Gamma Oscillations in the Hippocampus

Gamma oscillations are thought to temporally link the activity of distributed cells. We discuss mechanisms of gamma oscillations in the hippocampus and review evidence supporting a functional role for such oscillations in several key hippocampal operations, including cell grouping, dynamic routing, and memory. We propose that memory encoding and retrieval are coordinated by different frequencies of hippocampal gamma oscillations and suggest how transitions between slow and fast gamma may occur.

Many cognitive operations require dynamic coordination of activity across distributed groups of neurons. Several mechanisms exist for this purpose, but one of the best understood is synchronization of neuronal activity by oscillations. Oscillations can be readily studied using local field potential (LFP) recording techniques. LFPs are measured extracellularly and, for the most part, reflect the spatial integration of voltages generated by currents flowing in and out of the dendrites of many neurons within an area. When postsynaptic activity across many cells is periodically synchronized, oscillations appear in LFP recordings. Widespread use of LFP recording techniques over the last several decades has provided a great deal of evidence suggesting that oscillations are not merely an epiphenomenon but are instead important for temporal coordination of neural activity on a relatively fast time scale.

In the hippocampus, a brain region critically involved in encoding, storage, and retrieval of memory (75), two main types of oscillations synchronize neuronal activity during active waking behaviors. These two types of oscillations are termed theta and gamma rhythms, and their distinctive temporal properties fit well with different coordination functions. The theta rhythm is a large amplitude, relatively slow (4–12 Hz), and highly regular rhythm that plays an important role in spatial and episodic memory processing (see Ref. 10 for a review). Theta rhythms in the hippocampus correlate with theta in many hippocampal efferent and afferent structures, including the entorhinal cortex (54), septum (59), amygdala (66), parasubiculum (30), striatum (18), and prefrontal cortex (40). Synchronized theta oscillations are well suited for connecting widespread networks of neurons due to their ~100- to 200-ms-wide period that can tolerate long conduction delays. Hippocampal theta rhythms correlate with intake of sensory information during movements such as whisking and sniffing in rats and may temporally segment samples of stimuli from the environment, with each theta cycle providing a discrete unit for sensory information processing in the brain (see Ref. 44 for a review).

The second type of synchronization mechanism seen in the hippocampus during alert behaviors is the relatively fast gamma oscillation (∼25–140 Hz). Gamma oscillations in the hippocampus exhibit their largest amplitude when they are nested within the slower theta oscillations (5, 11, 49, 77). Although the two types of oscillatory activity often co-occur, hippocampal theta and gamma rhythms appear to be independently generated (48, 77). Unlike theta rhythms, which remain relatively stable throughout active behaviors, gamma oscillations occur in bursts at particular times within the theta cycle (5, 12, 14, 74, 77) and have been proposed to select particular cell assemblies for processing at those times (37, 38, 51, 68). Because of their high frequency, gamma oscillations are ideally suited for operations that require neuronal coordination on a time scale that is beyond the range of conscious perception. This type of fast coordination may be needed during many fundamental operations of the hippocampus, including rapidly selecting inputs, grouping neurons into functional ensembles, retrieving memories needed to correctly perform a previously learned task, and determining which aspects of an experience will later be remembered. All of these processes likely involve not only activating selected cell ensembles but also filtering out unnecessary inputs. Consistent with this idea, gamma oscillations in hippocampal LFP recordings are not associated with gamma-related firing in all principal neurons but rather only with a particular subset of neurons at a given time (14, 16, 68).

In this review, we will summarize evidence showing that gamma oscillations synchronize the activity of select ensembles of cells during many functions of the hippocampus. We will first describe results elucidating the origins and mechanisms of gamma generation in the hippocampus and discuss the functional significance of these
results. Experiments supporting a critical functional role for gamma oscillations in several key operations of the hippocampus will then be reviewed. To conclude, we will introduce novel hypotheses regarding the functional relevance of hippocampal gamma oscillations and suggest a number of unresolved questions for future testing.

