Rhythms of the hippocampal network

Laura Lee Colgin

Abstract | The hippocampal local field potential (LFP) shows three major types of rhythms: theta, sharp wave–ripples and gamma. These rhythms are defined by their frequencies, they have behavioural correlates in several species including rats and humans, and they have been proposed to carry out distinct functions in hippocampal memory processing. However, recent findings have challenged traditional views on these behavioural functions. In this Review, I discuss our current understanding of the origins and the mnemonic functions of hippocampal theta, sharp wave–ripples and gamma rhythms on the basis of findings from rodent studies. In addition, I present an updated synthesis of their roles and interactions within the hippocampal network.

Sleep spindles
Thalamocortical oscillations of 7–14 Hz that occur in bouts lasting for a few seconds and recurring approximately once every 10 seconds during slow-wave sleep, particularly around the onset of sleep.

Slow oscillations
Cortically generated oscillations of ~0.5–1 Hz, consisting of alternating depolarizing 'up' states and hyperpolarizing 'down' states that regulate the occurrence of other oscillations, including sleep spindles, during slow-wave sleep.

Center for Learning and Memory, Department of Neuroscience, The University of Texas at Austin, Austin, Texas 78712, USA.
colgin@mail.clm.utexas.edu

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Brain rhythms are periodically fluctuating waves of neuronal activity that are readily observed using local field potential (LFP) recordings. Such rhythms reflect the synchronized activity of large numbers of neurons because synchronous currents sum together to generate large-amplitude fluctuations in LFP, whereas non-synchronized currents do not sum together and thus remain too small to be detected. It is known that individual neurons are not capable of carrying out complex cognitive operations in isolation and instead must form functional networks with other neurons[1] and so synchronous neuronal activity is thought to be relevant to cognition.

One such cognitive operation that requires coordination across multiple neurons is memory. Memories are thought to be represented by distributed ensembles of neurons that are concurrently activated, a concept that can be traced back to Donald Hebb's cell assembly hypothesis[2]. Brain rhythms are thought to have a key role in memory formation by synchronizing, and thereby coordinating, the activity of distributed neurons during memory operations.

The hippocampus is essential for spatial and episodic memory[3] and thus is an ideal region in which to investigate how brain rhythms affect memory operations. In addition, several features of the hippocampus facilitate the study of brain rhythms. The hippocampus contains densely packed neurons that generate large LFPs and, in turn, generate large rhythms. This is especially true for area CA1 because the pyramidal cell dendrites are aligned in parallel. As a result of this, synaptic currents flow in the same direction and sum together to produce large amplitude signals that are easily detected in LFP recordings. Accordingly, many studies of the role of brain rhythms in memory have been carried out in the hippocampus.

Another reason why the hippocampus is an excellent model system for studying brain rhythms is that much is known about hippocampal interneurons[4]. Interneurons are important for rhythm generation because they are able to synchronize activity across large groups of neurons via their highly divergent projections[5]. Pyramidal cells — the principal excitatory neurons of the hippocampus, many of which have receptive fields for particular locations in space and thus are termed place cells[6,7] — are also both modulated by and participate in the generation of hippocampal rhythms.

The hippocampus has different types of brain rhythms including theta rhythms[8] (~4–12 Hz), sharp wave–ripple complexes[9,10] (~110–250 Hz ripples superimposed on ~0.01–3 Hz sharp waves) and gamma rhythms[9,11] (~25–100 Hz). Each type of rhythm is observed during particular behaviours, is generated by specific mechanisms and is associated with characteristic neuronal firing properties. It is therefore not surprising that these different rhythms are thought to carry out distinct functions. Theta rhythms are thought to allow the brain to take in and to learn new information[12], and sharp wave–ripples are thought to be responsible for stabilizing and consolidating memories[13]. There is less agreement in the field about the functional significance of gamma rhythms[14]. Other brain state-dependent rhythms, such as sleep spindles and slow oscillations, also influence hippocampal operations; these rhythms will not be discussed in depth in this Review, but have been reviewed elsewhere[15,16].

In this Review, I discuss new findings that have yielded insights into and challenged assumptions about the role of hippocampal theta, sharp wave–ripple and gamma rhythms in memory operations. These rhythms have been observed in humans and non-human primates, as well as in lower mammals (BOX 1). However, many of the findings described have been made in studies carried out in lower mammals, particularly rodents, partly because the measurement of brain rhythms in healthy human subjects within a deep-lying structure such as the hippocampus is difficult. I discuss the

Box 1 | **Hippocampal rhythms in humans and non-human primates**

The study of hippocampal rhythms in healthy humans using non-invasive techniques is challenging because of the large distance between hippocampal sources deep in the brain and sensors placed outside of the head, leading to questions of whether the same hippocampus rhythms occur in humans and rodents. However, findings from studies of patients undergoing neurosurgery that have had electrodes implanted directly in the hippocampus support the conclusion that hippocampal rhythms in humans share many similarities with those in rodents. Moreover, in non-human primates it is possible to implant depth electrodes and thereby confirm the presence of oscillations in healthy primate hippocampi.

