

# The Theta/Gamma Discrete Phase Code Occuring During the Hippocampal Phase Precession May be a More General Brain Coding Scheme

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**ABSTRACT:** In the hippocampus, oscillations in the theta and gamma frequency range occur together and interact in several ways, indicating that they are part of a common functional system. It is argued that these oscillations form a coding scheme that is used in the hippocampus to organize the readout from long-term memory of the discrete sequence of upcoming places, as cued by current position. This readout of place cells has been analyzed in several ways. First, plots of the theta phase of spikes vs. position on a track show a systematic progression of phase as rats run through a place field. This is termed the phase precession. Second, two cells with nearby place fields have a systematic difference in phase, as indicated by a cross-correlation having a peak with a temporal offset that is a significant fraction of a theta cycle. Third, several different decoding algorithms demonstrate the information content of theta phase in predicting the animal's position. It appears that small phase differences corresponding to jitter within a gamma cycle do not carry information. This evidence, together with the finding that principle cells fire preferentially at a given gamma phase, supports the concept of theta/gamma coding: a given place is encoded by the spatial pattern of neurons that fire in a given gamma cycle (the exact timing within a gamma cycle being unimportant); sequential places are encoded in sequential gamma subcycles of the theta cycle (i.e., with different discrete theta phase). It appears that this general form of coding is not restricted to readout of information from long-term memory in the hippocampus because similar patterns of theta/gamma oscillations have been observed in multiple brain regions, including regions involved in working memory and sensory integration. It is suggested that dual oscillations serve a general function: the encoding of multiple units of information (items) in a way that preserves their serial order. The relationship of such coding to that proposed by Singer and von der Malsburg is discussed; in their scheme, theta is not considered. It is argued that what theta provides is the absolute phase reference needed for encoding order. Theta/gamma coding therefore bears some relationship to the concept of "word" in digital computers, with word length corresponding to the number of gamma cycles within a theta cycle, and discrete phase corresponding to the ordered "place" within a word.

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**KEY WORDS:** hippocampus; neural code; oscillation; place cell

## INTRODUCTION

It has long been clear that the brain shows oscillatory activity in various frequency bands. The power in these bands can change as function

of behavioral state and task demands. Furthermore, the coupling between disparate brain regions can increase, as indicated by the task-dependent changes in the coherence of the oscillations in distinct regions. All this suggests that oscillatory activity is an integral aspect of brain function (for reviews see Engel et al., 2001; Niebur, 2002; Steriade, 2003; Buzsáki and Draguhn, 2004; Traub et al., 2004; Mann and Paulsen, 2005). However, despite considerable effort, the functional role of oscillations remains unclear. Indeed, there is no consensus regarding the fundamental question of why the brain oscillates. The most influential idea to date was proposed by Singer (2000) and von der Malsburg (von der Malsburg and Schneider, 1986) with regard to gamma frequency (30–100 Hz) oscillations. They proposed that each cycle of a gamma oscillation is a network phenomenon in which a group of cells fire together synchronously. In the version of such models shown in Figure 1, synchronous is defined as firing in same gamma cycle; different groups fire on different gamma cycles. This synchronizing effect could make downstream neuronal targets able to discriminate synchronized from unsynchronized groups. It was further suggested that gamma could subserve a cognitive role: cells representing groups of features that were part of the same object would fire synchronously, thus "binding" the parts into a meaningful whole. Thus, different assemblies firing in different gamma cycles or at different gamma frequencies could represent different entities that are simultaneously represented in the brain. These ideas regarding the cognitive role of gamma have been extensively investigated in sensory cortex (Engel et al., 2001), but remain controversial (Shadlen and Movshon, 1999).

A second major investigation of oscillations has focused on the hippocampus and the associated limbic region (see Vertes, this volume). In these regions, there are prominent oscillations in the theta frequency band (4–10 Hz). It was subsequently shown that the hippocampus also showed oscillations in the gamma frequency band (30–100 Hz). A particularly interesting discovery then followed: both theta and gamma could occur together; moreover, the theta modulation of gamma amplitude indicated that the oscillatory processes at the two frequencies were interacting rather

