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Memory circuits: CA2

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The hippocampus is a central region in the coding of spatial, temporal and episodic memory. Recent discoveries have revealed surprising and complex roles of the small area CA2 in hippocampal function. Lesion studies have revealed that this region is required for social memory formation. Area CA2 is targeted by extra-hippocampal paraventricular inputs that release vasopressin and can act to enhance social memory performance. *In vivo* recordings have revealed nonconventional activity by neurons in this region that act to both initiate hippocampal sharp-wave ripple events as well as encode spatial information during immobility. Silencing of CA2 pyramidal neurons has revealed that this area also acts to control hippocampal network excitability during encoding, and this balance of excitation and inhibition is disrupted in disease. This review summarizes recent findings and attempts to integrate these results into pre-existing models.

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Introduction

From a cellular and molecular perspective, area CA2 has many unique properties that unquestionably enable this small region to fulfill its role (as reviewed by [1]) in hippocampal function. In this review, we aim to present how the small region in the hippocampus is participating in two newly discovered roles: social memory formation and hippocampal spatial memory.

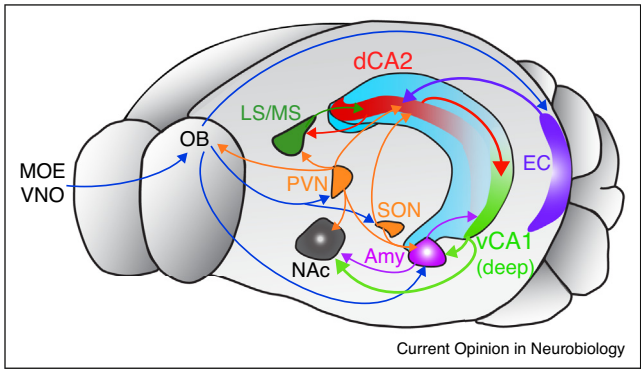
Hippocampal area CA2 and social memory

So far, activity in area CA2 has been linked to only a few hippocampal-dependent behaviors including social aggressivity and social recognition memory. A role for area CA2 in social memory was assessed using transgenic mice (AMIGO-cre) and viral injection to express tetanus toxin in CA2 pyramidal neurons and block synaptic transmission onto their targets [2••]. This study, as well as a study using excitotoxic lesion of dorsal CA2 [3••] have demonstrated that area CA2 is required for social memory formation. While the hippocampus is well acknowledged as being a key structure for spatial, temporal and episodic memory [4], the hippocampus is usually not included in brain circuitry underlying social cognition (for instance see [5]). Now that numerous studies have demonstrated a role of the hippocampus in social recognition memory, we will try to describe how the hippocampus, and in particular area CA2, can integrate into pre-existing models of social cognition (Figure 1).

Sensory inputs are key mediators in the recognition of a conspecific. In rodents, odors, pheromones and ultrasonic vocalizations are important cues for social memory. Processed sensory information is conveyed to the entorhinal cortex, and cells in layers II and III send inputs into the dentate gyrus and distal dendritic compartments of all CA regions. Recent studies have strongly implicated the lateral entorhinal cortex in olfactory learning [6,7]. Interestingly, it was shown that in contrast to other CA areas, CA2 pyramidal cells are very strongly excited by cortical input stimulation [8•]. Further studies revealed that the unique dendritic arborization of CA2 pyramidal cells as well as the composition of voltage-gated ion channels on the dendritic membrane allow for efficient transmission of synaptic input from distal dendrites [9,10]. Concomitantly with the cortical sensory information, CA2 pyramidal neurons receive inputs from numerous structures involved in social cognition such as the amygdala, the septum and the hypothalamic supraoptic and paraventricular nuclei (SON and PVN) [11]. Neurons from the SON and PVN synthesize and release oxytocin (OT) and vasopressin (AVP), two neuropeptides well-known to contribute to social behaviors and cognition [12]. Recently, it has been shown that area CA2 and nearby area CA3a is enriched in OT receptors in female mice [13]. Likewise, AVP V1b receptors are highly enriched in area CA2 [14]. Social memory formation was impaired in KO mice for V1b receptors or after removal of OT receptors in CA2/CA3a [15,16•]. Conversely, targeted optogenetic activation of AVP fibers in dorsal CA2 during a social interaction task strongly increased the duration of social recognition in mice [17••]. Therefore, the hypothalamic projection to dorsal CA2 appears to be a critical component of social memory formation.