In humans with epilepsy, hippocampal theta occurs as a traveling wave[166], as it does in rodents[167,168], and is associated with movement. However, theta recorded in humans during virtual movement is lower in frequency, less sinusoidal and less continuous[20,169,170] than theta in freely moving rats. Short bouts of theta rhythms also occur in the monkey hippocampus and correlate with eye movements[22]. Studies of hippocampus in individuals with epilepsy have shown that sharp wave–ripples occur in the hippocampal network during rest and slow-wave sleep[171], as in rats, and may promote memory consolidation[172]. Moreover, hippocampal ripples are coupled with neocortical spindles in humans with epilepsy[103,173], as they are in rats[102,108]. In the monkey hippocampus, sharp wave–ripples that appear very similar to their counterparts in rodents also occur during inactive and active states[174,175]. Finally, separate slow and fast gamma rhythms may occur in primates, as in rodents. In humans with epilepsy, lower and higher frequency gamma oscillations have been reported in the hippocampus, with the higher frequency variant associated with memory encoding[176]. In the monkey hippocampus, it has been shown that neuronal spiking is coordinated by separate slow and fast gamma rhythms, and that coordination by fast gamma is associated with successful memory encoding[177].

mechanisms underlying hippocampal rhythm generation and provide an overview of what is known about their mnemonic functions.

Theta

Theta rhythms are fairly low frequency sinusoidal waves that occur in all hippocampal subregions during active exploration and rapid eye movement (REM) sleep[8,12]. Theta rhythms were first discovered in rabbits[17] and have since been recorded in many species including cats, rats, mice, bats, monkeys and humans[8,18–22]. These waves of activity also occur in many cortical and subcortical regions[23–27]. Theta rhythms have been the most widely studied rhythm in the rodent hippocampus, in which high-amplitude theta is readily observed during locomotor behaviours[8]. The medial septum–diagonal band of Broca has long been thought to function as the pacemaker for theta rhythms since it was first shown that hippocampal theta is abolished by septal lesions[18]. These results have since been replicated many times and many further details have been revealed regarding the role of the medial septum–diagonal band of Broca in hippocampal theta generation.

Mechanisms. The GABAergic cells of the medial septum that function as theta pacemakers target interneurons in the dentate gyrus, CA3 and CA1 (REF. 28). The septal interneurons rhythmically disinhibit hippocampal pyramidal cells and thereby promote their theta rhythmic firing. Pacemaking medial septum interneurons express parvalbumin and also express hyperpolarization-activated cyclic nucleotide-gated (HCN) channels[29,30], which are likely to promote their pacemaker properties[31]. However, the mechanisms underlying theta generation are more complicated than this simple summary implies. Septal interneurons terminate on more than one type of hippocampal interneuron[28]. In addition, distinct classes of hippocampal interneurons are phase-locked in their firing to different phases of the theta cycle[32]. A recent study of hippocampal interneurons in awake, behaving mice found that parvalbumin-positive basket cells preferentially fire at an earlier theta phase (when place cells preferentially fire) than do somatostatin-positive interneurons in the oriens lacunosum-moleculare[33]. These findings suggest that different types of interneurons in the hippocampus have different functions at distinct phases of the theta cycle.

In support of this view are findings from a study in which different interneuron classes were silenced in head-fixed mice as they ran on a treadmill containing visual and tactile cues[34]. Silencing of parvalbumin-positive interneurons, which are mainly perisomatic-targeting, increased place cell spiking in the early part of a cell's place field, which corresponds to late phases of theta[35,36]. By contrast, inhibition of somatostatin-positive interneurons, which mainly target dendrites, tended to increase place cell firing in the later part of the place field[34], which corresponds to early phases of theta[35,36]. These findings suggest that parvalbumin-positive interneurons have a role in selecting which place cells become active during theta. The findings also suggest that somatostatin-positive interneurons could inhibit the activity of place cells as the animal reaches the end of their place fields, thereby allowing the network to update its representation of location according to ongoing behaviour and current environmental cues.

Consistent with the findings that different types of interneurons fire at different theta phases, it has been shown that different types of interneuron mechanisms are involved in theta generation. First, theta rhythmic inhibition of interneurons is crucial for theta rhythm generation, as described above. In addition, mice lacking functional GABA type A receptors ($GABA_A$Rs) in parvalbumin-positive interneurons show attenuated theta rhythms[37]. Another important interneuron-mediated mechanism of theta generation is the rhythmic suppression of pyramidal cell activity. In support of this mechanism, it was found that specifically silencing theta-modulated parvalbumin-positive and somatostatin-positive interneurons in behaving mice increased firing rates of place cells within their place fields[34]. In addition, place cells produced longer bursts

Neuronal ensembles
Co-active neurons that work together to carry out neuronal computations and operations such as stimuli coding or memory storage.

of spikes when somatostatin-positive interneurons were silenced[34]. Moreover, other studies have shown that theta-modulated interneurons not only inhibit spiking but also induce theta-synchronized firing in pyramidal cells. In hippocampal slices, theta rhythmic activation of interneurons induced post-inhibitory rebound spiking, which produced theta-synchronized firing across multiple pyramidal cells[5]. Consistent with these findings, in a recent study of parvalbumin-positive interneurons in mice that were freely behaving in their home cage, it was shown that theta rhythmic activation of parvalbumin-positive interneurons induced rebound spiking and theta rhythmic firing in pyramidal cells[38].

Non-GABAergic mechanisms are also involved in theta production. First, excitatory currents are essential during theta[39,40]. A study of head-fixed mice running on a cue-rich treadmill found that silencing interneurons did not affect place cells outside of their place fields[34], showing that excitatory inputs are necessary to activate specific place cells within a theta cycle. Second, the intrinsic properties of pyramidal neurons that promote theta resonance may also have a role in theta production. For example, HCN1 is thought to facilitate theta rhythmic firing in neurons[41,42] and HCN1 blockade reduces theta entrainment of pyramidal cell spikes induced by rhythmic activation of parvalbumin-positive interneurons[38]. However, the precise role of HCN channels in theta production remains unclear because it has also been reported that enhanced theta rhythms occur in HCN1-knockout mice[43]. Last, cholinergic inputs from the medial septum also contribute to theta generation. Cholinergic projections from the medial septum are required for theta rhythms that occur while the animal is not engaged in active behaviours, which are termed atropine-sensitive theta[44]. Cholinergic stimulation may provide excitation[45] to the hippocampus during such inactive states, when movement-related inputs that drive atropine-resistant theta[44] are absent. In addition, a major role for cholinergic inputs in theta generation may be the suppression of another type of rhythm, sharp wave–ripples, which function in a manner that is antagonistic to theta[46,47] (BOX 2).

