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Review

Memory formation by neuronal synchronization

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ABSTRACT

Cognitive functions not only depend on the localization of neural activity, but also on the precise temporal pattern of activity in neural assemblies. Synchronization of action potential discharges provides a link between large-scale EEG recordings and cellular plasticity mechanisms. Here, we focus on the role of neuronal synchronization in different frequency domains for the subsequent stages of memory formation. Recent EEG studies suggest that synchronized neural activity in the gamma frequency range (around 30–100 Hz) plays a functional role for the formation of declarative long-term memories in humans. On the cellular level, gamma synchronization between hippocampal and parahippocampal regions may induce LTP in the CA3 region of the hippocampus. In order to encode spatial locations or sequences of multiple items and to guarantee a defined temporal order of memory processing, synchronization in the gamma frequency range has to be accompanied by a stimulus-locked phase reset of ongoing theta oscillations. Simultaneous gamma- and theta-dependent plasticity leads to complex learning rules required for realistic declarative memory formation. Subsequently, consolidation of declarative memories may occur via replay of newly acquired patterns in so-called sharp wave–ripple complexes, predominantly during slow-wave sleep. These irregular bursts induce longer lasting forms of synaptic plasticity in output regions of the hippocampus and in the neocortex. In summary, synchronization of neural assemblies in different frequency ranges induces specific forms of cellular plasticity during subsequent stages of memory formation.

Contents

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1. Introduction

The basic unit of information processing in the human brain is an action potential. Action potentials of individual neurons are not independent from each other but are correlated by synchronized activity in neuronal assemblies. Because it has been shown in various systems that the exact spike times (and not just the firing rate) of individual neurons are a relevant measure of the activation of these neurons (Rieke et al., 1997), an increasing synchrony reduces the amount of information that the spike times of any individual neuron contains. Thus, synchronization in itself is unlikely to serve as a neuronal code. Instead of representing time-coded information on stimulus features, it rather appears to support specific processes during neural communication (Fries, 2005): the behavioral specificity of synchronization phenomena (e.g., in the gamma range between 30 and 100 Hz) suggests a functional role of synchronized activity for neural information processing (e.g., Ekstrom et al., 2003). Furthermore, changes in network oscillations during pathological states (e.g., during epileptic seizures) may impair normal brain function.

The mechanistic role of synchronized activity for information processing in single neurons is far from evident: primarily, the observation of synchronized activity in a given frequency band signifies just that neural activity is correlated. There may be a variety of mechanisms by which a neural network is synchronized in a certain frequency range, and each mechanism may have different effects. For example, theta oscillations (3–8 Hz) have been described both during pathological states in the human EEG and during episodes of memory encoding in specific areas of the medial temporal lobe in animals (e.g., Buzsáki, 2002). In general, an increasing synchrony may strengthen the impact of the synchronously firing neurons onto common target cells if these target cells integrate their inputs over small time scales (Fries, 2005). Furthermore, if the synaptic connections between the synchronously firing neurons are modifiable by spike-timing-dependent plasticity, an increasing synchronicity between these neurons may induce long-term potentiation of these synapses. As a result, the stimulus properties that have activated these neurons are associated with each other to form a new memory. In our article, we attempt to give a detailed description of this process, focusing on synchronous activity in the gamma and theta frequency range.

Accordingly, two main functions have been proposed for the synchronization of gamma oscillations. Many observations support the view that gamma synchronization binds participating neurons that represent attended (as opposed to background) features of a stimulus (e.g., Fries et al., 2001; Engel and Singer, 2001; Fell et al., 2003a). According to this view, precise synchronization in the gamma frequency range serves widely distributed networks of neurons to effectively activate common target cells. Only recently, a different (though perhaps related) function of gamma oscillation has been proposed: formation of declarative memories, i.e., long-term storage of consciously accessible information into memory (Fell et al., 2001; Gruber et al., 2004; Sederberg et al., 2003). More specifically, late (induced) gamma activity at an interval of more than 200 ms after the onset of stimulus presentation has been suggested to be crucial for long-term storage of information after its previous matching with already encoded memory contents by early (evoked) gamma activity (Herrmann et al., 2004). Lesion studies have demonstrated that structures within the medial temporal lobe, in particular within the hippocampus, are necessary for declarative memory formation (e.g., Scoville and Milner, 1957).

In the following, we will first focus on the potential role of medial temporal gamma activity for declarative memory formation. We will discuss why synchronization of neural firing in the gamma frequency range (rather than at lower or higher frequencies) might be specifically well suited for memory formation. We will further consider its connection with oscillations in the theta range that are phase and amplitude reset by stimuli triggering memory processes (Rizzuto et al., 2003; Mormann et al., 2005). Finally, we will discuss the function of fast oscillations (~200 Hz) and physiological hippocampal sharp waves for the specific types of neural plasticity during memory consolidation.

2. Gamma frequency hypothesis

The most parsimonious hypothesis for the role of synchronized gamma activity in memory formation is that gamma

synchronization is particularly well suited due to its specific frequency range. Interestingly, the definition of the gamma frequency range varies substantially across different studies. Whereas earlier human studies have mostly focused on activity around 40 Hz (e.g., Eckhorn et al., 1988; Joliot et al., 1994; Tallon-Baudry et al., 1996; Rodriguez et al., 1999), more recent research explicitly takes into account activity in higher frequency ranges (e.g., Crone et al., 2001; Muller and Keil, 2004; Lachaux et al., 2005). On the contrary, even earlier animal data have considered gamma activity in higher frequency ranges up to ~120 Hz (e.g., Bragin et al., 1995; Neuenschwander and Singer, 1996). A good overview of the literature is given in Engel and Singer (2001). The "gamma frequency hypothesis" implies that synchronized activity in the gamma range induces memory processes more successfully than both slower (e.g., beta-) and faster (e.g., ripple-) activity. How could, in general, correlated activity in a given frequency range support memory formation? Long-term potentiation (LTP) and depression (LTD) are widely considered to underlie the encoding of new declarative memories (e.g., Nakazawa et al., 2004; but see Shors and Matzel, 1997). More specifically, Hebbian learning – which depends on the correlated activity of the pre- and postsynaptic cell (Hebb, 1949) – is assumed to be implemented by a specific form of pairing-induced LTP which for most synapses depends on the presence of NMDA receptors. Other forms of NMDA-receptor-independent LTP which may only depend on the activity of the pre-, but not the postsynaptic cell, have been discovered at various synapses (e.g., Liu et al., 2004).