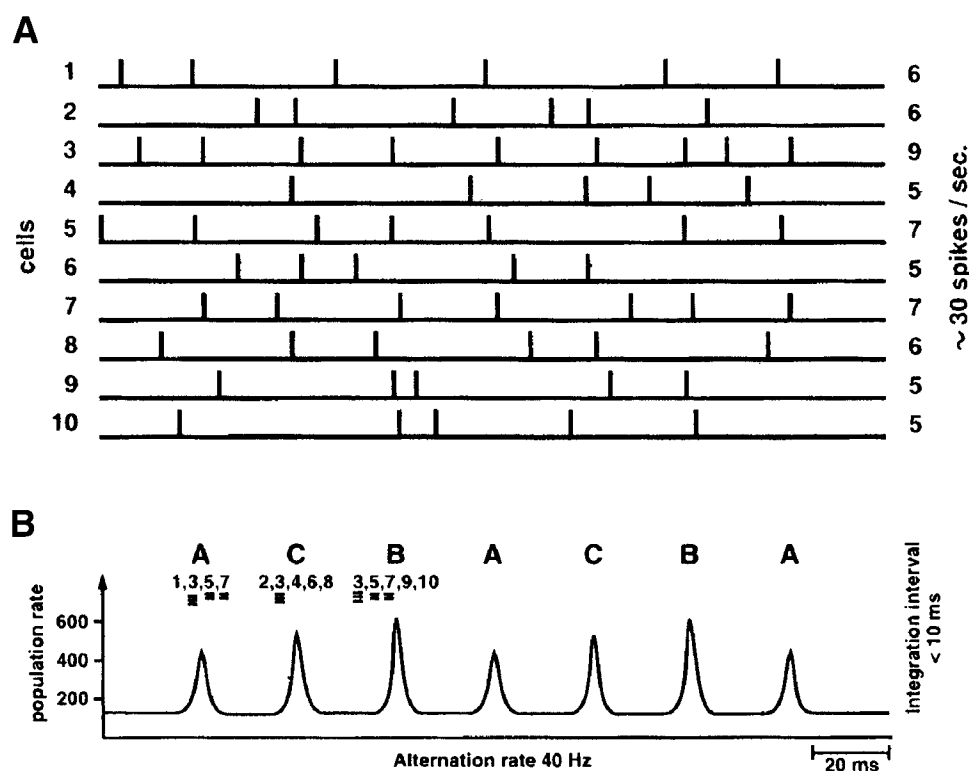
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**FIGURE 1.** A model proposed by Singer regarding the role of gamma as a synchronizing mechanism that differentiates multiple assemblies in cortex. **A:** Simultaneous spiking shown in 10 neurons. **B:** Overall rate (average of all cells) when rate is computed in a short window (<10 ms). This rate oscillates at gamma fre-

quency. Letters represent different assemblies. The particular cells that fire as part of a given assembly are listed. Note that within an assembly there is a small temporal jitter. Reproduced with permission from Singer (2000).

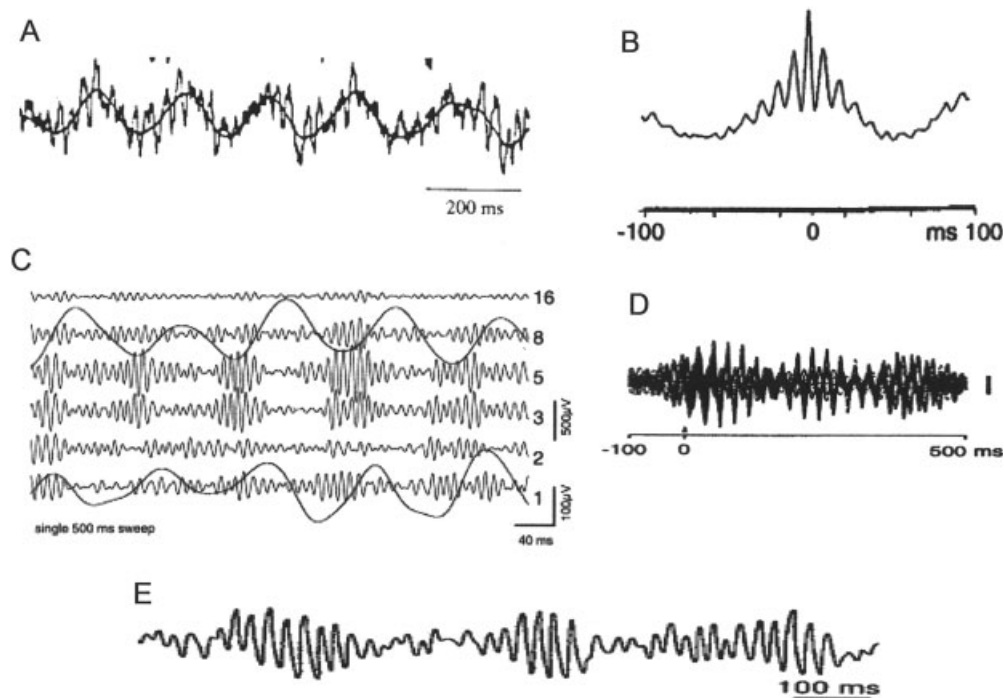
than independent processes (Figs. 2A,B) (Soltesz and Deschenes, 1993; Bragin et al., 1995). Other experiments show that gamma and theta frequency can each vary over a significant range, but that the frequency shifts of the two oscillations are correlated, providing additional evidence of their inter-related function (Bragin et al., 1995).

Although such dual interacting theta/gamma oscillations have been most extensively studied in the hippocampus, they are not unique to the hippocampus. Figure 2C–E shows examples from human midline cortical magnetoencephalography (MEG) and from rat entorhinal and olfactory cortex. Thus, whatever the function of these dual oscillations, it is unlikely to be specific to the hippocampus. In the hippocampus, however, there is sufficient evidence to make a reasonable inference about the role of these oscillations. This paper will first review that evidence and will then return to the question of what the more general function of dual oscillations might be.