Origins and Cellular Mechanisms of Hippocampal Gamma Oscillations

Entrainment by Two Oscillators

The results of several studies support the conclusion that there are two independent generators of hippocampal gamma oscillations, one located in the EC and another in CA3. A study conducted by Bragin and colleagues (5) in behaving rats employed current source density (CSD) analyses of hippocampal gamma activity and found the largest estimated excitatory currents in the middle third of the dentate gyrus molecular layer, i.e., the termination zone for medial entorhinal cortex (MEC) projections. Furthermore, CSD profiles for dominant currents during gamma oscillations resembled CSD profiles for responses evoked by medial perforant path stimulation, and lesions of the EC caused these gamma-associated excitatory currents to virtually disappear. The average frequency of the remaining gamma oscillations was lower in lesioned animals than in control animals, and the maximal gamma power shifted to CA1 with large excitatory currents appearing in stratum radiatum, a layer that receives CA3 projections. Additional support for an entorhinal generator of hippocampal gamma oscillations was provided by CSD studies in partially decorticated, anesthetized guinea pigs (13). In this study, large excitatory currents associated with gamma oscillations were observed in CA1 stratum lacunosum-moleculare, the target area for perforant path fibers from the EC. The gamma-associated currents were not disrupted by knife cuts between CA3 and CA1 but were completely eliminated by lidocaine or tetrodotoxin injections to the EC. A more recent study in awake behaving, non-lesioned rats further investigated the driving forces behind hippocampal gamma oscillations (16). In this study, gamma oscillation peaks were detected in EGG recordings, and gamma cycle averages were constructed. Gamma peaks were detected in two reference sites, the CA1 and dentate gyrus cell body layers, and CSD maps were constructed to estimate currents during gamma oscillations in these regions. When CA1 was used as the reference for detecting gamma, excitatory currents were seen in CA3 and CA1 in the layers that are targeted by CA3 projections. When the dentate gyrus was chosen as the reference site, gamma oscillations in the dentate gyrus were coherent with gamma in CA1 stratum lacunosum-moleculare, the layer that receives direct input from EC. The authors concluded that there are two generators of hippocampal gamma oscillations, one in the dentate gyrus that depends on input from EC and another that emerges in CA3 and propagates to CA1. The two gamma oscillators were reported to usually be independent but still able to couple at times. A recent study suggested that the two gamma generators may produce different frequencies of gamma oscillations in CA1 (14). Slow and fast gamma oscillations in CA1 were entrained by CA3 and MEC, respectively, and tended to occur on different phases of the underlying theta cycles. Taken together, the results of these studies suggest that gamma oscillations in the hippocampus are driven by CA3 inputs at some times and by entorhinal inputs at other times.