Recently, it has been reported that the exact relative timing of pre- and postsynaptic spikes within a time range of several milliseconds to tens of milliseconds is important for the induction of so-called spike-timing-dependent plasticity at various synapses (e.g., Levy and Steward, 1983; Markram et al., 1997; Dan and Poo, 2004). Synchronized network activity in the gamma frequency range relies on patterning of synaptic inputs within exactly these intervals of 10–30 ms. Slower oscillations do not impose sufficiently narrow time windows for the coincident activation of pre- and postsynaptic cell. Faster oscillations, on the other hand, have more than one cycle during the time window of the LTD/LTP shift: if these oscillations were to entrain action potentials at intervals <10 ms in two synaptically connected cells, the postsynaptic cell might receive inputs both before and after having generated a spike. Therefore, the effect on synaptic plasticity would be ambiguous. Furthermore, network oscillations of very high frequencies may result only from a small number of contributing neurons that are not sufficient to induce plasticity. Finally, the cellular events that are synchronized during very fast oscillations may not be full-blown action potentials but rather ectopic spikes not suited for backpropagating and thereby for pairing-induced plasticity (Traub et al., 2002).

The following section gives a detailed overview on how exactly synchronized gamma activity supports specific forms of long-term potentiation in the hippocampus.

2.1. *Hippocampal gamma synchronization and spike timing*

How is synchronized gamma activity generated? Neural networks can synchronize in the gamma range by a variety of mechanisms (Traub et al., 1998). According to the "interneuron-gamma" hypothesis, hippocampal gamma oscillations arise from networks of mutually interconnected GABAergic interneurons (Whittington et al., 1995). Both the excitatory (mainly glutamatergic) driving current to these interneurons and the time course of inhibitory postsynaptic potentials (IPSPs) determine the frequency of the network gamma oscillations. Following this hypothesis, pyramidal cells do not themselves contribute to the generation of hippocampal gamma oscillations (Whittington et al., 1995). However, the mechanisms of interneuron synchronization are still under debate; recent experimental data suggest that recurrent excitation in the CA3 region (cf. Fig. 1 for an overview of the hippocampal circuits) is a necessary prerequisite to ensure precisely synchronized gamma activity (Mann et al., 2005).

Synaptic currents arrive at pyramidal cell somata with variable latency, depending on the synaptic location and on dendritic integration properties. Furthermore, somatic excitatory postsynaptic potentials (EPSPs) do not induce spikes in hippocampal pyramidal cells after a precise delay but with considerable jitter (contrary to hippocampal interneurons; Fricker and Miles, 2000); only if the time window for action potential generation is constrained by subsequent activation of intrinsic outward currents is EPSP–spike coupling precise (Axmacher and Miles, 2004). Coupled interneurons that fire precisely synchronized in the gamma frequency range prevent pyramidal cells from firing as long as the pyramidal cell membrane is hyperpolarized after an IPSP has arrived. Thus, the interneurons can set time windows during which pyramidal cells cannot fire action potentials. Indeed, the time course of IPSPs has been shown to correlate with the frequency of the network (field) gamma oscillations that reflect the firing of various kinds of cells, but predominantly of the (more abundant) pyramidal cells (Pouille and Scanziani, 2001; Csicsvari et al., 2003). Taken together, gamma oscillations paced by interneurons are a network mechanism to induce precise timing of pyramidal cell action potentials.

If pyramidal cell firing is paced in the gamma frequency range, it still remains an open question how precise this control is: is spiking in a given pyramidal cell exact at the level of a gamma half-cycle (~10 ms) or even more precisely related to the phase inside this half-cycle? This question is important because control of LTP by network gamma activity requires temporal precision of cell firing in the range of few milliseconds, i.e., of different phases in a gamma cycle. In in vitro experiments, pyramidal cells fire predominantly during a specific phase of the gamma cycle, but with considerable jitter (Bragin et al., 1995; see Fig. 2, middle panel of the left column). Results from computer simulations suggest that the phase relationship of pyramidal cell action potentials in the hippocampus depends on the excitation of the respective pyramidal cell: more depolarized pyramidal cells appear to fire at an earlier gamma phase than less excited ones (Traub et al., 1997). As a consequence, pyramidal cells would encode the strength of their synaptic inputs by the phase of action potential timing with respect to gamma activity (gamma phase coding). Contrary to phase coding in the theta range, which will be dealt with later in the text, to date, there is no

