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Review

Gamma oscillations and episodic memory

Benjamin J. Griffiths[1,*] and Ole Jensen[1]

Enhanced gamma oscillatory activity (30–80 Hz) accompanies the successful formation and retrieval of episodic memories. While this co-occurrence is well documented, the mechanistic contributions of gamma oscillatory activity to episodic memory remain unclear. Here, we review how gamma oscillatory activity may facilitate spike timing-dependent plasticity, neural communication, and sequence encoding/retrieval, thereby ensuring the successful formation and/or retrieval of an episodic memory. Based on the evidence reviewed, we propose that multiple, distinct forms of gamma oscillation can be found within the canonical gamma band, each of which has a complementary role in the neural processes listed above. Further exploration of these theories using causal manipulations may be key to elucidating the relevance of gamma oscillatory activity to episodic memory.

Highlights

Gamma oscillations may coordinate pre- and postsynaptic neuronal firing to enhance plasticity within the hippocampus.

Cross-regional gamma synchronisation may communicate sensory information to the hippocampus during memory formation, and hippocampal representations to the cortex during retrieval.

Gamma oscillations nested within ongoing theta oscillations may encode and recall sequences of stimuli.

Multiple, distinct oscillations may exist within the canonical gamma band (30–80 Hz), each with complementary roles in episodic memory.

An established correlation between gamma oscillations and episodic memory

When we talk of **episodic memories** (see Glossary), we mean long-term memories relating to personally experienced events anchored to a specific moment in time and space [1]. Although these memories are, by definition, rich in detail and can last for decades, patterns of neural activity lasting mere seconds will dictate whether these memories are formed or recalled [2,3]. Many studies suggest that **gamma oscillations** (~30–80 Hz, although definitions can vary slightly among researchers) have a key role in both the formation and retrieval of an episodic memory. Supporting evidence comes from a range of species (including rodents [4–7], nonhuman primates [8,9], and humans [10–12]), and a variety of empirical techniques (ranging from studies of cell cultures *in vitro* [13,14] to behavioural responses in humans [15]). In our view, the extent of this evidence provides firm support for a link between gamma oscillations and episodic memory, and calls for a focus on understanding why this link exists. To address this question, we review three distinct neural mechanisms that may link gamma oscillations to fundamental aspects of episodic memory: (i) **spike timing-dependent plasticity**; (ii) **neural communication**; and (iii) **sequence encoding/retrieval**, with the aim of elucidating how gamma oscillatory activity supports episodic memory.

Gamma oscillations and spike timing-dependent plasticity

Our ability to form an episodic memory hinges upon **long-term potentiation** (LTP), a process through which synaptic connections between two neurons are strengthened [16,17]. Gamma oscillations have been proposed to play an important role in a type of LTP known as spike timing-dependent plasticity (STDP), which depends on a precise temporal delay between the firing of a presynaptic and a postsynaptic neuron. While there are numerous examples of gamma oscillatory activity enhancing STDP *in vitro* [13,18], *in silico* [19,20], and *in vivo* [21,22], the mechanistic explanation of this link is open to debate. Here, we discuss: (i) how STDP occurs; (ii) how gamma oscillations may facilitate this process; and (iii) how the interaction between STDP and gamma oscillations might result in the formation of complex, episodic memories.

STDP is thought to depend upon: (i) a presynaptic spike leading to the release of presynaptic glutamate, which promotes the opening of postsynaptic NMDA receptors; and (ii) the backpropagation of

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a postsynaptic spike leading to the unblocking of the Mg^{2+} block from the same postsynaptic NMDA receptors [16]. Some have suggested that the comparatively slow binding of glutamate to the NMDA receptor relative to the rapid removal of the Mg^{2+} block means that the presynaptic action potential must precede the postsynaptic action potential by ~10–20 ms for STDP to occur (e.g., [23]). Indeed, in slices of rat hippocampus, presynaptic spikes that lead postsynaptic spikes by ~15 ms result in synaptic strengthening, whereas presynaptic spikes that follow postsynaptic spikes by ~6 ms lead to synaptic weakening (known as long-term depression; LTD) [24]. STDP effects have been reported across a range of species, including rodents (*in vitro* [24–26] and *in vivo* [27]), nonhuman primates (*in vitro* [28] and *in vivo* [29]), and humans (*in vitro* [30]).

Although STDP depends upon correlated pre- and postsynaptic spiking, a solitary presynaptic spike is unlikely to induce postsynaptic spiking [16]. Instead, convergent input is required. Gamma oscillations may provide this convergent input in two ways. First, gamma oscillations can synchronise the firing of multiple presynaptic neurons so that they exert a stronger depolarising effect on the target postsynaptic neuron than if they were to fire in isolation [13,14]. Indeed, computational models show that the oscillation-driven synchrony of presynaptic activity increases the likelihood of a postsynaptic spike [31,32] (see also [33]). Moreover, *in vitro* studies show that synchronising multiple inputs to a postsynaptic neuron enhances the likelihood of LTP [13]. While an oscillation of any frequency could, in theory, synchronise neuronal firing, gamma oscillations are perhaps ideal because they provide a comparatively short window of excitability that ensures all neurons fire in near-perfect unison [34], while having oscillatory cycles that are long enough to ensure that neurons return to their resting potential before the next excitatory part of the oscillation. In support of the former claim, LTP has been demonstrated to be most effective when pre- and postsynaptic firing is coupled to a 50-Hz rhythm (relative to slower rhythms) [13], although it remains to be seen how LTP is affected when pre- and postsynaptic firing is coupled to a frequency greater than 50 Hz.