Role of Inhibition

In a system that relies on fast temporal correlations to link interactions among cells, the activity of most cells in the network at any given time must be suppressed because otherwise many cells would fire near synchronously just by chance (87). In accordance with this idea, many lines of evidence point to the conclusion that the primary driving force behind hippocampal gamma oscillations is rhythmic inhibitory postsynaptic potentials (IPSPs) in the pyramidal cells. In an early study, high correlations were consistently seen between interneuron spike times and the phase of gamma oscillations, whereas pyramidal cell firing was not consistently related to gamma phase (11). A later study investigated intracellular recordings from CA1 and CA3 pyramidal neurons during gamma oscillations in anesthetized rats to determine which intracellular currents correlated with gamma oscillations in the field potentials (74). Intracellular gamma oscillations were not immediately apparent, but intracellular injection of chloride ions induced gamma frequency (25–50 Hz) depolarizing potentials in pyramidal cells that were coherent with gamma oscillations in the field (FIGURE 1). Because chloride injection at resting potential converts IPSPs into depolarizing responses, the results indicated that the gamma oscillations reflect gamma frequency IPSPs in pyramidal cells. A later intracellular study using urethane-anesthetized rats found that the amplitude of intracellular gamma oscillations recorded in pyramidal cells was smallest in the range of the chloride equilibrium potential (i.e., between −60 and −80 mV), and the phase of the intracellular oscillations also reversed in this voltage range (62). Thus the results from pyramidal cell intracellular recording studies supported the conclusion that gamma oscillations reflect rhythmic IPSPs in pyramidal cells.
Recordings from interneurons during gamma oscillations further supported this conclusion. In the study by Penttonen and colleagues mentioned above (62), histologically verified basket cells burst at theta frequency, with gamma-frequency (20–80 Hz) firing occurring within the bursts. Importantly, the gamma-frequency firing of the basket cells was phase locked to the gamma oscillations in the field, suggesting that basket-cell firing directly contributes to gamma-associated IPSPs in pyramidal cells. Basket cells predominantly innervate the cell body and proximal dendritic region of pyramidal cells and thus are well situated to potently inhibit the pyramidal cell population. A more recent study of interneuron firing during gamma oscillations in anesthetized rats found that parvalbumin-expressing basket cells were not strongly modulated by gamma (81). However, various types of basket cells, with different neurochemical characteristics, are seen in the hippocampus (see Ref. 23 for a review), and other classes of basket cells may participate in gamma oscillation generation. In the study by Tukker and colleagues (81), juxtacellular recordings were also made from several other classes of hippocampal interneurons: O-LM cells, axo-axonic cells, cholecystokinin-expressing cells, and bistratified cells. Out of all of the interneuron classes that were investigated, bistratified cells showed the strongest gamma modulation, reliably firing on the ascending phase of nearly every gamma cycle. Bistratified interneurons receive input from CA3 and target the dendritic zones that receive input from CA3 (i.e., strata oriens and radiatum), and thus they may participate in the generation of CA3-driven gamma oscillations in particular. It is plausible to assume that the gamma oscillations in the Tukker study were driven by the CA3 generator because the recordings were performed in urethane-anesthetized animals (81), and EC input to the hippocampus is reduced during urethane anesthesia (91). Additionally, the average frequency of gamma oscillations in this study was ~40 Hz, which falls within the frequency range of gamma oscillations in CA1 that are coupled with gamma from CA3 (14). In any case, the above results indicate that there are at least two different types of interneurons that participate in the generation of gamma oscillations in the hippocampus.

If hippocampal gamma oscillations primarily reflect IPSPs in the pyramidal cells, the question remains as to how gamma rhythmicity arises in the interneurons. In a hippocampal slice model of gamma oscillations, periodic firing emerged at ~40 Hz in networks of interconnected interneurons (88). In this model, metabotropic glutamatergic transmission, in the absence of ionotropic glutamatergic transmission, provided sufficient excitatory drive to the network of interneurons to bring about IPSPs in intracellular recordings from CA1 pyramidal cells. In another slice study, ~40-Hz oscillations were induced in CA3 and CA1 by infusion of cholinergic agonists (22). However, in this preparation, the oscillations were completely abolished by AMPA receptor antagonists and were resistant to antagonists of metabotropic glutamate receptors. The cholinergically induced oscillations in CA3 were later shown to be generated by alternating cycles of AMPA receptor-mediated recurrent excitation followed by feedback inhibition from perisomatic-targeting interneurons (33, 52). There is also evidence that gap junctions between interneurons increase the power of gamma oscillations by

FIGURE 1. Gamma oscillations reflect inhibitory postsynaptic potentials in pyramidal cells
Example recordings from CA1 during periods of spontaneously occurring theta-gamma oscillations are shown under control conditions (A) and after addition of KCl to the intracellular recording pipette (B). In each panel, intracellular recordings from pyramidal cells (1) appear above simultaneously recorded extracellular field potentials (2). Note that intracellular gamma oscillations were not apparent until after injection of chloride ions. Intracellular gamma oscillations elicited by chloride ions (indicated by arrow) coincided with gamma oscillations in the extracellular recording and were largest in amplitude on a particular portion of the theta cycle. The arrowheads indicate the portion of the theta cycle when intracellular gamma activity was substantially lower in amplitude. Scale: 500 ms; 20 mV and 1 mV for intracellular and extracellular recordings, respectively. Figure is adapted from Ref. 74.
Functions of Gamma Oscillations in the Hippocampus