Adding to the range of complex mechanisms known to contribute to theta generation is the discovery that theta rhythms can occur in the absence of medial septum pacemaker inputs in a whole hippocampal *in vitro* preparation[48]. This finding suggests that theta can also emerge from local circuit interactions in the hippocampus. Nonetheless, it is clear that medial septum inputs are important for driving theta in behaving animals, as numerous studies have shown that medial septum lesions or inactivation disrupt theta generation[18,49–52].

Functions. In the 1970s, several fundamental studies showed that the extent to which theta was present in an electroencephalogram predicted how quickly animals learned or how well they remembered[53–55]. These findings led to the theory that theta has an essential role in learning and memory. Since then, much evidence for this theory has been provided by studies relating theta to mnemonic task performance and synaptic plasticity[50,56–67]. However, the theory has been called into question by a recent study[51] involving recordings from place cells. Place fields emerge as animals gain experience with new environments[68–70] and it is often assumed that the development of place cell representations corresponds to spatial learning. It was therefore surprising that this study[51] showed that, in rats, place fields were formed when the animal was in novel environments despite theta rhythms and theta entrainment of spikes being blocked by septal inactivation. In addition, flying bats have place cells even though these place cells show little to no theta rhythmicity in their firing[71]. These findings show that theta rhythmicity is not required for the formation of place fields and thus imply that theta is not necessary for the formation of spatial memory representations at the single cell level.

However, it is important to note that memory is a distributed process involving coordinated groups of neurons, not isolated neurons, and, accordingly, several studies suggest that theta is required for the formation of memories represented by neuronal ensembles. A recent study in rats showed that theta rhythm blockade by inactivation of the medial septum impaired performance on a delayed spatial alternation mnemonic

Box 2 | **Interactions between different hippocampal rhythms**

Hippocampal rhythms interact with each other in various ways. Sharp wave–ripples occur persistently in the absence of extrinsic input to the network[46,86–89]. As an animal shifts from inactive to active behaviours, extrinsic inputs, such as cholinergic inputs, may function to suppress sharp wave–ripples[10,46,47], allowing theta rhythms to predominate. Theta-rhythmic inhibitory events demarcate theta cycles, which correlate with actions that function to take in sensory information, such as sniffing and eye movements. In this way, each theta cycle may provide the hippocampus with a snapshot of the current environment as an animal actively samples external stimuli and the hippocampus encodes information about these stimuli. However, theta rhythms are also present during internal hippocampal operations such as the retrieval of previously stored memories[64,66] and envisaging future events[76]. During such intrinsic hippocampal network operations, each theta cycle may activate a coordinated ensemble of cells that represents a previously stored memory or an anticipated future trajectory. The switch between extrinsically and intrinsically driven network operations may depend on which type of gamma rhythms are nested within the theta cycle, with fast gamma promoting extrinsic inputs from medial entorhinal cortex (MEC) and slow gamma promoting intrinsic signals from CA3. Consistent with the idea that slow gamma promotes intrinsic signals from CA3, slow gamma rhythms also occur during sharp wave–ripples[100,148], which suggests that slow gamma may promote any state in which CA3 transmits information to CA1. For both fast and slow variants of gamma, the inhibitory events that comprise gamma cycles may function to select those cells receiving the most excitatory input[178] and thus carrying the most salient information at that time, while also filtering out noisy irrelevant inputs.

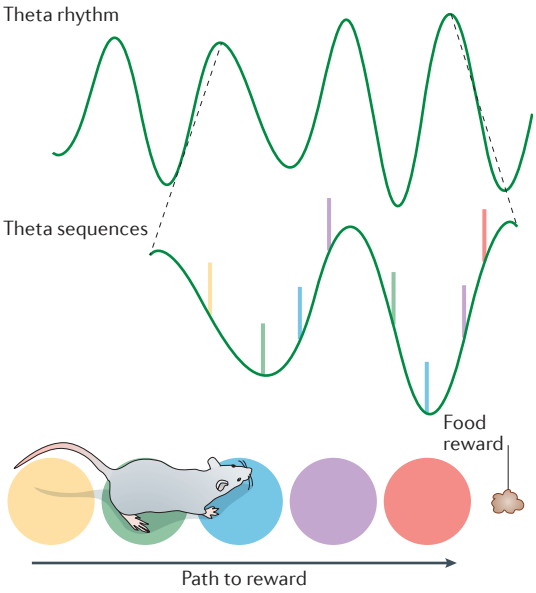

Figure 1 | **Theta sequences in the hippocampus during spatial memory operations.** Successive locations in an animal's trajectory are represented by an ordered series of CA3 or CA1 place cell spikes within individual theta cycles, termed a theta sequence. Shown in this figure is a schematic representation of a path to be taken by a rodent in order to reach a reward (bottom), an ongoing theta rhythm (top) and the theta sequence of place cells for two magnified theta cycles (middle), by which the place cells are colour coded according to the particular point in the path at which their place field is located. For individual place cells within a theta sequence, spikes occur at progressively earlier theta phases across successive theta cycles, a phenomenon termed theta phase precession[35]. As a result of this, spikes at early and late theta phases represent earlier and later locations, respectively, in the trajectory.

task and disrupted organized ensembles of place cells that are activated in a specific order[52]. Such organized neuronal ensembles are termed theta sequences[36,72,73] (FIG. 1) and this work suggested that theta sequences, rather than isolated place cells, are important for memory operations. In support of this view, theta sequences have been shown to be experience dependent[74] and to represent meaningful concepts that involve sequences of locations[75,76] (such as the path to a reward). In addition, theta sequences do not simply reflect hard-wired connections in the hippocampal network, but rather they change dynamically according to the behavioural intentions of the animal[76]. These results suggest that theta rhythms link different cells together in functional ensembles that support memory operations by providing integrated representations of complex concepts and experiences.