In addition to facilitating synchronised neuronal firing, gamma oscillations may also aid the postsynaptic depolarisation necessary for STDP by inducing subthreshold oscillatory fluctuations in postsynaptic membrane potential. For example, *in vitro* work has shown that pairing presynaptic spikes to the peak of a 40-Hz oscillation led to greater LTP than when spikes were paired to the trough of the oscillation [35], purportedly because the change in potential at the oscillatory peak adds an additional drive for depolarising the postsynaptic neuron. This may explain why, in humans and nonhuman primates, successful memory formation occurs when neuronal firing is coupled to particular phases of the ongoing gamma oscillation [9,36]. Considering all the above, it appears plausible that gamma oscillations can facilitate LTP by increasing the likelihood of postsynaptic spiking.

Gamma oscillations may also provide a spike-timing delay between the pre- and postsynaptic neurons that is optimal for STDP (~10–20 ms) [37]. However, little work has been conducted at the cellular level to demonstrate that observed links between gamma oscillatory activity and STDP are specifically due to gamma oscillations matching the optimal timing constraints of STDP. This may be because the spiking delays necessary for STDP can vary across brain regions, cell types, and even between individual cells (Box 1). Consequently, a gamma oscillation of a precise frequency cannot match the timing delay of every cell in a network. However, it remains possible that gamma oscillations match the average preferred delay of the network, meaning that STDP-like phenomena could be reliable on a macroscopic (e.g., behavioural) level. In line with this idea, humans are better able to learn pairings between stimuli that rhythmically fluctuate in intensity (at 37.5 Hz) when, during the initial pairing, the cue preceded the target by ~7 ms (matching traditional STDP delays) relative to when the cue and target are presented

Glossary

Associative binding: cornerstone of episodic memory formation that involves linking two previously unrelated concepts together.
Cell assembly: collection of interconnected neurons that are tuned to a particular stimulus.
Episodic memory: long-term memory relating to a unique experience, anchored to a single point in time and space, that can be explicitly recalled and re-experienced in vivid detail.
Gamma oscillation: fast, rhythmic change in the activity of a collection of neurons, often defined to be in the range of 30–80 Hz although definitions vary across the literature.
Long-term potentiation (LTP): neural phenomenon in which the strength of a synaptic connection between two neurons grows following repeated co-firing of the two neurons. LTP is thought to be key in binding distinct cell assemblies together to form an episodic memory.
Neural communication: process of routing information through the brain. Here, we use the term 'neural communication' to refer to both local (i.e., between local cells/assemblies) and interareal (i.e., between regions) communication.
Reinstatement: phenomenon in which patterns of neural activity observed during memory formation reoccur during memory retrieval. This reoccurrence is thought to allow an individual to vividly re-experience the memory.
Sequence encoding/retrieval: act of encoding/retrieving multiple, distinct stimuli in the order that they were presented. Sequence encoding/retrieval is critical to forming and recalling the temporal narrative of an episodic memory.
Spike-timing-dependent plasticity (STDP): form of LTP that relies on the precise firing of two neurons. Typically, STDP is thought to occur when the presynaptic neuron fires shortly (<20 ms) before the postsynaptic neuron.
Theta–gamma coupling: oscillatory phenomenon in which patterns of gamma oscillatory activity fluctuate as a function of theta oscillatory activity. Often, this involves the amplitude of gamma oscillations fluctuating as a function of theta oscillatory phase.

Box 1. Variations on the traditional STDP curve

The textbook STDP curve depicts pre-to-postsynaptic firing inducing LTP, post-to-presynaptic firing inducing LTD, and the strength of the effects diminishing as the delay between the firing of the two neurons increases. Depictions of this curve are based on NMDA receptor-dependent STDP in slices of the rat hippocampus (e.g., [24]), with the assumption that these curves generalise to other cells, brain regions, and even species. However, this may not be the case (Figure I).

For example, GABAergic neurons fail to display LTP [24] (and can even display LTD [134]) following pre-to-postsynaptic firing, suggesting that STDP curves vary based on cell type. In spiny stellate cells of the barrel cortex of rodents, pre-to-postsynaptic firing also induces LTD [135], hinting that STDP curves vary based on both brain regions and cell types. In human hippocampal tissue, LTP can be observed regardless of whether the presynaptic spike precedes or follows the postsynaptic spike, with LTD only being observed when the postsynaptic spike precedes the presynaptic spike by ~100 ms [30], suggesting variation across species. Even in cells of the same type and region, STDP curves can vary simply because of variation in the distance between the soma and the location where input arrives on the dendrite: short distances produce the stereotypical curves, while greater distances invert the curve [136]. Lastly, STDP curves of a single neuronal pair can vary based on the time difference between glutamate arriving at the NMDA receptor and the occurrence of a depolarising potential [137]. In short, STDP curves can take many forms, and one should exercise caution when generalising STDP curves to other cells, brain regions, and species.

This conclusion is also pertinent to the discussion of STDP and gamma oscillations: given that no two neurons are identical, it appears unlikely that there is a single oscillatory frequency that is optimal for enhancing STDP in all neurons. Indeed, variations in gamma oscillatory frequency across regions/species may well align with the differences in STDP curves that neurons in these regions/species exhibit.

