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Slow Gamma Takes the Reins in Replay

Laura Lee Colgin[1,*]
[1]Center for Learning and Memory, The University of Texas at Austin, 1 University Station Stop C7000, Austin, TX 78712-0805, USA
*Correspondence: colgin@mail.clm.utexas.edu
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The mechanisms supporting hippocampal memory reactivation are puzzling. Reactivation occurs during ripple oscillations, yet ripples are not coordinated across regions. In this issue of *Neuron*, Carr et al. (2012) report that another oscillation, slow gamma, coordinates memory reactivation across the hippocampal network.

In the hippocampus, a brain area critical for memories of events and experiences, one of the most prominent patterns of activity is the sharp-wave ripple complex (SWR; Girardeau and Zugaro, 2011, for a recent review). SWRs consist of waves of excitation that spread from hippocampal subfield CA3 to neighboring subfield CA1. SWRs are most often seen during periods of inactivity and slow-wave sleep. Perhaps the most fascinating feature of SWR activity is the phenomenon of "reactivation" (also known as "replay"; Carr et al., 2011, for a recent review). During SWRs, the neuronal firing patterns that occurred during active behaviors (e.g., exploration) reactivate in the same order but on a faster time scale. During spatial exploration, hippocampal neurons known as "place cells" fire selectively in particular regions of the environment known as "place fields" (Moser et al., 2008, for a review). As an animal moves through an environment, place cells with place fields along the animal's trajectory activate in sequence. Subsequent reactivation of such neuronal sequences during SWRs replays representations of spatial trajectories taken by the animal. Replay of neuronal sequences corresponding to earlier experiences is believed to facilitate transfer of memories from the hippocampus to the neocortex during the process of memory consolidation.

The hippocampus must possess a mechanism that enables precisely timed reactivation of neuronal sequences. A candidate mechanism for this function is neuronal oscillations. Oscillations reflect alternating periods of excitation and inhibition in neuronal networks. They can coordinate neuronal sequence activation by presenting successions of precisely timed windows of excitation interspersed with windows of inhibition. One would think that the oscillation regulating sequence reactivation across the hippocampus would be the high frequency (~150–200 Hz) ripple oscillation that accompanies sharp waves. However, high-frequency ripples are not correlated between CA3 and CA1 (Csicsvari et al., 1999). This is problematic because reactivation in CA1 requires properly timed input from CA3 (Nakashiba et al., 2009). Moreover, the large majority of replay events include neuronal activity from both CA1 and CA3 (Carr et al., 2012).

In this issue of *Neuron*, Carr et al. (2012) propose a solution to this problem. Their results indicate that low frequency ("slow," ~20–50 Hz) gamma oscillations regulate the precisely timed reactivation of neuronal sequences in CA3 and CA1. They report that SWRs are accompanied by increases in CA3 and CA1 slow gamma activity. In contrast to ripples, SWR-associated slow gamma oscillations occurred synchronously across CA3 and CA1. Moreover, CA3-CA1 slow gamma synchrony was stronger during SWRs than when no SWRs were present. Concurrent increases in CA3-CA1 synchrony were not seen in other frequency bands. CA3 slow gamma oscillations entrained spiking of neurons in both CA3 and CA1, and CA3 slow gamma entrainment of CA1 spiking was stronger during SWRs than when no SWRs were present.

The new findings by Carr et al. (2012) also imply that slow gamma oscillations in the hippocampus serve as an internal clock during sequence reactivation. The authors measured slow gamma phase intervals between spikes from pairs of place cells. They found that slow gamma phase intervals across successive gamma cycles were significantly correlated with distance between the neurons' place fields. Considering that distinctive places like cue-containing walls (Hetherington and Shapiro, 1997) and goal locations (Hollup et al., 2001) are heavily represented by place cell activity, the new findings raise the possibility that discrete locations are reactivated on separate slow gamma cycles.

Replay occurring during pauses in exploratory activity matches activation patterns from earlier experiences more accurately than replay occurring during extended periods of quiescence (Karlsson and Frank, 2009). Carr et al. (2012) found that quiescent SWR replay (i.e., relatively low-quality replay) was not associated with increases in slow gamma entrainment of cell spiking, a finding that supports the conclusion that enhanced slow gamma entrainment is necessary for high-fidelity replay. This conclusion received further support from their finding that large increases in CA3-CA1 slow gamma synchrony during SWRs were predictive of high fidelity replay events.