Is social information encoded in area CA2? One possibility is that CA2 pyramidal cell activity is modulated by

Figure 1



Area CA2 and the hippocampus as central components of the brain social network. Olfactory cues coming from the main olfactory epithelium (MOE) and the vomeronasal organ (VNO), as well as auditory cues (not depicted) are playing a key role in social recognition in rodents. The olfactory bulb (OB) sends inputs to diverse structures involved in social cognition as well as to the entorhinal cortex (EC). The EC sends processed sensory information to the hippocampus and in particular to CA2 pyramidal neurons that are strongly connected by EC layer II neurons. Pyramidal neurons in CA2 project to the ventral part of CA1 and in particular to the deep CA1 neurons. Deep pyramidal neurons in vCA1 participate in encoding social information [19] and project to the shell of the nucleus accumbens (NAc). Deep CA1 neurons also project to the amygdala (Amy), which sends connection back to the ventral hippocampus. Area CA2 also receives inputs from diverse structures involved in social cognition such as the lateral and medial septum (LS/MS), the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). The peptides oxytocin and vasopressin that are released by PVN and SON neurons play a key role in social memory [12]. Both oxytocin and vasopressin receptors are strongly enriched in area CA2 and are important for social memory formation [13,14]. Increasing vasopressin release in area CA2 strongly enhances the duration of social memory [17••]. Oxytocin and vasopressin are also released in most structures involved in social cognition such as the Amy, the NAc, the LS/MS and the OB.

numerous structures during social context, and this altered CA2 output acts on the hippocampal network as well as other brain areas to enable encoding of social information in other regions. Consistently, CA2 pyramidal neurons have been shown to directly project to several brain regions important for social cognition: the medial and lateral septum [11], and potentially cortical areas [18]. This hypothesis is supported by a recent study revealing the localization of social memory engrams in ventral CA1 pyramidal cells [19]. This paper made clever use of optogenetics, transgenic mouse lines and cfos: transactivator viral constructs to label and later manipulate unique populations of cells active during a particular social recognition task, that is, the social memory engram. The CA1 cells that were part of this engram were preferentially located in the deep pyramidal layer. This is of relevance because CA2 PNs were previously shown to contact deep CA1 cells more strongly than superficial cells [20•]. In addition, deep CA1 pyramidal neurons have been shown to project to the amygdala, prefrontal cortex and the nucleus accumbens [19,21], structures involved in social behaviors. Area CA3, which also receives and important input from area CA2 that acts to control network activity [22••] has also recently been found to play a necessary role in social recognition memory [23].