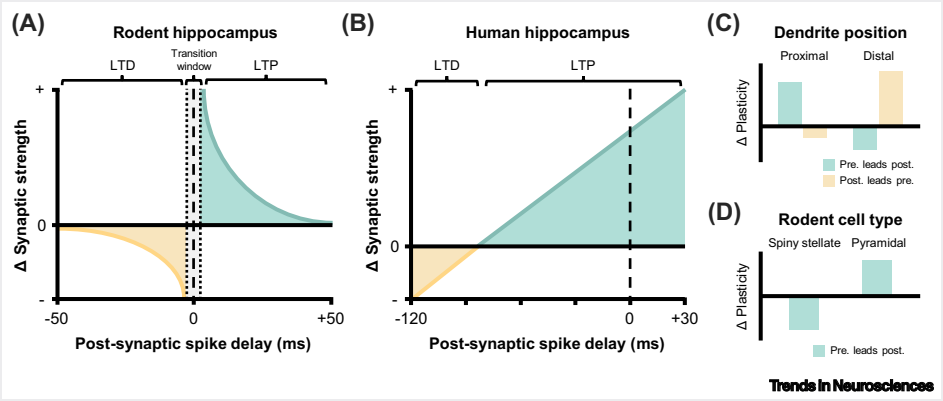

Figure I. Variations on the traditional spike timing-dependent plasticity (STDP) curve. (A) Depiction of perhaps the most common STDP curve, in which long-term potentiation (LTP) occurs when the presynaptic spike precedes the postsynaptic spike, and long-term depression (LTD) occurs when the presynaptic spike follows the postsynaptic spike. This curve was derived from observations made on slices of rat hippocampus [24]. (B) Depiction of an alternative STDP curve, observed in slices of human hippocampal tissue [30]. (C) Depiction of how STDP curves vary as a function of dendrite input location. When input is proximal to the postsynaptic soma, typical STDP patterns are observed, but when input is distal, the effect inverts [136]. (D) Depiction of how STDP effects differ as a function of cell type in the rodent barrel cortex. Pyramidal cells show the typical LTP effect when presynaptic spikes precede postsynaptic spikes, but LTD is observed in spiny stellate cells following the same pattern of firing [135].

simultaneously during encoding [15]. Based on this finding, perhaps it is not a matter of ensuring that synapses of every neuron pair undergo STDP, but rather that sufficient pairs undergo STDP to ensure that a memory can be reliably formed.

While the explanations explored in the preceding text suggest gamma oscillatory activity enhances STDP, they introduce an issue of firing order ambiguity. Specifically, if two neurons repeatedly and reliably fire as a function of gamma oscillatory phase, it becomes unclear which neuron leads which and, consequently, whether LTP or LTD will occur. In these instances, evidence suggests that LTP and LTD do not sum linearly [13,38,39], with LTP possibly

supplanting LTD [13]. This suggests that the relevant timing of pre- and postsynaptic spikes becomes irrelevant so long as both neurons fire regularly and in quick succession. Consequently, ambiguity in firing order does not undermine the idea that gamma oscillations can enhance STDP.

There is also the question of how gamma-facilitated plasticity scales up to the formation of fully fledged episodic memories. Unfortunately, linking gamma oscillations to both STDP and behavioural expressions of episodic memory in a single experiment is a troublesome endeavour: STDP is most easily observed in small cultures of cells and slice preparations, whereas behavioural expressions of episodic memory can only be observed in active individuals. That said, progress has been made. For example, in rodents, an increase in gamma oscillatory activity correlated with both an enhanced fear response to an auditory tone (i.e., a learned response) and a change in A1 receptive fields (a proxy for plasticity) [7]. Indirect links also exist in humans. For example, successful memory formation occurs when two conditions are met: (i) when the latency of firing between two neurons is ~20 ms (approximating the delay required for STDP); and (ii) when the co-firing neurons couple to an ongoing gamma oscillation [36]. This suggests that episodic memory formation is most probable when STDP-like delays in neuronal firing are coupled to an ongoing gamma oscillation. Together, these studies support the idea that gamma-facilitated STDP can lead to the formation of complex and highly detailed episodic memories.

In sum, STDP is intimately tied to gamma oscillatory activity, although the mechanistic explanation of this link is open to debate. Moreover, it remains an open question whether gamma oscillations are necessary for STDP to occur. These questions may benefit from causal interventions that quantify the relevance of gamma oscillatory activity to STDP.

Gamma oscillations and neural communication

Neural communication refers to the process of relaying information across the brain, be that between local cell assemblies or across large portions of the cortex. Neural communication is relevant to almost all aspects of cognition, from perception to action, but we focus here on its relevance to episodic memory. Effective neural communication ensures that, during memory formation, incoming information in sensory cortices activates the relevant cell assemblies in the hippocampus to ensure **associative binding**. Similarly, during retrieval, neural communication ensures that reactivated hippocampal cell assemblies induce neocortical activity to allow for the **reinstatement** of an episode. Here, we review key theories that link gamma oscillations to neural communication and assess whether they may, as a result, explain the link between gamma oscillatory activity and episodic memory.