## PROPERTIES OF THETA AND GAMMA IN THE HIPPOCAMPUS

Theta frequency oscillations are found throughout the hippocampus and are coherent over the entire structure. Both pyramidal cells and interneurons display firing that is modulated by theta frequency, but with important differences; pyramidal

cells are usually place-specific within the recording environment, whereas interneuron firing is largely position-independent (McNaughton et al., 1983). The mechanisms involved are also different. The theta rhythm requires an oscillatory input from the medial septal nucleus (reviewed in Vertes and Kocsis, 1997). Gamma oscillations can be driven by gamma frequency inputs from the entorhinal cortex (EC) (Bragin et al., 1995), but they can also be generated by intrinsic mechanisms, notably by feedback inhibition within hippocampal networks. Important early observations showed that gamma could be seen in intracellular recordings from hippocampal pyramidal cells. By altering the polarization of the cells, it was established that the gamma input into pyramidal cells was inhibitory (Soltesz and Deschenes, 1993). The source of this inhibition is from local interneurons, which are themselves excited by the pyramidal cells, thus forming a negative feedback loop (Fisahn et al., 1998; Penttonen et al., 1998; Csicsvari et al., 2003; Tamas et al., 2004). The inhibitory neurons fire at gamma frequency. Given the periodic inhibition of pyramidal cells, it would be expected that their firing would be modulated by gamma. Consistent with this, pyramidal cells in awake animals show a cross-correlation of firing with the gamma observed in field recordings. This cross-correlation has been shown in awake animals as they run (Fig. 3) (Csicsvari et al., 2003), an observation that has implications for the phase precession, as will be discussed later.



**FIGURE 2.** Recordings of dual theta/gamma oscillations in the hippocampus and various cortical regions. **A:** Intracellular recording from hippocampal neuron. Reproduced with permission from Soltesz and Deschenes (1993). **B:** Field recordings from hippocampus; average triggered on peak of the gamma frequency field potential oscillation. Reproduced with permission from Bragin et al. (1995). **C:**

Field recordings from EC. Highly filtered records show the theta component in isolation. Reproduced with permission from Chrobak and Buzsaki (1998). **D:** MEG from human midline cortex. Reproduced with permission from Llinas and Ribary (1993). **E:** Field recording from olfactory cortex. Reproduced with permission from Woolley and Timiras (1965).

It is important to understand that such cross-correlation does not imply that individual pyramidal cells fire at gamma frequency; in fact they do not. What the cross-correlation indicates is that if a cell fires, it will fire in certain phase range of gamma. More generally, although the relationship of cell firing to gamma, as measured in field potentiation potentials, can be detected (Fig. 3), this relationship is not as robust as the relationship to theta. One possible reason is simply that the detection of gamma in field potentials is compromised by noise, making it difficult to assign gamma peaks with confidence. Such peak detection is the basis of the best methods for relating spikes to network oscillations (see below regarding theta phase). Other methods for studying gamma, such as autocorrelation, assume that the oscillation has constant frequency, which is not the case.

An unresolved issue about hippocampal gamma is the extent of its coherence across the entire structure. Along the longitudinal axis of the dentate hilus, there is very high coherence ( $>0.5$ ) over long distances, suggesting that the entire dentate region is coordinately regulated by gamma (Bragin et al., 1995). In contrast, the gamma coherence between the dentate, CA3, and CA1 is generally low, even at the same longitudinal level. Importantly, this coherence can suddenly become high during brief epochs (the functional correlate of these epochs is not known). It thus appears that at least under some conditions, the entire hippocampus may be coordinately clocked by the same gamma and

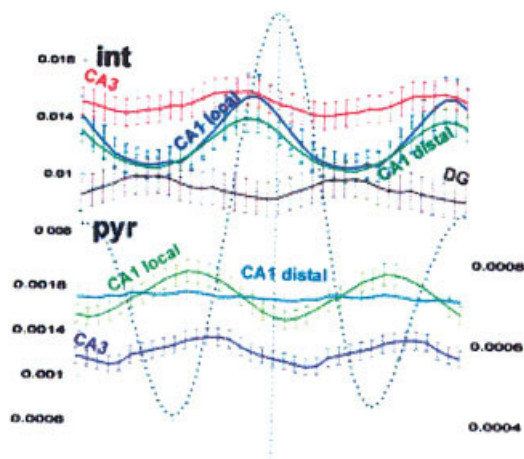
theta oscillations. It will be important to understand how and why this varies in different hippocampal states.

## THE PHASE PRECESSION OF HIPPOCAMPAL PLACE CELLS

The first indication that theta phase might be an important aspect of hippocampal information coding came from the work of O'Keefe and Recce (1993). They recorded single unit activity from place cells and simultaneously recorded theta in the field potentials. They identified the theta peaks on each cycle and could then assign a phase for every spike. It is noteworthy that because theta phase is calculated relative to each theta cycle, there is no assumption regarding the constancy of theta frequency. As the rat passes through a place field, there are on the order of 10 theta cycles during which firing occurs. Data was collected as rats repeatedly traversed the same region. The key observation was that the average theta phase systematically changes as the rat traverses the place field (Fig. 4).

## THE CONCEPT OF A THETA/GAMMA CODE

A coding model in which pyramidal cell firing is regulated by theta and gamma is shown in Figure 5 (Lisman and Idiart,



**FIGURE 3.** Pyramidal cell firing is influenced by gamma frequency oscillations. Gamma is evident in field potentials recorded in CA1 (dashed line). Other lines show the correlation of various parameters, including CA1 spiking, with the gamma field potential (see original paper for details (Csicsvari et al., 2003)). [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