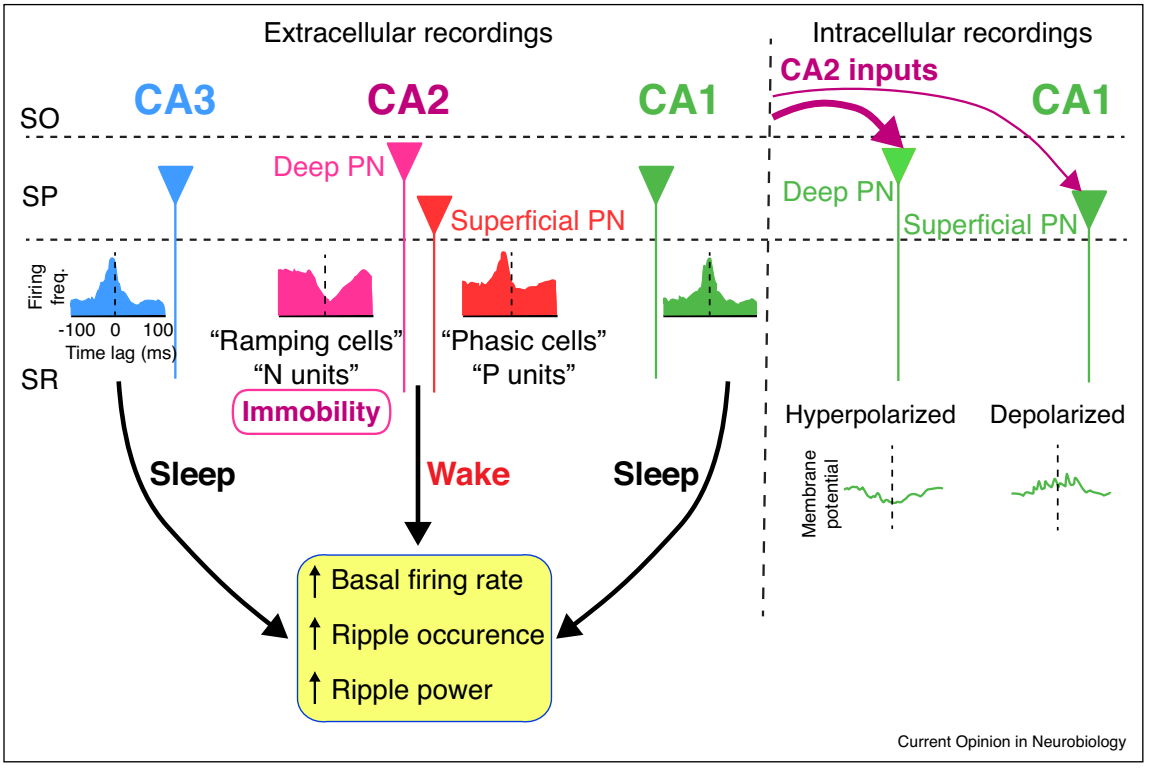
Thus, in conclusion, it is unlikely that area CA2 is itself encoding social information. Rather, this region is readily modulated by vasopressin during social interactions and equipped to serve as a hub, receiving numerous inputs and sending an array of outputs to influence information encoding in areas CA1 and CA3.

Does area CA2 encode spatial information?

In the past three years, several studies have examined area CA2 in the customary context of spatial encoding by hippocampal place cell activity [24–28]. The culmination of these *in vivo* recording studies has conclusively found that, in essence, place cells in area CA2 display low-precision spatial coding. CA2 place cells are more numerous, have larger and more place fields per place cell and fire more action potentials on average without an increased firing rate inside the receptive field. Furthermore, space representation by place cells in area CA2 is much poorer than neighboring CA1 and CA3, as CA2 place cells fail to remap with changing environment [24,26], or displacement of cues [25]. While contextual changes induced little remapping in area CA2, place cells in this region were found to remap in the same context on the order of minutes, thus motivating the authors to propose that CA2 cells do not encode spatial information like areas CA1 or CA3, but perhaps this remapping activity provides an internal representation of some other aspect of the episodic experience, such as time [26]. A separate study recording place cell activity in areas CA1 and CA2 reported global remapping only in area CA2 upon presentation of both novel and familiar social stimuli, as well as with novel object presentation [27]. From these results, the authors postulated that CA2 neurons act to modulate pre-existing hippocampal spatial representations by remapping with particular social and novel stimuli. Prior experiments using immediate-early gene expression to assess activity in different hippocampal regions also found evidence that only area CA2 contained different active ensembles of cells following presentation to very subtle contextual changes within tens of minutes of exposure [29]. This data supports the hypothesis that area CA2 may be acting as a conflict detector, displaying enhanced activity when the present context conflicts with established internal representation.