A prominent theory tying gamma activity to information exchange is 'communication through coherence' [40,41]. Communication through coherence proposes that information from one neural population can be relayed to another population when: (i) gamma oscillations in the two regions synchronise; and (ii) input from the 'sender' **cell assembly** arrives at the 'receiver' assembly when the 'receiver' assembly is at its most excitable oscillatory phase (Figure 1A). Similar to STDP, gamma oscillations are well suited for facilitating communication because they ensure tighter synchrony between neurons of the 'sender' cell assembly compared with slower oscillations [34], while also ensuring that neurons can return to their resting potential before the next excitatory phase of the oscillation. This may explain numerous findings linking gamma-band coherence to episodic memory. For example, when learning object–reward associations, primates display enhanced gamma-band coherence between inferotemporal areas (which represent the object) and prefrontal sites (which are thought to link the object to the reward) [8] (for similar effects in humans, see [12,42]). Moreover, when humans successfully recall a memory, gamma-band coherence between the hippocampus and lateral temporal cortex predicts the

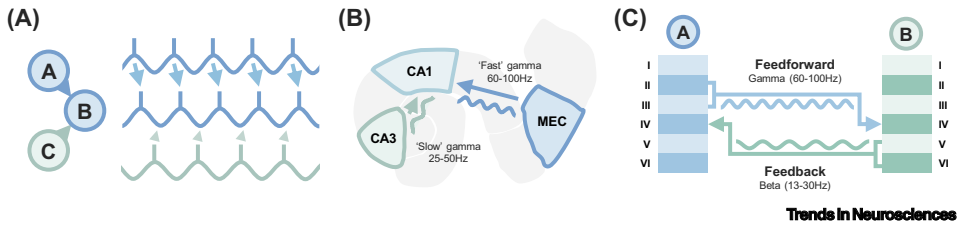

Figure 1. Theories of gamma-based neural communication. (A) Depiction of 'communication through coherence' [41]. Two brain regions can communicate when: (i) gamma oscillations in the two regions become coherent; and (ii) the transmission delay from sender to receiver ensures that the sender spike arrives at the moment when the receiver is most excitable. (B) Depiction of how two hippocampal gamma oscillations may coexist [45,46]. A 'fast' gamma oscillation, generated by the medial entorhinal cortex, can entrain cells in CA1. This allows to-be-encoded information to flow into the hippocampus. A 'slow' gamma oscillation, generated by CA3, can also entrain cells in CA1. This allows reactivated memory traces to be reinstated in CA1 (C) Depiction of how distinct oscillations allow information to be fed forward and backward [55]. Bottom-up, sensory information is passed forward by gamma oscillatory coherence present in superficial cortical layers (i.e., layer 2/3). Top-down influence is exerted via beta oscillatory coherence present in deeper cortical layers (i.e., layer 5/6).

degree of reinstatement observed in the lateral temporal cortex [43], with such retrieval-related coherence being absent in those with autobiographical amnesia [44]. Taken together, these empirical reports demonstrate a correlative link between gamma coherence and the ability to relay to-be-encoded and to-be-recalled information across the brain.

If gamma-band connectivity is involved in relaying both to-be-encoded and recalled information, how can interference between the two streams of information be avoided? One suggestion, based on observations from the rodent hippocampus, is that distinct gamma oscillations support the two processes: a fast gamma oscillation (~60–100 Hz; slightly above the canonical gamma band) facilitates encoding by allowing information to flow from the entorhinal cortex to the hippocampus, while a slow gamma oscillation (~25–50 Hz; slightly beneath the canonical gamma band) supports retrieval by allowing reinstated traces to propagate from CA3 to CA1 [45,46] (Figure 1B). These ideas have received empirical support from studies of rodents (e.g., [4,5,47,48]) and humans [10,49,50]. While contradictions exist in the rodent literature (e.g., [51,52]), these are often seen in studies in which encoding and retrieval overlap (e.g., at a decision point in a maze: a rat may either be retrieving a past trajectory or encoding the current trajectory for future reference), making it difficult to isolate encoding-/retrieval-specific neural processes. However, studies in humans sidestep this issue by explicitly directing participants to either encode or retrieve and then contrasting the resulting neural correlates. In these instances, the typical pattern of 'fast and 'slow' gamma activity is observed, with the former favouring encoding and the latter favouring retrieval [10]. That said, in both rodent and human studies, measurements of 'slow' gamma oscillations may be susceptible to distortion by theta harmonics [53], meaning open questions remain about what can be attributed to 'slow' gamma oscillations and what is attributable to theta. Taken together, 'fast' and 'slow' gamma oscillations may have separable roles in episodic memory, with the former biased toward encoding and the latter toward retrieval.

The spectral separation of encoding and retrieval may also arise in the cortex [54–57], with gamma oscillations feeding information forward to associative hubs (e.g., the hippocampus) for memory formation [58], while beta oscillations (15–30 Hz) exert top-down inhibitory influence over the same pathways to restrict activity to regions relevant to the processing of reactivated memory traces [59] (Figure 1C). While these frequency-specific cortical routes have been observed in low-level perceptual processes (e.g., [55–57]), these concepts are more difficult to

reconcile with episodic memory. For example, as described in the preceding text, gamma-band coherence between the hippocampus and lateral temporal cortex supports memory retrieval [43], suggesting that gamma oscillations are not the exclusively feedforward phenomenon that the cortical routing hypothesis would suggest (see also [60,61]). However, this concern could be addressed by hypothesising that hippocampal slow gamma oscillations and top-down cortical beta oscillations reflect the same rhythm. Oscillations tend to propagate from areas with faster intrinsic rhythms to areas with slower intrinsic rhythms [62]; thus, speculatively, a propagating hippocampal slow 'gamma' oscillation could slow to a beta-like rhythm in cortical areas as the reactivated memory trace propagates across the brain. Exploring the interactions between hippocampal 'slow' gamma and cortical beta oscillations using simultaneous recordings would allow for empirical testing of this idea.

