Published in final edited form as:
Neuron. 2013 March 20; 77(6): 1002–1016. doi:10.1016/j.neuron.2013.03.007.

The Theta-Gamma Neural Code

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Abstract

Theta and gamma frequency oscillations occur in the same brain regions and interact with each other, a process called cross-frequency coupling. Here, we review evidence for the following hypothesis: that the dual oscillations form a code for representing multiple items in an ordered way. This form of coding has been most clearly demonstrated in the hippocampus, where different spatial information is represented in different gamma subcycles of a theta cycle. Other experiments have tested the functional importance of oscillations and their coupling. These involve correlation of oscillatory properties with memory states, correlation with memory performance, and effects of disrupting oscillations on memory. Recent work suggests that this coding scheme coordinates communication between brain regions and is involved in sensory as well as memory processes.

Introduction

Multi-item messages must often be transmitted between brain regions. For instance, short-term memory may represent the last several events in the recent past; similarly, the sequence of events that constitute an episodic memory may be recalled from long-term memory. Handling such multi-item messages requires a neural code that specifies not only how items are represented, but also how different items are kept separate (e.g. the longer pauses that separate letters in the Morse code). Here, we evaluate the hypothesis that the neural code for multi-item messages is organized by brain oscillations. These oscillations can be observed in field potentials, a method of extracellular recording that provides a measure of average neural activity in a brain region (Buzsáki et al., 2012). Such recordings in rodents (Fig. 1A) have shown that gamma frequency (~40 Hz) oscillations are nested within slow theta frequency (~7 Hz) oscillations (Belluscio et al., 2012; Bragin et al., 1995; Colgin et al., 2009; Soltesz and Deschenes, 1993). A large number of experiments have investigated the role of theta/gamma oscillations, largely using physiological methods in rodents. More recently, the study of these oscillations in humans has become a focus of cognitive neuroscience (Axmacher et al., 2010; Canolty et al., 2006; Demiralp et al., 2007; Llinas and Ribary, 1993; Maris et al., 2011; Mormann et al., 2005; Sauseng et al., 2009; Voytek et al., 2010).

The specific hypothesis that we will evaluate here is shown in Fig. 1B (Lisman and Buzsaki, 2008; Lisman and Idiart, 1995). According to this coding scheme, the subset of cells that fire during a given gamma cycle (sometimes referred to as a cell assembly or an ensemble) form a spatial pattern that represents a given item. Formatting of multiple items is organized by theta/gamma oscillations as follows: largely non-overlapping assemblies are active in different gamma cycles, i.e., at different theta phases. Given that there are four to eight gamma cycles nested within a theta cycle, multiple items can be represented in a defined order. Here, we will first describe the evidence that jointly occurring theta and gamma oscillations can organize information in the way hypothesized in Fig. 1B. We will then describe experiments that address the following questions: 1) Do the oscillations and their interaction vary with cognitive demands, and do these changes predict behavioral performance? 2) Does interfering with (or enhancing) the oscillations affect function? 3) Are the oscillations used to coordinate communication between brain regions? We then turn to an analysis of the mechanistic role of gamma oscillations in the context of the theta-gamma code. In the final section, we discuss outstanding issues, notably the relationship of alpha and theta frequency oscillations in cortex and the possibility that the theta-gamma code contributes not only to memory processes, but also to sensory processes.

Theta-gamma coding in the hippocampus

The first indication that theta oscillations have a role in neural coding came from the study of rat CA1 hippocampal place cells. Such cells increase their firing rate when the rat is in a subregion of the environment called the place field; different cells have different place fields (O’Keefe and Dostrovsky, 1971). As the rat crosses the place field of a cell, there are generally five to ten theta cycles. On each successive cycle, firing tends to occur with earlier and earlier theta phase (Fig. 2A), a phenomenon termed the phase precession (O’Keefe and Recce, 1993; Skaggs et al., 1996). These and related results (Lenck-Santini et al., 2008; Pastalkova et al., 2008) suggest that the hippocampus uses a code in which theta phase carries information. Further analysis showed that CA1 place cells fire at a preferred phase of the faster gamma oscillations (Fig. 2B) (Senior et al., 2008). Thus, during a given theta cycle, firing will tend to occur at a preferred theta phase and at a preferred gamma phase.

If a place cell fires at a particular phase during a theta cycle (i.e., in a particular gamma cycle), other place cells representing different information presumably fire at other theta phases, collectively forming a multi-part message. The ability to record simultaneously from >100 cells (Wilson and McNaughton, 1993) has made it possible to directly observe such messages. As illustrated in Figure 3, during an individual theta cycle, different place cells fire in a temporal sequence. These sequences are called “sweeps” because the firing order correspond to the cells’ place field centers along the track (Gupta et al., 2012) see also (Dragoi and Buzsaki, 2006; Gupta et al., 2012; Harris et al., 2003; Skaggs et al., 1996). Such data show directly that different cells representing different information (i.e. positions) fire at different theta phases. Given that firing is also modulated by gamma (Fig. 2B), there can be little doubt that a theta-gamma code is used in the hippocampus to represent ordered multi-item messages.

An important property of sweeps is that that they are time compressed. Whereas the rat might take ~300 ms to move between positions a and b, cells representing these positions fire ~30 ms apart during a sweep (Skaggs et al., 1996). Furthermore, this time-compressed readout is often predictive (Battaglia et al., 2004), providing a way of rapidly informing downstream networks of the sequence of upcoming places (see Fig. 2 caption). The usefulness of such predictive readout is particularly evident for the sweeps that occur when a rat stops at the choice point of a familiar maze (Johnson and Redish, 2007). Under these conditions, one sweep may represent the sequence of positions down one arm of the maze (sweeps can turn corners and thus are dependent on memory rather than direct vision), and the next sweep may be down the other arm. Such rapid readout from memory presumably allows downstream brain regions to choose the arm leading to the goal.

To be useful for transmitting information, a code must be consistent over cell populations and stable over time. A procedure for examining these requirements utilizes one part of the recording period to correlate potential coding variables (such as firing rate or theta phase) to the observed position of the rat. Different codes can then be quantitatively compared by their ability to predict the rat's position from the firing patterns during the other part of the experiment (Harris et al., 2003; Jensen and Lisman, 2000). It was found that codes that take theta phase into account allowed the rat's position to be predicted with an accuracy of about 3 cm, while codes that did not use theta phase had less accuracy. Together, these and related results (Harris et al., 2003) show that the theta-phase code carries information, is stable over time, and is used consistently by cell populations.

Information is represented by an ensemble of cells rather than by single cells. Can a cell assembly that codes for a particular place be observed, and do the cells fire together in a gamma cycle, as postulated? Testing this prediction is difficult because the "true" place field (~3 cm; see Fig. 2 caption) is only a small fraction of the environment. Therefore, finding two place cells that code for the same position is difficult, but this has been achieved (Dragoi and Buzsaki, 2006). It can be seen if Figure 4 that two cells (red, green) have nearly identical place fields (Fig. 4A). The key observation is that these cells tend to fire in the same gamma cycle, as indicated by the fact that the cross-correlation of spiking in the two cells (Fig. 4B; red) has a peak that is very near 0 ms and a half-width of ±15 ms. These results and similar data in (Shapiro and Ferbinteanu, 2006; Skaggs et al., 1996) provide the few glimpses available of actual cell assemblies.