There is recent evidence that area CA2 may be playing a larger role in hippocampal network function and information encoding. It has been demonstrated by several recent studies that CA2 pyramidal neurons fire action potentials in a non-stereotypic manner during sharp-wave ripples (Figure 2) [30••,31••,32,33]. Sharp-wave ripples

Figure 2



Activity pattern of CA2 and CA1 pyramidal neurons during sharp-wave ripple. Illustration of the activity of pyramidal neurons (PN) in the different hippocampal areas as observed from *in vivo* extra-cellular and intra-cellular recordings. Based on extracellular recordings performed in [30••,31••], the histogram next to each population of cell illustrates the unit firing frequency of the neurons centered around a sharp-wave ripple complex (SWR). Time zero, indicated by a dotted line, corresponds to the trough of the SW recorded in CA1 *stratum radiatum* (*SR*). In these studies, the majority of CA3 and CA1 units increased their firing frequency during a SWR complex. In area CA2, units located close to *stratum radiatum* (*SR*) (Superficial PN) also increased their firing frequency during SWRs. These units were called 'Phasic cells' in [31••] and likely correspond to the P units recorded in [30••]. Strikingly, the CA2 units located close to *stratum oriens* (*SO*) displayed a drop in their firing frequency during SWR complex (called 'Ramping cells,' [31••] or 'N units,' [30••]). Interestingly, while CA3 and CA1 pyramidal neurons encode space during locomotion, 'N units' in area CA2 were found to encode space during immobility [30••]. Furthermore, the activity of pyramidal neurons was found to be state dependent, with both CA1 and CA3 units increasing their basal firing rate, SWR number and ripple power during sleep [31••]. In contrast, firing rate, ripple occurrence and ripple power were observed to be increased in CA2 units during wake. CA2 pyramidal neurons have been found to have a stronger excitatory connection to deep CA1 PNs [20•]. Interestingly, intracellular recordings of CA1 PNs during SWR events revealed that the membrane potential of superficial CA1 PNs tended to be depolarized and more likely to participate during the SWR than deep CA1 PNs, which were hyperpolarized during the SWR and unlikely to fire action potentials during the SWR event [32].

are brief massively synchronous network events due to rapid action potential firing of pyramidal cells and interneurons that occur in response to strong excitatory drive. These events occur broadly through the hippocampus and cortex, and are a critical component of memory consolidation [34]. Interestingly, area CA2 has been proposed to participate in the generation of hippocampal sharp-wave ripples. Experiments using multiple high-density silicon probes to simultaneously record from every CA region reported that deep CA2 cells, called 'ramping cells' decrease their firing activity before the sharp-wave. Furthermore, superficial cells in area CA2 were found to fire earliest during the sharp-wave ripple event as compared to CA3 and CA1 pyramidal neurons [31••]. Moreover, this study found that a large fraction of sharp-wave ripples were generated in area CA2 and then transferred to areas CA3, or directly transferred to CA1 [31••]. Furthermore, while the vast majority of CA1 and CA3 pyramidal neurons increase their action potential firing during sharp-wave ripple events occurring in areas CA1, both 'ramping cells' described by Oliva *et al.* and CA2 pyramidal neurons called 'N-units' by Kay *et al.* decrease their firing [30••,31••]. Consistently, sharp electrode recordings in area CA2 during SWR in area CA1 reported a reduction in firing rate [32], and *in vivo* whole-cell recordings in area CA2 showed that the membrane potential of PNs undergoes a hyperpolarization during SWR [33].

A substantial and intriguing finding by Kay *et al.*, was that CA2 'N-units' not only display unusual firing activity, but also encode spatial information with high fidelity during

periods of immobility and sleep [30••]. There was clear correspondence of 'N-unit' activity with behavior, as these cells fired at rates that inversely correlated with locomotion. Furthermore, while these cells did not display spatial coding during active exploration, individual N-units were found to fire at discreet spatial locations during immobility. Furthermore, during non-SWR periods when N-units were actively firing, their activity could be detected broadly throughout the hippocampal network by local field potential (LFP) recordings, resulting in a distinct pattern of activity called 'N-wave' [30••]. This finding, while providing mechanistic evidence of a distinct representation of location during immobility by the hippocampus, raises numerous questions. Is there a secondary hippocampal network encoding information during immobility? What role does N-unit firing activity play in social memory, novelty detection and other cognitive processes?