Theta may also integrate various types of sensory information received by the hippocampus — such as olfactory and visual input — by linking neurons that code different aspects of the same experience. Theta rhythms are well suited to coordinating multimodal sensory information because they correlate with movements used to acquire sensory stimuli, including sniffing and whisking[56,77]. These correlations may be important for the optimal intake of sensory information. For example, during an olfactory discrimination task, performance was poor when rats sniffed more slowly than theta frequency[78]. Moreover, theta rhythm in the hippocampus was not coupled to whisking when rats were merely whisking in air rather than actively sampling olfactory stimuli[79]. In addition, a recent study reported that saccade generation reset the phase of hippocampal theta in monkeys carrying out a visual memory task[22], which suggests that saccades prime the hippocampus to take in visual information. Together, these results suggest that theta coordination of neuronal activity and the active sampling of sensory stimuli produce an integrated representation of the current environment.

Furthermore, each theta cycle may represent a fundamental unit of information within an episodic memory. Support for this idea was provided by studies in rats showing that distinct representations of different environments[80], or of the same environment but with the location of rewards changed[81], were mainly segregated across separate theta cycles. Similar theta segregation occurred across head direction-coding neuronal ensembles in the medial entorhinal cortex (MEC) and the parasubiculum of rats[82]. Head direction cells that fired on the same theta cycles were tuned to similar head directions, whereas cells that fired on separate theta cycles preferred different head directions. Together, these studies suggest that spikes carrying related information are linked within a theta cycle, whereas dissimilar (and thus potentially conflicting) signals are segregated on different theta cycles.

The functions described above are associated with theta that occurs during active states. However, theta is also prominent in the hippocampus during REM sleep, albeit with a lower frequency and a different regional profile than theta that occurs during waking[83]. Interestingly, place cell spiking patterns that occur during active states have been shown to reoccur in theta during subsequent REM sleep, raising the possibility that REM sleep-associated theta may have a role in memory consolidation[84].

Sharp wave–ripples

Sharp wave–ripples are large amplitude, irregularly occurring LFP patterns that are observed in animals during waking immobility and during slow-wave sleep, as well as during consummatory behaviours[10]. These rhythms are mainly restricted to the hippocampal network, although they are also observed in the entorhinal cortex[85]. Sharp wave–ripples are widely presumed to originate in the hippocampus, as they occur persistently in hippocampal slices[46,86–88] and transplanted hippocampal grafts[89] in which afferents to the hippocampus are missing. In this section, I focus on how mechanisms of generation of sharp wave–ripples relate to their purported mnemonic functions. For additional details on mechanisms of sharp wave–ripple generation, I refer readers to a recent comprehensive review[90].

Theta sequences
Ordered series of place cell spikes that occur within theta cycles and that represent the succession of locations traversed during active behaviours.

Head direction cells
Neurons that fire when an animal's head is pointing in a particular direction and are found in several brain areas including the postsubiculum, the thalamus and the medial entorhinal cortex.

Replay
The phenomenon by which ordered place cell spike trains that occur during exploratory theta-related behaviours later reactivate in a temporally compressed manner during sharp wave–ripples while the animal is at rest and during slow-wave sleep.

Mechanisms. Although sharp waves and ripples are coupled, they are thought to be separate events with distinct origins. Sharp waves are excitatory events that are transmitted from CA3 to CA1 (REFS 10,91). By contrast, ripples are generated locally in CA1 by ripple-frequency spiking of perisomatically targeting basket cell interneurons[92–94]. It is unlikely that CA1 spiking during ripples is entrained by CA3, as CA1 place cell spikes are phase-locked to CA1 ripples, but CA3 spikes are not[91,95]. In addition, ripples are not coherent between CA3 and CA1; specifically, CA1 ripples are of higher frequency than CA3 ripples[91,95].

Nonetheless, sharp wave-associated spiking in CA3 is likely to affect CA1 cell firing during ripples, as shown by studies of place cell replay or reactivation. Replay refers to the phenomenon in which place cell firing patterns that occurred during active exploration are reactivated during subsequent sharp wave–ripples[96–99] (FIG. 2). A study has investigated replay in CA3 and CA1 place cells of rats, when ripples were detected in CA1 during wakefulness[100]. The data from this study imply that CA3 and CA1 place cells concurrently replay the same spatial memories. Moreover, another study has found that suppression of CA3 inputs to CA1 in transgenic mice impaired ripple-associated reactivation of CA1 place cell pairs[101]. Consistent with the idea that ripples are generated locally, the rate of ripple occurrence in CA1 did not change significantly when CA3 inputs were suppressed, although ripple frequency was lower.