The evidence we have described makes a strong case that the theta-gamma code is used to format multi-item messages about spatial information. We now turn to the question of whether this coding scheme can be linked to cognitive processes and to actual information transfer.

Changes in theta, gamma, and their interactions during tasks

Although the existence of brain oscillations has been known for many years, the idea that these oscillations provide a mechanistic framework for memory processes is relatively recent and has been controversial. One strategy has been to ask the simple question of whether oscillations are changed during memory processes. Another, more telling approach has been to test whether the observed change predicts the accuracy of subsequent memory performance. Initial studies focused on individual types of oscillation; more recent studies have examined the role of theta-gamma coupling. Below, we briefly review these studies---first those on long-term memory and then those on working memory.

Long-term memory

Gamma—Studies of long-term memory have focused on the hippocampus. It was found that gamma power and spike-gamma coherence in the monkey hippocampus were higher during successful encoding (Jutras et al., 2009). Similar correlations have been found in humans, both in the hippocampus (Sederberg et al., 2007) and cortical regions (Osipova et al., 2006; Sederberg et al., 2007)

Theta—In rats, hippocampal theta increases during locomotion or attention (Vanderwolf, 1969) and is necessary for memory function (Winson, 1978). In humans, the theta power *preceding* the stimulus predicted subsequent memory (Fell et al., 2011; Guderian et al., 2009). Using a somewhat different strategy, Rutishauser et al. showed that successful memory formation was predicted by how well spike timing was phase coupled to theta oscillations (Rutishauser et al., 2010). Recent work suggests that, in humans, “slow theta” (3–4 Hz) is predictive of correct recall (Lega et al., 2012; Watrous et al., In Press) and corresponds functionally to the 7 Hz theta of rats.

Theta-Gamma Coupling—Several signal processing tools have been developed to quantify theta-gamma coupling (more generally termed cross-frequency coupling) (Canolty et al., 2006; Cohen, 2008; Kramer et al., 2008; Onslow et al., 2011; Penny et al., 2008; Tort et al., 2010; Young and Eggermont, 2009). These measure the relationship between the phase of the theta oscillations and the envelope of the gamma power. Thus, high values of coupling indicate that gamma amplitude is a strong function of theta phase. Theta/gamma coupling has been shown to be functionally important for long-term memory processes (Tort et al., 2009). In this study, rats learned to associate contexts with the location of subsequent food reward (Fig. 5A). As learning progressed, there was an increase in cross-frequency coupling (Fig. 5B). Moreover, the strength of coupling predicted the probability of correct choice (Fig. 5C). These and related results (Shirvalkar et al., 2010) suggest that theta-gamma coupling in the rat hippocampus enables the recall of stored information. A recent study on humans points to a similar conclusion: long-term memory encoding was associated with increased cross-frequency coupling between frontal theta and posterior gamma oscillations (Friese et al., 2012).

Working memory

In a typical working memory experiment, subjects are presented with a list of several items. This is followed by a delay period (usually <10 s) during which no information is presented. Subjects are the shown a test item and must make a response based on the properties of the information stored in their working memory.

Gamma—In humans, MEG studies and intracranial recordings have reported an increase in gamma power during the delay period of working memory tasks. Importantly, this increase varies with the number of items being held in memory (Howard et al., 2003; Roux et al., 2012). An increase in spike-field coherence during the delay period has also been observed (Pesaran et al., 2002).

Theta—Several studies in humans have reported sustained theta band cortical activity during the delay period (Gevins et al., 1997; Jensen and Tesche, 2002; Raghavachari et al., 2001; Scheeringa et al., 2009), pointing to a role for theta in working memory. One objection to this conclusion is that single-unit recording of persistent firing during a working memory task did not reveal any obvious theta rhythmicity (Funahashi et al., 1991). However, rhythmicity can be difficult to detect by analysis of spikes alone and is more easily detected by determining whether spikes are phase locked to the oscillations in the local field potential (Wang, 2010). Consistent with this, experiments in monkeys have shown that persistent firing during a working memory task is phase locked to low-frequency (theta/delta) oscillations in the local field potential, both in extrastriate cortex (Lee et al., 2005; Liebe et al., 2012) and in prefrontal cortex (Siegel et al., 2009).

Theta-gamma coupling—Theta-gamma coupling during working memory has been demonstrated in humans both in cortex (Canolty et al., 2006; Lee et al., 2005) and in the hippocampus (van Vugt et al., 2010). Gamma power in the hippocampus is modulated by the phase of theta oscillations during working memory retention, and the strength of this cross-frequency coupling predicts individual working memory performance (Axmacher et al., 2010). Importantly, the particular cortical regions demonstrating cross-frequency coupling depend on the nature of the information being held in working memory. The spatial distribution of gamma band power in cortex can be used to predict whether working memory is maintaining an indoor or outdoor scene (Fuentemilla et al., 2010), and the gamma activity with this predictive capability is phase locked to the theta activity. In another study, gamma power at certain sites (primarily in occipital cortex) was shown to depend on the particular letter being viewed, and gamma was found to be phase locked to theta (Jacobs and Kahana, 2009).

The concept of the theta-gamma code (Lisman and Idiart, 1995) was originally proposed as a way of keeping multiple items active in working memory and there have been several related implementations of this idea (Jensen and Lisman, 1998; Koene and Hasselmo, 2007; Lisman and Idiart, 1995). Support for this class of models has come from the analysis of grid cells in the entorhinal cortex (de Almeida et al., 2012), a region that provides input to the hippocampus and has been previously implicated in working memory (Gaffan and Murray, 1992; Ranganath and D’Esposito, 2001; Stern et al., 2001; Suzuki et al., 1997; Young et al., 1997). It was found that the entorhinal cortex has a working memory mode in which grid cells represent the recent past (i.e., positions behind the animal). Consistent with the model of Fig. 1B, cells representing different positions fired in different gamma subcycles of the theta cycle.

Another way of asking whether the theta-gamma code underlies working memory is to relate the oscillations to the psychophysically measured properties of working memory. A classic result (Miller, 1956) is that working memory has a capacity limit (span) of 7±2 (see (Cowan, 2001) for a slightly lower value). The number of gamma cycles within a theta cycle may be what sets the capacity limitation for working memory (Lisman and Idiart, 1995). Initial efforts to test this concept sought to use the theta-gamma framework to quantitatively account for response time properties of the Sternberg task (i.e., time to respond to whether a given test item was on a short list presented several seconds before). The linear dependence of response time suggested that the list held in working memory was serially and exhaustively scanned at a rate of 20–30 ms per memory item (Sternberg, 1966), a time that approximately equals the duration of a gamma cycle. These and other quantitative results of the Sternberg task can be accounted for by models based on the theta-gamma code assuming either that theta phase is reset by stimuli or that theta frequency decreases with memory load (Jensen and Lisman, 1998). Experiments provide evidence for both effects (Axmacher et al., 2010; Moran et al., 2010; Mormann et al., 2005; Rizzuto et al., 2006). Recent work sought to determine whether properties of theta and gamma oscillations in individuals could explain their memory span. The ratio of theta to gamma (i.e., the maximum number of gamma cycles within a theta cycle) was found to correlate with span (Kaminski et al., 2011). However, the determinations of oscillation frequencies were very noise sensitive, raising doubts about the conclusion. Rigorous testing of this relationship will require resolution of the controversy about which brain regions are responsible for short-term memory maintenance and better methods for noninvasive measurement of the oscillatory frequencies at those locations.