While the theories outlined in the preceding text propose that coherence causes communication, some have questioned how general these causal mechanisms may be [63–65] (Box 2). For example, in macaques, coherence can be a product of communication if a 'sender' region projects to both itself and a 'receiver' region in a rhythmic fashion [64]. Moreover, computational modelling shows that two networks can communicate with one another without coherence, and such communication can, in fact, produce coherence [63]. These findings suggest that coherence is not necessary for communication but, nonetheless, could reflect instances when successful communication occurred.

Others have questioned how gamma-band coherence can support communication over distances of >1 cm, given factors such as variable axonal conduction delays [66]. Indeed, computational models suggest that this 'long-range' communication is better supported by slower

Box 2. The pros and cons of communication through coherence

Communication through coherence (CTC) has been an influential theory of neural communication over the past 20 years, but the generality of the mechanism has recently been questioned. Here, we consider some key critiques and enduring strengths of CTC.

Some critics of CTC propose that coherence may be a consequence, rather than the cause, of communication. Indeed, rhythmic spiking in the sender can produce postsynaptic potentials in both the sender and receiver area, which in turn produce gamma-band coherence in the local field potential between the two regions [64]. Computational models support this idea, showing that coherence follows, rather than causes, communication [63]. Others have demonstrated that excitatory neurons in the receiving region do not couple to the phase of the gamma oscillation despite the two regions becoming coherent [138], suggesting that coherence is not essential for neuronal communication. Lastly, the frequency and strength of gamma oscillations depend on stimulus properties (e.g., contrast) [139,140], resulting in multiple frequencies of gamma oscillation which may struggle to become coherent with one another. Altogether, these findings suggest that gamma oscillatory coherence may not be a prerequisite for neural communication.

That said, several aspects of CTC appear robust. For example, gamma coherence relates to performance in a range of cognitive tasks, including attention (e.g., [141]) memory (e.g., [8,42,43]), and navigation (e.g., [142]), with suboptimal phase delays between gamma oscillations in the sender and receiver regions impairing behavioural responses [143], all of which support the idea that coherence with optimised phase delays aids communication and its behavioural consequences. Moreover, while many investigations of CTC focus on the visual system of nonhuman primates, congruent findings can be found in the rodent hippocampus (e.g., [46,142]), suggesting that the principles of CTC generalise across brain regions and species. Lastly, while stimulus properties modulate gamma frequency and this frequency mismatch may hinder communication [139], this can be beneficial: following a phase reset, highly excited networks produce fast gamma oscillations that can quickly excite a connected region, with the resulting wave of inhibition suppressing inputs from less excited sender regions (which exhibit slower gamma oscillations). In other words, variation in oscillatory frequency allows selective communication, a key feature of CTC [41].

Given the evidence presented in the preceding text, it may be suggested that gamma-band coherence can support communication, although it may not be the only means of coherence within the brain. Consequently, investigating the specific conditions under which gamma coherence supports communication may prove fruitful.

(e.g., beta) oscillations [67]. However, these concerns may be addressed by cross-frequency coupling, a phenomenon in which gamma oscillations nest within a slower rhythm [68]. When the low-frequency oscillations of two distant regions become coherent, and local gamma oscillations phase lock to the coherent low-frequency oscillations, gamma-band coupling becomes more precise than what would occur based on long-range gamma-band interactions alone. In line with this idea, computational models [69], rodent hippocampal recordings [46], and nonhuman primate visual cortical/thalamic recordings [70] all suggest a link between neural communication and cross-frequency interactions. Consequently, future explorations into communication through cross-frequency coupling may prove prosperous.

In sum, distinct gamma oscillations may track the flow of to-be-encoded and to-be-retrieved information across the cortex. However, it remains to be seen whether gamma oscillatory activity has a causal role in such communication or is simply a by-product. Of course, even if it becomes apparent that gamma oscillations do not have a causal role in communication, this does not preclude the potential role of gamma oscillations in other subprocesses of episodic memory.

Gamma oscillations and sequence encoding/retrieval

Thus far, we have discussed episodic memories as though all information relevant to the memory was presented and processed simultaneously. This is not the case, however: episodic memories have an inherent temporal narrative, a property that gamma oscillations, nested in ongoing hippocampal theta rhythms (~3–7 Hz), may facilitate [46,71–75]. In this partnership, the theta oscillation defines the overarching episode (e.g., a birthday party), while nested gamma cycles represent and separate distinct elements of the sequence (e.g., the birthday cake, the presents). Here, we review how a theta–gamma code encodes and retrieves episodic memory sequences.