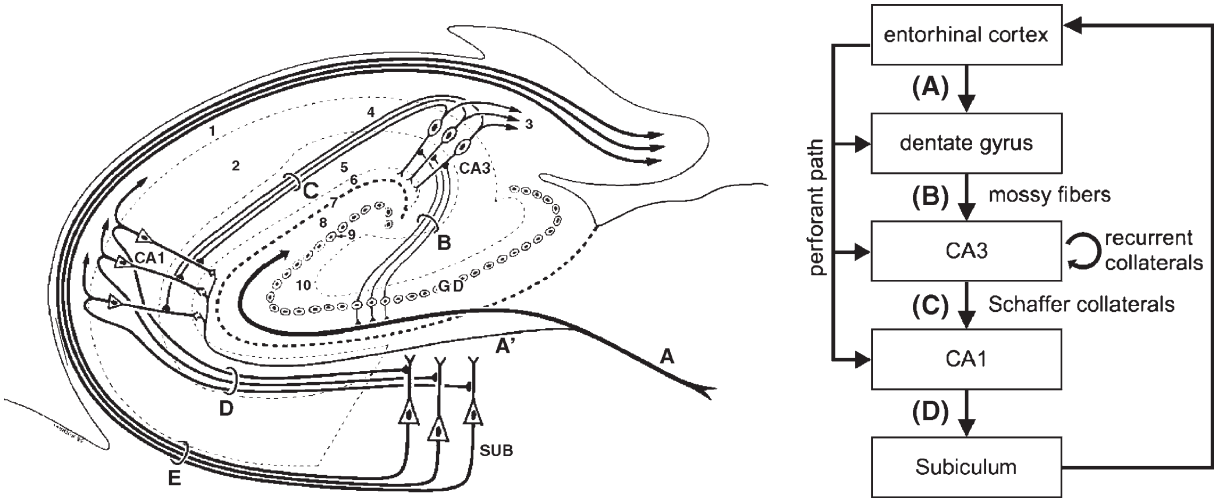

Fig. 1 – Pathways of the hippocampus. Left: Anatomical drawing adapted from Duvernoy (1988). GD, dentate gyrus; CA3, CA1 fields of the cornu ammonis; SUB, subiculum. Cornu ammonis: (1) alveus, (2) stratum pyramidale, (3) axon of pyramidal neurons, (4) Schaffer collateral, (5) stratum radiatum and lacunosum, (6) stratum moleculare, (7) hippocampal sulcus. Dentate gyrus: (8) stratum moleculare, (9) stratum granulosum, (10) polymorphic layer. Right: Schematic overview including a legend of hippocampal connections. (A) Connection from the superficial layers of the entorhinal cortex to the dentate gyrus, (A') perforant path, (B) mossy fibers, (C) Schaffer collaterals, (D) connection from CA1 to the subiculum, (E) connection from the subiculum to deep layers of the entorhinal cortex.

direct evidence for the idea of gamma phase coding. This idea would, however, imply that the phase relationships of pyramidal cell action potentials are rather diverse (depending on their input strength). Indeed, the gamma phase at which pyramidal cells fire is more variable than the gamma phase during which interneurons fire (because interneurons are the pacemaker of gamma oscillations; Bragin et al., 1995). A recent paper demonstrates that extracellular stimulation at gamma frequency induces either LTP or LTD, depending on the gamma phase of the incoming stimulus. Interestingly, the stimulated cell fired during the peak of the gamma oscillation in both cases (Wespatat et al., 2004). Taken together, some, but not all, experiments support the idea that the phase of network gamma oscillations at which a given pyramidal cells fires is determined by the strength of the synaptic input to this cell.

2.2. *Regional basis of rhinal–hippocampal synchronization*

In a recent study, the phase synchronization of gamma activity between the rhinal cortex and the hippocampus was found to increase in humans for successfully stored items (as opposed to subsequently forgotten items) (Fell et al., 2001). In that paper, the power of hippocampal gamma oscillations did not increase during successful encoding, consistent with human data on the firing rate of single hippocampal neurons (Cameron et al., 2001). Only a small subset of hippocampal pyramidal cells fires in phase with the network gamma oscillations (Csicsvari et al., 2003). (Similarly, the firing rate of specific interneuron types is modulated in a more pronounced manner by theta phase than the firing rate of pyramidal cells; Klausberger et al., 2003.) The subgroup of pyramidal cells whose firing rate is strongly modulated by the underlying network oscillation might specifically represent stimulus features that undergo long-term memory encoding. A decrease of the network gamma power may then correspond to the fact that a more specific subset of neurons is coherently activated and associated into a memory assembly.

Sederberg and colleagues found increases in the power of both gamma and theta activity during successful memory encoding in widespread neocortical regions (Sederberg et al., 2003); the hippocampus was not investigated in that study. For scalp EEG, an increase in the gamma power during successful encoding and retrieval has been reported (Gruber et al., 2004). However, in measurements with a coarse spatial resolution (e.g., scalp EEG data), synchronization between local assemblies may lead to an apparent increase of the net power measured at a more global level. Thus, it remains unclear whether the memory-related power and synchronization findings, which at first sight appear to be partially divergent, represent actual characteristics of the different brain structures or are caused by a methodological bias.

Is it possible to locate the synchronization changes between the rhinal cortex and the hippocampus more closely? Given the anatomical connectivities (Duvernoy, 1988), the synchronization changes could arise (a) between the rhinal cortex and the dentate gyrus; (b) between the dentate gyrus and CA3; or (c) between CA3 and CA1 (cf. Fig. 1). In rodents, it has recently been shown that gamma activity in CA3 and CA1 is driven by a common oscillator (Csicsvari et al., 2003) (see Fig. 1 for an overview of hippocampal circuits). This can be regarded as evidence against the possibility that alterations in gamma synchronization between the hippocampus and the rhinal cortex depend mainly on changes in synchronization between CA3 and CA1. The synchronization between this