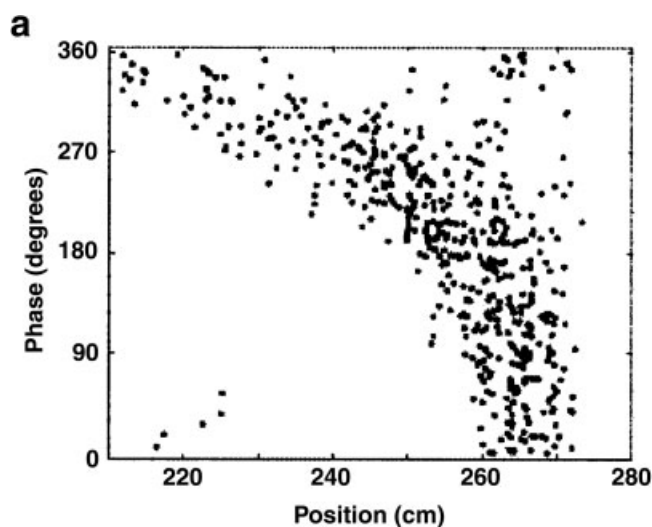
1995; Lisman, 1999). In describing this model, the term “ensemble” will be used to indicate a subset of cells that fire together and that jointly represent a given memory (e.g., for a given place or item). Because we are dealing here with a temporal code, it is crucial to be specific about what the term “together” means. Here “together” means firing in the same gamma cycle (i.e., within 10–20 ms, depending on gamma frequency). A corollary is that small offsets in firing time corresponding to different phases within a gamma cycle (i.e., jitters of <10 ms) are not important; the cells are still considered part of the same ensemble. The subset of cells that fire together on a given gamma cycle (an assembly) form a spatial code for a particular item. Different, but overlapping assemblies fire on different gamma cycles, thereby collectively forming a discrete sequence of assemblies within each theta cycle, each firing at a different theta phase. In discussing this coding scheme, it is useful to compare it with the scheme proposed by Singer and von der Malsburg (Fig. 1). The ideas regarding gamma and the role of synchronous firing are similar; what differs is the role of theta. As discussed in the last section of this review, what theta provides is an absolute phase reference that can be used to encode the order of items.

### TESTS OF THE THETA/GAMMA CODE

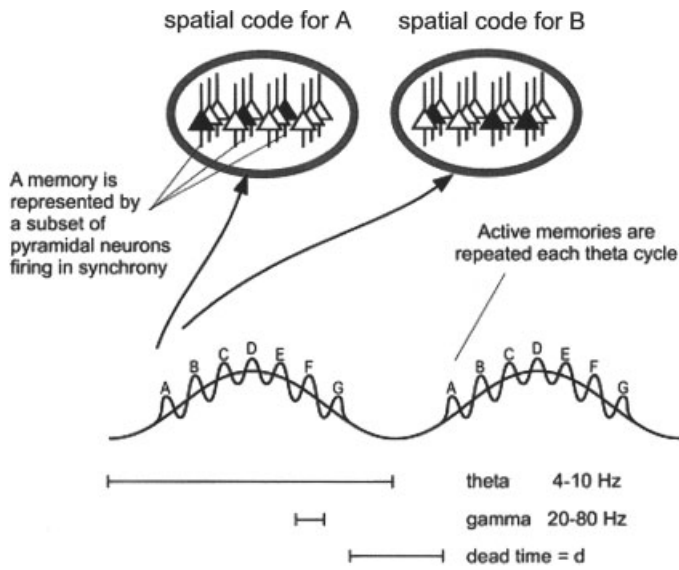
A critical test of theta/gamma coding is to determine whether different cell groups systematically fire at different phases of theta. Since phase varies with position, this test would have to be restricted to data taken from a given position, thereby strongly restricting the useable data. For this reason, a related test is more practical; a corollary of theta phase coding is that ensembles representing nearby places should fire with a fixed average phase difference, irrespective of the particular position

of the rat (so long as the rat is in both place fields). The specific prediction is that two cells coding for slightly different positions should show a cross-correlation with a peak offset equal to a significant fraction of theta. Obtaining data to test cross-correlation is not easy; the only expected cross-correlations would be from cells that are simultaneously active because they have nearby place fields. Because the position of place fields is not topographically mapped in the hippocampus, there is no way to pick two cells that are likely, a priori, to have overlapping place fields. With the advent of multi-electrode recording, however, so many cells are sampled that cells with overlapping place fields can be found. Skaggs et al. (1996) reported some examples of such pairs and found a cross-correlation with an offset in the 50–100 ms range (Fig. 6, lower). Similar results are reported by Dragoi et al. (2003). This directly shows that different cells have systematic theta phase difference.

But how finely is theta phase divided? Perhaps all that matters is whether a cell fires with early phase or late phase. In contrast, according to the theta/gamma model, there should be a number of phase division equal to the number of gamma cycles within a theta cycle. This is in the range of 5–7 (Fig. 1). To obtain information about this issue, Jensen and Lisman (2000) used a position reconstruction method based on the simultaneously recorded spikes from 38 cells. The data from the first half of an experiment was used to construct correlations of position and the firing phase of individual cells. For the second half, these correlations were used to reconstruct position from the observed spikes. The average distance between the reconstructed position and the actual position could be used as quantitative measure of the efficacy of different decoding schemes. Specifically, schemes based on different numbers of phase bins could be compared. As shown in Figure 7A–C, as finer phase bins were used, reconstruction accuracy improved, up to about 5 phase bins (corre-



**FIGURE 4.** The phase precession of a CA1 place cell. As the rat moves through a place field (position on the track is plotted on the x-axis), the phase of each spike is determined relative to the peaks of theta in the field potential, which are measured separately for each theta cycle (Mehta et al., 2002).