Hippocampal **theta–gamma coupling** may support episodic memory by iteratively representing elements of an episode in a manner optimal for LTP [73,76]. This process begins with a hippocampal cell assembly (i.e., a collection of cells tuned to an element of an event) firing in response to a combination of external and theta phase-dependent excitation [77]. This results in feedback inhibition that suppresses network activity momentarily (~20 ms). Once inhibition dissipates, the next assembly in the sequence fires. The back-and-forth between excitation and inhibition produces a gamma oscillation that helps segment elements of an event from one another [71] (Figure 2A) and facilitates STDP. STDP allows the temporal order of an event to be encoded in

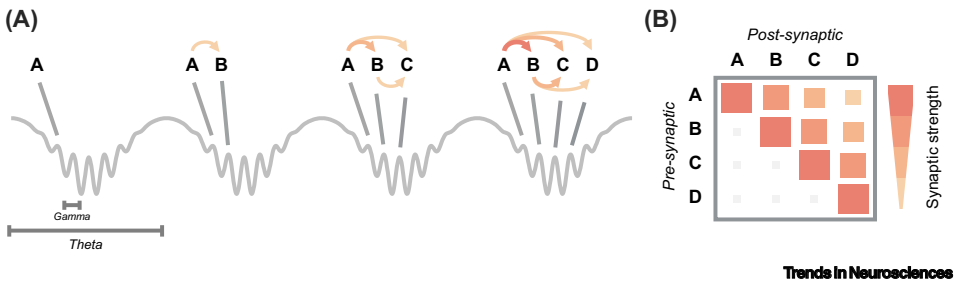

Figure 2. Depiction of the contribution of theta–gamma coupling to episodic memory. (A) Individual elements of an event are represented on individual gamma cycles, which are nested within an ongoing theta oscillation. Given the inhibitory nature of theta, individual elements of an event occur at the trough of the theta cycle. Given that early elements always precede later elements, unidirectional synaptic links can form between elements via asymmetric long-term potentiation (LTP). (B) Sequential learning establishes synaptic links between elements, such that early elements can induce firing in later elements, but not vice versa. Adapted from [88].

the asymmetric synaptic links between the neuronal representations of the event [78] (Figure 2B). The alternation between cell assembly excitation and feedback inhibition continues until theta reaches its inhibitory phase. This results in a gamma oscillation nested within the ongoing theta oscillation, which supports the formation of a temporally coherent memory.

Supporting these ideas, computational modelling demonstrates that elements represented in a biologically plausible theta–gamma code do indeed produce asymmetric synaptic connections that later predict successful retrieval [79,80]. While a direct demonstration is lacking in biological organisms, pairwise links between theta–gamma coupling, asymmetric LTP, and sequence encoding have been observed. First, as discussed earlier, gamma oscillatory activity can facilitate LTP [13,14], and LTP could be further enhanced if gamma couples to the phase of theta optimal for LTP [81–84], suggesting that theta gamma coupling can enhance LTP. Second, sequences of place cells representing a familiar path have been shown to fire more readily with each traversal [85], an effect attributed to enhanced asymmetric synaptic connectivity between sequentially firing place cells, linking sequence learning to LTP (for similar evidence in humans, see [86]). Lastly, in humans, the magnitude of theta–gamma coupling during object sequence learning predicts the accuracy of temporal judgements about the objects presented in the sequence [11], explicitly linking theta–gamma coupling to sequence memory. Weaving the strands together, it appears that theta gamma coupling helps encode temporally coherent episodic memories through asymmetric LTP.

With the sequence encoded through asymmetric synaptic connections, sequential recall is simply a matter of cuing one element in a sequence and allowing the asymmetric synaptic links to reactivate each remaining element in turn [72]. Given that memory reactivation is thought to preferentially arise at the peak of the hippocampal theta cycle [82], sequence recall will inherently be tied to this phase of theta. When this phase is reached, the cued assembly fires and excites connected assemblies. As with encoding, feedback inhibition prevents immediate activation of the connected assemblies, but as inhibition subsides, the most excited assembly (i.e., the one that shares the strongest synaptic links) can fire [87]. This process repeats for each element of the memory, resulting in theta–gamma-coupled activity that reflects the readout of sequential information from episodic memory.

Several empirical studies support this explanatory link between theta–gamma coupling and retrieval. For example, retrieval occurs at a preferred phase of theta in both rats (e.g., [88,89]) and humans (e.g., [90,91]), suggesting that recall is theta-phase dependent. Critically, disrupting theta by injecting muscimol impairs both memory retrieval and theta–gamma coupling [6], while optogenetically enhancing gamma boosts both memory retrieval and theta–gamma coupling [92], suggesting a causal role for both theta and gamma in sequence retrieval (although this may not be the only route to sequence retrieval; Box 3).

With evidence to suggest that theta–gamma coupling can carry codes related to both the past and the present, we must once again address how the brain separates to-be-encoded and to-be-retrieved information. This may be achieved by distinct hippocampal gamma rhythms nested in differing phases of theta [45,46,82,93,94]. In rats, indirect support for this idea has come from the observation that ‘fast’ gamma coupled to theta carries spatial sequences about where the rat currently is (which is thought to be pertinent to forming new memories based on current experience), while ‘slow’ gamma, coupled to a different phase of theta, represents sequences of where rats are planning to go (which is thought to reflect the reactivation of past sequences to aid navigation) [4,5]. Similar evidence has been reported in humans, with the two frequencies coupling to different phases of theta [49]. Taken together, one could speculate that sequential

Box 3. Sharp-wave ripples as an alternate route to sequence retrieval

Similar to theta-gamma coupling, sharp-wave ripples have also been linked to the retrieval of sequences [144,145], although it is unclear whether these two mechanisms are complementary or adversarial. Here, we briefly summarise the link between sharp-wave ripples and sequences, and then discuss how the nature of LTP and theta–gamma coupling may dictate which sequences sharp-wave ripples can retrieve.