In addition, CA1 ripple frequency in sleeping rats has been found to positively correlate with sharp wave magnitude[91], which suggests that stronger excitation from CA3 produces faster ripples in CA1. In this study, CA1 cell firing was phase-locked to ripples during sleep[91] and thus faster ripples would be expected to promote shorter interspike intervals in CA1. This could allow CA1 to send a more powerful output to its downstream targets. In support of this idea, hippocampal ripple activity has been reported to peak before neocortical spindles peak[102,103]. Thus, ripples could facilitate transfer of memories to the neocortex during memory consolidation, which is a commonly hypothesized function of sharp wave–ripples[96–99,101,104–107]. However, another study reported that neocortical spindles precede hippocampal ripples, which suggests that neocortical projections also influence the content of hippocampal ripples[108].

Mechanisms of ripple formation also support the idea that ripples have a memory consolidation function. During sharp wave–ripples, CA1 pyramidal cells are not only depolarized by sharp waves but also receive strong shunting inhibition from ripples[109]. This shunting inhibition raises spike thresholds and prevents most cells from firing. This suggests that ripples may function to select only the most strongly encoded memories for consolidation. That is, only the cells that receive sufficient excitation, which are likely to be those with synapses that were potentiated during earlier learning, would be able to overcome this inhibition and send their memory traces to long-term storage. While memories are being transferred to neocortical storage sites, the neural mechanisms encoding the memories may be depotentiated in synapses between CA3 and CA1. In support of this idea, long-term potentiation at the Schaffer collateral synapse was found to decay over time in hippocampal slices that showed sharp wave–ripples[87]. In addition, reactivation of events in CA1 does not increase, but rather decreases, over the course of slow-wave sleep following the events[96]. Moreover, experience-dependent plasticity in rat place cells has been shown to persist for days in CA3 but to disappear overnight in CA1 (REF. 110).

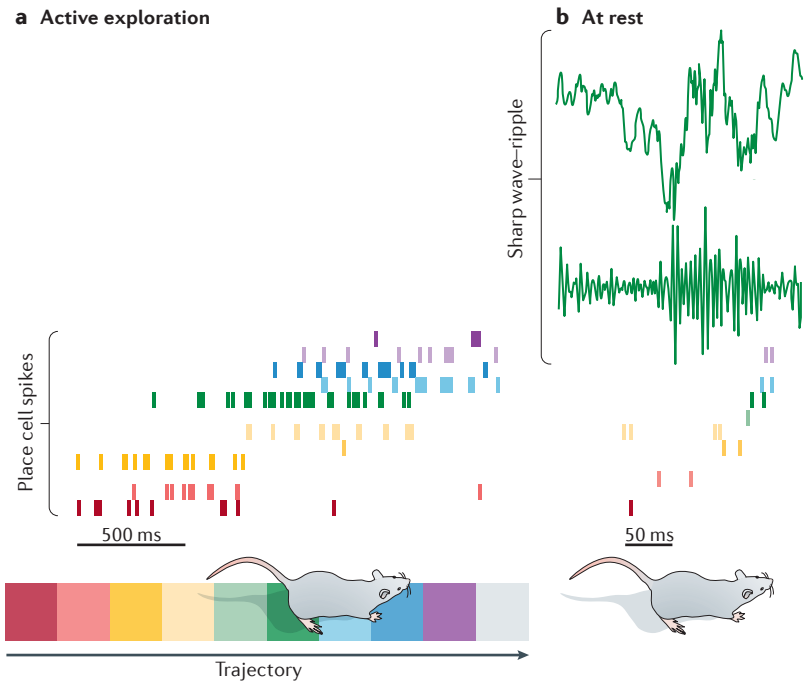

Figure 2 | **Replay during sharp wave–ripples. a** | Shown in this part of the figure are spikes from successively activated place cells (top) as a rodent passes through the cells' place fields in a particular trajectory on a linear track (bottom). Each row of coloured tick marks represents spikes from a different place cell (calibration: 500 ms). **b** | Shown in this part of the figure is an example of a sharp wave–ripple (top) recorded during subsequent rest at the end of the linear track; a bandpass filtered (150–300 Hz) version of the sharp wave–ripple is shown immediately below the raw recording. Spikes from the place cell ensemble are shown to reactivate during the sharp wave–ripple in the same order as in exploration but on a faster timescale (calibration: 50 ms).

Functions. Any hypothesized functions of sharp wave–ripples must be consistent with the unconscious nature of slow-wave sleep, the state during which sharp wave–ripples most often occur[10]. Accordingly, sharp wave–ripples have not been thought to be involved in the active sampling of incoming sensory information and in the corresponding encoding of memories of these sensory experiences. Instead, sharp wave–ripples have been traditionally hypothesized to carry out offline mnemonic functions, including memory consolidation[96–99,101–107,111] and erasure of hippocampal memory traces[87,112].

However, recent evidence suggests that sharp wave–ripples have a key role in certain aspects of active spatial navigation[111,113,114]. At times, place cells must convey representations of locations that are distinct from an animal's current location. During such times, place cells

cannot simply respond to inputs driven by stimuli in the immediate environment but instead must be activated by another form of excitatory input. Sharp waves have long been recognized as excitatory events[10], and recent intracellular recordings from behaving mice confirmed the presence of depolarizing events in pyramidal cells during sharp waves[109]. Moreover, in rats carrying out spatial memory tasks, place cells have been shown to represent locations distinct from the animal's current location when sharp waves occur between bouts of active navigation[99,115]. Thus, sharp waves are likely to provide the excitation that allows place cells to fire outside of their place fields, during waking behaviours that require representations of distant locations.

