Higuchi, S., and Miyashita, Y. (1996). Proc. Natl. Acad. Sci. USA *93*, 739–743.

Keysers, C., Xiao, D.K., Földiák, P., and Perrett, D.I. (2001). J. Cogn. Neurosci. *13*, 90–101.

Kreiman, G. (2007). Curr. Opin. Neurobiol. *17*, 471–475.

Logothetis, N.K. (1998). Philos. Trans. R. Soc. Lond. B Biol. Sci. *353*, 1801–1818.

Naya, Y., Yoshida, M., and Miyashita, Y. (2003). J. Neurosci. *23*, 2861–2871.

Potter, M.C., Wyble, B., Hagmann, C.E., and McCourt, E.S. (2014). Atten. Percept. Psychophys. *76*, 270–279.

Quian Quiroga, R.Q. (2012). Nat. Rev. Neurosci. *13*, 587–597.

Quian Quiroga, R., Kraskov, A., Mormann, F., Fried, I., and Koch, C. (2014). Neuron *84*, this issue, 363–369.

Reddy, L., Quiroga, R.Q., Wilken, P., Koch, C., and Fried, I. (2006). Curr. Biol. *16*, 2066–2072.

Schapiro, A.C., Kustner, L.V., and Turk-Browne, N.B. (2012). Curr. Biol. *22*, 1622–1627.

Squire, L.R., Stark, C.E., and Clark, R.E. (2004). Annu. Rev. Neurosci. *27*, 279–306.

Suzuki, W.A., and Eichenbaum, H. (2000). Ann. N Y Acad. Sci. *911*, 175–191.

Thorpe, S.J. (2012). Grandmother cells and Distributed Representations. In Visual Population Codes: Toward a Common Multivariate Framework for Cell Recording and Functional Imaging, N. Kriegeskorte and G. Kreiman, eds. (Cambridge: MIT Press), pp. 23–52.

Wirth, S., Yanike, M., Frank, L.M., Smith, A.C., Brown, E.N., and Suzuki, W.A. (2003). Science *300*, 1578–1581.

The Hippocampal Cacophony: Multiple Layers of Communication

James L. Butler[1] and Ole Paulsen[1,*]
[1]Department of Physiology, Development and Neuroscience, University of Cambridge, Physiological Laboratory, Downing Street, Cambridge CB2 3EG, UK
*Correspondence: op210@cam.ac.uk
http://dx.doi.org/10.1016/j.neuron.2014.10.017

Locally generated gamma oscillations synchronize spikes, but the nature of coupling between regions remains unclear. In this issue of *Neuron*, Schomburg et al. (2014) show that afferent gamma input fails to entrain hippocampal output, suggesting limited propagation of gamma waves.

The timing of signals in the brain is important for information transfer. Such temporal coding is facilitated by neural oscillations in many frequency bands, which provide a temporal framework within which information can be bound or segregated via oscillatory cycles (Buzsáki and Wang, 2012). Gamma oscillations (>30 Hz) in particular tightly synchronize the spiking output of a region, making a response in the downstream region more likely to be elicited than if the signals arrived asynchronously. This is known as coincidence detection, which is a widely accepted consequence of gamma activity (König et al., 1996). Additionally, downstream regions also produce gamma oscillations during information transfer, and it has been postulated that gamma oscillations that are coherent between the upstream and downstream regions facilitate successful information transfer between the two regions (Fries, 2005). New compelling evidence in this issue of *Neuron*, however, found that spiking of Cornu ammonis 1 (CA1) pyramidal neurons was not entrained by afferent gamma input, questioning whether this latter theory applies to hippocampal gamma oscillations.

CA1 in the hippocampus has spatially segregated inputs and different gamma oscillations that occupy distinct frequency bands (Csicsvari et al., 2003; Colgin et al., 2009), therefore making CA1 an excellent place within which to study gamma oscillations. Adopting a tour de force approach, Schomburg et al. (2014) implanted high-density silicon shanks containing an impressive total of up to 256 sites into the dorsal hippocampus of rats. This allowed for simultaneous recording of both gamma oscillations and spikes from all layers of CA1 and also along the majority of CA1's transverse (proximodistal) axis of the dorsal hippocampus. The high recording density increases the likelihood of capturing activity from matching dendritic and somatic compartments of the same neurons, which is an important factor to consider when interpreting the acquired data. CA1 receives afferent input from layer 3 of the entorhinal cortex (EC3) and CA3 of the hippocampus, from which they also recorded in concert with CA1. Complementing this state of the art technology, the investigators used advanced methods of source separation. Specifically, independent component analysis (ICA) was used in addition to conventional current-source density (CSD) analysis to pinpoint the precise location of gamma oscillations. ICA allows for the separation of linearly mixed sources into their independent components (Fernández-Ruiz and Herreras, 2013). This is useful when heterogeneous signals occur at the same site, such as gamma oscillations in CA1, where ICA has been employed to isolate and study the different current generators (Korovaichuk et al., 2010).

