The role of phase synchronization in memory processes

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Abstract | In recent years, studies ranging from single-unit recordings in animals to electroencephalography and magnetoencephalography studies in humans have demonstrated the pivotal role of phase synchronization in memory processes. Phase synchronization — here referring to the synchronization of oscillatory phases between different brain regions — supports both working memory and long-term memory and acts by facilitating neural communication and by promoting neural plasticity. There is evidence that processes underlying working and long-term memory might interact in the medial temporal lobe. We propose that this is accomplished by neural operations involving phase–phase and phase–amplitude synchronization. A deeper understanding of how phase synchronization supports the flexibility of and interaction between memory systems may yield new insights into the functions of phase synchronization in general.

Local field potential
A neural voltage fluctuation recorded from the extracellular space, which mainly originates from postsynaptic potentials.

Neural oscillation
A periodic and continuous (wave-like) variation of a neural signal.

Oscillatory phase
The angle that corresponds to the momentary deflection of an oscillation (referring to the cosine function; for example, 0° at the peak and 180° at the trough of an oscillation).

Gamma frequency range
The frequency range between 30–100 Hz.

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doi:10.1038/nrn2979

Neurons do not function in isolation. They are embedded in assemblies and networks, in which they influence each other through excitatory and inhibitory synaptic connections. As a result, the neurons in a network are rhythmically activated and inhibited[1]. This rhythmicity is reflected in oscillations of the extracellular field potential that can be measured through recordings of local field potentials and through electroencephalography (EEG).

The frequency of neural oscillations depends on various time constants and network properties and may range from slow activity, with oscillation periods of several seconds, to fast activity in which one cycle lasts a few milliseconds. Moreover, oscillations of different frequencies can occur at the same time in the same brain regions[2–4].

In networks of synchronized neurons, the oscillatory phase determines the degree of excitability of the neurons and influences the precise discharge times of the cells in the network[5,6] (although not each neuron discharges action potentials during every oscillatory cycle). Consequently, phase relationships between brain regions affect the relative timing of action potentials in those regions. One speaks of phase synchronization between oscillations in two regions when oscillatory phases in these regions are correlated (for example, if the peaks of oscillatory activity in region A invariantly occur at the same time as the peaks of oscillatory activity in region B; BOX 1 and FIG. 1).

Phase synchronization is a fundamental neural mechanism. It supports neural communication and neural plasticity and is probably relevant for many cognitive processes[7–11]. Despite a growing amount of empirical data, however, a fundamental understanding of these functions and their interplay is lacking. In this Review, we focus on the role of phase synchronization in memory processes, which is currently a matter of intense investigation. We hypothesize that understanding this role is particularly well suited to illuminating how the basic functions of phase synchronization might interact in other contexts.

We first describe the main basic functions of phase synchronization of high- and low-frequency oscillations: neural communication and plasticity. We then discuss the relevance of phase synchronization and related phase-based mechanisms — specifically, cross-frequency phase–phase and phase–amplitude synchronization — for working memory and long-term memory processes. Finally, we propose a model by which phase synchronization and related mechanisms may support the interaction between the two memory systems. We suggest that this model may also provide a basis for a general understanding of how phase synchronization promotes its functions of neural communication and plasticity in a cooperative manner.

Functions of phase synchronization

Supporting neural communication. Experimental evidence from the 1980s supports the hypothesis that phase synchronization, particularly in the gamma frequency range, establishes transient associations between brain

Box 1 | What is neural synchronization?

The term 'synchronization' (from the Greek 'syn', meaning 'together', and 'chronos', meaning 'time') may be used differently depending on the context. Animal experiments allow researchers to record extracellular action potentials. Here, 'synchronization' most often refers to correlations between spikes in two regions or to the coupling between spikes in one region and local field potentials in the same or a different region (this is known as spike–field coherence)[10,20,76]. In addition, some studies have analysed phase synchronization of local field potentials in two regions, and found a positive correlation between phase synchronization and inter-regional spike–field coherence[32,80].

Human scalp electroencephalography (EEG) studies do not measure action potentials. Here, 'synchronization' refers either to the phase relation of EEG oscillations between two regions (phase synchronization) or to an enhanced EEG power (that is, the square of the EEG signal amplitude) in one region. Local changes in power originate from synchronized postsynaptic potentials of millions of neurons, corresponding to more than 1 cm^2 of cortical surface. EEG power can vary across several orders of magnitude and depends on the degree of synchronization between the contributing neurons[132]. Therefore, phase synchronization and power effects cannot be separated unambiguously on a local scale (up to 1 cm). The terms 'event-related synchronization' and 'event-related desynchronization' are thus often used to describe an increase or decrease, respectively, in local power in response to a stimulus[133]. Importantly, there is no intrinsic relationship between power effects and phase synchronization on a larger spatial scale, and even inverse changes have been observed[26,67]. Furthermore, phase-based interactions are independent of the neural firing rate in each region[10,134] and thus provide an independent dimension of neural information processing.

When we use the term 'phase synchronization' in this Review we refer, for the sake of clarity, to relations between oscillation phases in different brain regions. Studies addressing spike–field coherence and spectral coherence are only mentioned where they are particularly instructive. Of note, the focus on phase synchronization is not intended to imply that other measures of synchronization (or, in general, other measures of neural activity) are not also relevant for memory processes.

Inactivation time constant
A variable controlling the temporal characteristics of the spontaneous inactivation of an ion channel, as described by an exponential decay function.

Coincidence-sensitive neurons
Neurons that predominantly discharge action potentials if simultaneously activated by multiple presynaptic neurons, defining a narrow time window for activation.

Hebbian learning
A cellular mechanism of learning, proposed by Donald Hebb, according to which the connection between a presynaptic and a postsynaptic cell is strengthened if the presynaptic cell is successful in activating a postsynaptic cell.

Spike timing-dependent plasticity
A special kind of neural plasticity that depends on time delays between the action potentials of the presynaptic and the postsynaptic neuron.

regions that represent specific attributes of a stimulus[12,13]. For example, when you perceive a red Ferrari sports car, information about its colour (red), the stimulus category (car) and its motion (moving fast) is processed in different subregions of the brain. These representations need to be linked by some mechanism to ensure that the brain assigns them to the same object. This 'binding function' of phase synchronization was later generalized to the view that phase synchronization supports neural communication (that is, 'communication through coherence')[14].

Phase synchronization may support neural communication by enabling several synaptic inputs to arrive at a postsynaptic neuron at the same time. Such coincident synaptic inputs enable rapid depolarizations to occur, and thereby increase the postsynaptic membrane potential to above the firing threshold[15]. Rapid depolarizations are more effective in triggering action potentials than slow depolarizations because of the fast inactivation time constants of sodium channels[16].

To facilitate neural communication, the temporal precision of these coincident synaptic inputs has to be in the millisecond range[15–17], and such precise spike timing has been observed during gamma oscillations[18–21]. Indeed, assemblies of neurons that show synchronized gamma oscillations can reliably trigger activity in target coincidence-sensitive neurons[15,22] (FIG. 1Ba). However, it should be noted that such coincidence detection depends on various neuronal properties such as the distribution of membrane channels, which may change depending on the history of neuronal activation[17]. Gamma oscillations may thus enhance information transmission from one brain region to another. Indeed, phase synchronization of gamma oscillations (also known as gamma phase synchronization) has been shown to facilitate the propagation of information during bottom-up (from lower-level sensory regions towards higher-level associative and control regions) and top-down (in the reverse direction) processing[9].

