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Hippocampal network oscillations — recent insights from *in vitro* experiments

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Network oscillations are present throughout the mammalian brain. They are important for certain cognitive functions, such as learning and memory. The hippocampus exhibits prominent oscillations similar to those seen in other parts of the cortex. Due to its highly organised lamellar structure, *ex vivo* and *in vitro* preparations from the hippocampus have provided experimental models within which to study network oscillations. As such, experiments in hippocampal slices continue to progress our understanding about both the mechanisms and functions of cortical network oscillations. Here, advances from the past two years are summarised, and the current state of the field discussed.

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Introduction

Network oscillations are ubiquitous throughout the mammalian brain. They are assumed to be important for various cognitive abilities, such as learning, memory, and attention, to name but a few. Understanding the mechanisms and functions of oscillations is therefore necessary in order to understand how the brain carries out complex behaviours. The hippocampus, famed for its role in memory and navigation, exhibits a heterogeneous collection of oscillations that are temporally similar to those found in other parts of the cortex. The hippocampus proper (herein referred to as the hippocampus) is a highly organised structure; consisting of the Cornu Ammonis (CA) regions 1, 2, and 3 [1,2]. The regular, well defined circuitry and lamellar organisation of the hippocampus make it an ideal region within which to study the mechanisms of network oscillations.

There are three well characterised types of oscillations present in the hippocampus, all of which also occur in the neocortex [3]. Rhythmic activity in the theta frequency range (4–12 Hz) occurs during movement and rapid eye movement sleep in mammals. Faster rhythmic oscillations in the 30–100 Hz frequency range, known as gamma oscillations, also occur during these behavioural states [4]. These are thought to serve various roles including, but not limited to, navigation [5], sensory association, and working memory [6–8]. A unifying feature of the aforementioned oscillations is that they occur during high cholinergic tone, which is thought to switch the hippocampus into an on-line 'processing' mode [9,10].

Conversely, acetylcholine levels in the hippocampus are low during rest and slow wave sleep [11,12]. During these states, irregular bursts of high frequency activity, known as sharp wave ripples (SWRs), are observed [13–15]. This is thought to be another main processing mode of the hippocampus, during which information is synaptically consolidated within the hippocampus, as well as transferred to the neocortex for longer term storage [9,16,17].

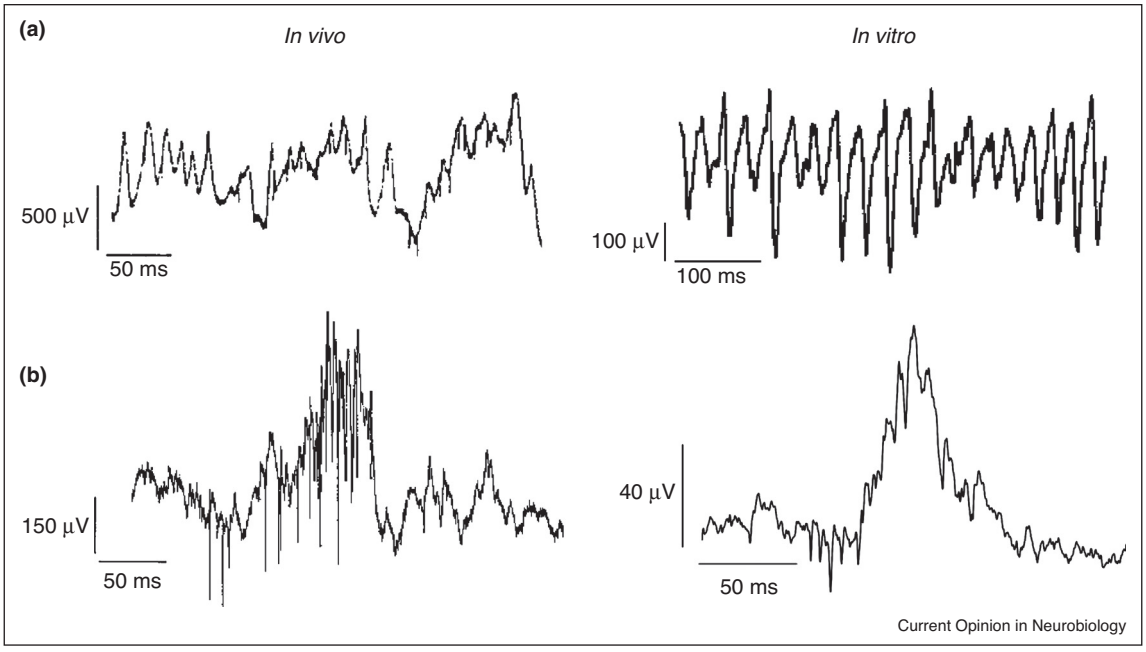
Hippocampal oscillations can be recorded *in vivo*, which allows behavioural correlates to be studied. Complementing these studies are *ex vivo* and *in vitro* approaches, here collectively referred to as *in vitro* investigations, whereby the hippocampus is studied outside of its normal biological context. This allows more careful experimental control, enabling detailed studies of circuit mechanisms and functions at the cellular level. The high degree of similarity between *in vivo* and *in vitro* recordings of hippocampal oscillations can be seen in Figure 1.