**FIGURE 5.** A model of theta/gamma. Each theta cycle is subdivided into 7 gamma subcycles, though the exact number could vary. Within a particular gamma cycle (e.g., A), certain cells will be active, thereby forming a spatial code for an item. Seven items are sequentially represented in the gamma subcycles. The entire pattern group of 7 patterns may repeat on the next theta cycle if this is a working memory network.

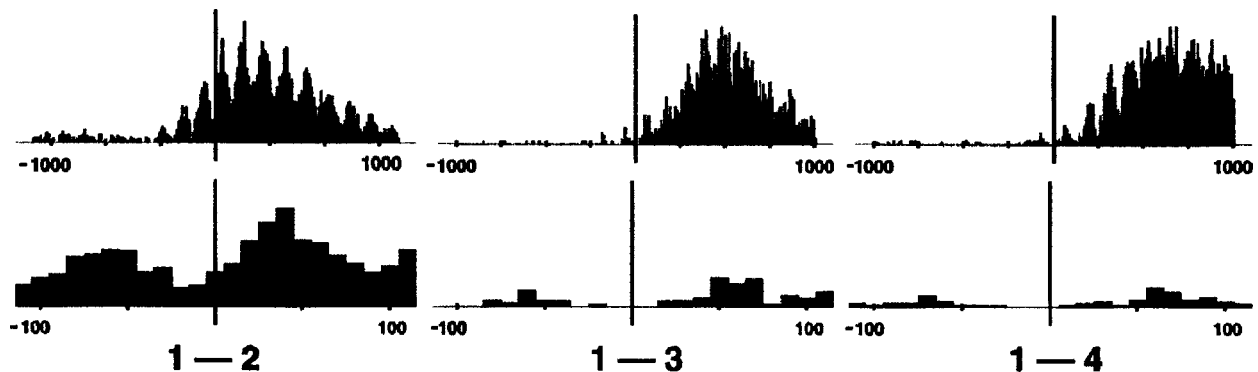
sponding to temporal differences of about 10–20 ms). If phase information corresponding to millisecond differences were important, then subdividing phase even more finely would improve prediction accuracy. However, it was found that with finer phase bins, reconstruction accuracy did not improve and may have actually declined. Related calculations by Harris et al. (2003) further confirmed this conclusion; using a somewhat different methodology they showed that maximum information was obtained by considering spiking in 25 ms phase bins (corresponding roughly to the period of a gamma cycle) (Fig. 7D). These results thus support the importance of coarse phase divisions (on the order of a gamma period) and suggest that finer phase variations are probably not important.

The existence of a theta/gamma coding does not preclude other forms of coding in the same brain structure. For instance, bursts might occur at early phases but not at late phases. If an organization of spiking of this kind occurred, the overall rate would vary as a function of phase and possibly encode additional information. One proposal of this kind has been put forward by Huxter et al. (2003), arguing that theta phase encodes the rat's position, as described above, while the overall rate encodes the rat's velocity.

**THETA/GAMMA CODING IN THE HIPPOCAMPUS: REMAINING ISSUES**

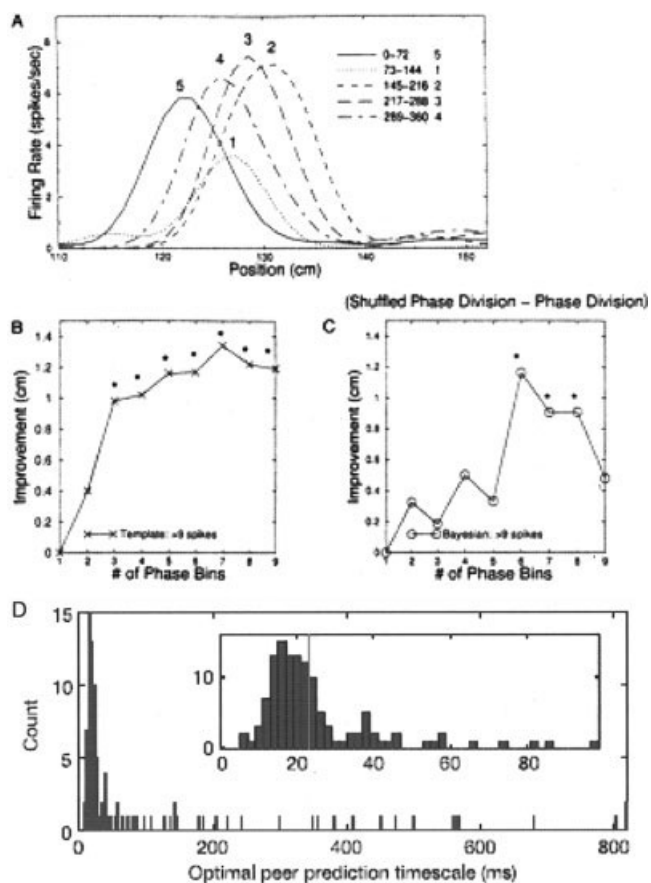
A summary of the experiments described above is as follows: (1) systematic changes in phase are observed in single cells; (2) when different cells are compared, their phase difference remains fixed even as phase changes; (3) the phase difference of different cells can be directly related to the difference in positions that the cells encode, i.e., to a cognitive dimension; and (4) when theta phase is taken into consideration, it improves prediction of the rat's position compared with analysis that does not take phase in consideration. Thus, theta phase is systematically mapping a cognitive variable and has demonstrable information content. Taken together, these findings firmly establish the phase code and it is not clear what further tests could provide.