Phase synchronization also provides windows for optimal communication between two or more brain areas[14] (FIG. 1Bb). Oscillations of local field potentials and EEG signals reflect fluctuations in neural excitability (that is, fluctuations in membrane potential shifts), and these fluctuations not only affect neural output but also the sensitivity to neural input[23]. Specifically, inverse phases of oscillations (for example, 0° versus 180°) in the extracellular space may correspond to membrane potential depolarizations (so-called up states) versus hyperpolarizations (so-called down states). If action potentials that occur during the depolarized (up) phase of an oscillation are transferred from one brain area to another and arrive again during the depolarized phase of an oscillation in the target area, they are likely to trigger action potentials in that area. By contrast, if there is no phase synchronization or if there is phase synchronization with an inappropriate phase lag, the action potentials will arrive at a phase in which sensitivity to neural input is non-optimal, and communication is likely to be blocked[20] (BOX 2).

Supporting neural plasticity. Studies in humans and animals have shown that phase synchronization is more precise during encoding of information that is later remembered than during encoding of information that is not well remembered[24–32]. These findings, together with the concept of Hebbian learning, led to the suggestion that phase synchronization may facilitate spike timing-dependent plasticity[33,34].

In common models of spike timing-dependent plasticity, synaptic long-term potentiation (LTP) occurs when postsynaptic neurons fire less than 10–20 ms after presynaptic neurons[35–37]. As action potentials occur predominantly during the depolarized phase of oscillatory field potential activity[14] (so-called spike–field coherence), synchronizing the phases of pre- and postsynaptic oscillations can enable such correlated timing of pre- and postsynaptic action potentials. Spike–field coherence has been shown to occur for oscillations in the theta frequency range[38,39] and the gamma frequency range [18–21,38,40] in the hippocampus and neocortex of rodents, cats, monkeys and humans. Moreover, spike–field coherence at a given frequency can occur simultaneously with coherence at a second, remote frequency[19], but may interfere with coherence at a similar frequency[19,21].

Thus, as a result of spike–field coherence, phase synchronization between two regions can promote the induction of LTP (FIG. 1Bc) (for reviews, see REFS 33,34). Importantly, the temporal windows in which spikes can occur become shorter with increasing oscillation

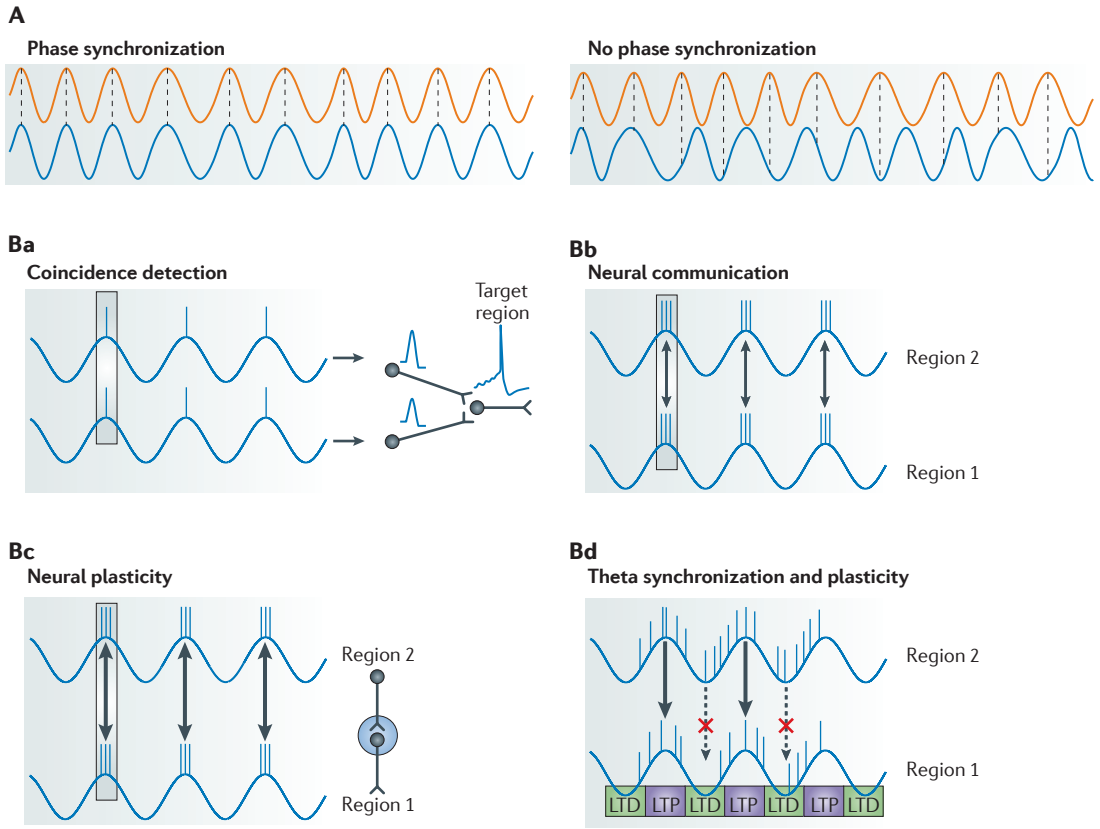


Figure 1 | **Putative functions of phase synchronization. A** | Neural oscillations may show phase synchronization (left; stable phase relationships) or may show no phase synchronization (right; variable phase relationships). Methods for the quantification of phase synchronization have been described extensively elsewhere[116,142]. **B** | Potential roles of phase synchronization in neural processing. Blue curves represent oscillations of neural assemblies in two brain regions, arrows denote interregional information transfer. **Ba** | Phase synchronization of neural assemblies coordinates the timing of synaptic inputs to a common target region. Coincident activity (indicated by the box surrounding two coinciding spikes) thus reliably induces action potentials. **Bb** | Phase synchronization between multiple brain regions allows for efficient information transfer (indicated by the arrows) during excitable periods (the box indicates the first such period). **Bc** | Precise timing of action potentials resulting from phase synchronization between two regions can induce spike timing-dependent plasticity of the synaptic connections (depicted on the right) between these regions. Consequently, communication is facilitated further (indicated by thicker arrows). **Bd** | The putative function of theta phase synchronization between two regions. The propensity of action potentials that are propagated from region 2 to region 1 (indicated by the arrows) to induce synaptic plasticity in region 1 depends on the theta phase in region 1 during which the action potentials arrive. Therefore, phase synchronization in the theta range may serve to recruit memory-related regions (for example, the hippocampus) during periods of high susceptibility to synaptic potentiation (solid arrows). LTD, long-term depression; LTP, long-term potentiation.

frequency. For example, the most excitable quarter cycle of an oscillation corresponds to a period of 6.25 ms for gamma oscillations at 40 Hz, and to 50 ms for theta oscillations at 5 Hz. Therefore, phase synchronization in the gamma range is associated with an especially precise timing of action potentials that is optimally suited to promote spike timing-dependent plasticity[33,34,36,37].

Notably, neural communication and plasticity may support each other[1]. Indeed, simultaneous activation of two brain regions communicating through phase synchronization will probably also induce synaptic plasticity between these regions. This is particularly likely when phase synchronization-mediated communication occurs repeatedly or for an extended period, such as during the maintenance of information in working memory. Moreover, if synaptic connections between two regions have been strengthened, phase synchronization may be more easily induced, and the two regions will be more likely to communicate with each other.

Phase synchronization below the gamma frequency range. As described above, effective neural communication and spike timing-dependent plasticity both require neural activity to be controlled on a millisecond timescale, which can be accomplished by phase synchronization of activity in the gamma range. However, synchronized activity in lower-frequency ranges, in particular in the theta range, has also been shown to play a part in memory functions[27,29,41–47] (discussed below), suggesting that phase synchronization of theta oscillations

Spike–field coherence
The preferential firing of action potentials predominantly during a specific phase range of field potential oscillations.

Theta frequency range
The frequency range between 3–8 Hz.

Spike doublets
Two action potentials that are separated by a brief temporal interval.