Why would slow gamma entrainment of place cell spikes increase during some SWRs (i.e., waking SWRs) but not others (i.e., quiescent SWRs)? It is possible that SWR-associated reactivation of place cell sequences is involved in several different functions and that only some of these functions require coordination of CA3 and CA1 by slow gamma oscillations. The discovery of "reverse replay" during wakefulness (Foster and Wilson, 2006), in which previously encoded place cell sequences are reactivated in reverse order, supports the idea that SWR-associated replay can serve various functions. Diba and Buzsáki (2007) found that while forward replay events often represent

upcoming paths, reverse replay events often represent recently traversed paths. These findings imply that forward replay may be related to planning of future trajectories (Diba and Buzsáki, 2007), while reverse replay may instead play a role in reinforcement learning (Foster and Wilson, 2006). Carr et al. (2012) did not distinguish between forward and reverse replay, but it is likely that most of their measurements were taken during forward replay events, considering that forward replay occurs more often than reverse replay (Diba and Buzsáki, 2007; Davidson et al., 2009). Still, the question remains as to whether forward and reverse replay differ with regard to associated slow gamma synchrony. It is plausible that the trajectory planning function ascribed to forward replay would involve retrieval of previously stored representations of space, a process that requires CA3 (Kesner, 2007, for a review) and would thus likely benefit from enhanced slow gamma entrainment of CA1 by CA3. With regard to reverse replay, activation of the ventral striatum via CA1 inputs to subiculum (Groenewegen et al., 1987) could conceivably support the proposed reinforcement learning function without requiring slow gamma coupling of CA3 and CA1. A hypothesis that follows from these conjectures is that CA3-CA1 slow gamma synchrony would be higher during forward replay than during reverse replay. It would be interesting to test this hypothesis in future studies in which slow gamma synchrony effects are assessed separately for forward and reverse replay events. The memory consolidation function of replay, on the other hand, is believed to take place during quiescent SWRs (Girardeau and Zugaro, 2011). Since quiescent SWRs were not associated with enhanced CA3-CA1 slow gamma synchrony, transmission of hippocampal memory representations to cortical sites during memory consolidation may not require slow gamma coordination of CA3 and CA1.

The new results also raise fascinating questions regarding potential functions of slow gamma oscillations. Although functions of slow gamma oscillations remain unknown, the results by Carr et al. (2012) suggest that SWRs and slow gamma oscillations may share some common functions. One such function may be memory retrieval. Gamma coordination of CA3 and CA1 is reportedly important for memory retrieval (Montgomery and Buzsáki, 2007), and replay during awake SWRs is thought to mediate retrieval of spatially or temporally remote experiences (Carr et al., 2011). But why would place cell sequences be retrieved in a time-compressed manner during SWR-related slow gamma and in "real time" during theta-associated slow gamma? One possibility is that SWR-related slow gamma mediates retrieval of distant memories, which are not directly related to what is currently happening and thus can be retrieved on a time scale faster than the time scale of ongoing experiences. Theta-associated slow gamma, on the other hand, may facilitate retrieval of stored representations that relate directly to the animal's current location. Such retrieval would have to occur on a noncompressed time scale (i.e., the time scale of behavior) in order to effectively encode new experiences happening in that location.

The authors found no relationship between CA3 slow gamma and the probability of observing a SWR during wakefulness. On the other hand, SWRs were likely to occur when strong slow gamma was measured in CA1, and slow gamma coupling of CA3 and CA1 was predictive of SWR occurrence. These findings suggest that SWRs arise, and replay occurs, when CA3 slow gamma effectively entrains slow gamma in CA1. What factors determine whether or not CA3 slow gamma entrains CA1? During awake SWRs, replay is more likely to involve place cells having place fields near an animal's current location (Davidson et al., 2009), suggesting that sensory inputs can influence reactivation. It is possible then that sensory input related to nearby locations can excite relevant place cell populations in CA1, enabling their entrainment by CA3 slow gamma and triggering reactivation of place cell sequences. Another possibility is that other inputs affecting CA1 excitability, such as the nucleus reuniens of the thalamus, modulate CA1's receptiveness to CA3 slow gamma and thereby influence CA3's ability to elicit SWRs and associated reactivation in CA1.

The new findings by Carr et al. (2012) support the conclusion that CA3-CA1 slow gamma synchrony facilitates activation of CA1 by CA3 during replay. The question remains as to whether accurate replay of place cell sequences benefits particularly from slow gamma timing or if any factor enhancing CA1's reception of CA3 inputs would suffice. An answer to this question may come from future experiments utilizing sophisticated molecular techniques to selectively silence or activate slow gamma machinery during reactivation. The results from Carr et al. (2012) pave the way for such experiments and many other exciting future investigations of the functions of slow gamma oscillations and hippocampal replay.

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