton and McHugh, 2019; Wintzer et al., 2014). 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 vs. 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 (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.

9.2.4. 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 4. Thus it remains unclear whether variability in CA2 place cell firing over time is a coding scheme or a byproduct of another process.

Recent work has further considered spatial vs. temporal coding as being separated in the hippocampal circuit (MacDonald and Tonegawa, 2021). In a *delayed spatial alternation* task, optogenetically silencing dorsal CA2 inputs to dorsal CA1 specifically during the 10 s delay period altered the sequential organisation of activity in CA1 and disrupted performance. MacDonald and Tonegawa (2021) suggest that this is indicative of CA2 involvement in "temporal coding", presumably since the animal was not moving through space during the delay. However, it is worth noting that animals are not required to keep track of time in this task. Instead, animals must remember which arm they previously traversed in order to choose the correct arm after the delay. Thus, it is conceivable that processes maintaining the memory of where the animal came from were disrupted, or perhaps planning processes were compromised, as unlike temporal coding, these faculties were required to solve the task.

Stronger effects on sequential firing patterns and behavior during the delay than while running along the track observed by MacDonald and Tonegawa (2021) could speak to CA2 involvement in intrinsic vs. externally driven hippocampal sequences. It has been suggested that self-organised, internal mechanisms generate sequential firing during a delay period in which a memory must be held and a plan established (Pastalkova et al., 2008). In contrast, during navigation, sequential patterns are likely driven by environmental/self-motion cues (Pastalkova et al., 2008). Pastalkova et al. (2008) suggest that during learning, the temporal order of external events should specify neuronal representations and then during recall, imagination, or action planning, the sequence identity would be determined by the intrinsic dynamics of the network. Taken together, these results point to a role for CA2 in the organisation of *internally generated* sequential firing patterns. It is noteworthy that this seems at odds with the suggestion of CA2 involvement in sensory-based processing (Middleton and McHugh, 2019). Instead, following this line of argumentation one might expect CA2 to be recruited in internally-driven memory-based processing or planning.

9.3. 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 5).

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 (Chevaleyre and Siegelbaum, 2010; Kohara et al., 2014). 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.

9.3.1. Prioritization of important experiences for replay

The hardware described above may support a unique function in the CA3-CA2 recurrent system. Stöber et al. (2020) propose that, together, CA3 and CA2 can select and prioritize important activity sequences for replay. Neuromodulator release during an important experience may 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).

A core prediction of the proposal by Stöber et al. (2020) is that the interplay between CA3 and CA2 controls which events are replayed during memory consolidation. Indeed, recent experimental findings support this hypothesis (He et al., 2020). Chemogenetically silencing CA2 pyramidal cells during the second of two novel spatial experiences affected occurrence and fidelity of reactivation events in subsequent rest (see Section 7). In particular, this intervention led to aberrant co-reactivation of both experiences during individual sharp wave ripple events. These findings can be explained by a critical role of CA2 for mediating competition between activity sequences in CA3 (Stöber et al., 2020).

10. 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 place cells and spike timing in CA3 and CA1, (c) organising internally-generated sequential firing patterns in CA1, (d) 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), working memory (MacDonald and Tonegawa, 2021), 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 (Alexander et al.,

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Box 1
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.

1. 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 units which are either positively or negatively modulated by sharp wave ripples a consequence of physiological heterogeneity in pyramidal cells?
2. 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).
3. Release of the various neuromodulatory substances need to be characterized in naturalistic behaviors, for example by optical imaging of neuromodulation (Ravotto et al., 2020).
4. 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 cellular 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?

2016; Donegan et al., 2020; 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 → CA2 and CA3 → CA2, 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 (see Box 1). 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.

Acknowledgments

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