(also known as theta phase synchronization) may also support neural communication and synaptic plasticity. In principle, the effect of spike timing on plasticity is greater if the pre- and postsynaptic cells discharge at a high firing rate, as cells firing at a low rate contribute less to spike timing-dependent plasticity[48,49]. However, although high firing rates are associated with high spike–field coherence with respect to gamma oscillations[21], they are associated with low spike–field coherence with respect to theta oscillations[50] (BOX 3). In other words, if cells fire at an increasing rate, their action potentials tend to be concentrated at increasingly narrow phase ranges of the gamma cycle (resulting in a high spike–field coherence), but at broader phase ranges of the theta cycle (resulting in a low spike–field coherence)[39] compared with cells with a lower firing rate. Therefore, unlike gamma phase synchronization, theta phase synchronization is not ideally suited to promote precise relative timing of action potentials across two brain regions.

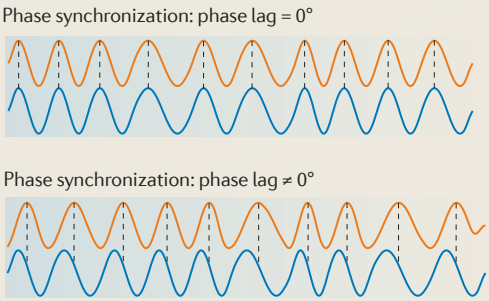
So, through what mechanisms might theta phase synchronization support working memory and long-term memory? There are several possibilities, which all require further investigation. First, it has been shown that the phase of the theta oscillation during electrical stimulation determines the direction and magnitude of the synaptic plasticity induced by that stimulation: in rats, stimulation at the peak of hippocampal theta oscillations induces LTP, whereas stimulation at the trough induces long-term depression (LTD)[51,52]. Thus, only inputs that arrive at the appropriate theta phase induce LTP and are encoded into long-term memory. Phase synchronization in the theta range may define instances when information transfer is likely to result in long-term memory formation[53]. For example, theta phase synchronization between the hippocampus and, for example, the prefrontal cortex may lead to the induction of hippocampal plasticity during time windows that are appropriate for stimulus encoding (FIG. 1Bd).

Second, theta phase synchronization is usually more spread across the brain than gamma phase synchronization[1], and this spread may ensure that different local assemblies — each synchronized in the gamma range — are activated simultaneously. This idea is consistent with the proposed top-down control function of theta phase synchronization exerted by the prefrontal cortex on parietal and temporal regions[43,45], and with the role of cross-frequency coupling between theta and gamma oscillations that we propose below. This mechanism may be relevant for the maintenance of information in working memory, whereas the first mechanism suggests a role for theta phase synchronization in long-term memory processes.

Phase synchronization in memory processes

Memory processes rely on neural communication and plasticity. For example, working memory — such as the memorizing of a telephone number until it is being used — depends on the communication between material-specific storage systems and executive control modules[54]. Long-term memory is probably implemented by modifications of synaptic strength[55–57], and depends on communication between the neocortex

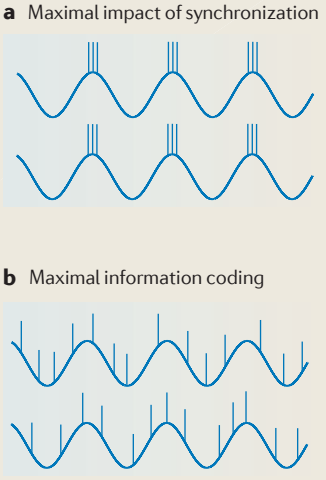
Box 2 | The problem of zero-lag phase synchronization



If phase synchronization is related to information transfer between two brain areas, one would expect oscillations in the two regions to show a phase lag corresponding to the conduction delay between these regions (see the figure). This has indeed been observed in animal studies for theta phase synchronization between the hippocampus and medial prefrontal cortex (with the hippocampus leading)[32,80] and for gamma phase synchronization between the frontal eye field and visual area V4 (with the frontal eye field leading)[135]. However, many other studies reported a phase lag of approximately 0° — for example, for theta phase synchronization between the amygdala and hippocampus[77,78]; for gamma phase synchronization between the rhinal cortex and hippocampus[26] and between visual areas V1 and V2 (REF. 136); and even for long-range beta phase synchronization between the visual, parietal and motor cortices in cats[7] and for gamma phase synchronization between various neocortical regions in humans[8].

There are several possible explanations for these results. First, two regions might receive a common input from other areas without direct interactions between the two regions. Second, several computer models[137–139] have derived zero-lag phase synchronization scenarios from mutual interactions between only two brain regions. Zero-lag phase synchronization may occur due to delayed interactions between excitatory pyramidal cells and inhibitory interneurons[137] and may be implemented physiologically through spike doublets in interneurons[138]. Without spike doublets, gamma phase synchronization in such networks develops at phase lags of around 180° (REF. 139). Third, zero-lag phase synchronization may emerge if two neural assemblies are connected via a third relay assembly[140]. For example, the thalamus may act as a relay region for cortico-cortical phase synchronization[140]. It should be noted that, in common models of spike timing-dependent plasticity, a time lag of exactly zero (in the presence of small levels of noise or deviations from the average phase difference in individual trials) may result in either synaptic enhancement or depression[35–37]. With regard to the precise spike timing associated with gamma oscillations[18,19], it is therefore an open question how unequivocal plasticity changes are accomplished by zero-lag phase synchronization[21].

Box 3 | **Trade-off between the impact of phase synchronization and phase coding**



For phase synchronization between two brain areas to affect neural communication and plasticity, action potentials must occur predominantly during a particular phase range of a neural oscillation (see the figure, part **a**). This phenomenon has been demonstrated for different frequency bands and may even emerge in a nested fashion, such that action potentials are concentrated at specific phases of both high- and low-frequency oscillations[4,19]. Information may also be encoded in the specific phase at which action potentials occur. For example, when a rat approaches a specific location in a familiar environment, the hippocampal place cell representing this location discharges at increasingly earlier phases of the theta band oscillations[109]. The amount of information that can be represented by such a 'phase code' would be maximal if the entire phase range were used to encode information (see the figure, part **b**). However, this would minimize the impact of phase synchronization on neural communication and plasticity: if action potentials occur with the same probability during the entire phase range in two brain regions, phase synchronization between these regions does not lead to an alignment of action potentials.

For theta activity, in which phase coding has been demonstrated, spikes have been observed to occur for as long as the entire cycle[39,50,141]. For gamma activity, the phase during which action potentials occur depends on the strength of neural activation: in the visual cortex of monkeys, cells with a high firing rate (that is, cells receiving input from their preferred stimulus) discharge at an earlier phase of gamma band oscillations than cells with a low firing rate[21]. It has been suggested that such shifts of action potentials with respect to the phase of gamma oscillations result in a leading or lagging of pre- versus postsynaptic spikes, which is necessary for unequivocal spike timing-dependent plasticity[21] (BOX 2). However, such variations of spike timing with respect to gamma oscillation phases have not been observed in other studies[113]. The reasons for this divergence are currently not clear and are possibly due to differences between the species, the brain regions and/or the cognitive functions under investigation.

and specialized archicortical regions such as the hippocampus[58]. As phase synchronization seems to facilitate both neural communication and neural plasticity, one might expect that it has a role in both working memory and long-term memory.

Working memory. Working memory has been defined as "a limited-capacity store for retaining information over the short term (that is, over several seconds) and for performing mental operations on the content of this store"[59]. According to a classical model, working memory depends on the interaction of an attentional control system — the 'central executive' — for which activity in the prefrontal cortex is probably essential, and material-specific buffers for short-term storage[54]. More recent theories question the need for specialized short-term buffers and propose that working memory depends on the activation of perceptual or long-term memory representations[60–63]. According to either theory, the neural signature of working memory should be sustained throughout the maintenance period, even in the absence of direct sensory input[62]. Moreover, it should depend on the number of items that are being maintained — that is, on working memory load — as well as on the complexity of the manipulations performed on the information that is being maintained[64].