Interfering with oscillations

The experiments described in the previous section make the strong case that theta and gamma oscillations are modified during memory tasks and that these modifications are predictive of performance. However, such experiments are only correlational; a stronger confirmation would require showing that disruption of the oscillations interferes with memory. Experiments of this kind are beginning to be possible because of increased understanding of the mechanisms that underlie oscillations and new optogenetic methods for perturbing the oscillations.

Gamma oscillations are generated by a feedback loop in which firing of pyramidal cells excites fast-spiking interneurons, which then rapidly inhibit the entire population of pyramidal cells (reviewed in (Buzsáki and Wang, 2012). Pyramidal cell firing is reinitiated after the GABAergic inhibition decays, thereby generating the next gamma cycle. Genetic methods have been used to block the excitation of fast-spiking interneurons by reducing their AMPAR-mediated input or by preventing firing using halorhodopsin. Both methods produce a decrease in gamma amplitude and result in memory deficits (Fuchs et al., 2007; Sohal et al., 2009).

There is substantial information about the processes that generate theta oscillations in the hippocampus. One important influence is the external input from the medial septal nucleus, a structure that shows theta rhythmicity (King et al., 1998; Zhang et al., 2011). This nucleus contains cholinergic and GABAergic neurons that impose a rhythmic drive onto the hippocampus. However, theta oscillations can also be generated by intrinsic mechanisms, as demonstrated by experiments on the isolated rat hippocampus (Goutagny et al., 2009) and on hippocampal slices (Fellous and Sejnowski, 2000; Fischer et al., 2002; Gloveli et al., 2005). The result of extrinsic and intrinsic influences is a theta frequency inhibition of pyramidal cells, which at its maximum strongly inhibits pyramidal cell firing and reduces the amplitude of gamma oscillations.

Shirvalkar et al. have shown that theta-gamma coupling increases during memory recall (Shirvalkar et al., 2010). They also found that inhibiting the medial septum with muscimol reduced theta-gamma coupling and interfered with recall. Remarkably stimulating the medial septum at theta frequency partially restored recall. Further evidence for the importance of theta-phase coding has come from experiments examining the effects of the cannabinoid receptor agonist CP5590 (Robbe et al., 2006). This agent strongly disrupted rats' performance on a hippocampal-dependent delayed spatial alternation task. Recordings showed that hippocampal place fields were normal. However, the theta-phase precession normally seen in these cells was completely absent, suggesting that phase-coded information is necessary for this task.

Role of theta and gamma oscillations in communication between regions

A strong possibility is that the communication between regions is affected by the coherence of the oscillations in the sender and receiver networks (Buzsáki, 2010). Coherence occurs when the phase difference in a given frequency band is consistent over time. Coherence varies between 0 and 1, and high values are realistic. For instance, theta coherence can be 0.95 between different parts of the hippocampus (Penley et al., 2011), while theta coherence is in the range of 0.5 between hippocampus and interaction regions in the PFC, amygdala and striatum (Seidenbecher et al., 2003; Sirota et al., 2008; van der Meer and Redish, 2011). The theta coherence between two structures can be elevated in specific phases of a task (Benchenane et al., 2010; Kim et al., 2011; Young and Shapiro, 2011). Importantly, it has been found that during periods of decision, theta coherence between the hippocampus and striatum could be >0.8 and that the magnitude of coherence was predictive of learning (DeCoteau et al., 2007).

As we have argued, the importance of the theta rhythm is to provide a way of ordering multi-part messages, an ordering that is exemplified by the phase precession. Phase precession is found both in the structures that provide input to the hippocampus (e.g., the entorhinal cortex and subiculum) (Hafting et al., 2008; Kim et al., 2012; Mizuseki et al., 2009) and in structures to which to which the hippocampus projects (e.g., the PFC and striatum). Notably, firing in the rat mPFC shows phase precession coupled to that seen in the hippocampus (Jones and Wilson, 2005). Similarly, theta-phase precession can be seen in the striatum (Fig. 6; (Jones and Wilson, 2005; van der Meer and Redish, 2011). The strong coherence between the hippocampus and its targets and the existence of phase coding in target structures strongly suggest that theta oscillations organize communication between the hippocampus and distant brain regions.

Theta-phase coding is also implicated in communication that does not involve the hippocampus. Theta-phase synchronization occurs between V4 and PFC and is predictive of task performance (Liebe et al., 2012). Although volume conduction confounds are often difficult to assess in human EEG and MEG studies, there are several encouraging findings indicating theta synchronization between frontal and posterior regions in working memory and error-monitoring tasks (Brzezicka et al., 2011; Cavanagh et al., 2009; Cohen and Cavanagh, 2011; Palva et al., 2010; Sarnthein et al., 1998; Sauseng et al., 2005; Schack et al., 2005).

The findings summarized above make the strong case that theta oscillations are important for long-range communication and that a signature of such communication is a high level of coherence, as originally proposed by (von Stein and Sarnthein, 2000). How this high level of coherence is achieved remains unclear. Within the hippocampus, high theta coherence occurs because the entire structure is driven by a theta generator in the medial septal nucleus of the basal forebrain. A nearby structure, the nucleus basalis, innervates cortex and is a good candidate mechanism for synchronizing cortical theta (Alonso et al., 1996; Lee et al., 2005). However, bidirectional interactions between cortex and thalamus (da Silva et al., 1973; Hughes and Crunelli, 2005; Lopes da Silva et al., 1980; Lorincz et al., 2009; Poulet et al., 2012; Saalmann and Kastner, 2011) and intrinsic mechanisms may also be involved (Alonso et al., 1996; Blatow et al., 2003; Flint and Connors, 1996; Jones, 2004; Raghavachari et al., 2006).

There is now substantial evidence suggesting that gamma synchronization between regions can also change during a task. Gamma coherence between monkey parietal and prefrontal areas has been shown to increase from 0.1 to 0.18 during an attention task (Gregoriou et al., 2009). Colgin et al. found alternating modes in which CA1 became coherent either with entorhinal cortex (through the fast gamma characteristic of the entorhinal region) or with CA3 (through the slower gamma characteristic of CA3) (Colgin et al., 2009). A recent study by Bosman and colleagues provides compelling evidence that gamma coherence reflects the selectivity of attention-mediated communication (Bosman et al., 2012). Two regions in V1 were studied that converged onto V4. When attention was turned to one V1 region, the coherence of this region with V4 was increased from 0.02 to 0.12 (the other V1 region was not affected). Granger analysis indicated that this change was due to the influence of V1 on V4. Changes in coherence have been correlated with memory performance. A study analyzing data from depth electrodes in epileptic patients showed that gamma synchronization between rhinal cortex and hippocampus predicted memory formation (Fell et al., 2001). In a rat study, gamma band synchronization between CA3 and CA1 reflected performance in a spatial memory task of the behaving rat (Montgomery and Buzsaki, 2007).