Dynamic Grouping

It has long been known that gamma oscillations emerge in sensory cortices in response to sensory stimulation (1, 67). Interest in gamma oscillations increased in the 1980s when researchers began to suspect that gamma oscillations in sensory cortices offered a possible solution to the so-called “binding problem.” Complex stimuli are broken down during sensory processing, with spatially disparate cells coding different aspects of the stimuli (e.g., color, shape, direction of motion, etc.). The binding problem is the question of how the brain puts these pieces back together to end up with a coherent perceptual experience (see Ref. 86 for a review).

In 1989, experimental evidence was obtained in Wolf Singer’s laboratory, suggesting that gamma oscillations provided the precise temporal synchrony necessary for binding distributed cells involved in coding various aspects of a particular stimulus. Gamma synchronized firing was recorded across neurons in separate columns of primary visual cortex when cells responded to different aspects of the same stimulus, a single light bar simultaneously passing through the different receptive fields of the neurons (31). When two separate and independent light bars were passed through the receptive fields, the same cells responded but did not show gamma synchronized firing. These results were widely interpreted as an indication that neurons that respond to the same sensory object synchronize their firing at gamma frequency and additionally that neurons that are activated by different objects in the sensory space do not show synchronized firing. The original experiments were conducted using anesthetized animals, but the general hypothesis has since been supported by subsequent studies using different experimental paradigms in awake animals (e.g., Refs. 26, 46, 47, but see also Ref. 69). The results obtained from this line of research suggested a neural mechanism for how the brain integrates and segregates neural activity into functional neuronal ensembles during perceptual processing.

As the relationship between gamma synchronization and perception was studied further, work from Robert Desimone’s laboratory revealed that gamma oscillations were also important for selecting which visual inputs would be processed in higher visual areas. They found that when animals attended to one of two stimuli in the visual field, phase synchronization was enhanced between LFP gamma oscillations and spikes from neurons in cortical area V4 only when the stimulus inside the neurons’ receptive field was being attended to but not when it acted as a distractor to be ignored (25).

They concluded that gamma synchronization of
neurons activated by attention to stimuli leads to a very powerful output because the spikes from these cells converge at the next stage of visual processing at roughly the same time. In this way, the synchronous cells, and not the asynchronous cells, will most effectively activate the downstream neurons (see Ref. 24 for a review). Subsequent results showing that enhanced power of gamma oscillations and gamma synchrony of spikes in V4 were associated with increased reaction times in a change detection task supported this conclusion (89). This neural mechanism likely allows the brain to select the most behaviorally relevant stimuli for processing downstream, while at the same time ensuring that noisy and irrelevant stimuli are filtered out.

Gamma synchronization of neurons could also mediate attentional selection processes in the hippocampus. Selecting the environmental cues that are important for performing hippocampal-dependent tasks and ignoring extraneous cues that are task-irrelevant requires attention (21, 57) and thus likely activates attentional selection mechanisms involving gamma oscillations in the cortex (described above, and see also Ref. 24). Gamma-facilitated transfer of inputs related to the task-relevant cues would provide an excitatory advantage to the hippocampal cells involved in coding these cues, enabling them to be activated more reliably. In support of this idea, place cell discharges are more reliable when animals are trained to attend to a particular set of environmental cues (21, 43, 61). It is possible that this increased reliability is brought about by gamma oscillations because in one of these studies place cell spikes became phase-locked to gamma oscillations after animals learned to attend to the relevant stimuli (57). Considering that attention largely determines which experiences will be remembered (see Refs. 43, 56 for a review), cell selection by gamma oscillations likely also plays a major role in regulating the information that will be retained in long-term storage.