These requirements seem to be fulfilled by theta phase synchronization (FIG. 2a). Several human scalp EEG studies show that theta phase synchronization between the prefrontal cortex and the temporal lobe occurs not only during encoding and retrieval[43], but persists during the maintenance interval of working memory[41,44]. Theta coupling between parietal and prefrontal cortices is increased during experimental conditions that require more complex manipulations[45], indicating that it might reflect a recruitment of executive control functions. In addition, several studies have observed a link between theta phase synchronization and working memory load. For example, theta coherence between frontal and temporal–parietal regions increases with memory load[47] and predicts individual working memory capacity[46]. These results are consistent with the idea that long-range theta phase synchronization organizes local assemblies, defined by faster oscillations, that encode object representations (discussed in more detail below).

Studies have also shown the relevance for working memory of phase synchronization in the beta frequency range and gamma frequency range. In particular, coherence between frontal and parietal areas is enhanced in these frequency ranges during maintenance of information in working memory compared with control conditions in humans[65,66]. Intracranial EEG data from patients with epilepsy revealed a sustained enhancement of beta phase synchronization between different extrastriate visual areas during maintenance of complex visual shapes compared with a purely perceptual control condition[67]. Furthermore, beta phase synchronization increased between the fusiform face area and the medial temporal lobe with higher working memory load (maintenance of four faces versus a single face)[68]. Interestingly, beta phase synchronization was accompanied by increases in the power (that is, the square of the EEG signal amplitude) of gamma oscillations in the visual cortex[67] and in gamma phase synchronization in the medial temporal lobe[68]. These phenomena may reflect inter-regional associations, mediated by beta phase synchronization,

Material-specific buffer for short-term storage
A specialized short-term maintenance system for verbal (phonological loop) or spatial (visuo-spatial sketchpad) information.

Beta frequency range
The frequency range between 12–30 Hz.

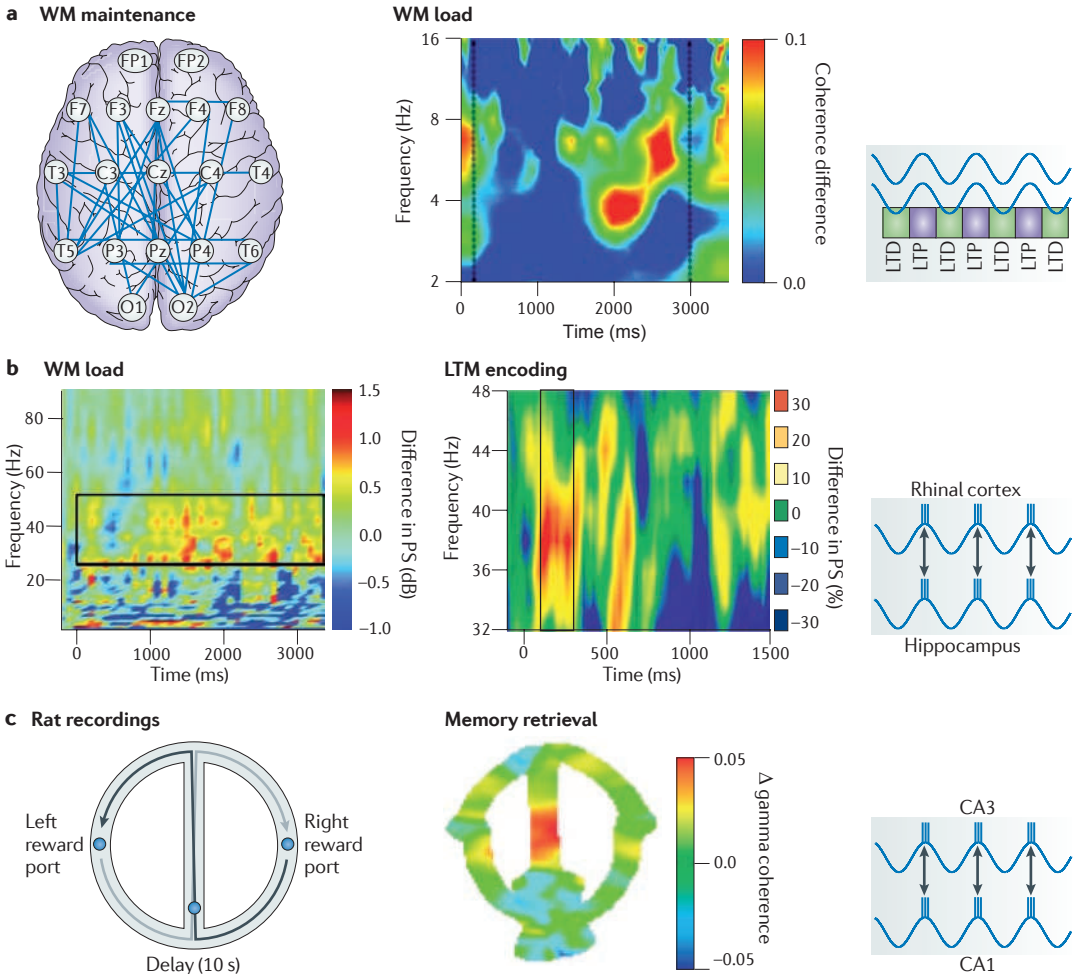


Figure 2 | **Patterns of phase synchronization during working and long-term memory. a** | Theta coherence between brain regions. In the left panel, the blue lines are based on data from scalp electroencephalography (EEG) recordings and reflect changes in inter-regional coherence — in particular, enhanced fronto-temporal theta coherence — during a working memory (WM) task compared with a control task. The middle panel shows that fronto-temporal EEG coherence in scalp EEG data increases further when memory load is enhanced (maintenance of six versus four letters in working memory). The figure shows the difference in coherence between the six- versus four-letter conditions, with warm and cold colours indicating increases and decreases in coherence, respectively. Increases were most obvious at 4 Hz and ~2000 ms and at ~6 Hz and ~2500 ms after stimulus presentation. As depicted in the right panel, this increase in theta coherence may be related to the recruitment by the frontal cortex (indicated by the top curve) of synaptic plasticity in the temporal lobe (indicated by the bottom curve) at appropriate theta phases, inducing long-term potentiation (LTP) rather than long-term depression (LTD). **b** | Intracranial EEG studies show increased gamma phase synchronization (warm colours within the black boxes) between the rhinal cortex and hippocampus during both multi-item working memory (left panel) and long-term memory (LTM) formation (middle panel). The left panel shows the difference in rhinal–hippocampal phase synchronization during working memory maintenance of four versus one item. There is a long-lasting enhancement of phase synchronization with working memory load during maintenance of multiple items in the frequency range between 26–50 Hz. The middle panel depicts the difference in rhinal–hippocampal phase synchronization during encoding of words into long-term memory for subsequently remembered versus subsequently forgotten items. Successful encoding is associated with a transient increase of gamma phase synchronization at ~40 Hz at ~200 ms after stimulus presentation. The right panel shows that, mechanistically, these increases in gamma phase synchronization may be associated with facilitation of neural communication between the rhinal cortex and hippocampus, as well as with promotion of spike timing-dependent plasticity in the medial temporal lobe in the LTM experiment. **c** | The left panel shows a spatial memory task in which rats alternate left and right turns in each trial at the junction point of a modified T-maze to retrieve a reward. In this 'delayed alternate choice task', intrahippocampal gamma coherence between CA1 and CA3 was elevated just before rats reached the decision point (indicated by the warm colour on the central arm), when they presumably used previously acquired information to determine in which direction to turn (middle panel). This task may rely on working memory and LTM processes. Mechanistically, this increase in coherence may facilitate neural communication and plasticity between CA1 and CA3 (right panel). The left panel of part **a** is modified, with permission, from REF. 45 © 2005 Elsevier; the middle panel is reproduced, with permission, from REF. 47 © 2009 Elsevier. The left panel of part **b** is reproduced, with permission, from REF. 68 © 2008 Society for Neuroscience; the middle panel is reproduced, with permission, from REF. 26 © 2001 Macmillan Publishing Ltd. All rights reserved. The left and middle panels of part **c** are reproduced, with permission, from REF. 81 © 2007 National Academy of Sciences.

of stimulus representations encoded in local assemblies that are themselves synchronized in the gamma range (for additional papers on the relationship between beta oscillations and working memory, see for example REFS 69–71).