Network oscillations are often measured extracellularly as local field potentials. Mechanistically, one can distinguish between rhythm generators, which set the frequency of the oscillation, and current generators, which move ions across membranes causing the shape of the waveform seen in the local field potential [18]. *In vitro* models have recently unveiled important new information regarding both rhythm and current generators in the hippocampus.

Spontaneous SWRs and GABAergic interneurons

When acute slices of the hippocampus are prepared from the rodent brain they can spontaneously produce SWRs originating in the CA3, under control conditions or conditions with slightly elevated excitability [19–21].

Figure 1



Similarities between hippocampal oscillations recorded *in vivo* and *in vitro*. **(a)** Hippocampal gamma oscillations recorded *in vivo* (left [4]) and *in vitro* (right [22]). **(b)** Hippocampal sharp-wave ripples recorded *in vivo* (left [15]) and *in vitro* (right [25]). In both cases there is a striking similarity between the oscillations in the two recording conditions. Traces reproduced with permission from [4,15,22,25].

It has therefore been a longstanding consensus that the hippocampus intrinsically generates SWRs and therefore contains a rhythm generator. These SWRs are replaced by gamma oscillations when acetylcholine is applied to the slice [22,23], reinforcing the theory that the switch between these two processing modes in the hippocampus is mediated *via* cholinergic tone.

SWRs are associated with reactivation of ensembles of neurons that have been active during a previous behaviour. By using immediate-early gene transcription, it is possible to target cells that become active during exploration of a novel environment [24••]. By then preparing acute hippocampal slices from these animals, it was revealed that these cells received strengthened excitatory input during SWRs [24••]. Whether these strengthened inputs are preselected, or selected during the exploration process, is still to be elucidated.

There have also been significant advances in our understanding of interneuron involvement in SWRs. Perisomatic-targeting interneurons can control the initiation of SWRs [25] and recent work has shown that interneuron firing preceded sequential activation of pyramidal cells [26]. There have also been advances regarding interneuron involvement during SWRs, with both parvalbumin-expressing interneurons [27•] and O-LM interneurons [28•] found to be active during SWR events in hippocampal slices.

It was recently reported in hippocampal slices that a subset of subicular neurons were active immediately preceding hippocampal SWRs [29], suggesting that hippocampal SWR events may be controlled by external inputs.

There have also been advances in research relating SWRs to epileptiform events. Karlocai *et al.* [30] characterised the differences between SWRs and interictal-like events *in vitro*. Again, PV-expressing interneurons seem to be important, with a decrease of their inhibition onto pyramidal cells preceding epileptiform events. Further work has since suggested that just small changes in extracellular calcium levels, and therefore the excitability of the network, are capable of causing the switch between these two network states [31].