By replaying previously experienced sequences, sharp-wave ripples are thought to facilitate processes such as systems consolidation (e.g., [144]), reward learning (e.g., [146]), and creative planning (e.g., [147]). Intriguingly, this replay can occur in a forward, backward, or novel order [146,148,149]. However, the observation of replay in any other direction than forward is difficult to explain with any neural mechanism that implements asymmetric LTP because the latter does not provide the synaptic connections necessary for traversing a sequence in any order other than the original. A possible resolution to this problem comes from recent work indicating that, within CA3, symmetric STDP can occur [150]. Symmetric STDP is ambivalent about which cell fired first, meaning it forms reciprocal connections between two cells. When applied to theta–gamma coupling, this would see a sequence build both forward and backward connections. Importantly, synaptic connections would still be moderated by temporal distance; thus, element C will have stronger connections to B and D than to A and E, meaning that some degree of temporal order is retained. While symmetric LTP, relative to asymmetric LTP, may make it more difficult to recall the exact order in which a sequence unfolded, it would provide additional flexibility for mentally navigating elements of a sequence to understand unexpected rewards or exploring unexperienced sequences of events [146,147]. It remains an open question whether theta–gamma coupling makes preferential use of either asymmetric or symmetric LTP and, consequently, whether theta–gamma coupling principally creates memory traces with a strict temporal narrative or traces that can be flexibly replayed and rearranged by sharp-wave ripples. Addressing this question will help elucidate whether theta–gamma coupling and sharp-wave ripples reflect two complementary learning mechanisms or a single cooperative mnemonic phenomenon [151].

information relating to the to-be-encoded present and to-be-remembered past is segregated by nesting distinct gamma oscillations at different phases of ongoing theta activity.

Notably, the links made between theta–gamma coupling and sequence encoding/retrieval and those made to neural communication may be complementary. For example, following the theta–gamma-coupled reactivation of a sequence in CA3, theta-band coupling between the CA3 and CA1 could ensure that gamma oscillations within the two regions become coherent and, consequently, help the reactivated sequence propagate toward the cortex for reinstatement. This highlights how theta–gamma coupling need not be thought of as solely aiding either communication or sequence representation, but may indeed facilitate both.

In sum, theta–gamma coupling provides the temporal scaffolding necessary for episodic memory. This may be achieved by distinct gamma oscillations, nested in differing phases of theta, supporting the encoding and retrieval of sequences. That said, much of the supporting evidence for this latter claim comes from studies of rodent navigation. Therefore, it will be of interest to see how these findings generalise to humans and nonhuman primates, which depend less on locomotion to build representations of space (relative to rodents) and instead explore space using different means (e.g., saccades; [95,96]).

From fundamental mechanisms to fully fledged episodic memories

So far, we have explored how gamma oscillations support low-level neural phenomena (i.e., plasticity, communication, and sequence representation), which, in turn, can facilitate episodic memory. However, because much of this work relies on the study of single cells *in vitro* or anthropomorphising the behaviour of rodents navigating a maze, it is unclear how well these concepts generalise to the behavioural expression of episodic memories that we, as humans, experience. Here, we explore recent work conducted in humans that directly links gamma oscillations to the behavioural expression of episodic memories.

Fortunately, there is no shortage of studies linking gamma-band activity to human episodic memory formation (e.g., [10,11,15,36,42,97–108]) or retrieval (e.g., [10,43,49,58,61,106,109–117]).

Many of these studies involve studying a series of stimuli and later recalling them on cue. These stimuli are then split based on whether they were recalled and the associated neural activity is contrasted. In doing so, these approaches isolate memory-related activity by minimising contributions from other cognitive phenomena (e.g., stimulus perception, motor response) that arise regardless of whether encoding/retrieval was successful. Indeed, lab-based studies utilising these approaches have demonstrated that inter-regional gamma-band coherence aids both memory formation [42] and retrieval [43,116], while theta–gamma coupling predicts episodic sequence encoding [11,98,106] and retrieval [106]. Moreover, the retrieval of real-life autobiographical memories has been linked to enhanced gamma coherence [44] and theta–gamma coupling [114,115], suggesting that gamma oscillations and the mechanisms they support have critical and specific roles in life-like episodic memories.

While these studies have an advantage over cell- and animal-based studies in quantifying the behavioural expression of episodic memory, they are at a disadvantage when quantifying gamma oscillations. Specifically, there is difficulty in delineating oscillations from arrhythmic signals [118] that also correlate with episodic memory (e.g., [119]). Therefore, an analysis of spectral power that does not attempt to separate out the contributions of gamma oscillatory activity from broadband aperiodic activity will struggle to provide informative insights into the oscillatory underpinnings of episodic memory. However, analytical advances have been developed to tackle this issue [118,120] and studies implementing these methods continue to suggest that narrowband gamma oscillations relate to episodic memory formation/retrieval (and also highlight separable contributions from lower-frequency oscillations; Box 4) [10,98,121].

Taken together, numerous human studies demonstrate that gamma oscillatory activity specifically maps onto the formation and retrieval of life-like episodic memories, further strengthening the link between the two phenomena.

Future directions

While there are numerous threads that relate gamma oscillatory activity to synaptic plasticity, neural communication, and sequence representation, further research is required to fully elucidate these links. Here, we discuss how investigating multiple oscillations, causality, and neuropathology may help address such open questions.