Long-term memory. Long-term memory is a system with a massive capacity for quasi-permanent storage of information. In experiments, long-term memory-related processes can be investigated separately from working memory-related processes by separating encoding and retrieval stages with long time intervals[72] (in the order of several minutes or more) or with a distraction task that interrupts working memory[26,27]. Surface EEG studies in humans have indicated enhanced long-range phase synchronization and spectral coherence — in particular between anterior and posterior brain areas — during encoding into[25,27,29] and retrieval from[73] declarative memory (a form of long-term memory) of visually presented objects. This phase synchronization may represent the cooperation between material-specific posterior regions with prefrontal control areas. Increases in memory-related phase synchronization (and coherence) have been observed in the theta[27,29] and gamma range[73], as well as in various frequency bands between the delta frequency range and the beta frequency range[25].

Medial temporal structures, in particular the rhinal cortex and the hippocampus, are crucial for the formation of declarative long-term memory[74]. The rhinal cortex is an anatomical 'bottleneck' and is the 'functional gatekeeper' for the information flow between the neocortex and the hippocampus, whereas the hippocampus supports synaptic plasticity and associative encoding more directly[75]. If phase synchronization has a role in communication and plasticity related to long-term memory, then an enhancement of rhinal–hippocampal and intrahippocampal phase synchronization would be expected during successful memory formation. Indeed, in a series of studies based on intracranial recordings in patients with epilepsy, a transient enhancement in the precision of rhinal–hippocampal gamma phase synchronization was found ~200 ms after the presentation of subsequently remembered, but not subsequently forgotten, words[26,30] (FIG. 2b). Individual differences in the increase in gamma phase synchronization were positively correlated with differences in spectral coherence in the theta frequency range[42]. In macaque monkeys, enhancements in intrahippocampal gamma spike–field coherence — also peaking at ~200 ms after stimulus presentation — predicted memory performance in a picture recognition task[76]. Furthermore, in humans, the ability to recall dreams is correlated, across subjects, with the level of broad-band (1–44 Hz) rhinal–hippocampal and intrahippocampal phase synchronization[28]. The enhancements of phase synchronization observed in these studies possibly reflect long-term memory-related information transfer between the rhinal cortex and the hippocampus[9,14], as well as the facilitation of spike timing-dependent plasticity[33,34].

Increases in phase synchronization have also been reported using non-declarative long-term memory paradigms. During retrieval of a fear memory after aversive conditioning in rats, theta phase synchronization between the amygdala and the hippocampus is enhanced[77]. This increase develops on an intermediate timescale (24 h after training), but not on a short timescale (the first 2 hours after training)[78], possibly reflecting the late stages of LTP[79]. Furthermore, gamma band coherence (measured in surface EEG recordings) increases during pain conditioning in humans[24]. These findings indicate that phase synchronization not only predicts subsequent memory performance, but is also enhanced as a result of learning.

Tasks involving working memory and long-term memory. In maze-learning experiments in rats, animals show increased theta phase synchronization between the prefrontal cortex and the hippocampus[32,80] and enhanced gamma phase synchronization between hippocampal areas CA1 and CA3 (REF. 81) when they decide which direction to take at the branching point of a T-maze (FIG. 2c). These decisions depend on previous knowledge of the environment, which might have been retrieved from either working memory or from long-term memory stores.

Similarly, in some experiments with human subjects, it is not entirely clear whether learning is based on working or long-term memory processes. For example, an increase in the coherence of theta and gamma oscillations in the hippocampus, amygdala and neocortex was predictive of immediate recall performance in a verbal learning task[31]. Such immediate recall probably involves a combination of working memory and long-term memory processing. The engagement of the amygdala in this task might be related to the role of this structure in modulating hippocampus-dependent long-term memory processes as a function of emotional arousal (although words were not explicitly selected to be emotionally arousing in this study)[82]. As working memory and long-term memory have traditionally been considered separate systems, it might seem surprising that they can both be supported by phase synchronization. In the next section, we describe recent data suggesting that working memory and long-term memory processes might interact in the hippocampus.

The hippocampus as a site of working memory–long-term memory interactions? As patients with hippocampal damage show impaired long-term memory but are not impaired in simple working memory experiments such as the delayed matching-to-sample task[83], it has long been assumed that the hippocampus is not necessary for working memory, and that working memory and long-term memory therefore represent distinct systems. More recently, however, a number of studies have cast doubt on this traditional view.

The first series of investigations was based on the observation that monkeys with lesions of the medial temporal lobe are impaired in working memory tasks[84], and that electrophysiological recordings from the (intact) monkey medial temporal lobe revealed sustained changes in cellular activity during delay periods in

Spectral coherence
A traditional measure of synchronization between two brain regions, which comprises both the synchronization of phases and the co-variation of power (squared amplitude) of neural oscillations.

Declarative memory
Memory of consciously accessible content — for example, memory of experiences with their specific temporal and spatial contexts (episodic memory), and memory of facts (semantic memory).

Delta frequency range
The frequency range between 1–3 Hz.

Aversive conditioning
A type of unconscious (non-declarative) learning that occurs when a stimulus (for example, a specific tone) is repeatedly accompanied by an unpleasant sensation such as an electric shock. After learning, presentation of the stimulus alone induces the physiological response associated with the unpleasant sensation.

Delayed matching-to-sample task
A typical working memory paradigm in which information about a single test item has to be maintained for several seconds. Afterwards, subjects have to indicate whether a probe item matches the test item.