An interesting possibility is that changes in gamma coherence may actually control the routing of information (Bressler, 1995; Fries, 2005; Siegel et al., 2012; Varela et al., 2001). This mechanism has been termed the communication through coherence (CTC) hypothesis (Fries, 2005). The general idea is that there are cycles of excitability in oscillatory networks; inputs will be most effective if they arrive at peaks of excitability. Thus, a mechanism that made gamma oscillations in two regions synchronous might selectively route information from one region to the other. However, several difficulties with this hypothesis must be noted, particularly. First, the measured levels of long-range gamma coherence are generally very low (0.1–0.2), so any matching of input with the local phase of gamma will be weak (it remains possible that coherence is high but is made low by signal-to-noise problems). Computational studies suggest that strong coherence is required for selective routing (Akam and Kullmann, 2012). Second, there is no indication of an external driver that can impose coherent gamma oscillations in two communicating regions; it is thus thought that coherence develops because of entrainment or resonance mechanisms, processes that develop over many gamma cycles. This process is thus too slow to explain the routing changes that occur during changes in covert attention, which occur in a time period of about a single gamma cycle (Buschman and Miller, 2009; Treisman and Gelade, 1980). These difficulties pose a challenge to the CTC hypothesis; perhaps, to the contrary, increases in gamma coherence are not the cause of selective routing but rather the consequence of some other routing mechanism (see also (Rolls et al., 2012). It is unclear what the alternative mechanism might be. One possibility is suggested by recent work showing that the thalamus (pulvinar) can coordinate coherent activity in the alpha bands between parts of visual cortex and produce the routing changes that are required for selective attention (Saalmann et al., 2012).

In summary, the presence of information coded by theta phase in the striatum and PFC, together with the strong coherence of theta between the hippocampus and these regions, point to the importance of theta phase coding in long-range communication between brain regions. The role of gamma coherence in long range communication is less clear. In the next section we discuss various postulated roles of gamma. This is followed by a summary section in which we attempt to bring the available information together.

What does gamma contribute to the theta-phase code?

Clocking

Gamma is sometimes referred to as the brain’s clock. According to this view, a given gamma cycle would occur at a predictable time that was a multiple of the gamma period. This view now seems unlikely. Gamma frequency in visual cortex changes with the contrast of visual stimuli (Ray and Maunsell, 2010). Moreover, the gamma period even varies from cycle to cycle (Burns et al., 2011; Henrie and Shapley, 2005; Ray and Maunsell, 2010). This variation occurs in a predictable way: the amplitude of gamma during one cycle (presumably reflecting the number of active cells) determines the duration of the next gamma cycle (Atallah and Scanziani, 2009). The variation of gamma frequency with intensity implies that two parts of the same object having different intensity cannot be synchronized in the same gamma cycles (Ray and Maunsell, 2010), as required if gamma has a binding role in perception (Engel and Singer, 2001). In the model of Fig. 1B, there is also a concept of binding (cells that represent the same item fire in the same gamma cycle), but it is not assumed that different cells represent different components of the item.

Synchronization and inter-item separation

Firing occurs during only part of the gamma cycle, a synchronization that allows downstream networks to use coincidence mechanisms to detect ensembles (Konig et al., 1996). Less recognized is the importance of the pauses that separate the firing that occurs in sequential gamma cycles. As noted earlier, information formatting is a critical aspect of coding that allows downstream “receiver” networks to interpret the coded message (Buzsáki, 2010). In Figure 7, we compare two schemes for organizing the multi-item message in the “sender” network. In one scheme, the sender rapidly switches from a state representing one item to a state representing the next item, i.e., there is no inter-item separation. In the other scheme, the sender clusters spikes so that they fire in about one-third of a gamma cycle, thereby creating inter-item separation. Now consider the fact that, for a cell to process input, there must be a window over which it integrates input. Experimentally, this window is shorter than a gamma cycle (Losonczy and Magee, 2006; Pouille and

Scanziani, 2001). Without inter-item separation, receiver cells will integrate inputs that are part of different items. These cells may therefore detect conjunctions that do not correspond to those in either of the items present. Such false positives are avoided if the pauses generated by gamma frequency inhibition are present.

Selecting which cells fire

A second critical role for gamma is in the *selection* of which cells fire, thereby forming the representation that is active during a gamma cycle. According to one major theory (van Vreeswijk and Sompolinsky, 1996), cells receive large excitation that is balanced by a comparable inhibition; what determines whether a cell fires is stochastic deviations from this balance. However, this theory is not applicable to networks with oscillating inhibition, as discussed by (Isaacson and Scanziani, 2011). An alternative theory (“E%-max”) posits that, in networks with dynamic inhibition, a network process rather than a single-cell process determines which cells fire (de Almeida et al., 2009). According to this theory, the critical step is a “search” for the most excitable cells in the network that occurs as inhibition decays during a gamma cycle. The most excited cells in the network will reach threshold first and trigger global feedback inhibition of less-excited cells (Fig. 8). However, this inhibition occurs with a delay of a few milliseconds, allowing somewhat less-excited cells to fire before feedback inhibition arrives. Thus, gamma allows the firing of not only the most excited cell, but also somewhat less-excited cells. As a result of this process, the most excited cell (i.e., best tuned to the stimulus) will fire first in a gamma cycle followed by cells that are slightly less well-tuned. This prediction has been recently confirmed: it was found that orientation tuning in V1 is highest early in a gamma cycle but becomes slightly lower later in the cycle (Womelsdorf et al., 2012).

Summary

There is now little doubt that multi-item information is formatted by a theta-gamma code in the hippocampus: different spatial locations are represented at different theta phases, and firing is clustered into discrete periods by the gamma rhythm. These oscillations and their interactions are altered during both long-term and working memory processes, as would be expected if different neural operations make different use of these oscillations. That said, we lack a clear understanding of why different tasks (or no task) result in the observed quantitative changes. A critical test of whether the theta-gamma code has an important role in memory is to determine whether inhibiting the oscillations interferes with memory. The available results suggest that this is the case, but more precise experiments are needed. Recently, optogenetic methods have been used to show that odor recognition can be disrupted by selectively interfering with information processes at particular phases of the sniff cycle (Smear et al., 2011). If the hypothesis we are proposing is correct, disrupting information at a particular theta phase should affect information represented at that phase, but not information represented at other phases.

Theta is critical for the transmission of multi-item messages because it provides a phase reference that signifies the onset of the message. This phase reference must be shared by sender and receiver; the high observed theta coherence between communicating regions appears to satisfy this requirement. The role of gamma is to define an item in a multi-item message. Gamma contributes to this in three ways: 1) it helps to form the message by allowing only the most excited cells to fire, 2) it synchronizes spikes (clustered spiking can be effectively detected in downstream regions), and 3) it creates pauses between items that prevent errors in decoding the message. The communication of the multi-part messages to downstream networks may be aided by coherence in the gamma band, but this is probably not required. We suspect that the small increases in gamma coherence that occur during communication are probably a *result* of effective communication rather than the cause.

Because gamma cycles are not of the same duration, detection methods based on exact clocking are not plausible. Thus, although phase-dependent detectors (Jensen, 2001) can be used to detect early versus late items, detection of the information in a specific gamma subcycle does not appear possible. However, many useful functions do not require exact clocking. For instance, according to one model (Fukai, 1999), the sequence of actions to be executed is sent from the hippocampus to the striatum by a theta-gamma code; the striatum stores this sequence and then executes the actions in order, using other information to orchestrate the exact timing of each action. Another useful operation would be the recall of a sequence that contained a salient element such as reward. The detection of this element could be important to downstream networks even if the exact position of that element in the recalled sequence was uncertain. Finally, the entire recalled sequence may be processed (chunked) to represent a higher-level item. Network models that perform such chunking depend on the ordering of items rather than on exact timing (Sanders et al., 2012).