Recent theoretical work has proposed a winner-take-all mechanism to explain how gamma oscillations could regulate cell selection in the hippocampus (17). In the model, each gamma cycle evokes inhibitory postsynaptic potentials in the pyramidal cells, consistent with experimental data described above (74). This inhibition strongly suppresses spikes from the pyramidal cell population. As the inhibitory potentials decay, the pyramidal cells with the most excitatory input at that time will be the first cells to fire. These cells trigger feedback inhibition in the other pyramidal cells within a few milliseconds so that the less-excited cells quickly lose their chance to fire. This mechanism can differentiate cells with only small differences in levels of excitation and may contribute to selection of hippocampal neurons during attentional states.

Dynamic Routing

Recently, Pascal Fries suggested another hypothesis of gamma oscillation function, “neuronal communication through neuronal coherence” (24), which describes a mechanism for how synchronized gamma oscillations facilitate transmission of information from one level of processing to the next. Gamma oscillations, like neural oscillations in general, consist of alternating periods of higher excitability and periods of higher inhibition. Thus, when gamma oscillations between a “sending” neuronal group and a “receiving” neuronal group are synchronized, their periods of high excitability coincide, and this leads to more effective communication between the regions. Experimental evidence supporting this hypothesis was later obtained from simultaneous paired recordings across visual cortical areas in cats and monkeys during presentation of visual stimuli (90). The authors found that gamma power correlations in the paired recordings were high during trials when gamma oscillations between the regions were classified as having a “good” phase relationship (i.e., phase difference close to the mean phase difference across trials). Gamma power correlations were low during trials when gamma oscillations between the regions had a “bad” phase relationship (i.e., out of phase with the mean). This study provided experimental evidence for the idea that synchronized gamma oscillations promote interregional communication during transmission of sensory information.

The hypothesis that synchronized gamma oscillations facilitate communication between brain regions has recently been supported by findings in the hippocampal network. These findings further suggest that the frequency of gamma oscillations plays a critical role in routing the flow of information in the hippocampal network. In a study in freely behaving rats, different frequencies of gamma oscillations were shown to synchronize CA1 with two of its main sources of input, CA3 and MEC (14). Specifically, slow gamma oscillations in CA1 were coupled with slow gamma in CA3, and fast gamma oscillations in CA1 were coherent with fast gamma in MEC (FIGURE 2). A significantly higher proportion of CA3 cells were phase locked to slow gamma oscillations in CA1 than to fast gamma oscillations in CA1, suggesting that CA3 was communicating with CA1 more effectively during slow gamma oscillations. A substantial proportion of cells in layer III of the MEC were phase locked to fast gamma oscillations in CA1, but none were phase locked to CA1 slow gamma, suggesting that MEC was transmitting its signals to CA1 more effectively during fast gamma. Slow and fast gamma oscillations preferentially occurred at significantly different phases of theta in CA1,
consistent with earlier results showing that excitatory currents from CA3 and EC are maximal at different phases of theta (6, 35, 42). Segregation of CA3 and EC inputs to the hippocampus may be critical for preventing interference from previously learned associations during encoding of new associations (35), and gamma oscillations may play a role in this segregation of inputs by facilitating transfer of information from one region while filtering out inputs from the other. The above results point to the conclusion that different frequencies of gamma oscillations serve to dynamically route information transfer to CA1 and further suggest that gamma-mediated routing of inputs is regulated by underlying theta oscillations. Gamma-modulated activity may also be induced in other brain areas at particular phases of hippocampal theta oscillations, and this may serve to facilitate communication between the hippocampus and structures such as the striatum and the prefrontal cortex (72, 80).