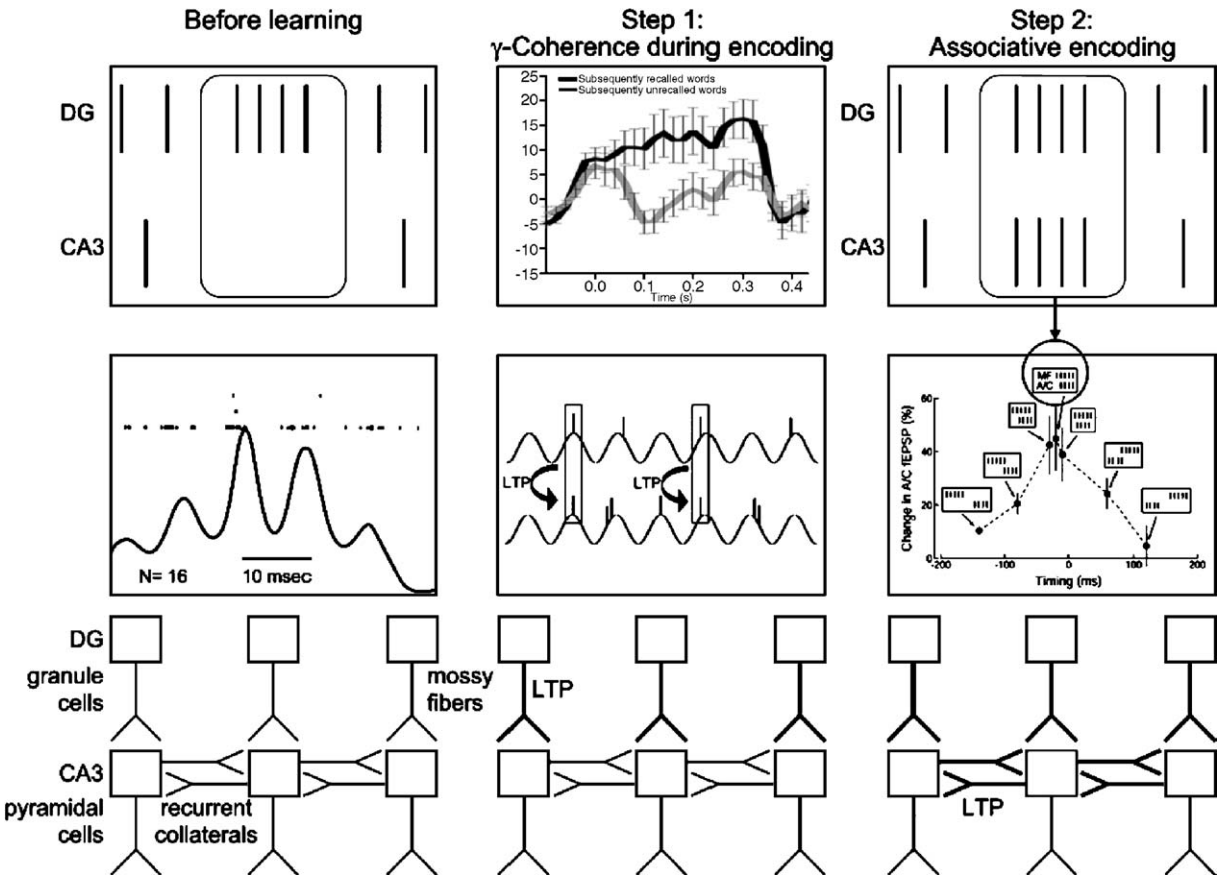

Fig. 2 – Associative encoding during hippocampal gamma activity occurs in a two-step process. Left: Before learning, action potentials in the dentate gyrus and CA3 are uncorrelated (upper panel). In each of these regions, the discharge probability depends on the phase of gamma field oscillations (middle panel, adapted with modification from Bragin et al., 1995): discharge frequency is maximal at the peak of the field oscillations. The lower panel shows a schematic drawing of the feedforward and recurrent connections in the input layers of the hippocampus (dentate gyrus (DG) and the CA3 region). Middle: During successful declarative memory encoding, gamma oscillations in the rhinal cortex and the hippocampus are synchronized, that is, they occur with a fixed phase relationship of zero degrees. The upper panel has been adapted with modification from Fell et al. (2001) and shows the coherence of network oscillations in dentate gyrus and hippocampus in the gamma frequency range during successful (black) and unsuccessful attempts to memorize items. The middle panel depicts schematically how the coherence of network oscillations influences spike-timing-dependent synaptic plasticity: as spikes occur predominantly during a specific gamma phase, cells in the synchronized networks also fire at similar times, which leads to Hebbian (paring-dependent) LTP at major input pathways towards CA3 (mossy fibers and the perforant path; middle panel). As a result, feedforward connections to CA3 are enhanced (lower panel). Right panel: After this first step of synaptic plasticity, activity in the dentate gyrus and CA3 is correlated (upper panel). The correlated activity induces heterosynaptic LTP at associative connections inside CA3 (middle and lower panel; middle panel adapted with modification from Kobayashi and Poo, 2004). The ordinate in the middle panel depicts the percentage increase of the field EPSP slope in CA3 as a measure of the strength of recurrent connections inside CA3 (for details, cf. Kobayashi and Poo, 2004).

intrahippocampal gamma oscillator and another gamma oscillator in the dentate gyrus, on the other hand, is variable (Csicsvari et al., 2003). Furthermore, gamma activity in the entorhinal cortex and the dentate gyrus is also synchronized and dentate gamma power decreases significantly after surgical removal of the entorhinal cortex, suggesting that it is driven from there (Bragin et al., 1995). Consequently, synaptic plasticity due to synchronization changes between the rhinal cortex and the hippocampus is most likely to occur at the junction between these two oscillators (entorhinal cortex–dentate gyrus and CA3–CA1), i.e., at afferent synapses to the CA3 region.

2.3. *Rhinal–hippocampal gamma synchronization supports LTP in CA3*

Pyramidal cells in CA3 receive synaptic inputs from both upstream regions (from the dentate gyrus via mossy fibers and from the entorhinal cortex via the perforant path) and abundant recurrent collaterals inside CA3. In this paragraph, we will discuss possible modifications at both types of synapses induced by synchronization of gamma activity. The suggested mechanism by which synchronization of gamma activity between rhinal and hippocampal structures modifies synaptic connections inside the hippocampus

critically depends on the form of LTP at afferent synapses into the hippocampus: an increased synchronization of firing in the gamma frequency range affects LTP at these synapses only if this LTP depends on pairing of pre- and postsynaptic activity (spike-timing-dependent Hebbian LTP; Dan and Poo, 2004). If, on the other hand, LTP at these synapses solely depends on the activity of the presynaptic site, the synchronization of pre- with postsynaptic activity is irrelevant. This distinction between different forms of LTP is particularly important: one of the major inputs to the CA3 region is transferred via highly specialized mossy fiber terminals from the dentate gyrus, and controversial findings exist concerning the existence of pairing-dependent LTP at these fibers (Urban and Barrionuevo, 1996; for a recent review, see Nicoll and Schmitz, 2005). In addition, pyramidal cells in CA3 receive direct inputs from the entorhinal cortex via the perforant path synapse. This connection has been clearly shown to be modifiable by pairing-induced synaptic plasticity (McMahon and Barrionuevo, 2002). These data suggest that afferents to CA3 are indeed modified by LTP that depends on paired pre- and postsynaptic activity.