Mechanisms of hippocampal theta oscillations

Due to the high coherence (synchrony) of theta oscillations across large distances in the brain, it is logical to think that a single rhythm generator is responsible for the oscillation. Due to the medial septum's (MS) far reaching projections, it was thought this area was responsible for theta oscillations throughout the hippocampus [32]. An absence of spontaneous theta oscillations in hippocampal slices reinforced this theory.

However, with the advent of the whole isolated hippocampus preparation, it was found that spontaneous

oscillations at theta frequency could indeed occur without the MS present [33]. This result questions the concept of a single pacemaker rhythm generator in the MS, and has resulted in new theories of theta generation based on a large network of individual theta generators. If these generators are just weakly coupled, they would entrain one another explaining the high synchrony that is seen across the brain (for review, see [34]).

Indeed, hippocampal pyramidal cells, as well as some interneuron subclasses, have a preferred resonance frequency in the theta range [35,36]. The conductance underlying the I_h current is important for this resonance profile [36–38], and this has enabled the demonstration that these resonance properties are important *in vivo* [39]. Hippocampal pyramidal cells have dendrites receiving tens of thousands of inputs at a range of distances from the soma [40]. A gradient of HCN channels across the dendrites compensates for differences in the location of input [41••], and, by filtering the signal this way, the net input at the soma can conceivably drive a coherent unified oscillation across hippocampal pyramidal cells.

Multiple gamma oscillation rhythm generators

Gamma oscillations are often divided into slow gamma (around 40 Hz, gamma_s), medium gamma (around 80 Hz, gamma_M), and fast gamma (around 120 Hz, gamma_F) [42]. They occur during different behaviours and are thought to perform different roles within the hippocampus [42–44].

Increasing tonic excitation pharmacologically through acetylcholine receptors [22], kainate receptors [45], or metabotropic glutamate receptors [46] elicits gamma_S in the CA3 area of hippocampal slices. This revealed a gamma rhythm generator in CA3, which has been confirmed *in vivo* [47]. Moreover, a medium gamma rhythm generator in the upstream medial entorhinal cortex (mEC) has been identified [48], which can drive gamma_M in the hippocampus [4,43].

Recently, it was discovered that CA1 can independently generate medium gamma oscillations [49•]. These oscillations were induced by carbachol and persisted when the connections between CA3 and CA1, and the mEC and CA1 were cut. Indeed, it has recently been shown *in vitro* that the subiculum, the gateway between the hippocampus and the mEC, also contains a gamma rhythm generator [50].

With these recent discoveries of additional gamma generators, it appears that each subregion can generate gamma oscillations independently, which has important implications for our understanding of communication throughout the hippocampus. Each region appears to contain its own generator and uses it during transfer of information to the next downstream region, where a new local generator takes over control of propagation of the signal. Thus, the oscillation frequency may be a signature of activity in a specific pathway.

Recent optogenetic studies have also helped further our understanding of gamma oscillations. A ramp of blue light stimulation of channelrhodopsin-2 (ChR2)-expressing CA3 pyramidal neurons produces robust gamma oscillations [51•]. Interestingly, the frequency of these gamma oscillations would categorise them as gamma_M, rather than gamma_S, despite their location in CA3. By applying a sinusoidal waveform on top of the stimulation ramp, the oscillations could be entrained to the frequency of the sinusoidal waveform, and this frequency could span the slow - medium gamma range [51•]. Therefore, local networks appear to be able to resonate across the whole gamma frequency range, regardless of the local oscillation frequency. *In vivo* recordings will be required to confirm whether such network resonance assists in the propagation of oscillations through feedforward inhibition [52•], or might contribute to bi-directional coupling of oscillators [43,53], for example *via* inhibitory interactions [54], or to synchrony of oscillations driven by a common input [8]. New advances in *in vitro* models could contribute to a more thorough understanding of the mechanisms involved.