Outstanding Questions

How is the coherence of hippocampus, cortex, and basal ganglia produced?

As described above, when the hippocampus communicates with target regions, the theta in the two regions becomes high. Virtually nothing is known about how this coherence is produced. It seems likely that the basal forebrain and/or the thalamus may be involved, but this remains to be investigated.

What mechanism underlies changes in cross-frequency coupling?

The method for studying cross-frequency coupling are strictly operational and thus do not give insight into the underlying mechanism. For instance, a change in cross-frequency coupling could be explained either by a change in the number of gamma cycles per theta cycle (the duty cycle) or by a change in gamma amplitude with a constant number of gamma cycles per theta cycle. New analytical methods may be helpful in providing a clearer view of what is happening during the observed changes in theta-gamma coupling.

Is there also a super-fast gamma-phase code?

According to our hypothesis, a representation is formed by all of the cells that fire in a gamma cycle, regardless of their gamma phase. Thus, differences in gamma phase (amounting to only milliseconds) are thought to be unimportant and would be averaged over by the time window of integration in receiver networks. Consistent with the unimportance of gamma phase, position reconstruction methods did not show any advantage to using small theta phase differences that correspond to fractions of a gamma cycle (Harris et al., 2003; Jensen and Lisman, 2000). As noted above, V1 cells with millisecond differences in gamma phase have slightly different orientation tuning. We suspect that such millisecond differences are not important because they are integrated by downstream regions. In memory circuits, an important computation, pattern completion, can be performed during a gamma cycle (de Almeida et al., 2007); dealing with multiple input items within a gamma cycle would be disruptive of this processing. Still, the possibility that the brain uses a superfast code based on millisecond differences in gamma phase must be considered (Fries et al., 2007; Nikolic et al., 2013). Indeed, millisecond differences are important in specialized auditory circuits (Wagner et al., 2005; Yang et al., 2008). Furthermore, possible support for a gamma-phase code comes from single-unit recordings during multi-item working memory in monkeys (Siegel et al., 2009). It was found that neurons representing different memories fired maximally at a different gamma phases, consistent with a superfast gamma-phase code. However, given the analysis method used, it cannot be excluded that cells firing with a different gamma phase were actually firing in different gamma cycles (i.e., with a different low-frequency phase). Indeed, this would be consistent with results showing that hippocampal neurons that fire with different theta phase also fire with different gamma phase (Senior et al., 2008). Further work will thus be needed to clarify this important issue.

What is the signature of engaged neocortex (role of alpha and theta)?

The properties of theta in the neocortex are much less understood than those in the hippocampus. In the hippocampus, increases in theta power are associated with engagement, but whether this is also true in neocortex is unclear. As shown in Figure 9, there are some sites where theta increases and others where it decreases during a working memory task. Which one is the engaged region? A further critical question is whether oscillations in the theta frequency range should be considered fundamentally different from those in the alpha range? In the hippocampus, these frequencies are lumped together as “theta” but is this also appropriate for cortex? In the following paragraphs, we discuss these questions.

A classic observation is that alpha power in occipital cortex is high when the visual system is not engaged (Adrian and Matthews, 1934). A cue indicating that attention must be turned to one hemifield leads to a sharp drop in alpha power in the engaged (contralateral) cortex (Worden et al., 2000). In contrast, alpha power in ipsilateral visual cortex may actually increase. This increase is associated with suppression of information that is irrelevant to the task (Thut et al., 2006) and with improved performance (Handel et al., 2011). Further evidence that high alpha power is associated with inhibition is that firing rates, phosphene detection, and the BOLD signal are all reduced (Haegens et al., 2011; Ritter et al., 2009; Romei et al., 2008). One characteristic of alpha is that neural activity is limited to only about half of the cycle (Bollimunta et al., 2008; Bollimunta et al., 2011; Lakatos et al., 2005). This low-duty cycle (for comparison, see high-duty cycle of firing in Fig. 2) probably accounts for why perception is dependent on alpha phase (Busch et al., 2009; Dugue et al., 2011; Mathewson et al., 2009). The suppression of alpha power has also been observed in other sensory and motor regions when they become engaged (Fontanini and Katz, 2005; Hari and Salmelin, 1997; Pfurtscheller et al., 1997). Importantly, the suppression is even specific to the particular motor subregion that is engaged (Pfurtscheller et al., 1997) (see also (Miller et al., 2009)). Thus, in cortex, high alpha power is an inhibited state, and low alpha power appears to be an indicator of engagement.

Do these “alpha rules” also apply to the only slightly slower cortical oscillations in the theta range? It is important to recall that the frequency bands corresponding to alpha and theta were assigned arbitrarily without consideration of function. Consider Figure 9. If we use hippocampal theta as a model, the elevated theta state would be the engaged state. But based on the “alpha rules”, the lowered theta state would be the engaged state. In favor of the latter, work combining EEG and fMRI has demonstrated that the BOLD signal is high when theta power is low (Michels et al., 2010; Scheeringa et al., 2009). Another perspective on this issue comes from consideration of gamma activity. Gamma is present during the high alpha power state and is phase locked to alpha. As alpha power is decreased, gamma power is increased (Spaak et al., 2012). Importantly, when alpha power falls during task engagement, gamma and its modulation by low-frequency oscillations remain (Sauseng et al., 2009). Indeed, the importance of this cross-frequency coupling was demonstrated by the fact that the coupling varied with memory load up to saturation and that this saturating load correlated with memory span.

Putting these experimental observations together, we suggest that a signature of engaged cortex is a reduction in the power of alpha/theta (perhaps with a lowering of frequency), modulation of gamma amplitude by the remaining alpha/theta oscillations, and an increase of the gamma duty cycle, as in Figure 9. Thus, the engaged sites in Figure 9 may be the ones at which alpha/theta decreases, but cross-frequency coupling is nevertheless important. Consistent with this view, cross-frequency coupling between gamma and alpha/theta correlates with the BOLD signal better than other available EEG variables (Wang et al., 2012).

Are there single theta cycle messages?

There are several reports showing brief periods of gamma activity (gamma bursts) in cortex and striatum (Berke, 2009; Edwards et al., 2005; Freeman, 2003; Howe et al., 2011; Jacobs and Kahana, 2009; Sirota et al., 2008; Yang et al., 2012). The duration of these "gamma bursts" is 100–200 ms. Gamma bursts of similar duration underlie sharp waves in the hippocampal CA3 region (Carr et al., 2012). It is curious that this duration is similar to that of a theta cycle. One could thus argue that, even though continuous theta oscillations are not present in these states, a single theta cycle (and associated gamma) is what is occurring. Indeed, during fast behavioral reactions, there may be time for only a single theta cycle. It will thus be of interest to determine whether perturbations that affect the frequency of continuous theta also affect the duration of gamma bursts.

Is there a role of theta-gamma in sensory processing?

Early work in the olfactory cortex provided evidence that theta-gamma interactions are involved in cortical sensory processing (Woolley and Timiras, 1965), and there has recently been renewed interest in this possibility. Recordings from awake, behaving rodents have been made from mitral cells, the output neurons of the olfactory bulb. It was found that a given odor produced brief bursts at a particular phase in the sniff (theta) cycle; different cells had different preferred phases (Shusterman et al., 2011). Firing in the bulb is also phase locked to gamma phase (Sanders et al., 2012). These results and related work in insects (Laurent et al., 2001) suggest that the signature of an odor is a discrete sequence of ensembles organized by theta-gamma oscillations.