This allows for a hypothesis on the functional relevance of synchronized gamma oscillations between CA3 and upstream regions of the hippocampus that is depicted in Fig. 2 (for an overview of the relationship between hippocampal plasticity and network oscillations also, see Table 1). Before learning, there is very variable and generally rather weak synchronization of gamma frequency network oscillations between input regions of the hippocampus and hippocampal CA3 (Csicsvari et al., 2003). As discussed above, action potential discharges occur predominantly during a specific phase of these network gamma oscillations in both regions (Bragin et al., 1995; Chrobak and Buzsáki, 1998) (Fig. 2, left column, middle panel). Uncorrelated network activity therefore leads to uncorrelated action potentials in the dentate gyrus and hippocampus (Fig. 2, left column, upper panel).

Declarative memory formation occurs when gamma oscillations in rhinal cortex and hippocampus are synchronized (Fell et al., 2001) (Fig. 2, middle column, upper panel), so that the phase relationship between these oscillations is constant. As a consequence, the times when action potentials occur are also correlated between these regions (Fig. 2, middle column, medium panel). Hebbian LTP (i.e., LTP induced by pairing of pre- and postsynaptic activity) strengthens the synaptic connections between these cells (specific mossy fiber boutons and/or perforant path synapses; Fig. 2, middle column, medium and lower panel).

Table 1 – Overview of learning rules related to gamma and theta frequency oscillations

	Gamma	Theta
Synapses	Feedforward and recurrent collaterals	Feedforward
Temporal precision	High	Low
Hebbian plasticity?	Yes	No
Specificity for strong inputs?	No	Yes
Stimulus-locked?	No	Yes
Sequence encoding	Individual items	Multiple items

As a result of this first step of learning-induced plasticity, action potential discharges in the dentate gyrus lead to action potential discharges in CA3 because the reliability of synaptic transmission between these regions has increased at specific synaptic connections: enhancement of inputs by LTP should lead to subsets of CA3 pyramidal cells firing in correlation with dentate granule cells (Fig. 2, right column, upper panel). Apart from these feedforward connections towards CA3, recurrent collaterals inside CA3 might be modified by synchronized gamma activity. This would require that these recurrent connections are modified by heterosynaptic plasticity following changes in gamma synchronization between parahippocampal regions and CA3: synaptic connections inside CA3 would have to depend not only on the activity inside CA3 (as during homosynaptic plasticity), but also on the activity at synapses between a downstream region and CA3. Indeed, Kobayashi and Poo (2004) recently found that associated activation of mossy fibers and CA3 neurons in the gamma frequency range induces LTP at recurrent synapses in CA3. Interestingly, the precise relative timing of the two inputs was found to be rather unimportant in this study, in contrast to earlier results in slice cultures (Debanne et al., 1998) (cf. Fig. 2, right column, middle panel). The resulting modifications of recurrent collaterals in CA3 may be the substrate of associative memory encoding (Marr, 1971; Nakazawa et al., 2002).

Taken together, synchronized gamma network activity in the dentate gyrus and CA3 may first induce spike-timing-dependent plasticity at mossy fiber terminals and/or perforant path synapses that depends on the exact phase relationship of spikes to gamma activity. Subsequently, when dentate granule cells successfully activate these cells, recurrent collaterals between them are enhanced irrespective of their exact temporal relationship with dentate granule cells. The hypothesized rules of gamma activity-related synaptic plasticity are summarized in Table 1.

2.4. *Unresolved issues*

The data on synaptic modifications by induced gamma synchronization discussed so far cannot provide a full explanation of the mechanisms underlying declarative memory formation: gamma synchronization is not necessarily time-locked to a stimulus so that the specificity of memory encoding has to be guaranteed by an additional mechanism, in particular when multiple items are processed. In the second part of our review, we will therefore discuss data indicating that an interaction of gamma and theta oscillations can provide a mechanism to meet the required conditions.

Furthermore, the idea of gamma phase coding leads to problematic consequences: Hebbian plasticity occurs if pre- and postsynaptic action potentials are correlated. If the gamma phase of action potentials were to encode the input strength of the respective cell, two cells with equally weak input would be correlated. Thus, the synaptic connections between these cell would be strengthened by LTP (Table 1). It is well known, however, that selective attention towards a stimulus enhances neural responses and allows for more reliable memorization (Rees et al., 1999)—enhancing the

connections between cells that only respond weakly to a stimulus is of no use. As a consequence, LTP induced by synchronized gamma activity alone is not sufficient to account for realistic learning rules.

3. Theta–gamma hypothesis

According to this hypothesis, gamma activity is well suited for memory encoding because it interacts with theta oscillations during a specific state of the hippocampal network characterized by predominant theta.

3.1. *Theta-phase-dependent encoding*

Hippocampal theta oscillations have been observed both in humans and animals (Buzsáki, 2002). In rodents, hippocampal theta activity with a maximum power in the CA1 region is associated with gamma activity during exploratory behavior. In this state, recurrent excitation within area CA3 is largely blocked, whereas a specific subset of CA3 pyramidal cells remains active (Buzsáki, 1989). Various data on the exact mechanisms responsible for hippocampal theta oscillations have been discussed in an excellent review by Buzsáki (2002). One classical hypothesis is that cholinergic excitation from the septum and the diagonal band of broca activates inhibitory interneurons, which in turn induce rhythmic IPSPs on the soma of pyramidal cells (Petsche et al., 1962). More recent data indicate that theta activity can also be generated intrinsically in the CA1 region of the hippocampus (Gillies et al., 2002; Rotstein et al., 2005). Pyramidal cell dendrites in the stratum radiatum are rhythmically depolarized in phase with the somatic hyperpolarizations (Kamondi et al., 1998). Somatic hyperpolarizations correspond to theta peaks in the pyramidal cell layer and theta troughs in the stratum radiatum, where the distal dendrites of pyramidal cells are located (cf. Fig. 1, left).