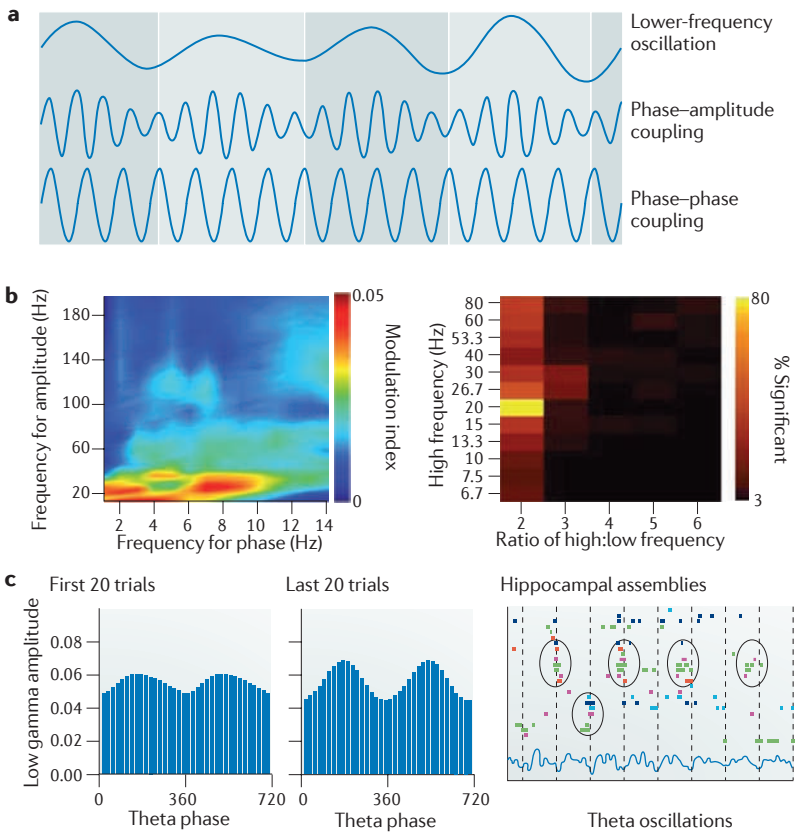


Figure 3 | **Cross-frequency phase–phase and phase–amplitude coupling. a** | Schematic overview of two cases in which oscillatory activity of a higher-frequency oscillation may be related to the phase of a lower-frequency oscillation. Dark and light boxes separate consecutive cycles of the lower-frequency oscillation. The lower-frequency oscillation of fluctuating amplitude (top) shows phase–amplitude coupling with a higher-frequency oscillation of fluctuating amplitude (middle). In this example, amplitudes of the higher-frequency oscillation are maximal during the up-phase of the lower-frequency oscillation. A higher-frequency oscillation of stable amplitude (bottom), shows phase–phase coupling with the low-frequency oscillation. Here, peaks of the higher-frequency oscillation always coincide with the same phase values of the lower-frequency oscillations. **b** | Cross-frequency coupling during working memory processing. The left panel shows phase–amplitude coupling in intracranial electroencephalography data from the human hippocampus. The magnitude of this coupling ('modulation index') was calculated for various pairs of phases of low-frequency oscillations (between 1–14 Hz; horizontal axis) and amplitudes of higher-frequency oscillations (between 14–200 Hz; vertical axis). Warm colours indicate higher values of phase–amplitude coupling, and the coupling was strongest between the phases of 7-Hz oscillations and the amplitudes of 28-Hz oscillations. The right panel shows phase–phase coupling in magnetoencephalography data. Bright colours indicate a higher percentage of channels with statistically significant coupling between low-frequency phases (horizontal axis) and high-frequency phases (vertical axis, between 6.7–80 Hz). Labels on the horizontal axis indicate frequency ratios. **c** | Acquired phase–amplitude coupling in rodents after learning. The graphs in the left panel show that hippocampal phase–amplitude coupling increases with learning of item–context relationships, as indicated by the higher amplitude of the right versus the left graph. The right panel shows that hippocampal assemblies synchronized in the gamma band preferentially fire during theta phase ranges around the troughs of theta cycles (dashed lines). This synchronized activity may allow for cued recall of sequences. Each coloured box represents a different hippocampal place cell. The blue trace represents theta oscillations in the extracellular field. Neurons representing similar information belong to a common assembly (assemblies indicated by circles). Part **a** is modified, with permission, from REF. 106 © 2007 Elsevier. The left panel of part **b** is reproduced, with permission, from REF. 70 © 2010 National Academy of Sciences; the right panel is reproduced, with permission, from REF. 118 © 2005 Society for Neuroscience. The left panel of part **c** is reproduced, with permission, from REF. 108 © 2009 National Academy of Sciences; the right panel is reproduced, with permission, from REF. 113 2003 © Macmillan publishers Ltd. All rights reserved.

working memory tasks[85]. It was reasoned that one important difference between experiments in monkeys and human subjects is that working memory in monkeys is usually tested with novel, trial-unique stimuli, whereas studies in humans are based on familiar material such as numbers or letters. Indeed, several functional MRI studies subsequently showed that working memory tasks involving novel stimuli are accompanied by sustained activation in the human medial temporal lobe[86–90]. Moreover, behavioural data have indicated that patients with medial temporal lobe lesions show impaired performance in such working memory tasks[87,91]. Together, these studies suggest that the hippocampus and neighbouring structures support certain working memory processes.

A second series of studies built on the so-called relational memory theory of the hippocampus[92,93]. This theory posits that the hippocampus specifically supports memory processes that involve sequences of items or associations of multiple item features, possibly based on the associational network properties of area CA3 (REFS 1,92,93). Several studies using intracranial EEG[86] and fMRI[86,94] reported increased hippocampal activation in working memory tasks that require subjects to maintain associations between multiple objects or object features. Again, patients with lesions of the medial temporal lobe are impaired in these tasks[95–97].

These results suggest that the medial temporal lobe, particularly the hippocampus, has a role in working memory processes that involve novel items or associations between multiple items and item features[92,93] (but see also REF. 98). Being involved in both memory operations, the hippocampus may represent a locus of interaction between working memory and long-term memory. That is, it may support the transfer of information from working memory to long-term memory and the retrieval of information from long-term memory into working memory. Indeed, a number of studies showed that working memory and long-term memory are not only supported by overlapping brain regions, but that activation of the medial temporal lobe during maintenance of information in working memory is predictive of successful subsequent long-term memory recall[88,99].

Complementary phase-based mechanisms

In addition to phase synchronization of oscillations in different brain regions, other synchronization mechanisms facilitate the representation of multiple objects in memory. They include cross-frequency phase–amplitude coupling and cross-frequency phase–phase coupling — two phenomena that may occur independently[100] and may have different underlying mechanisms and different functional consequences, as described below.

Cross-frequency phase–amplitude coupling. The phase of a low-frequency oscillation may be synchronized not only with the phase, but also with the amplitude, of another (high-frequency) oscillation (FIG. 3). This phenomenon was initially described based on recordings

from the rat hippocampus[40] and from the monkey auditory cortex[4]. Recently, phase–amplitude coupling was also observed in the human brain using scalp[100,101] and intracranial EEG recordings[102,103]. Although the factors that contribute to these mechanisms are still not completely understood, it has been suggested that the phases of low-frequency oscillations reflect fluctuations of membrane potentials in a brain area and thus represent changes in neural excitability, which affect the amplitude of high-frequency oscillations in that area[5,6].

Phase–amplitude coupling seems to be relevant for memory processes. According to an influential model of working memory that elegantly explains its limited capacity, multiple objects are simultaneously maintained in working memory by consecutive gamma cycles associated with specific theta phase ranges[104,105]. This model assumes that individual items are represented by assemblies of neurons that are synchronized in the gamma frequency range (the binding function of gamma oscillations described above).

Assuming gamma band activity at 40 Hz (corresponding to oscillation periods of 25 ms), this model suggests that the first item in a sequence is represented by a gamma oscillation during a first 25-ms range of a theta cycle, the second item by a gamma oscillation during the next 25 ms, and so on. As a result if, for example, three items are being maintained in working memory, gamma oscillations occur during the first 75 ms of a theta cycle, and the remaining 125 ms (for theta band activity of 5 Hz, one cycle lasts 200 ms) is void. This results in a high gamma amplitude during the first 75 ms and a low (in this case zero) amplitude during the remaining 125 ms of the theta cycle. Thus, the amplitude of a high-frequency (for example, gamma) oscillation is modulated by the phase of a low-frequency (for example, theta) oscillation[105,106].

Such phase–amplitude coupling has recently been detected in working memory tasks. First, phase–amplitude coupling was enhanced in the hippocampus of rats approaching the branching point while navigating through a T-maze. At the branching point, rats have to decide which direction to take and thus recruit working or long-term memory processes[107]. Second, phase–amplitude coupling between theta phase and beta–gamma (20–40 Hz) amplitude was increased in the hippocampus of patients with epilepsy when they maintained novel information (faces) in working memory[70]. Third, in the prefrontal cortex of monkeys, neural firing during object maintenance in working memory was concentrated at specific phases of beta and delta oscillations, and the amplitude of the beta oscillations varied with the phase of the delta oscillation[69]. Taken together, these findings suggest that phase–amplitude coupling mechanisms in both the hippocampus and prefrontal cortex may support phase-dependent coding of objects in working memory.