Area CA2 is set up to be an integrator in the hippocampal network. This region receives input from CA3 pyramidal neurons, the dentate gyrus, entorhinal cortex as well hypothalamic regions and projects broadly to contralateral and ipsi-lateral areas CA3 and CA1 as well as extra-hippocampal structures [11,18,20•]. A recent study that employed both chronic and transient synaptic silencing of CA2 pyramidal neurons revealed that the expansive CA2 network plays a critical role in balancing levels of excitation and inhibition in the hippocampus [22••]. In experiments in which tetanus toxin light-chain was expressed selectively in CA2 pyramidal cells to chronically silent CA2 output, a striking loss of feedforward inhibition between CA2 and CA3 was observed. This excitatory/inhibitory imbalance transformed normal CA1 and CA3 place field firing into spatially triggered network hyperexcitability events. Furthermore, SWRs in areas CA3 and CA1 were partially replaced with epileptiform-like discharges. In addition to showing deficits in social memory, these animals also had impairments of contextual habituation. By transiently silencing CA2 pyramidal neurons with chemogenetic methods, Boerhinger *et al.* observed abnormal remapping of CA1 and CA3 place cells. Altogether, these findings reveal a central role of CA2-mediated inhibition of CA3 that curtails hippocampal network excitability and allows for physiological levels of excitability inside a place field. Hence, area CA2 is involved in shaping place field activity in CA1 and CA3.

As indicated by the Boerhinger *et al.* results, as well as the unorthodox action potential firing behavior of CA2 pyramidal neurons during SWR events [30••,31••], the control and CA2 pyramidal neuron activity by the local inhibitory network is playing a profoundly important role. Fitting with the unusual behavior of this hippocampal region, the inhibitory neurons in area CA2 have several unusual properties. Area CA2 contains a higher density of several subclasses of interneurons [35] with unique morphologies and axonal projections [36–38]. It has been demonstrated in slice physiology that the feedforward inhibition recruited by CA3 stimulation completely prevents CA3 input from evoking action potentials in CA2 pyramidal neurons [8•,39]. Unlike CA3 excitatory inputs onto CA2 pyramidal neurons [40], inhibitory inputs from parvalbumin-expressing interneurons in area CA2 are highly plastic, undergoing a long-term depression upon activation of delta-opioid receptors on the axon terminals [41]. This plasticity can be induced by stimulus of both cortical inputs as well as CA3 [42], indicating that activity-dependent modulation CA2 output could be multi-modal. Furthermore, block of delta-opioid mediated plasticity in the hippocampus has been shown to impair social memory formation [43].

It is important to note that contribution of area CA2 to hippocampal network formation is likely highly relevant in numerous psychiatric and neurodegenerative diseases [44]. In a rodent model of the 22q11.2 deletion syndrome, both the pyramidal cells and interneurons in area CA2 were found to undergo numerous age-dependent changes [45] that correspond to post-mortem findings in patients [46,47]. In summary, in this disease model, the CA2 inhibitory network had reduced plasticity, and the pyramidal neurons were hyperpolarized and inactive. Consistent with lesion and plasticity studies, social recognition memory was found to be disrupted in this model [45]. How the hippocampal network activity and spatial coding is altered in this disease model merits further study.

Conclusion

In the last 5 years, hippocampal area CA2 has been revealed as a necessary component for social memory formation. Much work still remains in order to better understand how area CA2 works in parallel with other CA regions to detect, integrate and encode social information. With this, there is striking evidence that neurons in area CA2 are playing a complex and unexpected role in spatial encoding and sharp-wave ripple generation. Further studies are needed to better understand how activity in area CA2 translates to and modifies intra-hippocampal and extra-hippocampal structures. This will lead to a better understanding of memory formation and also have an important impact on understanding the mechanisms underlying psychiatric disease development.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Dudek SM, Alexander GM, Farris S: **Rediscovering area CA2: unique properties and functions**. *Nat Rev Neurosci* 2016, **17**: 89-102.