Data from both rodents (O'Keefe and Dostrovsky, 1971; Muller et al., 1987) and humans (Ekstrom et al., 2003) demonstrate that hippocampal pyramidal cells increase their firing rate when a specific spatial location is approached. Furthermore, not only the firing frequency, but also the timing of action potentials relative to the ongoing field theta activity is related to the location of a rat (O'Keefe and Recce, 1993): when approaching a specific location, "place cells" specific for this location fire earlier with respect to the underlying theta oscillation. They first fire during the trough of theta activity as recorded in the pyramidal layer and later (when the rat is closer to the respective place field center) gradually earlier, so that finally firing already starts during the peak of pyramidal layer theta activity. This so-called *theta phase precession* (Skaggs et al., 1996; Mehta et al., 2002) suggests that the phase relationship of action potentials to network theta oscillations encodes spatial locations. Whereas in the case of gamma activity, the relevance (or even the existence) of phase coding is still under debate, in the case of theta activity, it has been clearly demonstrated.

In an influential series of theoretical papers starting with a 1995 *Science* article by Lisman and Idiart (1995), Jensen, Lisman and colleagues have suggested that different items are represented by cells firing at different gamma periods during one theta cycle (Lisman and Idiart, 1995; Jensen et al., 1996; Jensen and Lisman, 2005). More specifically, the frequency relationship between gamma and theta oscillations is supposed to explain the content of the working memory buffer (for instance, 7 ± 2 for digits) that is transferred into long-term memory during encoding. The relationship between working and long-term memory currently has become a strongly debated issue: theta phase coding has been shown to be not only relevant for long-term memory formation, but also for working memory (e.g., Lee et al., 2005; Siapas et al., 2005). Sustained activity of cellular assemblies during working memory (Egorov et al., 2002) may be efficient for the induction of LTP, especially if this activity is correlated in the gamma frequency band (Rizzuto et al., 2003). Further support for the role of working memory maintenance on long-term memory formation arises from recent experiments using functional magnetic resonance imaging (Schon et al., 2004; Ranganath et al., 2005; for a review, see Ranganath and Blumenfeld, 2005). On the other hand, it can be argued that the mechanisms of the two memory types are dissociable: whereas working memory maintenance relies on persistent activity of a given subset of neurons to enable immediate access and might be supported by rhinal regions (Fransen et al., 2002; Tang et al., 1997), encoding into longer-lasting traces involves the complementation of previous experience by new information, a function specifically dependent on the hippocampus proper (e.g., Lorincz and Buzsáki, 2000; Davachi and Wagner, 2002). Regardless of how this interesting issue will be resolved by further research, findings indicate that not only spatial locations, but also sequences of items of various modalities are represented by activity in mediotemporal areas.

3.2. *Theta activity and LTP*

Action potentials during different theta phases are the measurable correlate of spatial representations encoded in the synaptic weights of neural assemblies in rodents. During learning of new environments, these connections are subject to synaptic modifications. Findings from human recordings show an increased synchronization of hippocampal and parahippocampal theta activity during successful learning (Fell et al., 2003b). In contrast to the synchronization of gamma activity, which is not related to a prominent evoked (i.e., phase-locked) response, the learning-dependent synchronization of hippocampal and rhinal theta activity (Fell et al., 2003b) is associated with large event-related rhinal and hippocampal potentials with frequency contents in the theta and delta range (Fernández et al., 1999). These potentials appear to result from phase reset of theta activity occurring both in the rhinal cortex and in the hippocampus at a fixed interval after stimulus onset (Rizzuto et al., 2003; Mormann et al., 2005; Makeig et al., 2004). If these modifications in the theta range were to occur with a variable delay after the stimulus, the resulting oscillations with variable phases across trials would cancel out. Whereas the mechanism underlying the induced gamma synchronization is unknown so far, phase reset of theta activity is able to produce theta synchronization: It has been shown both in animals (Givens, 1996; McCartney et al., 2004) and in humans (Tesche and Karhu, 2000; Mormann et

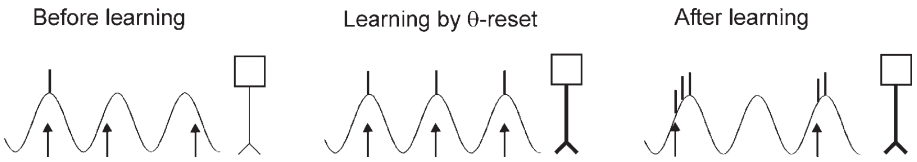

Fig. 3 – Stimulus specificity of memory encoding is enhanced by phase reset of theta activity. Left: Before learning, only stimuli occurring during the depolarized phase of the cell elicit spikes (first arrow). Middle: Learning occurs when a salient stimulus induces a theta reset so that this stimulus impinges on the cell at a defined theta phase. Right: After synaptic potentiation, even stimuli occurring during hyperpolarized membrane potentials initiate bursts of action potentials. This situation corresponds to a place cell after spatial learning.

al., 2005) that stimuli presented during learning lead to a fixed theta phase after a given delay. In rats, the same effect can be elicited by electrical stimulation of fornix and perforant path (McCartney et al., 2004; Moser et al., 2005).