In the auditory system, a model has been proposed in which ongoing syllables and words are segmented by an oscillatory cortical decoder based on nested theta and gamma oscillations (Ghitza, 2011; Giraud and Poeppel, 2012; Peelle and Davis, 2012). This process may involve yet slower oscillations tied to larger lexical units, a hypothesis that relates to an important study (Lakatos et al., 2005) showing that theta oscillations can be nested within slower delta frequency oscillations. This and other recent findings (Fujisawa and Buzsaki, 2011) raise the possibility that a hierarchy of oscillations that include gamma, theta, and delta oscillations organizes sensory and memory functions.

Interest in oscillations in the visual system has been stimulated by the finding that the phase of a stimulus with respect to ongoing cortical alpha/theta oscillations is predictive of the perception threshold, at least for attended stimuli (Busch et al., 2009; Mathewson et al., 2009). This finding was corroborated by a TMS/EEG study in which the perception of phosphenes was modulated by the phase of both frontal and posterior rhythms in the theta and alpha band (Dugue et al., 2011). Furthermore, the phase of oscillations in the theta-alpha band has been implicated in saccade onset (Drewes and VanRullen, 2011; Hamm et al., 2012). Given that covert attention can move very rapidly (Buschman and Miller, 2009), one possibility is that a theta cycle may be subdivided by faster oscillations, with each of these subcycles representing a different component of the visual scene (Miconi and Vanrullen, 2010).

Conclusion

Neurophysiological studies have provided evidence that a theta-gamma code is used to organize information in the hippocampus and to transmit it to targets in the PFC and striatum. Cognitive studies have shown a strong linkage between theta-gamma oscillations and successfully recalled memories. This body of work lays a foundation for understanding the general problem of how multi-item messages are sent between brain regions, including sensory and possibly motor areas. There is now little doubt that brain oscillations will have an important role in these processes, but important questions remain. The ongoing integration of neurophysiological and cognitive approaches is likely to provide new insights into how the theta-gamma code contributes to brain function.

Acknowledgments

The authors gratefully acknowledge The Netherlands Organization for Scientific Research (NWO) VICI grant number: 453-09-002, NIH grants awarded to JL - 5R01MH086518 from the National Institute Of Mental Health and 1R01DA027807 from the National Institute On Drug Abuse. The authors thank Michael Kahana, John Maunsell, Don Katz, Nikolai Axmacher, Dan Pollen, and Honi Sanders for comments on the manuscript.

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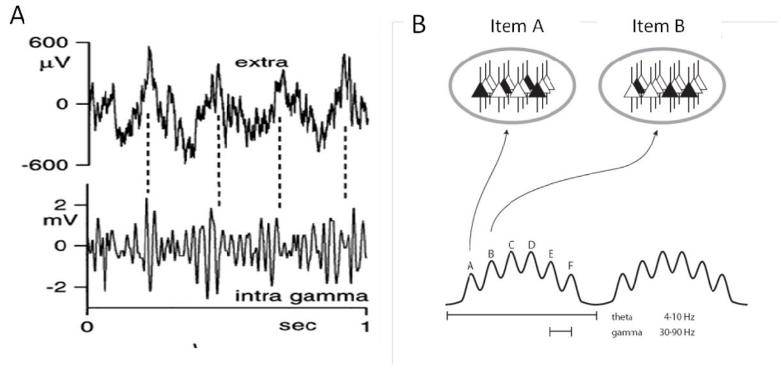

Fig. 1.

Neural code organized by theta and gamma oscillations. (A) Simultaneous extracellular (top) and intracellular (bottom) recordings from the hippocampus. Intracellular gamma is due to IPSPs, the amplitude of which is modulated by the phase of theta. From Fig. 4C of (Penttonen et al., 1998). (B) Schematic of the theta-gamma code. The ovals at top represent states of the same network during two gamma cycles (active cells are black and constitute the ensemble that codes for a particular item). Different ensembles are active in different gamma cycles.

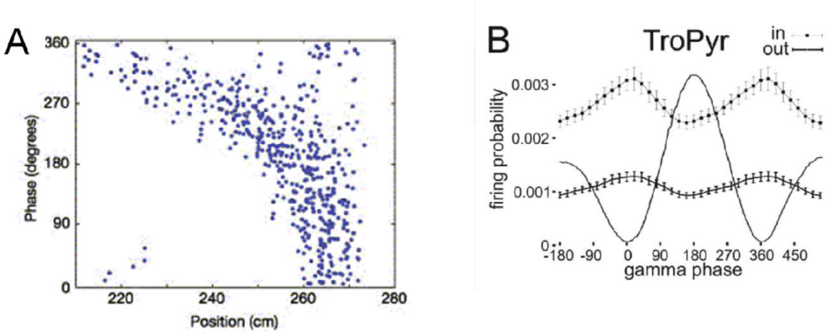

Fig. 2.

Spiking in the rat CA1 region depends on the phase of both theta and gamma oscillations. (A) Phase precession: as the rat runs through a place field, a process that takes several seconds, theta phase becomes progressively earlier (closer to zero phase) on successive theta cycles. From Fig. 1A of (Mehta et al., 2002). The phase precession can be understood as cued, time-compressed readout of the sequences of places ahead of the animal. Such “sweeps” provide information to other brain regions of what is to come. Consider that the place field (210 cm to 270 cm) can be divided into seven subregions, **a, b, c, d, e, f,** and **g**. The rat enters the field from the left at position **a**, which cues the ordered prediction of upcoming positions (Battaglia et al., 2004), thereby producing a “sweep.” The “true” place field of this cell is the position **g**; the firing of this cell at position **a** represents a prediction that **g** is ahead of the animal. By the time of the second theta cycle, the rat has moved to **b**, so **b** is the cue and produces the sweep **b, c, d, e, f, g, h** in the second theta cycle. One can see from this example why the **g** cell fires with earlier theta phase on each successive theta cycle. According to one hypothesis, the successive activation of cells during a sweep results from simple chaining of excitation between the ensembles (Burgess and O’Keefe, 2011; Jensen and Lisman, 1996; Tsodyks et al., 1996). The results shown are combined data from many passages through the place field; the linkage of phase to position is even more exact when individual passages are analyzed (Schmidt et al., 2009), perhaps because theta can occur during different modes (see below) having different phase-position relationships. (B) Many CA1 place cells fire at a preferred phase of gamma cycles (‘in’ and ‘out’ refer to the firing probability as a function of gamma phase when the rat is respectively inside or outside of the place field; the line with no error bars is the LFP filtered in the gamma band). From Fig. 6B of (Senior et al., 2008). Because the analysis averages over different functional modes (Colgin et al., 2009; de Almeida et al., 2012; Gupta et al., 2012; Senior et al., 2008) and gamma generators (Belluscio et al., 2012), the actual modulation by gamma phase may be stronger than shown.)