Memory Encoding

If gamma oscillations play a role in selection of inputs during memory formation in the hippocampus, as hypothesized above, then there should be a link between hippocampal gamma oscillations and memory encoding processes. Indeed, a number of recent studies point to the conclusion that hippocampal gamma oscillations facilitate effective memory encoding. In intracranial recordings from human subjects asked to remember lists of random words, increased gamma power in the hippocampus during encoding of individual words was correlated with a high probability that a word would be subsequently recalled (64, 65). In another study involving intracranial recordings from patients who were asked to memorize word lists, gamma synchronization was significantly higher between EEG recordings from hippocampus and rhinal cortices during encoding of words that were later remembered compared with words that were later

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**FIGURE 2.** Dynamic routing of inputs by slow and fast gamma oscillations

A: example recordings of slow (top) and fast (bottom) gamma oscillations, overlying theta oscillations, in CA1. B: coherence spectra for example pairs of CA3-CA1 local field potential recordings (top) and MEC-CA1 local field potential recordings (bottom). Note that CA3 and CA1 are more coherent in the slow gamma frequency range (<60 Hz) and that MEC and CA1 are more coherent in the fast gamma frequency range (>60 Hz). C: schematic illustrating how slow and fast gamma oscillations route different inputs. Slow gamma is maximal on the descending portion of the theta wave and serves to synchronize CA1 with slow gamma-mediated inputs arriving from CA3. Fast gamma peaks near the theta trough and synchronizes CA1 with MEC input transmitted by fast gamma waves. Figure is adapted from Ref. 14.
forgotten (20). In a later study of neural activity and gamma oscillations in monkey hippocampus, coherence between spiking activity and local field potentials was higher in the gamma band during encoding of stimuli that were later well recognized compared with stimuli that were poorly recognized (41). As in the human studies, gamma power in the local field potentials was also significantly enhanced during encoding of stimuli that were well remembered later.

In accord with the hypothesized link between hippocampal gamma oscillations and memory encoding, we recently suggested that fast gamma synchronization between MEC and CA1 may facilitate memory encoding. Fast gamma oscillations in CA1 are coherent with fast gamma oscillations in layer III of MEC (14), the layer that provides direct input to CA1. The direct MEC projection to CA1 conveys information about the animal’s current position in the environment (7, 8, 28, 32). Thus it is possible that fast gamma oscillations transmit information about environmental stimuli from the EC to the hippocampus for encoding.

There is a plausible mechanism for how the timing of fast gamma oscillations would make them particularly well suited for memory encoding. Consider a scenario in which a depolarizing input is carried to a particular cell by fast gamma, and the same cell is activated again ~10–15 ms later on the next excitatory phase of fast gamma, this time leading to spiking. In this hypothetical scenario, the timing of the initial depolarization and the subsequent spiking would lead to long-term plasticity because of spike-timing-dependent plasticity in hippocampal neurons (4). This may explain why high frequencies of gamma oscillations may be ideal for transferring information about ongoing experiences from the entorhinal cortex to the hippocampus during memory encoding.

**Memory Retrieval**

It is also possible that gamma oscillations are required to link the distributed cells that represent a memory episode during memory retrieval processes in the hippocampus. In line with this idea, several studies have provided evidence supporting a role for hippocampal gamma oscillations during memory retrieval. In a recent study, local field potentials were recorded as rats learned to perform a delayed spatial alternation task in which they were required on each trial to retrieve information about the trajectory they traversed on the previous trial to decide which way to turn to receive a reward (55). Increases in gamma coherence between CA3 and CA1 and in gamma power in CA1 were observed on the center arm, the region that the rats traversed after the delay and before the turning choice point. This was thought to be the region where memory retrieval processes were engaged, and thus the authors proposed that gamma oscillations facilitate transfer of retrieved memories from CA3 to CA1. Studies demonstrating that memory retrieval requires intact projections from CA3 to CA1 are in accord with this conclusion (29, 58, 76, 78). In another study, CA3 place cell representations of possible future trajectories were activated when animals paused at a choice point (39). These activations may have reflected memory retrieval processes during prospective coding and were associated with strong gamma oscillations that were not seen during other pauses, suggesting another possible link between gamma oscillations and memory retrieval. In a later study, the amplitude of slow gamma (30–60 Hz) oscillations in CA3 increased as animals learned to accurately perform a task that involved retrieval of learned associations between items and contexts (79). In another study, CA1 place cell firing in mice was phase locked to slow (20–60 Hz) gamma oscillations only when mice had to suppress odor cues and retrieve a stable representation of the visuospatial environment to receive a reward (57). Gradual increases in gamma power were also seen as the animals learned to correctly perform the task. It is interesting to note that the gamma reported in the Tort et al. (79) and Muzzio et al. (57) studies was in the slow gamma frequency range. Both slow gamma oscillations (14) and memory retrieval (55) are associated with increased gamma coherence between CA3 and CA1, raising the possibility that slow gamma oscillations promote the CA3-CA1 communication that leads to successful memory retrieval.