2. •• Hitti FL, Siegelbaum SA: **The hippocampal CA2 region is essential for social memory**. *Nature* 2014, **508**:88-92.
This paper used the transgenic mouse line, Amigo-Cre to silence transmission CA2 pyramidal neurons. A wide array of behavioral tests revealed that CA2 transmission is required for social memory.

3. •• Stevenson EL, Caldwell HK: **Lesions to the CA2 region of the hippocampus impair social memory in mice**. *Eur J Neurosci* 2014 http://dx.doi.org/10.1111/ejn.12689.
This study performed elegantly targeted lesions of area CA2 in rat, and demonstrated that social recognition memory is compromised.

4. Squire LR, Wixted JT, Clark RE: **Recognition memory and the medial temporal lobe: a new perspective**. *Nat Rev Neurosci* 2007, **8**:872-883.

5. Fernández M, Mollinedo-Gajate I, Peñagarikano O: **Neural circuits for social cognition: implications for autism**. *Neuroscience* 2017 http://dx.doi.org/10.1016/j.neuroscience.2017.07.013.

6. Leitner FC, Melzer S, Lütcke H, Pinna R, Seeburg PH, Helmchen F, Monyer H: **Spatially segregated feedforward and feedback neurons support differential odor processing in the lateral entorhinal cortex**. *Nat Neurosci* 2016, **19**:935-944.

7. Igarashi KM, Lu L, Colgin LL, Moser M-B, Moser EI: **Coordination of entorhinal–hippocampal ensemble activity during associative learning**. *Nature* 2014, **510**:143-147.

8. • Chevaleyre V, Siegelbaum SA: **Strong CA2 pyramidal neuron synapses define a powerful disynaptic cortico-hippocampal loop**. *Neuron* 2010, **66**:560-572.
This study demonstrated multiple features of CA2 pyramidal neurons that set the stage for further studies: CA2 pyramidal cells are strongly excited by distal cortical inputs and strongly inhibited by feedforward inhibition from CA3.

9. Sun Q, Srinivas KV, Sotayo A, Siegelbaum SA: **Dendritic Na(+) spikes enable cortical input to drive action potential output from hippocampal CA2 pyramidal neurons**. *eLife* 2014, **3**:7750.

10. Srinivas KV, Buss EW, Sun Q, Santoro B, Takahashi H, Nicholson DA, Siegelbaum SA: **The dendrites of CA2 and CA1 pyramidal neurons differentially regulate information flow in the cortico-hippocampal circuit**. *J Neurosci* 2017, **37**: 3276-3293.

11. Cui Z, Gerfen CR, Young WS: **Hypothalamic and other connections with dorsal CA2 area of the mouse hippocampus**. *J Comp Neurol* 2013, **521**:1844-1866.

12. Johnson ZV, Young LJ: **Oxytocin and vasopressin neural networks: implications for social behavioral diversity and translational neuroscience**. *Neurosci Biobehav Rev* 2017, **76**: 87-98.

13. Mitre M, Marlin BJ, Schiavo JK, Morina E, Norden SE, Hackett TA, Aoki CJ, Chao MV, Froemke RC: **A distributed network for social cognition enriched for oxytocin receptors**. *J Neurosci* 2016, **36**:2517-2535.

14. Young WS, Li J, Wersinger SR, Palkovits M: **The vasopressin 1b receptor is prominent in the hippocampal area CA2 where it is unaffected by restraint stress or adrenalectomy**. *Neuroscience* 2006, **143**:1031-1039.

15. Wersinger SR, Ginns EI, O'carroll A-M, Lolait SJ, Young WS: **Vasopressin V1b receptor knockout reduces aggressive behavior in male mice**. *Mol Psychiatry* 2002, **7**:975-984.