Why might theta synchronization evoked by theta reset be a substrate of memory encoding? It determines the theta phase at which a given stimulus impinges on a cell (i.e., the relationship of presynaptic inputs with respect to theta). Before the synaptic inputs to a cell have undergone learning-induced strengthening, only inputs arriving during the depolarized state of the membrane potential may elicit an action potential; this situation is depicted in the left panel of Fig. 3. Thus, the cell always fires during a similar theta phase; no phase coding exists before it is acquired by experience (Mehta et al., 2002). During learning, the phase relationship of inputs with respect to theta is fixed by the theta reset, so that appropriate stimuli arrive during the peak of the theta oscillation (McCartney et al., 2004). This situation leads to LTP of the respective synapses: It has been shown that inputs arriving at this theta phase induce LTP, while inputs arriving during the trough of the theta cycle induce LTD (Huerta and Lisman, 1993; Huerta and Lisman, 1995; Holscher et al., 1997) (Fig. 3, middle panel). After learning, the same stimulus impinges on potentiated synapses so that it evokes action potential discharges even when it does not occur during the most depolarized state of the cell (during the peak of network theta activity; right panel of Fig. 3).

This learning mechanism depends solely on the timing of the presynaptic stimulus with respect to theta; it is independent on the firing of the postsynaptic cell (cf. Table 1). However, as discussed above, the theta phase at which hippocampal pyramidal cells (e.g., in CA1) discharge corresponds to the spatial location of an animal. Furthermore, the theta phase at which pyramidal cells in the hippocampus fire depends on the strength of an input, with stronger inputs leading to discharges during earlier theta phases (Kamondi et al., 1998).

Which mechanisms may appropriately modify the afferent synapses to hippocampal pyramidal cells (e.g., place cells)? When a rat enters an unfamiliar environment, new place maps have to be formed. Near the center of a place field, a theta reset may occur (maybe by a single input to CA1 via the perforant path) (Moser et al., 2005) so that some of the inputs representing the actual environmental cues arrive during the peak phase of theta activity in the stratum radiatum. The synaptic connections activated by these inputs could be strengthened by LTP so that subsequently the same afferents evoke responses of the new place cell earlier in the theta cycle. Similar inputs (close to, but not exactly at the center of a place field) would be less strengthened. After learning, the place cell would fire only weakly and only during the peak of network theta activity when the rat is at the border of a place field. When it approaches the place field center, the environmental cues match the optimal stimulus of the place cell more closely so that the place cell now gets activated via potentiated synapses. Therefore, it fires earlier during the theta cycle, and theta precession can be observed.

Let us now summarize the main differences between gamma- and theta-dependent synaptic plasticity: in contrast to gamma-dependent LTP, theta-phase-dependent synaptic plasticity is non-Hebbian as it is independent of the firing rate of the postsynaptic cell: the direction of synaptic modification depends solely on the timing of inputs with respect to network theta activity. However, theta-phase-dependent synaptic plasticity changes direction if an input arrives during the trough of the theta cycle, whereas inputs during the trough of the gamma cycle may evoke LTP if paired with postsynaptic action potentials. In other words: network gamma activity leads to LTP because it synchronizes pre- and postsynaptic activity so that the relative timing of pre- and postsynaptic action potentials is important. Network theta activity, on the other hand, leads to LTP only if a presynaptic action potential arrives at the appropriate theta phase. That is, the theta phase determines the direction of synaptic plasticity (LTP or LTD). The relationship with the postsynaptic action potential is irrelevant. Furthermore, the strength of the synaptic input is important for theta-, but not gamma-, activity-dependent LTP: if two cells receive a correlated weak input, their connections may be strengthened by spike-timing-dependent LTP; a weak input, on the other hand, does not induce a theta phase reset. Table 1 gives a systematic overview of the different rules of gamma- and theta-activity-dependent synaptic plasticity.

3.3. *Theta–gamma interaction*

So far, we have described how both gamma and theta activity could serve as timing devices for synaptic plasticity associated with memory formation. As discussed in the first part of the review, both inputs to CA3 and recurrent collaterals inside CA3 are modified by induced gamma synchronization of the hippocampus with parahippocampal regions. Theta activity occurs both in CA3 and (with an even higher power) in CA1, and stimulus presentation at an appropriate interval after theta reset leads to theta-phase-dependent plasticity. The

combination of the specific forms of synaptic plasticity associated with neural synchronization in the gamma and theta frequency range is a necessary condition for the complex learning rules during realistic declarative memory formation (see Table 1): Whereas gamma-dependent plasticity alone may not distinguish between correlated weak and strong inputs and occurs not necessarily time-locked to a given stimulus, plasticity during theta reset has these features. Theta-dependent plasticity alone, on the other hand, is too coarse to encode stimulus features with a high temporal resolution: at least Hebbian LTP requires precise spike timing. Moreover, sequence encoding (sequences of items as well as spatial paths) has been suggested to depend on action potentials during subsequent theta phases, with gamma periods binding each item (Jensen et al., 1996; Jensen and Lisman, 2005).

4. Memory consolidation by high-frequency oscillations

4.1. *Memory replay and consolidation*

During immobility and consummatory behavior as well as during slow-wave sleep, the recurrent collaterals of the CA3 region of the hippocampus are released from subcortical inhibition so that activation of a small subset of CA3 cells gives rise to synchronous population discharges (Miles and Wong, 1983) known as sharp waves. CA3 sharp waves propagate to the CA1 region where they induce similar population bursts but also activate inhibitory basket cells that discharge short trains of action potentials during the sharp wave (see Fig. 4, left column). These action potentials induce inhibitory post-synaptic currents (IPSCs) in target pyramidal cells and constrain pyramidal cells to fire during very short (2–3 ms) temporal windows. The coordinated activation of pyramidal cells and interneurons during the sharp wave is reflected by extracellular fast "ripple" oscillations (~200 Hz; Buzsáki et al., 1983). In order to allow for the highly coherent discharges during ripple oscillations, the participating cells are coupled via gap junctions (Ylinen et al., 1995; Draguhn et al., 1998). Ultra-fast ripple oscillations above the gamma frequency range have first been described in animals (O'Keefe, 1976; Buzsáki et al., 1992). Because of the peculiar architecture of the hippocampus, hippocampal EEG is not detectable with surface electrodes, so that in humans hippocampal activity is only assessable in epilepsy patients that have intracranial EEG electrodes for presurgical seizure monitoring. Even with these electrodes, it was difficult to distinguish between pathological (epilepsy-related) and physiological sharp wave–ripple activity for a long time. Recently, physiological ultra-fast oscillations in the frequency range between 100 and 200 Hz have been described (Bragin et al., 1999). Pathological ultra-fast oscillations, on the other hand, were reported to occur in even higher frequency ranges between 200 and 500 Hz (Bragin et al., 2002; Staba et al., 2004).