The timing of slow gamma may work better for memory retrieval than memory encoding. In a study of spike-timing-dependent plasticity in hippocampal synapses, postsynaptic spikes occurring more than 20 ms after the onset of EPSPs in the postsynaptic cell were not effective at eliciting synaptic changes (4). This suggests that repetitive activation carried to CA1 by slow gamma oscillations (with a period of ~25 ms) would be outside of the optimal time range for effectively inducing long-term potentiation. Thus slow gamma oscillations may be fast enough to link distributed cells during memory retrieval yet also slow enough to avoid re-encoding of previously stored memories.

**Working Memory**

Several studies have suggested that hippocampal gamma oscillations play an important role in working memory, defined as the short-term internal maintenance of information that is required for impending decisions or actions but no longer present in the external environment (19, 27). In a study of intracranial recordings from human
epileptics, the power of gamma oscillations in the hippocampus increased with increasing working memory load (83). Another recent study using similar techniques found enhancement of the coupling between theta phase and gamma power in the hippocampus during the maintenance period of a working memory task (3). Working memory processes rely on a distributed network of brain regions, including the hippocampus and the prefrontal cortex (19, 27, 63). Thus gamma-related working memory effects in the hippocampus may involve gamma synchronization with other regions involved in working memory operations, including the prefrontal cortex. A recent study showed that prefrontal neurons synchronized their activity at gamma frequencies (~30 Hz) as monkeys remembered two objects during a brief delay period in a short-term memory task (71). During working memory, the hippocampus and prefrontal cortex show enhanced theta coherence (40), and prefrontal cortex neurons fire phase locked to hippocampal theta rhythms (36, 40, 70). Considering that the amplitude of gamma oscillations in the prefrontal cortex is modulated by the phase of theta oscillations in the hippocampus (72), it is plausible to hypothesize that gamma oscillations may also be involved in the coupling between prefrontal cortex and hippocampus during working memory.

**Representations of Spatial Sequences**

Gamma oscillations in the hippocampus may also be important for representing movement trajectories. A recent study in rats found a distinct class of pyramidal cells in CA1 that fires phase locked to the trough of gamma cycles (“TroPyr” cells; Ref. 68). This class of place cells exhibited clear theta phase precession, a phenomenon that is thought to provide a temporal code for spatial sequences (53, 60, 73). The TroPyr class of place cells was separated from another group of cells, termed “RisPyr,” which fired on the rising phase of gamma oscillations. RisPyr cells did not show normal theta phase precession when gamma oscillations were present. Interestingly, fast gamma-modulated place cells fire on the fast gamma trough and are a largely separate population from slow gamma-modulated cells, which fire on the ascending phase of slow gamma (14). Thus fast and slow gamma-modulated place cells may correspond to the TroPyr and RisPyr classes of cells, respectively, in the Senior et al. study (68). The firing properties of TroPyr gamma-modulated cells indicate that they may link codes for discrete places on each gamma cycle and thereby encode temporal sequences during theta phase precession, as has been suggested previously (50). If TroPyr cells and fast gamma-modulated cells correspond to the same class of place cells, it may suggest that fast gamma oscillations help maintain the temporal code for spatial sequences during theta phase precession.

**Transitions Between Different Gamma Mechanisms**

It is reasonable to assume that different mechanisms exist for hippocampal gamma oscillations that are employed for distinct purposes such as memory encoding and memory retrieval. We hypothesized that synchronization of CA3 and CA1 during slow gamma oscillations and synchronization of MEC and CA1 during fast gamma oscillations selectively promote retrieval and encoding, respectively. However, it remains unclear what causes the transition between the different synchronization mechanisms.