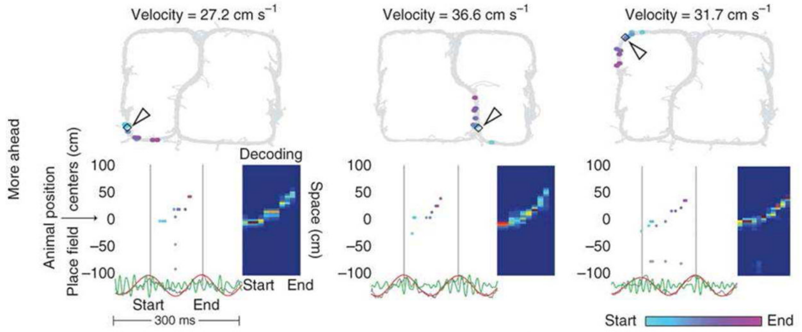

Fig. 3.

Cells that fire in sequence during a theta cycle form a sweep. Three examples are shown. (Top) Top panels show track. Current position of rat is marked by arrowhead, and it is at this position that the sweep shown below occurs. Different cells active during the sweep have place field centers marked by the colored dots. (Bottom) The spikes of different cells during a theta cycle (start to end). Cells are positioned on the y axis according to the position of their place field centers. In these examples, activity sweeps represent positions along the path ahead of the animal. From Fig. 3 of (Gupta et al., 2012).

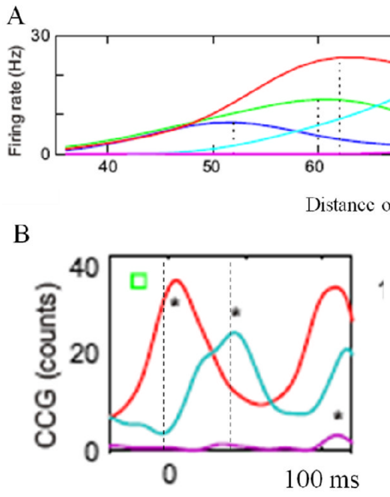

Fig. 4.

Cells that code for the same position (part of a cell assembly) and then fire in synchrony (within a gamma cycle). (A) Firing rate as a function of distance on a linear track for five place cells in CA1 (different colors). Green and red cells have peak firing rates at nearly the same position. (B) The cross-correlation between green and red cells (in A) has a peak very near 0 ms (red line), indicating that the cells tend to fire in the same gamma cycle. This is true even though the particular gamma subcycle changes during the theta-phase precession. Green and blue cells (in A) have different place field centers and tend to fire with a temporal offset that peaks at 40 ms (cyan line) (i.e., in different gamma cycles). From Fig. 1 of (Dragoi and Buzsaki, 2006).

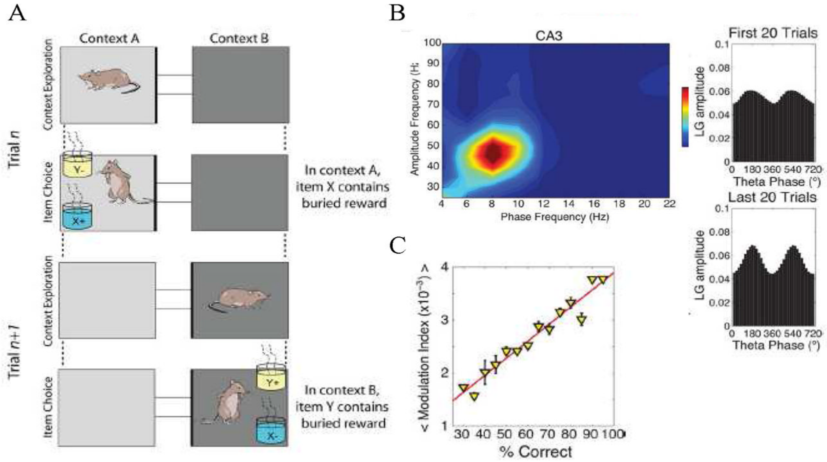

Fig. 5.

Theta-gamma cross-frequency coupling in CA3 predicts behavior. (A) Exposure to empty context A or B (light gray/dark gray) cues the rat about which cup (blue/yellow) when subsequently presented will contain reward. (B) While exploring context, cross-frequency coupling occurs (left) and can vary in the degree to which theta phase modulates gamma power (right). (C) Theta-gamma modulation occurs during recall of the association between the context and the type of rewarded cup; this modulation is predictive of whether the rat correctly goes to the rewarded cup. From Fig. 1 and 2 of (Tort et al., 2009).

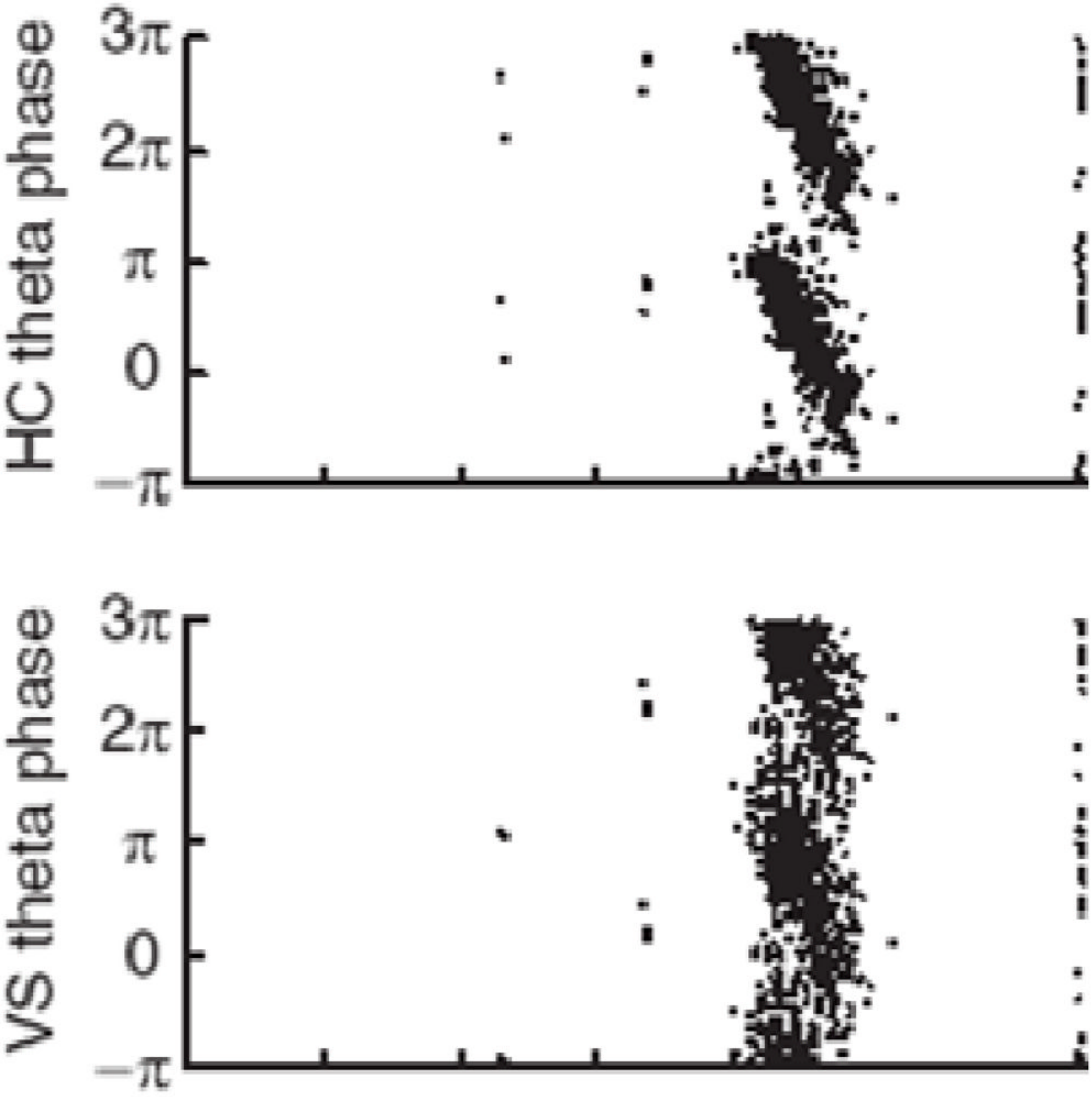

Fig. 6.