Sharp wave–ripples (SWR) occur during behavioral states characterized by the absence of external stimulation. How do they relate to the previously described theta–gamma oscillations? Activation (by theta–gamma related behavior) of place cells with overlapping place fields leads to an increased correlation in their discharges during the subsequent period of slow-wave sleep, known as the behavioral state with the highest abundance of SWR (Wilson and McNaughton, 1994). Even sequences of three spikes during wheelrunning are repeated in subsequent slow-wave sleep (Nádasdy et al., 1999), and information about the order in which the cells were activated is maintained (Skaggs and McNaughton, 1996). Furthermore, longer activity patterns are not only replayed during slow-wave sleep, but also during REM sleep (Louie and Wilson, 2001), a period of sleep characterized by theta and gamma activity.

4.2. *Memory consolidation via sharp wave–ripple complexes*

Taken together, there is evidence that newly acquired activity patterns are replayed during different sleep states; most research has focused on SWR activity during slow-wave sleep. What might be the functional relevance of

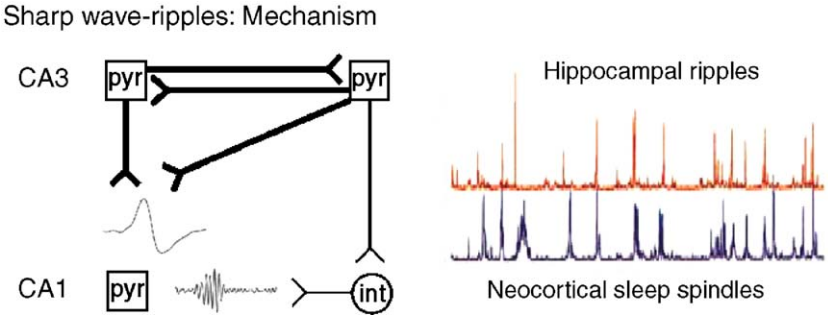

Fig. 4 – Memory consolidation by sharp waves and high frequency "ripple" oscillations. Left: Putative mechanism of sharp waves and ripples. After release from subcortical inhibition, networks of CA3 pyramidal cells (with recurrent connections strengthened by previous gamma-activity-related LTP) induce population bursts in CA1. Simultaneously, CA3 interneurons are activated and discharge with high-frequency trains of action potentials (~200 Hz), thereby controlling pyramidal cell activity on a millisecond time scale (adapted from Maier et al., 2003). Right: Hippocampal ripples are correlated with neocortical sleep spindles during slow-wave sleep that modify neocortical synapses via slow forms of LTP (adapted from Siapas and Wilson, 1998). Pyr = pyramidal cell; Int = interneuron.

these experience-dependent SWR complexes for memory formation? First, Yun and colleagues have compared the efficiency of different stimulus patterns (sharp-wave-like bursts, theta bursts and high-frequency trains) to induce LTP in different layers of the entorhinal cortex that are known to either project into the hippocampus (superficial layers) or receive input from the hippocampus (deep layers) (Yun et al., 2002). They found that deep layers are most efficiently modified by bursts reminiscent of sharp waves (rather than by theta bursts or high-frequency trains), whereas LTP in superficial layers is most susceptible to theta burst stimulation. This suggests that the activity patterns that naturally occur in the respective regions are optimal for the induction of LTP. Second, even apart from the direct role of sharp waves in LTP induction, sharp waves may act as a trigger of neocortical events: Memory consolidation, the gradual strengthening of a memory trace after its initial encoding, depends on the transfer of information from the hippocampus to the neocortex (Frankland and Bontempi, 2005). While this theory was primarily suggested on the basis of clinical observations in patients with hippocampal or neocortical lesions, it has recently been validated by physiological data. Sleep spindles, a thalamocortical rhythmic activity, are mutually connected with hippocampal ripples: longer patterns of sleep spindles appear to be driven by ripples (Siapas and Wilson, 1998) (Fig. 4, right panel), while on a millisecond level, ripples follow sleep spindles (Sirota et al., 2003).

The above data were recorded in rodents, and so far replay of hippocampal activity patterns has not been shown in humans, possibly because in vivo single cell recordings in humans have only recently become available. However, sleep spindles have been shown to be globally affected by learning: after having performed a declarative memory task, the density of sleep spindles is enhanced (Gais et al., 2002). Sleep spindles have been suggested to play a role for the induction of long-term plasticity in the neocortex by triggering Ca^{2+} entry through dendritic depolarizations (for review, see Sejnowski and Destexhe, 2000). Taken together, neuronal activity patterns learned during theta–gamma states are replayed by SWR complexes during slow-wave sleep; these SWR complexes may then either directly initiate plastic changes in structures downstream of the hippocampus or may interact with sleep spindles that modify synaptic connections in the neocortex.

5. Conclusions

Associated activity in the gamma and theta frequency range selectively modifies both feedforward connections (mossy fiber boutons and perforant path synapses) and CA3 recurrent collaterals by different mechanisms. While synchronized gamma activity can accomplish hippocampal plasticity between neurons with similar input strength, spatial locations and multiple items are more likely coded by the timing of gamma cycles and action potentials with respect to theta phase. Thus, gamma and theta oscillations may interactively represent a cellular basis for the initial steps of declarative memory formation. Subsequent memory consolidation appears to depend on irregular sharp wave–ripple complexes that may induce more durable forms of LTP in output regions of the hippocampus.

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