16. • Raam T, McAvoy KM, Besnard A, Veenema A, Sahay A: **Hippocampal oxytocin receptors are necessary for discrimination of social stimuli**. *Nat Commun* 2017, **8**:2001.
Recent advance in the field using oxytocin receptor cre line to demonstrate the role oxytocin signaling in social stimuli discrimination.

17. •• Smith AS, Avram SKW, Cymerblit-Sabba A, Song J, Young WS: **Targeted activation of the hippocampal CA2 area strongly enhances social memory**. *Mol Psychiatry* 2016 http://dx.doi.org/10.1038/mp.2015.189.
This study used optogenetic activation to demonstrate that vasopressin release to area CA2 during social interaction dramatically enhances social memory performance.

18. Rowland DC, Weible AP, Wickersham IR, Wu H, Mayford M, Witter MP, Kentros CG: **Transgenically targeted rabies virus demonstrates a major monosynaptic projection from hippocampal area CA2 to medial entorhinal layer II neurons**. *J Neurosci* 2013, **33**:14889-14898.

19. Okuyama T, Kitamura T, Roy DS, Itohara S, Tonegawa S: **Ventral CA1 neurons store social memory**. *Science* 2016, **353**: 1536-1541.

20. • Kohara K, Pignatelli M, Rivest AJ, Jung H-Y, Kitamura T, Suh J, Frank D, Kajikawa K, Mise N, Obata Y *et al.*: **Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits**. *Nat Neurosci* 2014, **17**:269-279.
This paper performs a comprehensive and elegant mapping of intra-hippocampal and extra-hippocampal inputs and outputs of CA2 pyramidal neurons.

21. Lee S-H, Marchionni I, Bezaire M, Varga C, Danielson N, Lovett-Barron M, Losonczy A, Soltesz I: **Parvalbumin-positive basket cells differentiate among hippocampal pyramidal cells**. *Neuron* 2014, **82**:1129-1144.

22. •• Boehringer R, Polygalov D, Huang AJY, Middleton SJ, Robert V, Wintzer ME, Piskorowski RA, Chevaleyre V, McHugh TJ: **Chronic loss of CA2 transmission leads to hippocampal hyperexcitability**. *Neuron* 2017, **94** 642–655.e9.
This study performs *in vivo* and hippocampal slice experiments to explore the role of CA2 in hippocampal network activity, revealing that CA2 recruits a feed-forward inhibition in area CA3 that is critical in maintaining physiological levels of excitability during spatial navigation.

23. Chiang M-C, Huang AJY, Wintzer ME, Ohshima T, McHugh TJ: **A role for CA3 in social recognition memory**. *Behav Brain Res* 2018 http://dx.doi.org/10.1016/j.bbr.2018.01.019.

24. Lu L, Igarashi KM, Witter MP, Moser EI, Moser M-B: **Topography of place maps along the CA3-to-CA2 axis of the hippocampus**. *Neuron* 2015, **87**:1078-1092.

25. Lee H, Wang C, Deshmukh SS, Knierim JJ: **Neural population evidence of functional heterogeneity along the CA3 transverse axis: pattern completion versus pattern separation**. *Neuron* 2015, **87**:1093-1105.

26. Mankin EA, Diehl GW, Sparks FT, Leutgeb S, Leutgeb JK: **Hippocampal CA2 activity patterns change over time to a larger extent than between spatial contexts**. *Neuron* 2015, **85**:190-201.

27. Alexander GM, Farris S, Pirone JR, Zheng C, Colgin LL, Dudek SM: **Social and novel contexts modify hippocampal CA2 representations of space**. *Nat Commun* 2016, **7**:10300.

28. Oliva A, Fernández-Ruiz A, Buzsáki G, Berényi A: **Spatial coding and physiological properties of hippocampal neurons in the Cornu Ammonis subregions**. *Hippocampus* 2016, **26**: 1593-1607.

29. Wintzer ME, Boehringer R, Polygalov D, McHugh TJ: **The hippocampal CA2 ensemble is sensitive to contextual change**. *J Neurosci* 2014, **34**:3056-3066.