Planning of future trajectories requires the internal representation of maps of distant locations and new evidence indicates that sharp wave–ripples are important for retrieving such maps. One recent study found that blockade of sharp wave–ripples in rats that were learning a spatial memory task impaired task performance, which suggests that sharp wave–ripples in awake animals are involved in memory-guided trajectory planning[114]. Another study examined sharp wave–ripples during a spatial memory task in which rats foraged for a randomly placed reward and then returned to a predictable goal location[116]. During rest periods of the task, sequences of place cell spikes during sharp wave–ripples were found to represent paths towards the goals. Importantly, paths represented during sharp wave–ripples matched the paths that were subsequently taken to reach the goals. Another recent study investigated sharp wave–ripples in rats that were learning a spatial alternation maze[117]. Sharp wave-related spiking was examined during periods when rats were deciding which path to take. As task performance improved, it was found that pairs of place cells representing maze locations were more likely to co-activate during sharp waves that occurred before correct choices were made than during sharp waves that occurred before incorrect choices were made.

It is likely that spatial route planning is not the only waking function in which sharp wave–ripples have a role. It is possible that sharp wave–ripples emerge when the hippocampal network engages in intrinsically driven processes, but not during processes driven by the immediate sensory environment. Such intrinsic operations may include memory retrieval[100,113], envisioning the future (such as in trajectory planning, as discussed above) or imagining experiences that have never happened. With respect to imagining experiences that have never happened, it has been shown that place cell sequences during sharp wave–ripples can represent paths that were not previously experienced or subsequently traversed[115]. The temporal compression of spatial memories during sharp wave–ripples[97,98,118] is consistent with this set of functions, because memories are retrieved (or imagined) on a faster timescale than the timescale in which they were experienced[113].

However, it is important to note that current sensory stimuli can nonetheless influence which place cells fire during sharp wave–ripples. For example, in awake rats, paths that are represented by place cell sequences in both forward and reverse order during sharp waves often begin at or near an animal's current location[115,118–120]. Moreover, sensory stimuli can bias selection of the place cell ensembles that fire during sharp waves while the animal is sleeping. In a recent study in rats carrying out an auditory–spatial association task, auditory cues were associated with particular place cell firing patterns during waking[121]. The subsequent presentation of these auditory cues during non-REM sleep led to preferential reactivation of the place cell ensembles that were activated by the cues during earlier learning.

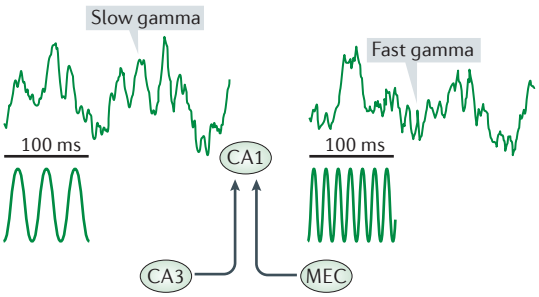

Figure 3 | **Slow and fast gamma rhythms.** Two distinct subtypes of gamma rhythms, termed slow and fast gamma, occur in the hippocampal network. Slow gamma rhythms couple activity in hippocampal subregion CA1 to inputs from CA3. By contrast, fast gamma rhythms in CA1 are entrained by inputs from medial entorhinal cortex (MEC). Typically, the two subtypes of gamma rhythm do not occur at the same time within CA1 (REF. 123). Slow and fast gamma rhythms are also observed in CA3, where fast gamma rhythms are also entrained by inputs from MEC[123]. Examples of slow and fast gamma rhythms recorded from CA1 in a freely behaving rat are shown at the top (calibration: 100 ms) in order to show their somewhat irregular appearance and stylized versions of the rhythms are shown below.

Gamma

Gamma rhythms are recorded in the hippocampus during a variety of behaviours but are of lower amplitude than the theta rhythms and sharp waves with which they occur[9,122]. Perhaps for this reason, gamma rhythms have received less experimental attention than theta rhythms and sharp wave–ripples, at least *in vivo*. The high variability of gamma frequency[11,123] also complicates its measurement in behaving animals.

Multiple researchers have recently begun to agree that rhythmic activity across the broad range of frequencies that are defined as gamma (~25–100 Hz) in CA1 actually encompasses more than one type of brain rhythm (FIG. 3). Activity in the lower end of the frequency range (~25–55 Hz) has been termed 'low gamma' or 'slow gamma' and is driven by CA3 (REFS 123–126). A second type of gamma rhythm shows a higher range of frequencies (~60–100 Hz) and is entrained by inputs from MEC[123–126]; this type of activity has been termed 'fast gamma' in some studies[123,125] and 'mid-frequency gamma' in others[124,126] ('fast gamma' is used in this Review). Gamma rhythms also occur in many other brain regions besides the hippocampus, with similar gamma subtypes showing low and high frequencies[127–131].

Mechanisms. There is much evidence to indicate that inhibitory interneurons are crucial for gamma generation[14,132]. Gamma rhythms in the LFP of rats have been shown to reflect inhibitory events recorded intracellularly in CA3 and CA1 pyramidal cells[133] and in dentate gyrus granule cells[40]. In addition, interneuron spikes consistently phase-lock to gamma oscillations, whereas pyramidal cell spikes do not[9,122–124,134,135]. Moreover, CA1 basket cells that were recorded intracellularly in anaesthetized rats were found to fire bursts of action potentials at gamma frequencies that were locked to gamma rhythms in the LFP[136]. Gamma phase-locked firing has been observed in several types of hippocampal interneurons including axo-axonic cells, bistratified cells, parvalbumin-positive basket cells and cholecystokinin-expressing cells[134]. Together, these findings suggest that gamma-frequency spiking of fast-spiking interneurons produces the observed gamma rhythms.