Cross-frequency coupling of hippocampal oscillations

There is also a lack of clear understanding regarding the relationships between different concomitant oscillations. When a brief period of gamma oscillations was induced against a background of ongoing SWRs in hippocampal slices, this caused a change in the firing rate and interplay of the neurons within the SWR assembly [55]. The exact function of this relationship, and its possible relation to the two-stage memory model [16], still needs to be determined.

As theta and gamma oscillations occur simultaneously during high levels of acetylcholine *in vivo*, it is thought there is an intimate relationship between the two. They are both phase and amplitude coupled [56,57]. In fact, theta-frequency sinusoidal stimulation of ChR2-expressing principal cells in the mEC is sufficient to induce theta-nested gamma oscillations in the local field potential [58••]. However, the exact nature of these relationships remains unclear, for example gamma_S and gamma_F have been reported to often co-occur in the same theta cycle [57] or to be restricted to different theta cycles [43].

New advances in *in vitro* models have already started to increase our understanding of cross-frequency coupling. The isolated hippocampal preparation revealed a change in theta-gamma cross-frequency coupling in a mouse

model of Alzheimer's disease [59•]. Hopefully, this marks the start of a new avenue of *in vitro* research into cross-frequency coupling.

Concluding remarks

Thanks to consistent progress in *in vitro* research, our understanding of hippocampal oscillations has steadily grown. We are now at a stage where we understand the mechanisms and functions of the individual oscillations relatively well. New advances in technology, such as the high spatial and temporal resolution of optogenetics, will be able to answer new questions about hippocampal oscillations. For example, this can be used to activate and silence the different identified generators at will, and examine the interactions between neighbouring, reciprocally connected, generators. It will be exciting to follow this field in the near future.

Conflict of interest

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. Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J: *The Hippocampus Book*. Oxford University Press; 2007.

2. Kohara K, Pignatelli M, Rivest AJ, Jung HY, Kitamura T, Suh J, Frank D, Kajikawa K, Mise N, Obata Y, Wickersham IR, Tonegawa S: **Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits**. *Nat Neurosci* 2014, **17**:269-279.

3. Leung LW, Lopes da Silva FH, Wadman WJ: **Spectral characteristics of the hippocampal EEG in the freely moving rat**. *Electroencephalogr Clin Neurophysiol* 1982, **54**:203-219.

4. Bragin A, Jandó G, Nádasdy Z, Hetke J, Wise K, Buzsáki G: **Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat**. *J Neurosci* 1995, **15**:47-60.

5. O'Keefe J, Recce ML: **Phase relationship between hippocampal place units and the EEG theta rhythm**. *Hippocampus* 1993, **3**:317-330.

6. Singer W: **Synchronization of cortical activity and its putative role in information processing and learning**. *Annu Rev Physiol* 1993, **55**:349-374.

7. Lisman J: **The theta/gamma discrete phase code occuring during the hippocampal phase precession may be a more general brain coding scheme**. *Hippocampus* 2005, **15**:913-922.

8. Yamamoto J, Suh J, Takeuchi D, Tonegawa S: **Successful execution of working memory linked to synchronized high-frequency gamma oscillations**. *Cell* 2014, **157**:845-857.

9. Buzsáki G:: **Two-stage model of memory trace formation: a role for "noisy" brain states**. *Neuroscience* 1989, **31**:551-570.

10. Zhang H, Lin SC, Nicolelis MA: **Spatiotemporal coupling between hippocampal acetylcholine release and theta oscillations in vivo**. *J Neurosci* 2010, **30**:13431-13440.

11. Kametani H, Kawamura H: **Alterations in acetylcholine release in the rat hippocampus during sleep-wakefulness detected by intracerebral dialysis**. *Life Sci* 1990, **47**:421-426.