These powerful methods separated CA1 LFPs into three distinct components: a dendritic sink in the stratum radiatum (Rad; the location of excitatory CA3 input), another current sink in the stratum lacunosum-moleculare (L-M; the location of direct EC3 input), and a current source in the stratum pyramidale (Pyr; the location of the CA1 output neurons). Each of the isolated LFP components was found to be preferentially coupled to a different gamma oscillation: Rad to slow gamma (gammaS, 30–80 Hz), L-M to medium gamma (gammaM, 60–120 Hz), and Pyr to fast gamma (gammaF, >100). Reassuringly, gamma coherence between the afferent regions and their terminal fields was consistent with known anatomical projections. Using such powerful methods, the authors have unequivocally identified the sinks and sources of gamma oscillations in CA1, thereby confirming previous suggestions that Rad, L-M, and Pyr exhibit three distinct gamma oscillations, of which the dendritic oscillations share the same frequency band as their upstream regions (Csicsvari et al., 2003; Colgin et al., 2009; Lasztóczi and Klausberger, 2014).

CA1 gamma oscillations have an intimate relationship with theta oscillations (3–12 Hz), being phase-amplitude coupled (Buzsáki and Wang, 2012). The different CA1 gamma oscillations had different theta-phase preferences. GammaM occurred on the peak of each theta cycle, followed by gammaS on the descending phase, and lastly, GammaF occurred at the trough of the theta cycle (Figure 1A). This order of theta-phase preference disagrees with a previous study also looking at in vivo CA1 oscillations, where gammaS and gammaM were maximal at the early descending phase and trough of theta, respectively (Colgin et al., 2009). This study, however, did not use multisite recordings, precluding accurate source identification.

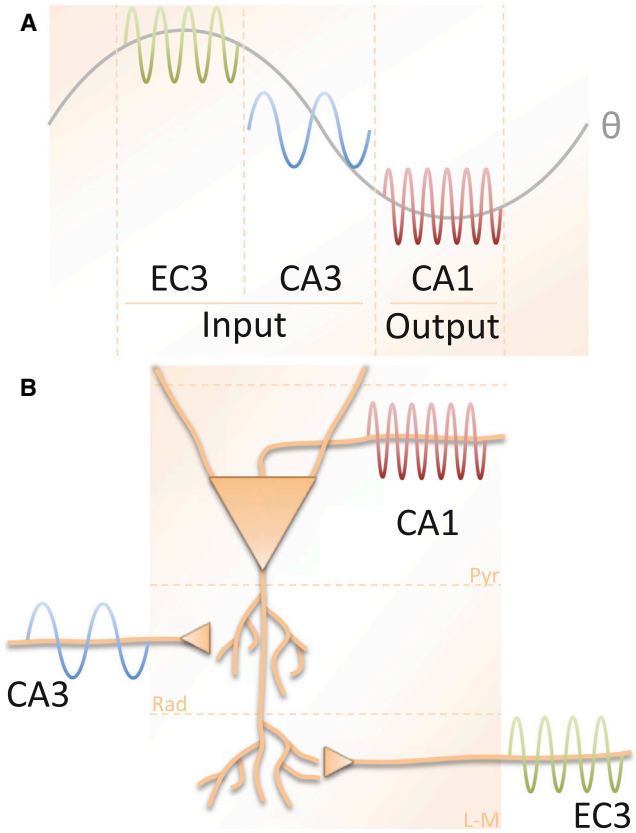

Figure 1. Spatiotemporal Segregation of Hippocampal Gamma Oscillations
(A and B) The different gamma oscillations in CA1 are segregated in the temporal domain by theta oscillations (A) and in the spatial domain whereby the dendritic layers inherit the gamma oscillations of their afferent regions (B).

The sequence of distal activity occurring before proximal activity is important for dendritic integration in CA1 pyramidal cells. Distal input from EC3 can both increase or decrease the probability of CA3 input to cause CA1 pyramidal cell spiking, and this depends on the timing of the EC3 input (Remondes and Schuman, 2002). Schomburg et al. (2014) have therefore revealed a potential model of information processing in CA1 whereby at the start of each theta cycle there is incoming afferent information from EC3 followed by input from CA3, and then at the trough of the theta cycle the CA1 pyramidal cells start firing, producing both CA1's output and the gammaF seen in the LFP. This clearly defined order of CA1 information transfer can help guide future computational models of CA1 information processing.

Do EC3 and CA3 inputs entrain the CA1 output, or is the output independent of the two preceding gamma oscillations that occur in each theta cycle? To investigate this question, the authors looked at the relationship between cell spikes and the oscillations seen in the LFP. If the oscillations did indeed couple the two regions, then one would expect the spiking of pyramidal neurons in both regions to adhere to the same oscillation. As expected, spiking of pyramidal neurons in both CA3 and EC3 was strongly coupled to LFP oscillations in both their respective local region and in the layer of CA1 that they innervate. However, the spiking of CA1 pyramidal cells showed only weak coupling to the oscillations in the afferent regions but strong coupling to gammaF in Pyr.