The case for discrete phase coding organized by gamma is not yet as strong. Although there is no doubt that gamma occurs in the hippocampus and can influence the spiking of principle cells as the rat runs through a place field, the strength of this modulation is not clear. Strong modulation implies a pause on each gamma cycle. Such a pause clearly separates ensembles and allows downstream cells to identify neuron groupings using simple coincidence detection (Perez-Orive et al., 2004). As argued above, methods based on temporal averaging may produce smearing because gamma frequency is not fixed. The best approach for detecting strong gamma modulation will therefore be ones that do not do such averaging. For instance, recording of many units should show that the instantaneous rate of the



**FIGURE 6.** Cross-correlation between 4 place cells (pairwise 1–2, 1–3, and 1–4) representing nearby places. Upper traces are at slow time base and show correlation across theta cycles; lower traces are on faster time base and show the correlation within a

theta cycle. Importantly, the peak cross-correlation has a temporal offset in the 40–80 ms range. Reproduced with permission from Skaggs et al. (1996).



**FIGURE 7.** Theta phase carries information, but phase differences corresponding to intervals less than 10–20 ms do not appear to carry information. **A:** Rate vs. position for overlapping place fields. **B and C:** Accuracy of position reconstruction from cell ensemble activity improves as phase is more finely divided up to 7 bins. (**B and C**) are two technically different reconstruction methods (Jensen and Lisman, 2000). **D:** Spike phase is used to predict other spikes, based on an optimal window (inset summary), which is ~20 ms (Harris et al., 2003).

group fluctuates strongly at gamma frequency. What makes this technically difficult to achieve is that a very large number of cells must be recorded to ensure that a large number are firing simultaneously (e.g., have nearby place fields).

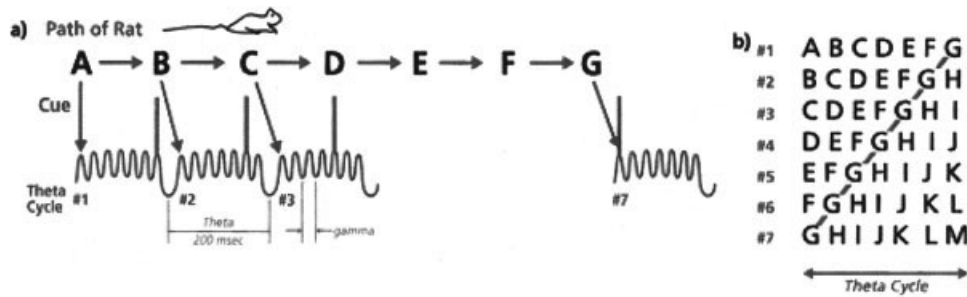
## FUNCTIONAL INTERPRETATION OF THE PHASE PRECESSION AS CUED SEQUENCE RECALL

The interpretation of the phase precession as cued sequence recall was developed by Jensen and Lisman (1996), Tsodyks et al. (1996), and Skaggs et al. (1996). The general idea of these models is similar, however the Jensen and Lisman model is the only one to explicitly include gamma modulation. The interpretation of the phase precession as cued sequence recall is illustrated in Figure 8. According to this interpretation, the cell's "true" place is a very small subregion of the apparent place field at the far side of the place field (e.g., position G in

the example shown). The overall place field firing occurs in positions A–G. Because the animal has learned about the sequence of places on the track based on previous experience, synaptic connections have been modified to allow asymmetrical excitatory connections between cells representing sequential positions along the track. This allows a chaining process that will recall the upcoming positions based on a sensory cue regarding current position. This chaining process is envisioned to be rapid and to occur within a theta cycle, discretized into steps by gamma. On the first theta cycle in a place field, the sensory input (cue) into the hippocampus corresponds to position A. This cue enters the hippocampus at the early part of the theta cycle and stimulates a chaining process, the end result of which is the firing of cell G in the last gamma cycle (Fig. 8B). The phase precession occurs because of the animal's movement during each theta cycle. As a result of this movement, the sensory cue at the beginning of the next theta cycle will correspond to position B; the consequent chaining will cause cell G to now fire in the next to last gamma cycle, i.e., with earlier phase (for further details regarding changes in phase variance during the phase precession, see Lisman et al. (2005)). It should now be obvious why theta phase should advance systematically as the animal progresses through the place field (Fig. 8B). According to this scheme, firing with late phase is a prediction that the animal is likely to come to position G. Firing with early phase indicates that the animal is at or near position G.

A testable aspect of this model is that the phase precession is driven by movement-dependent changes in the spatial cue. Consistent with this idea, phase depends on position within the place field and not on time within the place field, which varies with the rat's velocity (O'Keefe and Recce, 1993; Skaggs et al., 1996). What is found is that if the animal runs twice as slowly, the number of theta cycles on which there is firing will increase. An interesting further test of position cueing was reported by Czurko et al. (1999). They put rats on a running wheel, which decouples the movements of the legs from movement through space. Consistent with the lack of change in spatial cue, there was no phase precession. A recent report by Harris et al. (2002) indicates that phase precession can occur during REM sleep and it is unclear how this should be interpreted; perhaps it is simply a replay of rat's previous movements.