12. Marrosu F, Portas C, Mascia MS, Casu MA, Fà M, Giagheddu M, Imperato A, Gessa GL: **Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats**. *Brain Res* 1995, **671**:329-332.

13. O'Keefe J, Nadel L: *The Hippocampus as a Cognitive Map*. Oxford University Press; 1978.

14. Buzsáki G, Horváth Z, Urioste R, Hetke J, Wise K: **High-frequency network oscillation in the hippocampus**. *Science* 1992, **256**:1025-1027.

15. Csicsvari J, Hirase H, Czurkó A, Mamiya A, Buzsáki G: **Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat**. *J Neurosci* 1999, **19**:274-278.

16. Buzsáki G: **The hippocampo-neocortical dialogue**. *Cereb Cortex* 1996, **6**:81-92.

17. Káli S, Dayan P: **Off-line replay maintains declarative memories in a model of hippocampal-neocortical interactions**. *Nat Neurosci* 2004, **7**:286-294.

18. Buzsáki G: **Theta oscillations in the hippocampus**. *Neuron* 2002, **33**:325-340.

19. Maier N, Güldenagel M, Söhl G, Siegmund H, Willecke K, Draguhn A: **Reduction of high-frequency network oscillations (ripples) and pathological network discharges in hippocampal slices from connexin 36-deficient mice**. *J Physiol* 2002, **541**:521-528.

20. Colgin LL, Jia Y, Sabatier JM, Lynch G: **Blockade of NMDA receptors enhances spontaneous sharp waves in rat hippocampal slices**. *Neurosci Lett* 2005, **385**:46-51.

21. Hájos N, Ellender TJ, Zemankovics R, Mann EO, Exley R, Cragg SJ, Freund TF, Paulsen O: **Maintaining network activity in submerged hippocampal slices: importance of oxygen supply**. *Eur J Neurosci* 2009, **29**:319-327.

22. Fisahn A, Pike FG, Buhl EH, Paulsen O: **Cholinergic induction of network oscillations at 40 Hz in the hippocampus *in vitro***. *Nature* 1998, **394**:186-189.

23. Fischer V, Both M, Draguhn A, Egorov AV: **Choline-mediated modulation of hippocampal sharp wave-ripple complexes *in vitro***. *J Neurochem* 2014, **129**:792-805.

24. •• Mizunuma M, Norimoto H, Tao K, Egawa T, Hanaoka K, Sakaguchi T, Hioki H, Kaneko T, Yamaguchi S, Nagano T, Matsuki N, Ikegaya Y: **Unbalanced excitability underlies offline reactivation of behaviorally activated neurons**. *Nat Neurosci* 2014, **17**:503-505.
This paper used immediate-early gene transcription to target cells that became active during exploration of a novel environment. Slices were then made and these cells received strengthened excitatory input during SWRs.

25. Ellender TJ, Nissen W, Colgin LL, Mann EO, Paulsen O: **Priming of hippocampal population bursts by individual perisomatic-targeting interneurons**. *J Neurosci* 2010, **30**:5979-5991.

26. Sasaki T, Matsuki N, Ikegaya Y: **Interneuron firing precedes sequential activation of neuronal ensembles in hippocampal slices**. *Eur J Neurosci* 2014, **39**:2027-2036.

27. • Hájos N, Karlócai MR, Németh B, Ulbert I, Monyer H, Szabó G, Erdélyi F, Freund TF, Gulyás AI: **Input-output features of anatomically identified CA3 neurons during hippocampal sharp wave/ripple oscillation in vitro**. *J Neurosci* 2013, **33**:11677-11691.
An in-depth analysis of the different hippocampal interneurons and their behaviours during SWRs in acute slices. It was concluded that PV-expressing interneurons were important contributors to SWR current sources.