Phase precession, an indicator of theta-gamma coupling, is evident in the hippocampus (HC) (top) but is also evident in a hippocampal target area, the ventral striatum (bottom). The data are taken as the rat begins its approach to the reward site. Taken from Fig. 3B (van der Meer and Redish, 2011).

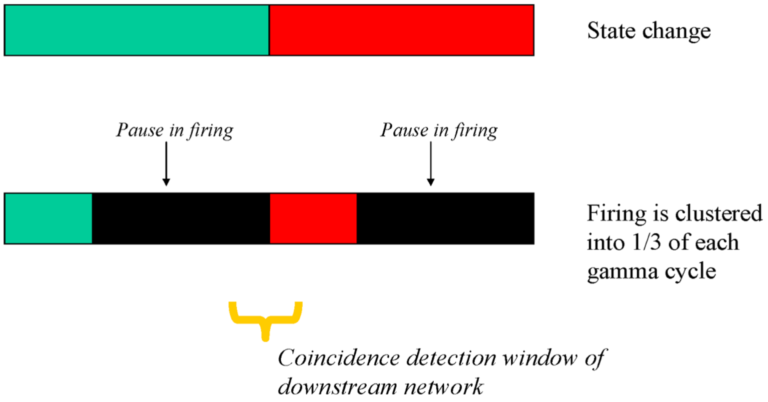

Fig. 7.

Role of the firing pause between items. Firing as a function of time for two sequential items in schemes with or without a firing pause between items. (Top) An ensemble representing one item (green) followed by rapid state change to an ensemble representing another item (red). (Bottom) Firing for the first item is clustered in one-third of a gamma cycle followed by a pause. Firing for the second item then occurs in the first part of the second gamma cycle, followed by another pause. Downstream networks detect patterns by integrating inputs that arrive within the coincidence detection window (yellow bar). If green is represented by cells 1,2,3, red by cells 4,5,6, and blue by 1,2,6, then the message detected in the state-change case is green, blue, red. In contrast, when firing is clustered, the message is correctly read as green, red.

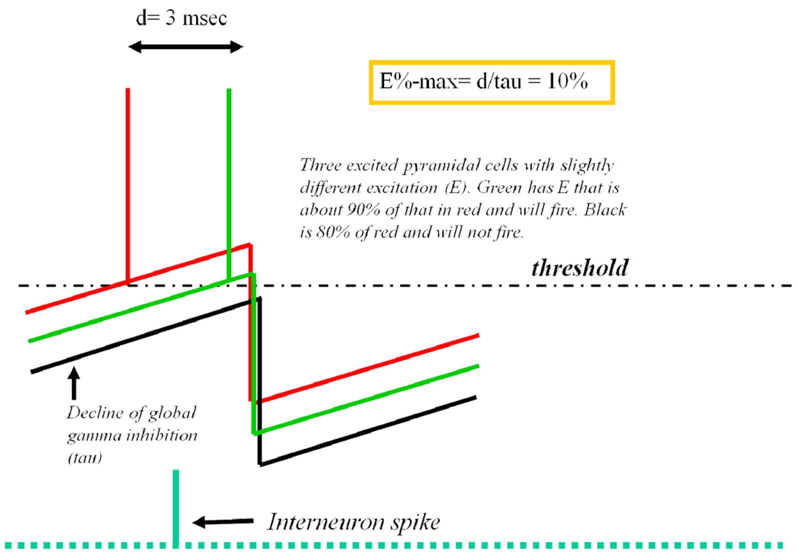

Fig. 8.

How inhibition during gamma oscillations determines which cells fire. Interneurons fired during a previous gamma cycle (left) and generated global inhibition in pyramidal cells. Inhibition decays with the time constant of the IPSP (tau; this equals the membrane time constant) (left). The voltage in three pyramidal cells having different tonic excitation is shown (red/green/black). As inhibition decays, the most excited cell (red) reaches threshold. This triggers an interneuron spike and feedback inhibition, which arrives at all pyramidal cells with delay, d. During this delay, the cell (green) with excitation that is close to that of the most excited cell will also fire.

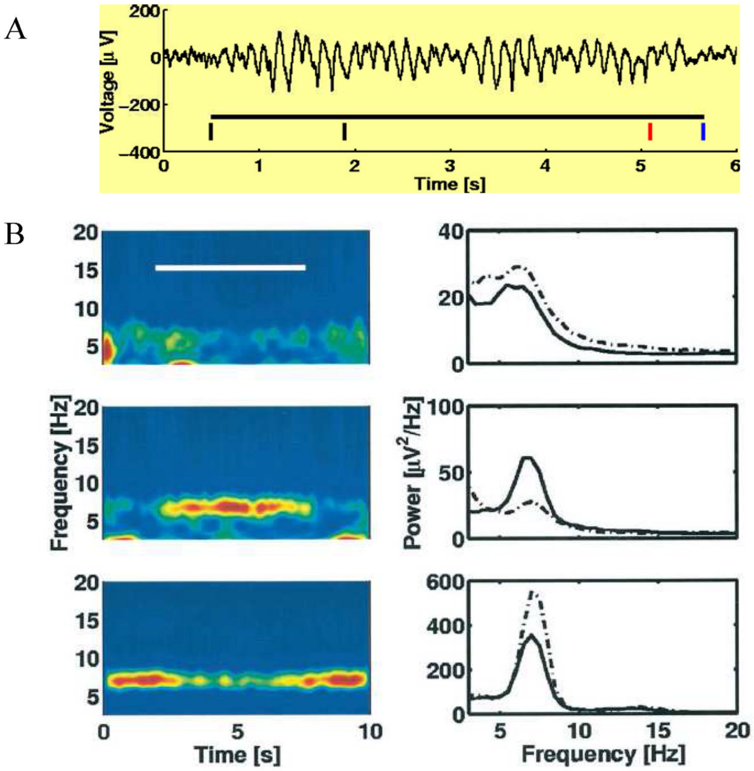

Fig. 9.

Theta power is gated up at some cortical sites and down at others during the period of working memory. (A) With intracranial recordings, large-amplitude theta can be observed in single trials of the Sternberg task. First black bar is the time of cue presentation; second black bar indicates presentation of the item to be remembered; at the red bar, the test item is presented and the subject indicates (at the blue bar) whether it is the same as the remembered item. In other trials, more items were presented. (B) Recordings from three sites where task (white bar) had little effect on theta power (top), where it produced an increase in theta power (middle), or where it produced a decrease in theta power (bottom). Color code at right indicates theta power. From Fig. 8 of (Raghavachari et al., 2001).