Perhaps the most parsimonious explanation of how gamma mechanisms could transition is that different interneurons are recruited by different inputs during different functions. Diverse classes of interneurons can be characterized by their distinct pattern of inputs, outputs, and firing patterns during hippocampal oscillations (see Ref. 45 for a review). It is possible that the interneuron circuits activated by CA3 inputs generate oscillations at lower frequencies than do the interneuron circuits activated by EC inputs. However, for the sample of interneurons recorded in the pyramidal cell body layers of the hippocampus in the Colgin et al. study (14), the majority were phase locked to both slow and fast gamma oscillations in CA1. It is possible that other types of interneurons with soma in other layers participate selectively in one or the other gamma subtype, but still the finding that so many interneurons participate in both types of gamma suggests that there is likely another mechanism involved in transitioning the network from one gamma state to the other.

A recent study has suggested a novel mechanism for how changes in gamma coherence across regions could be regulated (2). In CA3, large variations in gamma oscillation amplitude and frequency were observed, as has been reported previously (5, 14). However, the Atallah and Scanziani study (2) additionally reported that the instantaneous frequency of a gamma cycle could be predicted based on the amplitude of the preceding gamma cycle. Specifically, a particularly large amplitude gamma cycle was likely to be followed by a slow gamma cycle. Correlated increases in both excitatory and inhibitory synaptic currents in CA3 pyramidal cells were involved in the large amplitude gamma cycle. This effect may lead to a situation where a very long gamma cycle, involving increased excitation of CA3 pyramidal cells and interneurons, triggers a transition to slow gamma oscillations in the hippocampal network. Examples
of factors that could possibly produce a heightened activation of CA3 are increases in neuromodulatory inputs from the lower brain or enhanced firing in the CA3 associative network resulting from pattern completion processes (15). A transition to slow gamma oscillations in CA3, instigated by increased activation of CA3, would likely also entrain slow gamma oscillations in CA1 and may provide a cellular mechanism for how memory retrieval is initiated in the hippocampus.

In the absence of particularly strong activation of CA3, the default gamma mode in CA1 during active behaviors may be fast gamma oscillations. In accord with this idea, fast gamma oscillations were observed on a significantly higher percentage of theta cycles than were slow gamma oscillations (14). Thus it is possible that the hippocampus is automatically geared toward encoding current events during exploration, provided that the EC stimulation is properly timed and powerful enough to initiate synaptic plasticity processes. However, a particularly strong activation of CA3 may trigger a transition to slow gamma oscillations and memory retrieval in CA1. Interestingly, slow and fast gamma oscillations were rarely seen to co-occur on the same theta cycles (14), suggesting that the time course of transitions between different gamma mechanisms was often slower than the time course of a single theta cycle. Still, the behavioral conditions of this study were limited to free exploration of a highly familiar environment, a condition in which there is no need to compare ongoing events with previously stored memories. It is possible that slow and fast gamma oscillations occur more often on the same theta cycles during behaviors requiring comparisons between current conditions and previously stored memories. This suggestion is consistent with the hypothesis that the theta cycle is the organizing module for comparing current events with predictions based on previous experiences (84, 85).

In conclusion, the studies discussed here demonstrate that a large body of continually accumulating evidence points toward a critical role for gamma oscillations in many hippocampal operations. Still, the exact mechanisms responsible for their generation during different functions and the factors involved in switching between these mechanisms remain unknown. Future studies employing hippocampal-dependent tests will be essential for dissociating the contributions of gamma oscillations to various types of memory processing and to determine the validity of the hypotheses discussed in this review. Results of future studies are likely to impact theories of memory operations in the hippocampus and may lead to novel therapeutic strategies for diseases that involve aberrant gamma synchrony, such as schizophrenia (see Ref. 82 for a review).

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