28. • Pangalos M, Donoso JR, Winterer J, Zivkovic AR, Kempter R, Maier N, Schmitz D: **Recruitment of oriens-lacunosum-moleculare interneurons during hippocampal ripples**. *Proc Natl Acad Sci U S A* 2013, **110**:4398-4403.
This paper reports that inputs to O-LM interneurons, along with their firing, was phase locked to SWRs in acute hippocampal slices.

29. Norimoto H, Matsumoto N, Miyawaki T, Matsuki N, Ikegaya Y: **Subicular activation preceding hippocampal ripples *in vitro***. *Sci Rep* 2013, **3**:2696.

30. Karlócai MR, Kohus Z, Káli S, Ulbert I, Szabó G, Máté Z, Freund TF, Gulyás AI: **Physiological sharp wave-ripples and interictal events *in vitro*: what's the difference?** *Brain* 2014, **137**:463-485.

31. Aivar P, Valero M, Bellistri E, Menendez de la Prida L: **Extracellular calcium controls the expression of two different forms of ripple-like hippocampal oscillations**. *J Neurosci* 2014, **34**:2989-3004.

32. Vertes RP, Kocsis B: **Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus**. *Neuroscience* 1997, **81**:893-926.

33. Goutagny R, Jackson J, Williams S: **Self-generated theta oscillations in the hippocampus**. *Nat Neurosci* 2009, **12**:1491-1493.

34. Colgin LL: **Mechanisms and functions of theta rhythms**. *Annu Rev Neurosci* 2013, **36**:295-312.

35. Pike FG, Goddard RS, Suckling JM, Ganter P, Kasthuri N, Paulsen O: **Distinct frequency preferences of different types of rat hippocampal neurones in response to oscillatory input currents**. *J Physiol* 2000, **529**:205-213.

36. Zemankovics R, Káli S, Paulsen O, Freund TF, Hájos N: **Differences in subthreshold resonance of hippocampal pyramidal cells and interneurons: the role of h-current and passive membrane characteristics**. *J Physiol* 2010, **588**:2109-2132.

37. Hu H, Vervaeke K, Storm JF: **Two forms of electrical resonance at theta frequencies, generated by M-current, h-current and persistent Na^+ current in rat hippocampal pyramidal cells**. *J Physiol* 2002, **545**:783-805.

38. Borel M, Guadagna S, Jang HJ, Kwag J, Paulsen O: **Frequency dependence of CA3 spike phase response arising from h-current properties**. *Front Cell Neurosci* 2013, **7**:263.

39. Stark E, Eichler R, Roux L, Fujisawa S, Rotstein HG, Buzsáki G: **Inhibition-induced theta resonance in cortical circuits**. *Neuron* 2013, **80**:1263-1276.

40. Megías M, Emri Z, Freund TF, Gulyás AI: **Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells**. *Neuroscience* 2001, **102**:527-540.

41. •• Vaidya SP, Johnston D: **Temporal synchrony and gamma-to-theta power conversion in the dendrites of CA1 pyramidal neurons**. *Nat Neurosci* 2013, **16**:1812-1820.

This paper demonstrated that irrespective of the distance of the stimulation site in the dendrites to the soma of CA1 pyramidal neurons, the soma always receives the peak excitation at the same time. This was shown to be due to a gradient of HCN channels along the dendrites, which act to filter signals.

42. Buzsáki G, Wang X-J: **Mechanisms of gamma oscillations**. *Annu Rev Neurosci* 2012, **35**:203-225.

43. Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser MB, Moser EI: **Frequency of gamma oscillations routes flow of information in the hippocampus**. *Nature* 2009, **462**:353-357.

44. Bieri KW, Bobbitt KN, Colgin LL: **Slow and fast gamma rhythms coordinate different spatial coding modes in hippocampal place cells**. *Neuron* 2014, **82**:670-681.

45. Fisahn A, Contractor A, Traub RD, Buhl EH, Heinemann SF, McBain CJ: **Distinct roles for the kainate receptor subunits GluR5 and GluR6 in kainate-induced hippocampal gamma oscillations**. *J Neurosci* 2004, **24**:9658-9668.