Results from two lines of animal experiments suggest that phase–amplitude coupling is also employed during the cued recall of spatial information from long-term memory. First, experiments in which rats had to learn reward contingencies of odour cues as a function of spatial context showed that coupling of gamma amplitude to theta phase in the hippocampus is more precise after learning item–context associations than before learning[108].

Second, results from rodent studies on spatial recall[105,106] showed that, when a rat approaches a particular location within a familiar environment, hippocampal place cells representing this location fire during increasingly earlier phases of the theta oscillation with decreasing distance from this location, a phenomenon known as phase precession[50,109]. As individual neurons fire preferentially during a specific gamma phase, the firing of neurons during phase precession is modulated by the phase of simultaneous gamma oscillations[110]. As a result, phase precession occurs in discrete steps, each corresponding to approximately one gamma cycle[111,112]. At the neuronal population level, it was found that neural assemblies representing individual locations are active throughout the duration of one gamma cycle[113]. It was suggested that each location is represented by one gamma cycle occurring during a specific theta phase range — which may correspond to phase–amplitude coupling — and that this provides a cue for the recall of the next location[111,112,114,115], although a link between phase–amplitude coupling and phase precession is still somewhat speculative. In summary, these studies suggest that coupling of gamma cycles to specific theta phase ranges is a mechanism that is employed during both multi-item working memory maintenance and long-term memory retrieval.

Cross-frequency phase–phase coupling. Phase synchronization can also occur between oscillations of different frequencies, an effect known as '*m:n* phase coupling' or '*m:n* phase synchronization'[116]. It addresses the phenomenon that not only entire cycles, but even the individual phases of a single cycle of an oscillation with a higher frequency are locked to specific phases of an oscillation with a lower frequency (FIG. 3a). Typically, the two frequencies have an integer relationship such that, for example, a theta oscillation of 5 Hz and a gamma oscillation of 40 Hz exhibit a 1:8 phase coupling. In this example, gamma phases of 0° can, for example, be locked to theta phases of 0°, 45°, 90°, 135°, 180°, 225°, 270° and 315°. Similar to 1:1 phase synchronization, *m:n* coupling can be quantified by evaluating the distribution of phase differences between *n* times the phase of the lower frequency oscillation and *m* times the phase of the higher frequency oscillations (in our example, 8 x theta phase and 1 x gamma phase).

Several studies have described *m:n* coupling during working memory processing. Surface EEG recordings in humans suggested that there is coupling between oscillations in the theta frequency range (in the left frontal cortex) and oscillations in the alpha frequency range (in the central-parietal cortex)[117], and between oscillations in the theta and upper gamma (> 50 Hz) frequency ranges[100] (at parietal sites) during working memory maintenance. The load-dependent increase of theta–upper gamma coupling during working memory maintenance predicts a subject's working memory capacity[100]. Additionally, magnetoencephalography (MEG) data in

Place cell
A hippocampal neuron that specifically responds to stimuli in certain spatial locations. Its firing rate increases when an animal or subject approaches the respective location.

Alpha frequency range
The frequency range between 8–12 Hz.

an arithmetic task requiring maintenance and manipulation of information in working memory have suggested a load-dependent enhancement of alpha–gamma coupling[118].

We propose that working memory-related phase–phase coupling may reflect the coordinated recruitment of a lower-frequency rhythm and higher-frequency oscillations. As phase–phase coupling reflects the synchronization of the phases of lower-frequency and higher-frequency oscillations, it involves a timing of phases that is more precise than the duration of individual cycles of the high-frequency oscillation. For example, if the theta phase is synchronized to the phases of 40-Hz gamma activity, such phase–phase coupling involves the timing of phases that is more precise than 25 ms. By contrast, phase–amplitude coupling only corresponds to synchronization with the amplitude of a high-frequency oscillation. As the amplitude of oscillations is usually modulated across several cycles, phase–amplitude coupling is less precise than phase–phase coupling. The high temporal precision of cross-frequency phase–phase coupling may, for example, be necessary for non-interfering representations of multiple items in working memory via consecutive gamma cycles, which are locked to specific theta phases[104,105].

Working memory–long-term memory interactions

Interactions based on phase synchronization. Sustained phase synchronization between higher-order sensory, frontal and temporal areas[41,44,45,47,65–67], as well as between the rhinal cortex and hippocampus[68], represents a neural correlate of working memory maintenance. Such phase synchronization is likely to facilitate communication between brain regions, as proposed by the 'communication through coherence' hypothesis[14]. In addition, fronto-temporal phase synchronization[25,27,32] and phase synchronization within the medial temporal lobe[26,28,30,31] are a neural signature of long-term memory formation, corresponding to the idea that phase synchronization facilitates neural plasticity[33,34].

It could therefore be proposed that processes associated with working memory maintenance may support long-term memory formation (FIG. 4). Indeed, fMRI findings indicate that enhanced activity in the medial temporal lobe during working memory maintenance is associated with successful long-term memory encoding, as it predicts subsequent long-term memory retrieval[88,99]. Based on the well-known importance of the hippocampus for declarative long-term memory processes[74], one may speculate that engagement of this region during working memory — which occurs predominantly when novel items[87–90], associations and multiple items[94] are maintained in working memory — is a necessary prerequisite for long-term memory encoding. Indeed, rehearsal of inter-item relationships in working memory results in superior long-term memory performance compared with rehearsal of individual items[119,120]. In addition, intracranial EEG activation patterns in the hippocampus of patients with epilepsy that resemble patterns during hippocampus-dependent working memory facilitate long-term memory encoding[121].

Conversely, it is possible that phase synchronization may be enhanced as a result of plasticity-related changes that are associated with long-term memory[73]. Such enhancement has been observed between posterior and frontal sites in human scalp EEG recordings during recall of previously learned associations between different line drawings[73], and in medial temporal lobe recordings in rats following fear conditioning[77,78]. This enhancement of phase synchronization may in turn support working memory operations. Indeed, working memory maintenance of familiar items for which representations in long-term memory already exist is superior to working memory of novel items[122,123]. However, no studies have directly addressed how phase synchronization during working memory maintenance affects subsequent long-term memory outcome or how phase synchronization during long-term memory operations affects subsequent working memory performance.

Interactions based on phase–amplitude coupling. As described above, several studies suggest that phase–amplitude coupling supports multi-item working memory, for which it may be necessary to separate the representations of individual objects[70,100]. Furthermore, animal data indicate a role for phase–amplitude coupling in the cued recall of spatial sequences from long-term memory[113–115]. Do these two functions of phase–amplitude coupling for working memory and for long-term memory recall interact? And, if so, how?

It has been proposed that sequences of object representations arranged by theta–gamma coupling are bound together through activation of neurotransmitter receptors known to be involved in LTP, particularly NMDA receptors[124], and that this arrangement facilitates encoding. The time constant of NMDA receptors is below ~100 ms. If objects within a sequence are presented separately with temporal intervals >100 ms, which is generally the case, their neural representations would need to be brought together closer in time before they can be associated with one another. This requirement would be fulfilled if objects were represented by gamma cycles (corresponding to a temporal separation of object representations by ~20–30 ms) during successive phase ranges within a theta oscillation[105]. In other words, this model proposes that sequence representations first have to be temporally condensed through a working memory-related mechanism before the items can be linked to each other in long-term memory, so that both the individual items and their sequential relationship can be stored in long-term memory[105,124]. Again, this model explains why neural activity during working memory maintenance supports long-term memory encoding[88,99]. The recall of such object sequences from long-term memory may then be accomplished by an inverse mechanism based on theta–gamma coupling[113–115].