Gamma amplitude in freely behaving rats is largest during theta states[122], and gamma-generating mechanisms can also be modulated by theta; that is, gamma amplitude[11,123,133,136] and gamma phase[124,137] are coupled to theta phase. Theta phase modulation of gamma amplitude may involve inhibition of gamma-generating interneurons at a particular theta phase. In support of this idea, theta phase–gamma amplitude coupling was decreased when $GABA_A$R-mediated conductances in parvalbumin-positive interneurons were blocked in freely moving transgenic mice[37]. Gamma-generating circuits are also likely to be influenced by theta-modulated excitatory inputs. Theta–gamma phase-locking, which has been observed in rats during both running- and REM-associated theta[124], is consistent with the idea that excitation at a particular theta phase triggers the onset of gamma by inducing gamma-frequency bursting in interneurons.

It should be noted that most of the studies described above did not differentiate between different frequency variants of gamma and it is possible that slow and fast gamma are generated by different mechanisms. Recordings in freely exploring rats have shown that slow and fast gamma rhythms of CA1 show phase synchrony with CA3 and MEC, respectively[123]. Accordingly, different gamma frequencies have been shown to be prevalent in different layers of CA1 in rats carrying out spatial navigation tasks[126]. Specifically, slow gamma (~30–80 Hz) activity dominated in stratum radiatum, whereas ~60–100 Hz gamma dominated in stratum lacunosum-moleculare. In addition, different CA1 interneurons have been found to be preferentially modulated by different frequencies of gamma in both behaving and anesthetized rats[126,138]. These findings suggest that CA3-activated interneurons drive slow gamma and MEC-activated interneurons drive fast gamma. In further support of this, fast gamma rhythms were reduced when the MEC projection to CA1 was blocked in mice carrying out a spatial memory task[139]. Moreover, in mouse brain slices, optogenetic stimulation of MEC at theta frequency generated bursts of fast gamma oscillations that corresponded to fast gamma spiking in MEC interneurons[140].

Nonetheless, it has been shown that a substantial proportion of CA1 interneurons phase-lock to both slow and fast gamma[123,126]. Such interneurons may be part of a network that can generate either slow or fast gamma, depending on the state of the network. Theoretical work has shown that the frequency of gamma rhythms generated by networks of hippocampal interneurons can vary depending on the strength of excitatory and inhibitory inputs[141]. Specifically, in simulations of gamma activity in a model neuron network, gamma frequency was found to increase with increased excitatory drive onto the interneurons and was found to decrease with increased GABA conductances in the interneurons. The increased excitatory drive onto interneurons that is needed to produce fast gamma may be provided by increased spiking in MEC projection neurons. In support of this idea, both spiking activity in MEC neurons in rats and mice[142–144] and the power of fast gamma in rats[125,142,145] have been shown to increase with increased running speed. However, a different mechanism may promote slow gamma firing in gamma-generating interneurons. One possibility is that a certain class of interneurons projects to gamma-generating interneurons, thereby increasing their GABA-mediated conductances and reducing their spike rates to slow gamma frequencies. However, these hypotheses are tentative and much work remains to be done to uncover mechanisms underlying slow and fast gamma rhythms.

Functions. Several studies have recently begun to address the question of whether slow and fast gamma carry out different functions and a few main hypotheses have emerged from these studies. Evidence for and against each of these hypotheses is discussed below.

The entorhinal cortex processes sensory information and transmits this information to the hippocampus[146], and fast gamma is driven by inputs from MEC in rats and mice[123–126,139]. Therefore one plausible function for fast gamma is the encoding of current sensory information in memory and some results from recent studies are consistent with such a function. In one study, systemic administration of scopolamine, a muscarinic antagonist that blocks memory encoding, was shown to reduce fast gamma in rats running on a circular track[147]. It has also been shown that, in rats running on a linear track, place cells tended to encode recent locations and ongoing trajectories during fast gamma, rather than predicting future locations[137,148]. In addition, several studies have linked changes in fast gamma to variations in ongoing behaviour. Studies have shown that in rats, fast gamma frequency increases as a function of running speed during random foraging, performance of a spatial alternation task or running on a linear track[142,145]. This may allow spatial representations within gamma cycles to transition more quickly across successive locations as running speeds increase. In addition, fast gamma power increased relative to slow gamma power when mice used cues in the external environment to navigate towards the location of a reward[149]. In another study, fast gamma power was found to be high when rats attended to stimuli that signalled the beginning of a trial in a spatial alternation task[150]. However, other results do not support the hypothesis that

Stratum radiatum
Apical dendritic layer in CA3 and CA1 in which axons from CA3 pyramidal neurons terminate.

Stratum lacunosum-moleculare
Distal apical dendritic layer in CA3 and CA1 in which perforant pathway fibres from the entorhinal cortex terminate.

fast gamma has a memory encoding function. For example, a recent study has found that fast gamma is linked to working memory, but not memory encoding, in mice carrying out a delayed nonmatching-to-place task[139].

Another plausible hypothesis is that slow gamma promotes memory retrieval. Memories are thought to be stored in and retrieved from the CA3 network[151–154] and it is known that slow gamma rhythms in CA1 of behaving rats are entrained by inputs from CA3 (REFS 123–126). It has been shown in rats carrying out an associative memory-based task that coupling between theta phase and slow gamma amplitude in CA3 at the time when memory retrieval was expected to occur was correlated with task performance[155]. A subsequent study also found that coordination between slow gamma and theta was related to successful memory retrieval in rats[156]. In a recent study in which rats learned an odour–place association, ~20–40 Hz coupling between lateral entorhinal cortex (LEC) and CA1 was found to develop as the animals learned the task[157]. The LEC–CA1 coupling was observed during the odour-sampling period, which is likely to correspond to the time when animals recalled the place association and was not seen during error trials. However, the observed ~20–40 Hz activity overlapped with both beta and slow gamma frequency bands and thus may reflect either beta (which has been reported in the rat hippocampus during odour sampling)[158], slow gamma or a combination of both.