46. Pálhalmi J, Paulsen O, Freund TF, Hájos N: **Distinct properties of carbachol- and DHPG-induced network oscillations in hippocampal slices**. *Neuropharmacology* 2004, **47**:381-389.

47. Csicsvari J, Jamieson B, Wise KD, Buzsáki G: **Mechanisms of gamma oscillations in the hippocampus of the behaving rat**. *Neuron* 2003, **37**:311-322.

48. Cunningham MO, Davies CH, Buhl EH, Kopell N, Whittington MA: **Gamma oscillations induced by kainate receptor activation in the entorhinal cortex in vitro**. *J Neurosci* 2003, **23**:9761-9769.

49. • Pietersen AN, Ward PD, Hagger-Vaughan N, Wiggins J, Jefferys JG, Vreugdenhil M: **Transition between fast and slow gamma modes in rat hippocampus area CA1 *in vitro* is modulated by slow CA3 gamma oscillations**. *J Physiol* 2014, **592**:605-620.

This study discovered that gamma oscillations can be generated intrinsically in an isolated CA1 preparation.

50. Jackson J, Goutagny R, Williams S: **Fast and slow gamma rhythms are intrinsically and independently generated in the subiculum**. *J Neurosci* 2011, **31**:12104-12117.

51. • Akam T, Oren I, Mantoan L, Ferenczi E, Kullmann DM: **Oscillatory dynamics in the hippocampus support dentate gyrus–CA3 coupling**. *Nat Neurosci* 2012, **15**:763-768.

The first report of optogenetic-induced oscillations in acute hippocampal slices. It was revealed that CA3 is capable of producing gamma oscillations over the entire gamma range, despite having quite a narrow range *in vivo*.

52. • Zemankovics R, Veres JM, Oren I, Hájos N: **Feedforward inhibition underlies the propagation of cholinergically induced gamma oscillations from hippocampal CA3 to CA1**. *J Neurosci* 2013, **33**:12337-12351.

During carbachol-induced gamma oscillations, CA1 interneurons discharge after CA3 pyramidal neurons with a delay consistent with monosynaptic connections between the two.

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

54. Melzer S, Michael M, Caputi A, Eliava M, Fuchs EC, Whittington MA, Monyer H: **Long-range-projecting GABAergic neurons modulate inhibition in hippocampus and entorhinal cortex**. *Science* 2012, **335**:1506-1510.

55. Zylla MM, Zhang X, Reichinnek S, Draguhn A, Both M: **Cholinergic plasticity of oscillating neuronal assemblies in mouse hippocampal slices**. *PLoS One* 2013, **8**:e88071.

56. Tort AB, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ: **Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task**. *Proc Natl Acad Sci U S A* 2008, **105**:20517-20522.

57. Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsáki G: **Cross-frequency phase-phase coupling between θ and γ oscillations in the hippocampus**. *J Neurosci* 2012, **32**:423-435.

58. •• Pastoll H, Solanka L, van Rossum MC, Nolan MF: **Feedback inhibition enables θ-nested γ oscillations and grid firing fields**. *Neuron* 2013, **77**:141-154.

Theta-rate stimulation of ChR2-expressing principal neurons in the mEC caused theta-nested gamma to occur. The paper also revealed a lack of recurrent excitation between mEC principal stellate neurons.

59. • Goutagny R, Gu N, Cavanagh C, Jackson J, Chabot JG, Quirion R, Krantic S, Williams S: **Alterations in hippocampal network oscillations and theta-gamma coupling arise before Aβ overproduction in a mouse model of Alzheimer's disease**. *Eur J Neurosci* 2013, **37**:1896-1902.

This study used the isolated hippocampal preparation to demonstrate a change in theta-gamma cross-frequency coupling in a mouse model of Alzheimer's disease.