A common theme in the research reviewed in the preceding text is that multiple distinct oscillations, with differing frequencies and distinct mechanistic functions, sit (more or less) within the canonical gamma band. For better understanding of the role of gamma oscillations in episodic memory, it would be beneficial to account for these different forms of oscillation. This could be achieved analytically by distinguishing putative gamma oscillations from aperiodic components

Box 4. Synchronisation versus desynchronisation

While this review has principally focused on the relevance of gamma oscillatory synchrony in episodic memory formation and retrieval, growing evidence suggests that a second oscillatory correlate has an equally important role: widespread cortical power decreases, predominately in the lower frequencies (<30 Hz; e.g., [10,101–103,121,152–157]), but also within the gamma-band itself (e.g., [116]). While one might be led to believe that gamma-band power increases and low-frequency cortical power decreases are inversely correlated, several studies suggest that these two electrophysiological phenomena have distinct roles in episodic memory formation and retrieval [10,98,121]. For example, these cortical power decreases may be involved in information processing [158], decreasing inhibition [159], and/or moderating top-down control (e.g., [55,57]). Based on these functions, one could differentiate low-frequency oscillations from gamma oscillations by suggesting that the former support the allocation of resources (e.g., attention), while the latter reflect active processing (e.g., plasticity, neural communication, or sequence representation) (e.g., [55,160]). Consequently, low-frequency power decreases may complement gamma oscillations in the formation and retrieval of episodic memories. For further discussion on this point, see [3].

of the power spectrum (e.g., [118,122]) or by using spatial separation methods (e.g., independent components analysis; ICA) to distinguish hippocampal and cortical gamma rhythms (e.g., [43,55]). Complementing this, experimental paradigms could be finessed to better isolate distinct gamma oscillations. For example, matching sensory input/motor output between encoding and retrieval would ensure that only the internal state differs between encoding and retrieval, allowing direct comparison of the distinct rhythms associated with each state (e.g., [10]). Ultimately, these approaches may help separate the many forms of gamma oscillation that have critical roles in episodic memory.

With numerous studies demonstrating a correlative link between gamma oscillations and episodic memory, and mechanistic links proposing almost unanimously that gamma oscillatory activity results in memory formation and/or retrieval, causality also needs addressing. Fortunately, numerous promising techniques can help establish causality, including optogenetic manipulation of gamma oscillations in rodents (e.g., [92]), and sensory stimulation in humans (e.g., [15]). Of course, it is a challenge to determine absolute causality between gamma oscillations and episodic memory because this requires total control over a system that can generate and recall episodic memories. Therefore, cross-disciplinary approaches are essential. For example, combining computational models that explore the impact of gamma oscillations in a controlled system with behavioural experiments exploring how exogenous gamma stimulation impacts real episodic memories will provide deeper insights into the causal role of gamma oscillations in episodic memory compared with either approach in isolation.

Lastly, it is worth considering how cognition changes in the face of pathological gamma oscillations. While fundamental research linking gamma oscillations to episodic memories has been used to inform potential interventions for neurological disorders (e.g., Alzheimer's disease; [123–127]; however, see [128,129]), we propose that studies of clinical populations can also inform fundamental research. As discussed throughout this review, the brain does not execute a singular 'episodic memory' process but rather executes a whole host of processes (e.g., plasticity, neural communication, and sequence representation) from which episodic memory emerges. Neurological disorders are similarly ambivalent to psychological constructs such as episodic memory: neurological disorders principally associated with memory-related problems (e.g., dementia) often entail non-memory-related problems, while disorders that are not typically thought of as memory-related disorders can, nonetheless, involve memory issues (e.g., schizophrenia). Considering the commonalities and idiosyncrasies between disorders may provide an alternative view into the link between memory and gamma oscillations. For example, gamma oscillatory dysrhythmia can be observed in Alzheimer's disease [130] and autism [131], but memory function is markedly different between the two [132,133]. Understanding why gamma oscillatory dysrhythmia may relate to mnemonic impairment in some instances but not others may help elucidate the mechanistic role of gamma oscillations in episodic memory, complementing those provided by fundamental research conducted on healthy participants.

Concluding remarks

The well-documented link between gamma oscillations and episodic memory is likely to come from not one but many underlying mechanisms, including synaptic plasticity, neural communication, and sequence representation. However, whether gamma oscillations have a causal role in these mechanisms remains to be seen (see Outstanding questions). Consequently, future research that causally manipulates gamma oscillatory activity may be the best step forward to advance our understanding of the link between gamma oscillations and episodic memory.

Outstanding questions

Do gamma oscillations provide any additional benefit to plasticity above and beyond what is provided by arrhythmic but synchronous neural activity?

How do NMDA antagonists (e.g., ketamine) influence the interaction between gamma oscillatory activity and STDP?

Does gamma oscillatory coherence support the flow of information from the cortex to the hippocampus during memory formation? Does the phase delay between the sender and reader dictate whether a memory can be formed?

Can separable 'fast' and 'slow' gamma oscillations be observed outside of the medial temporal lobe? How do they relate to feedforward gamma and feedback beta rhythms observed in the sensory cortices?

Can individual elements of an episodic memory be decoded from human theta–gamma sequences during memory formation and/or retrieval?

Is there a trade-off between accurate temporal order memory and flexible thinking? Do asymmetric synaptic links between elements favour the former while symmetric synaptic links favour the latter?

Does the magnitude of theta–gamma coupling during memory formation predict the intensity and/or frequency of replay events during later offline periods (e.g., sleep)?

Can gamma-band sensory stimulation modulate memory? Given that 'fast' gamma sits above the flicker fusion threshold, does this mean that gamma-band sensory stimulation offers an imperceivable memory intervention?

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Declaration of interests

The authors declare no competing interest.

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