30. •• Kay K, Sosa M, Chung JE, Karlsson MP, Larkin MC, Frank LM: **A hippocampal network for spatial coding during immobility and sleep**. *Nature* 2016, **531**:185-190.
This paper presents compelling evidence that a subset of CA2 pyramidal neurons encode spatial information during immobility.

31. •• Oliva A, Fernández-Ruiz A, Buzsáki G, Berényi A: **Role of hippocampal CA2 region in triggering sharp-wave ripples**. *Neuron* 2016, **91**:1342-1355.
This work uses multiple electrode arrays to simultaneously measure hippocampal network activity in all three CA subregions, finding that a large fraction of sharp-wave ripple events originate in area CA2.

32. Valero M, Cid E, Averkin RG, Aguilar J, Sanchez-Aguilera A, Viney TJ, Gomez-Dominguez D, Bellistri E, la Prida de LM: **Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples**. *Nat Neurosci* 2015, **18**:1281-1290.

33. Matsumoto N, Okamoto K, Takagi Y, Ikegaya Y: **3-Hz subthreshold oscillations of CA2 neurons in vivo**. *Hippocampus* 2016, **26**:1570-1578.

34. Buzsáki G: **Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning**. *Hippocampus* 2015, **25**:1073-1188.

35. Botcher NA, Falck JE, Thomson AM, Mercer A: **Distribution of interneurons in the CA2 region of the rat hippocampus**. *Front Neuroanat* 2014, **8**:104.

36. Mercer A, Botcher NA, Eastlake K, Thomson AM: **SP–SR interneurones: a novel class of neurones of the CA2 region of the hippocampus [Internet]**. *Hippocampus* 2012, **22**:1758-1769.

37. Mercer A, Eastlake K, Trigg HL, Thomson AM: **Local circuitry involving parvalbumin-positive basket cells in the CA2 region of the hippocampus**. *Hippocampus* 2012, **22**:43-56.

38. Mercer A, Trigg HL, Thomson AM: **Characterization of neurons in the CA2 subfield of the adult rat hippocampus**. *J Neurosci* 2007, **27**:7329-7338.

39. Nasrallah K, Piskorowski RA, Chevaleyre V: **Inhibitory plasticity permits the recruitment of CA2 pyramidal neurons by CA3 (1,2,3)**. *eNeuro* 2015, **2**:1-12.

40. Zhao M, Choi Y-S, Obrietan K, Dudek SM: **Synaptic plasticity (and the lack thereof) in hippocampal CA2 neurons**. *J Neurosci* 2007, **27**:12025-12032.

41. Piskorowski RA, Chevaleyre V: **Delta-opioid receptors mediate unique plasticity onto parvalbumin-expressing interneurons in area CA2 of the hippocampus**. *J Neurosci* 2013, **33**:14567-14578.

42. Nasrallah K, Piskorowski RA, Chevaleyre V: **Bi-directional interplay between proximal and distal inputs to CA2 pyramidal neurons**. *Neurobiol Learn Mem* 2017, **138**:173-181.

43. Leroy F, Brann DH, Meira T, Siegelbaum SA: **Input-timing-dependent plasticity in the hippocampal CA2 region and its potential role in social memory**. *Neuron* 2017, **95** 1089–1102.e5.

44. Chevaleyre V, Piskorowski RA: **Hippocampal area CA2: an overlooked but promising therapeutic target**. *Trends Molec Med* 2016, **22**:645-655.

45. Piskorowski RA, Nasrallah K, Diamantopoulou A, Mukai J, Hassan SI, Siegelbaum SA, Gogos JA, Chevaleyre V: **Age-dependent specific changes in area ca2 of the hippocampus and social memory deficit in a mouse model of the 22q11.2 deletion syndrome**. *Neuron* 2016, **89**:163-176.

46. Benes FM, Kwok EW, Vincent SL, Todtenkopf MS: **A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives**. *Biol Psychiatry* 1998, **44**:88-97.

47. Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF, Stanley Neuropathology Consortium: **Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium**. *Mol Psychiatry* 2004, **9**:609-620 544.