Thus, during communication of information, gamma oscillations entrain local pyramidal neurons, and the downstream region inherits these oscillations in the layers that are innervated by the afferent projections (Figure 1B). However, these afferent inputs fail to entrain the downstream pyramidal cells. Inputs are low-pass filtered as they travel along the apical dendrites to the soma of CA1 pyramidal cells (Vaidya and Johnston, 2013), explaining how it is possible for a distinct oscillation to be produced by the CA1 pyramidal cells, which can occupy a phase and frequency different from those of their input.

Interneurons in CA1 showed a stronger coupling to the afferent gamma oscillations than the pyramidal neurons did. This is consistent with their coincidence detector properties and also confirms previous research in vitro that found that feedforward inhibition underlies the propagation of gamma oscillations to the CA1 perisomatic layer (Zemankovics et al., 2013).

These findings therefore suggest that coherence between gamma oscillations in the upstream region and gamma oscillations of the output of the downstream region is not important for information

transfer in the entorhinal-hippocampal system. It would seem that entorhinal-hippocampal gamma oscillations are a unidirectional process, with little importance of the oscillation in the downstream region for the receipt of information from upstream regions. This suggests that neural information is not bound to a single specific gamma wave that carries it along multiple steps of its neural pathway. Rather, the information is received and processed by each region and then assigned to a new gamma cycle from the local generator for the subsequent step along the neural pathway.

GammaM and gammaS inputs into CA1 could be competitive, cooperative, or independent of one another. Schomburg et al. (2014) compared gamma oscillations between rapid eye movement (REM) sleep and awake states. During REM sleep, CA3 pyramidal firing decreased, and this was accompanied by a decrease in gammaS power in both CA3 and CA1 Rad. These changes were mirrored by increases in both EC3 pyramidal cell firing and gammaM power. Importantly, the coupling between CA1 and its afferent regions also changed, whereby CA1–CA3 coupling decreased and CA1–EC3 coupling increased. This suggests, therefore, that there is competition within CA1 between the two gamma oscillations and their respective inputs.

Lastly, the authors looked at the physiological relevance of these findings using a behavioral test that examined the effect of memory recall. In contrast to REM sleep, where CA3 pyramidal cell firing fell, this time it increased. This increase was accompanied by an increase in power of all three gamma oscillations, with gammaS in Rad showing the biggest increase. Furthermore, some CA1 pyramidal cells increased their firing at the peak of the theta cycle, demonstrating that changes in EC3 and CA3 input into CA1 influences CA1 theta-gamma coupling.

As with all good papers, Schomburg et al. (2014) raise a number of interesting new questions. Pyramidal neurons also have basal dendrites in stratum oriens, which receive inputs from multiple sources. How is this information sorted when the spatial segregation of inputs as seen in L-M and Rad is absent? Moreover, this study suggests that CA1 pyramidal cell spiking causes gammaF in the perisomatic region, but what mechanisms underlie the spiking and associated gamma activity? An important point to consider is that this study analyzed average spike coupling over multiple cycles, whereas a cycle-by-cycle analysis might reveal transient coupling of CA1 pyramidal spiking to afferent gamma oscillations that was obscured by group averages. This would be particularly interesting for gammaS during the descending phase of theta, when individual CA1 pyramidal cells show phase precession relative to the ongoing theta activity (O'Keefe and Recce, 1993).

To summarize, there is now clear evidence that the CA1 layers Pyr, Rad, and L-M each possess a distinct gamma oscillation. These oscillations are differentially phase-amplitude coupled to theta oscillations, and the phase preference is task dependent. Furthermore, the output of CA1 (pyramidal cell spiking) is coupled to its own unique gamma oscillation that is distinct from gamma oscillations originating from the afferent inputs. These findings were attained using impressive hardware and analytical techniques and set a new standard for future research into neural oscillations.

REFERENCES

Buzsáki, G., and Wang, X.J. (2012). Annu. Rev. Neurosci. *35*, 203–225.

Colgin, L.L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.B., and Moser, E.I. (2009). Nature *462*, 353–357.

Csicsvari, J., Jamieson, B., Wise, K.D., and Buzsáki, G. (2003). Neuron *37*, 311–322.

Fernández-Ruiz, A., and Herreras, O. (2013). Front. Comput. Neurosci. *7*, 5.

Fries, P. (2005). Trends Cogn. Sci. *9*, 474–480.

König, P., Engel, A.K., and Singer, W. (1996). Trends Neurosci. *19*, 130–137.

Korovaichuk, A., Makarova, J., Makarov, V.A., Benito, N., and Herreras, O. (2010). J. Neurophysiol. *104*, 484–497.

Lasztóczi, B., and Klausberger, T. (2014). Neuron *81*, 1126–1139.

O'Keefe, J., and Recce, M.L. (1993). Hippocampus *3*, 317–330.

Remondes, M., and Schuman, E.M. (2002). Nature *416*, 736–740.

Schomburg, E.W., Fernández-Ruiz, A., Mizuseki, K., Berényi, A., Anastassiou, C.A., Koch, C., and Buzsáki, G. (2014). Neuron *84*, this issue, 470–485.

Vaidya, S.P., and Johnston, D. (2013). Nat. Neurosci. *16*, 1812–1820.

Zemankovics, R., Veres, J.M., Oren, I., and Hájos, N. (2013). J. Neurosci. *33*, 12337–12351.