Interactions based on* m:n *phase coupling. A working memory load-dependent enhancement of theta–gamma phase coupling has been observed[100]. Specifically, the timing of individual gamma cycles at certain phases of theta oscillations becomes more precise with increasing

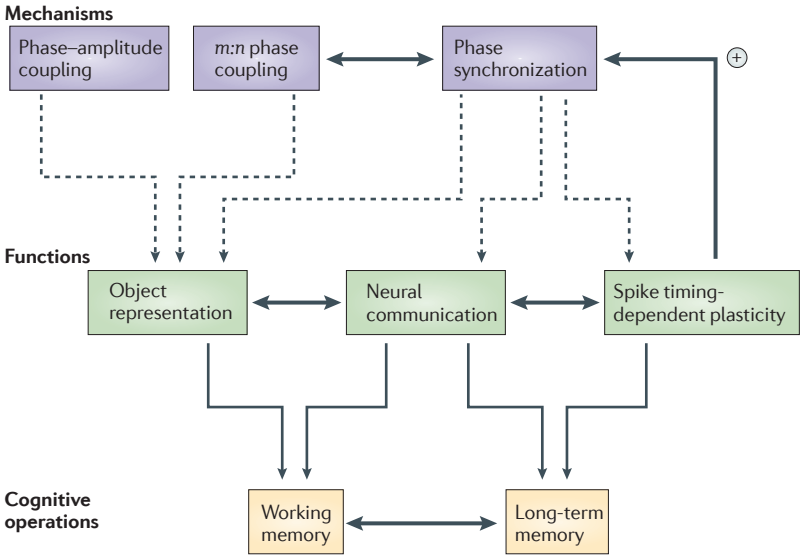


Figure 4 | **An integrative view of memory-related synchronization mechanisms.** In this schematic overview, dotted arrows point to the functions that are supported by the different neural mechanisms. Thin black arrows indicate that functions contribute to cognitive operations. Thick double-headed arrows represent interactions between mechanisms, functions or cognitive operations. Of note, 'phase synchronization' strictly refers to a bivariate measure of interaction between two brain regions, and '*m*:*n* phase coupling' refers to interactions between different frequencies — that is, $m \neq n$. In general, all three synchronization mechanisms are probably related to both working memory and long-term memory (and to the interaction between these memory processes). We propose that this relationship between mechanisms and memory operations is exerted through different primary functions of the three mechanisms: first, the mechanism of phase synchronization supports two general functions — namely, neural communication and spike timing-dependent plasticity. In addition, phase synchronization probably supports object representation — for example, through feature binding. This function also relies on neural communication (as indicated by the double-headed arrow). Neural communication facilitates both working memory and long-term memory processes, whereas spike timing-dependent plasticity specifically contributes to long-term memory. Synaptic enhancement resulting from spike timing-dependent plasticity also leads to increased phase synchronization. Second, the complementary mechanisms of phase–amplitude coupling and *m*:*n* phase coupling are crucial for a non-interfering representation of multiple objects in working memory. Synchronization processes, particularly within the medial temporal lobe, probably support the interaction of working memory and long-term memory operations.

working memory load. Furthermore, the variability of theta phases at which beta–gamma activity is maximal decreases with increasing working memory load[70]. These results suggest that object representations are more precisely locked to certain phases of theta oscillations when working memory load is high[105]. This phenomenon may reflect the necessity for an accurate arrangement of gamma cycles to guarantee temporally adjacent but non-overlapping representations of multiple objects.

An increase of theta–gamma phase coupling within two regions will automatically lead to enhanced gamma phase synchronization between these regions if there is already theta phase synchronization between the two regions. For example, if gamma phases of 0° are locked to theta phases of 0°, 45°, 90°, 135° and so on, and if theta phases are synchronized across regions (for example, with zero lag), then gamma phases of 0° will occur in both regions simultaneously. In other words, gamma oscillations are phase-synchronized between these regions (in this case, with zero lag). As described above, increased theta phase synchronization has been detected during both working memory maintenance[47] and long-term memory encoding[29]. Enhanced gamma phase synchronization, in turn, is likely to facilitate spike timing-dependent plasticity[33,34].

In this way, the complementary mechanisms of theta–gamma phase coupling and theta phase synchronization may support the transfer of items maintained in working memory into long-term memory by enhancing gamma phase synchronization. Indeed, a simultaneous increase of theta and gamma phase synchronization and theta–gamma phase coupling has been observed during successful long-term memory encoding in humans[125]. Furthermore, across subjects, rhinal–hippocampal theta phase synchronization associated with successful long-term memory formation was found to be correlated with rhinal–hippocampal gamma phase synchronization[42]. However, experimental evidence for these cooperative effects based on paradigms that directly address interactions between working memory and long-term memory is still needed.

Open questions and future perspectives

Although our understanding of synchronization mechanisms underlying memory processes has advanced considerably during recent years, there remain many unresolved issues. In general, gamma phase synchronization probably supports two major functions — namely, neural communication and plasticity. However, it is likely that not all regions involved in the transfer of information show neural plasticity. Hence, it is an open question how interference between communication and plasticity can be avoided or whether communication and plasticity are supported by different types of gamma phase synchronization. Similarly, it is currently unclear how phase synchronization can simultaneously support memory-related processes and other cognitive operations without interference.

It was recently reported that fast gamma oscillations (around 100 Hz) in CA1 specifically synchronize with fast gamma oscillations in the entorhinal cortex, whereas slow gamma oscillations (around 45 Hz) in CA1 synchronize with slow gamma oscillations in CA3 (REF. 126). Such a mechanism could enable simultaneous but non-interfering communication within memory networks. Directional coupling and network analyses may help to reveal the information flow and interaction schemes during working memory and long-term memory[127].

As described in this Review, empirical data suggest that synchronization-based mechanisms have a role in both working memory and long-term memory processing. We have described some ideas regarding the synchronization-based interplay between both functions for which evidence is accumulating, although such evidence is still indirect. A better understanding of these mechanisms requires experimental paradigms that directly address the interaction between working memory and long-term memory — that is, the transfer of information maintained

Microelectrode recording
An electrophysiological recording with a microelectrode (which has a diameter of several μm) that enable researchers to measure individual action potentials in animals or humans.

Macroelectrode recording
An electrophysiological recording using macroelectrodes (contact size in the mm range), which allow electroencephalography recordings from within the animal or human brain.

in working memory into long-term memory, but also the retrieval of information from long-term memory into working memory. Examples of such paradigms are delayed matching-to-sample tasks with subsequent long-term memory recall, and the working memory-dependent manipulation of multiple items that have already been stored in long-term memory.

Elucidating the functions of phase synchronization for memory operations requires an integration of evidence from different methodological domains. The extreme poles are cellular recordings in rodents under simple experimental situations versus EEG and MEG data from humans performing complex tasks. The recently developed methodology combining microelectrode recordings with macroelectrode recordings in patients[128] may close this gap by allowing the simultaneous investigation of human memory processes at both a cellular and a systems level.

Finally, it is well known that several psychological factors, including attention[57], novelty[129] and reward[130], control memory functions[131]. The neurophysiological processes that support the modulation of working memory and long-term memory by these factors are not sufficiently understood and the role of phase synchronization-based mechanisms therein has yet to be unravelled.

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Acknowledgements
This work is supported by grants from the German Research Foundation (SFB TR3, project A9 and DFG project FE366/5-1). We thank J. Jitsev, P. Klaver, N. Maier, L. Melloni, P. Sauseng and B. Staresina for valuable comments on an earlier draft of this manuscript.

Competing interests statement
The authors declare no competing financial interests.

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