The interpretation of the phase precession as sequence recall makes sense, given the increasing evidence that the hippocampus has a special role in the memory for sequences. Indeed, because the memory for sequences requires different network processes than those involved in item storage, it should not be surprising that special brain structures have developed for the storage and recall of sequences. There is now a substantial body of data, indicating that the hippocampus is required for the memory of the sequence of events such as would make up an "episode." Honey et al. (1998) trained rats on tone-light sequences and then measured the orienting of the rat to changes (mismatches) in the order of these sequences. Rats increased their orienting about 2-fold to mismatches, but only if their hippocampus was intact. In more specific tests of sequence recognition (Fortin et al., 2002), rats were presented with a se-



**FIGURE 8.** Interpretation of the phase precession as the cued recall of the sequence of upcoming places (see text for explanation).

ries of odors; if presented with a pair of these odors, normal rats know the order in which they were presented, whereas hippocampal rats do not. In contrast, if the rat is merely required to recognize whether a test item had been previously presented (regardless of order), the hippocampus is not required. Additional evidence is provided by electrophysiological recordings, indicating the replay of sequences by the hippocampus. For instance, sequences of CA1 cell firing that occurred during the awake theta state were seen again during the sharp waves of slow wave sleep (Skaggs et al., 1996; Nadasdy et al., 1999; Lee and Wilson, 2002). The replay that occurs during SWS is about twenty times faster than the sequence observed during awake theta (Lee and Wilson, 2002). In contrast, a replay that has been observed during REM sleep appears to be real time and involve temporal segments on the minute time scale. This process involves both a preservation of the sequence of firing of different cells and the time course of theta modulation that occurred in the waking state (Louie and Wilson, 2001). Thus, both lesion work and in vivo recordings support the hypothesis that the hippocampus is involved in the episodic memory of sequences (to be distinguished from striatal habit memory, which also involves sequences). This involvement meshes well with the interpretation of the phase precession as cued sequence recall from long-term memory.

## MECHANISM OF THE PHASE PRECESSION

It should be emphasized that the informational content of the theta phase could potentially be generated by a variety of different mechanisms. Four classes of hypotheses have been proposed: (1) interaction of dual oscillations with slightly different frequency (O'Keefe and Recce, 1993; Bose and Recce, 2001; Lengyel et al., 2003); (2) interaction between excitation that has the spatial dependence of a sawtooth with theta-frequency inhibition (Mehta et al., 2002); (3) interaction of gaussian excitation with theta-frequency inhibition (combined with intrinsic conductances that prevent firing on the downward phase of the excitation that is tuned to position by a Gaussian) (Kamondi et al., 1998); and (4) the chaining model (described above) in which each ensemble of neurons stimulate the next ensemble in the sequence (as in a synfire chain). Recent efforts (Harris et al., 2003) to distinguish among these models appear to rule

out versions of model 1 in which both oscillations are generated within the hippocampus (Zugaro et al., 2005).

A related question is the location within the hippocampus where the phase precession is generated. The precession has been observed in the dentate gyrus (DG) (Skaggs et al., 1996), arguing against models based on CA3/CA1 interactions. It is generally assumed that the phase precession develops in the hippocampus, but recordings from the EC are needed to establish this point with certainty. It has been proposed that the precession is generated through reciprocal interaction between the dentate and CA3 (Lisman, 1999). It is envisioned that this dual network system allows for network interactions that perform both chaining steps (heteroassociative, A to B') and autoassociative steps that corrects minor errors (B' to B). Such errors are likely to occur at each chaining step and only by correcting such errors can a recall process involving multiple chaining steps be accurately performed. It was originally suggested that the chaining step occurs in CA3, but more recent analysis suggests that they occur at feedback synapses from CA3 back to the dentate (Lisman, 2003; Lisman et al., 2005). The key new argument is that the time for information about memory 1 to go from the dentate to CA3 and back to the dentate may allow it to arrive at the dentate at the same time that memory 2 enters the dentate from the EC. This coincident arrival is optimal for induction of long-term potentiation (LTP) and will produce selective incorporation of heteroassociative information into the synaptic weights of feedback synapses (autoassociative weights will not be incorporated into feedback synapses because the timing is wrong). According to this revised model, recurrent synapses in CA3 are the synapses where autoassociative information about individual items is formed, as long suspected (Marr, 1971; Gardner-Medwin, 1976; Hopfield, 1982; McNaughton and Morris, 1987; Rolls, 1989) and as supported by recent experimental work (Nakazawa et al., 2002).

## THETA/GAMMA IN THE CORTEX

As mentioned in the introduction, the coexistence of theta and gamma oscillations has also been observed in cortical regions, including the entorhinal and olfactory cortex (Fig. 2). These are not regions where the function attributed to theta/gamma in the hippocampus cued recall of sequences from

long-term memory, is plausible. What then might the cortical role of these cortical oscillations be and is there nevertheless a relationship to theta/gamma in the hippocampus?

Not much can yet be said about the function of theta/gamma in olfactory cortex, but in the temporal cortex, a hypothesis has been developed and tested to some degree. The EC and other temporal lobe regions show persistent firing during the delay period of a working memory task. A fundamental property of working memory is that multiple items can be stored; in humans, the capacity limit for digits is  $7 \pm 2$ . This raises the question of how multiple items can be actively stored in brain networks and there are two broad ranges of possibilities. One, by analogy to digital computers, is to use different addresses; there would be a network for the first item, a different network for the second item, etc. A second class of hypothesis is temporal multiplexing; an ensemble of cells in a network fire representing the first item; then, a different ensemble fire representing the second item and so forth. When this process is completed, it simply repeats, thereby keeping active the short-term memory of multiple items.