Recent findings from studies of place cell ensemble activity suggest that slow gamma facilitates the activation of previously stored representations of spatial sequences, providing further support for the hypothesis that slow gamma is involved in memory retrieval. In rats traversing a familiar linear track, place cell ensembles preferentially represent upcoming locations, rather than recent locations, during periods of slow gamma[148]. In addition, sequences of locations were represented in a temporally compressed manner during slow gamma, which may help to explain how events are experienced in real time but subsequently retrieved in a time-compressed form[137]. In another study, slow gamma coupling between CA3 and CA1 was observed during sharp wave–ripples in awake resting rats and the fidelity of replay increased as this slow gamma coupling increased[100]. A subsequent study also investigated replay during awake rest in rats and found that representations of sequences of locations jumped from one discrete location to another across slow gamma cycles within sharp waves[159]. These findings suggest that slow gamma is important in memory retrieval, as replay is thought to reflect reactivation of memories of earlier experiences.

However, not all findings from studies of slow gamma fit with this memory retrieval hypothesis. Specifically, some studies have described novelty-related increases in slow gamma in rats[125,160,161]. One possible explanation for these observations is that slow gamma generally promotes interactions between CA3 and CA1 and that these interactions are heightened when the animal is in novel environments. These apparent incongruities across studies highlight the need for further investigation into the functions of slow gamma rhythms.

Conclusions and future directions

Although findings from recent studies have provided many important insights into the functional significance and origins of hippocampal rhythms, some important questions remain. For example, what exactly is the functional significance of variations in theta frequency? Specifically, is there any functional significance to the lower frequency of theta that occurs during novel experiences compared with familiar ones[162]? Furthermore, sharp wave–ripple replay often occurs in an order that is reversed relative to the order of cell activation from earlier behaviour[119,163], particularly for memories of recent experiences[164]. Why would memories be stored or consolidated in reverse order? Do forward and reverse

Box 3 | **Abnormal brain rhythms in schizophrenia**

Deficits in neuronal synchrony have been reported in several human brain disorders, including schizophrenia and Alzheimer disease[165]. Brain rhythm abnormalities have also been reported in rodent models of these diseases, which suggests that their underlying mechanisms can be discovered and treated. Rodent models of schizophrenia are particularly informative in this regard.

In the Df(16)A$^{+/-}$ mouse model of schizophrenia, hippocampal and medial prefrontal cortex (mPFC) theta rhythms were less correlated than in wild-type mice[179]. These mutant mice also showed working memory impairments that correlated with hippocampal-mPFC theta synchrony impairments. In another study, rats prenatally exposed to maternal immune activation[180], a risk factor for schizophrenia, were found to have reduced theta and slow gamma synchrony between hippocampus and mPFC, and these slow gamma deficits correlated with deficits in sensorimotor gating. Another study used a rat model of schizophrenia in which schizophrenia-like cognitive deficits are induced by causing a lesion of the ventral hippocampus[181]. The rats were trained on a slowly rotating arena on which they had to learn to avoid a shock zone that was defined according to distal room cues, not local arena cues. Successful performance of this task requires the animals to attend to relevant stimuli while ignoring irrelevant stimuli and it is known that such attentional functions are impaired in schizophrenia. Performance on this task was impaired in the rat model of schizophrenia and theta oscillations were less coordinated across the hippocampus in rats that showed impaired task performance. Remarkably, deficits in both task performance and hippocampal synchrony were prevented by pre-training rats on the task during adolescence.

Abnormalities in sharp wave–ripples may also occur in individuals with schizophrenia, on the basis of evidence from animal models. Animal models that show neuronal deficits (for example, parvalbumin-positive neuron dysfunction) or behavioural abnormalities associated with schizophrenia show augmented ripples and impaired reactivation[182,183]. Together, these findings suggest that oscillatory coordination in the hippocampal network is disrupted in schizophrenia and that treatments that increase oscillatory coordination may alleviate cognitive deficits.

Delayed nonmatching-to-place task
A behavioural task that assesses memory by first allowing animals to visit one of two goal locations and then, after a delay period, requiring animals to navigate to the other goal location in order to receive a reward.

replay have different functions? Another crucial gap in knowledge exists regarding the memory consolidation hypothesis of replay function. According to this hypothesis, replay functions to transfer memories from the hippocampus to the neocortex. However, it remains unknown whether coordinated sequence replay occurs between the hippocampus and its major downstream cortical target, the deep layers of the entorhinal cortex. Last, do different frequencies of gamma represent different functional states of the hippocampal network, as proposed above, and, if so, are different circuits involved in their generation or is the same circuitry simply entrained by different inputs?

Recent innovations in experimental methods provide us with the tools to address these and other important questions. For example, optogenetic activation of septal pacemaker interneurons will allow researchers to drive theta at particular frequencies in order to determine how memories are affected by theta frequency variations. In addition, researchers are now able to examine large numbers (that is, >100) of simultaneously recorded neurons across different hippocampal sites in rats[159], which allows for better and more precise decoding of neuronal activation patterns. Experiments using such high-density recordings can determine whether coordinated replay occurs across different regions. Furthermore, optogenetic and pharmacogenetic techniques permit selective silencing of particular interneurons. Such manipulations should reveal whether slow and fast gamma rhythms are mechanistically distinct. If so, these same tools can then be used to selectively silence slow or fast gamma in order to shed light on their functions. Such results may pave the way towards novel treatments for diseases associated with aberrant rhythms[165] (BOX 3).

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The author declares no competing interests.