In order for such a multiplexing network to operate, it would require clocking. Lisman and Idiart (1995) proposed that cortical theta and gamma might provide such clocking in cortical networks responsible for short-term memory. Two lines of psychophysical evidence are broadly consistent with this proposal. First, the number of gamma cycles within a theta cycle is about seven, suggesting a basis for the capacity limit of short-term memory. Second, measurements of memory scanning indicate that the time necessary to scan through a memory is about the period of a gamma cycle. The reader is referred to a review of this hypothesis (Jensen and Lisman, 2005) and recent relevant experimental findings (Raghavachari et al., 2001; Jensen and Lisman, 2005; Lee et al., 2005). If this hypothesis is correct, the function of theta/gamma in the temporal lobe is to provide a way of representing sequentially presented items in short-term/working memory; the item presented first is represented in the first gamma cycle of a theta cycle, the items presented second in the second gamma cycle, etc.

In discussing the possible role of theta and gamma in sensory cortex (Fig. 1E), a comment about gamma in sensory cortex is in order. Comparison of Singer's coding scheme for V1 (Fig. 1) with the theta/gamma scheme, we have proposed (Fig. 5) shows that both posit that different assemblies fire with temporal offset corresponding to an integral number of gamma periods. Singer's coding scheme (Fig. 1) depends only on gamma. However, recent work indicates that early visual areas also demonstrate theta. For instance, in monkey V4, theta can be seen in the field potential and single-unit activity is phase-locked to this oscillation (Lee et al., 2005). Intracranial EEG recordings in human visual sensory cortex show large amplitude theta (Raghavachari et al., 2001). Other work points to a role of theta in a variety of sensory regions. As shown in figure 2E, theta is present in rat olfactory cortex, where it is linked to theta-frequency sniffing. Whisking and licking in rats also occurs at theta frequency and generates theta in somatosensory and gustatory cortex. These findings raise the possibility that

joint theta/gamma oscillations may be quite widespread in sensory regions. In the case of licking and sniffing, it would seem that gamma might provide a way of separating short latency sensory information from long. Perhaps in olfaction and taste, the molecular components of a mixture are transduced with differing latencies and are represented in different gamma cycles. Relevant to this are theories of olfactory coding that utilize theta phase as a coding variable (Hopfield, 1995). In whisking theta latency differences correspond to different positions in space and are thus of obvious importance.

## A GENERAL THEORY OF THETA/GAMMA CODING

We can now turn to the question posed at the beginning of this article; what could be the common function of theta/gamma that accounts for why it is found in multiple brain regions. The present work suggests that it is a fundamental coding strategy for representing multiple units of information in a way that preserves information about order. Each unit of information is represented by cells that fire within a gamma cycle. The ensemble of cells that fire in a given gamma cycle form a spatial code. Different ensembles fire in different gamma cycles. What theta provides is a phase reference that allows assignment of order. In the context of the readout of information from long-term memory, as may be exemplified by the phase precession, early phase corresponds to a place that is nearby whereas late phase corresponds to a more distant place. This capability would, for instance, allow a decoding system to establish proximity to a goal (Burgess et al., 1994). In the context of short-term memory processes in temporal cortex, the utilization of phase coding is somewhat different; the earliest phase corresponds to the item that was presented first and the last phase to the last presented item. This coding may be what underlies our ability to recall lists in order from short-term memory. Theta/gamma may thus be a general coding scheme for ordered units of information, which can be used by different brain regions for different types of processes.

One may focus more specifically at what it is that the presence of theta provides. Suppose two assemblies (A,B) fire in sequential gamma cycles (Fig. 5). One could argue that their order is apparent without theta. Although this is true if the pattern does not repeat, it is not true when there is the repetition characteristic of short-term memory networks; it is now impossible to say whether A precedes B or vice versa. Even if no repetition occurs and one can therefore say that B follows A, it is only the relative order that can be determined, not the absolute position in an ordered set. In contrast, with theta coding, phase is absolute and can convey information. Thus if A and B occur sequentially during late parts of the theta cycle, one knows not only their relative order, but also that they are both late elements in an ordered set.

This line of thinking provides a potential explanation of why it is that the brain oscillates. It is temporal clocking system for a neural code designed for handling ordered units of information. The widespread use of this code may reflect the necessity



for different parts of the brain to use a common formatting system during information exchange. The information coding of digital computers provides a limited, but useful analogy. The elementary unit of information in digital computers is a bit. To represent a complex item, a formatting scheme is required. Computers use multiple (8 bits = 1 byte) ordered bits in parallel to represent an item as a "word." Note that in early computers, the byte corresponded to "word length"; in modern computers, word length is much higher. Each bit represents a "place" in an ordered list within a word of fixed length. In theta/gamma coding, the series of gamma cycles may similarly represent a "place" in an ordered list within a theta cycle. The list elements occur sequentially in space in a computer register, but sequentially in time according to the theta/gamma model. The "word length" is about seven in the brain (seven gamma cycles within a theta cycle), but 64 in modern computers. The digital computer can represent only a one bit item in each "place"; in the brain, the item represented in each gamma cycle can be complex because it is encoded by the large set of cells that fire within a gamma cycle. The information content of such an item will depend on the number of cells in the network, but will certainly be enormously higher than one bit. Because of the high information content of a theta/gamma "word," it can convey rich information, e.g., about a sequence of events recalled from memory, as in the phase precession. It is hoped that this analogy is helpful in seeing that all forms of computation require information formatting and that the theta/gamma oscillatory mechanisms of the brain may be a particular solution to this problem.

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