HIPPOCAMPUS 15:853–866 (2005)

Dual Phase and Rate Coding in Hippocampal Place Cells: Theoretical Significance and Relationship to Entorhinal Grid Cells

John O'Keefe[1]* and Neil Burgess[1,2]

ABSTRACT: We review the ideas and data behind the hypothesis that hippocampal pyramidal cells encode information by their phase of firing relative to the theta rhythm of the EEG. Particular focus is given to the further hypothesis that variations in firing rate can encode information independently from that encoded by firing phase. We discuss possible explanation of the phase-precession effect in terms of interference between two independent oscillatory influences on the pyramidal cell membrane potential, and the extent to which firing phase reflects internal dynamics or external (environmental) variables. Finally, we propose a model of the firing of the recently discovered "grid cells" in entorhinal cortex as part of a path-integration system, in combination with place cells and head-direction cells. © 2005 Wiley-Liss, Inc.

KEY WORDS: theta; oscillation; computational model; cognitive map; hippocampus

INTRODUCTION

The original impetus for the development of the cognitive map theory was the discovery of spatially-coded neurons in the hippocampus of freely-moving rats. The primary correlate of pyramidal cell firing is the animal's location in an environment. These cells were termed "place cells," and their firing fields "place fields" (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976). Neighboring place cells might be active in markedly different parts of environment such that a small group of them provide coverage of an entire environment. Some cells respond solely to location whereas others incorporate information about objects in that location. Most importantly the cells signal that the animal has entered the preferred location irrespective of its heading direction: they provide what is termed allocentric spatial information, which is independent of the orientation of the body axis and can be contrasted with egocentric spatial information within which objects are located relative to body-centered frameworks such as the eye, the head, or the body. On the basis of these findings, O'Keefe and Nadel (1978) proposed that the hippocampal formation functioned as a cognitive map, consisting of a set of place representations that completely covered an environment and that were linked together by vectors that specified the directions and distances between places. According to the theory, once the animal had located itself in the environment, movements that took it in a particular direction for a particular distance would activate the place cell that corresponded to the new location. The discovery of the head direction cells in the neighboring subicular area a few years later (Ranck, 1984; Taube et al., 1990a) and the demonstration that the place-cell firing rate varies as a function of the animals' running speed (McNaughton et al., 1983; Czurko et al., 1999) have provided strong support for the cognitive map theory, since they confirm that the information required by a mapping system is available to the hippocampus. The recent startling discovery of a collection of entorhinal cortical "grid cells," which lay regular spaced grids of activity upon each environment, by Hafting et al. (2005) may show how speed and direction can be combined to give the distance metric postulated by the cognitive map theory, see later.

However, the relationship between the global oscillatory EEG theta activity and the highly individuated activity of the place cells has been problematic for the spatial theory of hippocampal function since its initial proposal. On the one hand, the theta signal was similar across large areas of the hippocampal formation (Mitchell and Ranck, 1980; Fox et al., 1986; Bullock et al., 1990) and clearly involved the synchronized activity of thousands of cells; it was not difficult to imagine that it served the function of tying together distant parts of the hippocampus into a single unified processor. Moreover the EEG signal was clearly not an artifact: it was reflected in membrane fluctuations in intracellular recordings and in the phase correlations of the interneurons— cells that Jim Ranck had named "theta cells" in recognition of their strong and consistent phase correlation with the EEG theta signal. Most theta cells increased their firing rates during a wide variety of active behaviors. On the other hand, pyramidal cell activity was highly specific: each cell remaining silent most of the time, only becoming active when the animal visited a particular patch of environment. They exhibited a degree of specificity which was hard to reconcile with the global behavior of the EEG theta and the interneuronal theta cells.

Here we review the way in which we think that place-cell firing and the theta rhythm might cooperate to represent both spatial and nonspatial information, and comment on the relationship of these ideas to the recent discovery of "grid cells" in one part of the immediate input to the hippocampus: the medial entorhinal cortex (EC) (Hafting et al., 2005). First, we briefly review some of the ideas relating to the functional significance of the theta rhythm.

[1]**Department of Anatomy and Developmental Biology;** [2]**Institute of Cognitive Neuroscience, University College London, London**
Grant sponsors: MRC and the Wellcome Trust, UK.
*Correspondence to: John O'Keefe, Department of Anatomy and Developmental Biology, University College London, London.
E-mail: j.okeefe@ucl.ac.uk
Accepted for publication 3 June 2005
DOI 10.1002/hipo.20115
Published online 19 September 2005 in Wiley InterScience (www.interscience.wiley.com).

The original cognitive map theory suggested that the theta system provides part of the mechanism for moving from one part of the spatial representation (or cognitive map) to another on the basis of the animal's movements. Support for this came from Vanderwolf's (1969) observation that there were two components to theta, only one of which was sensitive to anticholinergics such as atropine. The second noncholinergic component was disrupted by lesions in the EC. A major correlate of this noncholinergic theta in the rat was a class of "voluntary" behaviors that included walking, running, swimming, and jumping: roughly equating to those behaviors which changed the location of the animal's head in an environment. On this view, either the frequency or amplitude of theta would correlate with running speed, and theta would be seen not as part of the spatial representation of the environment but as part of the mechanism for shifting the focus within the map on the basis of movement-correlated signals. Changes in the frequency of theta activity are correlated with either the animal's speed of movement through the environment (Rivas et al., 1996; Slawinska and Kasicki, 1998) or the rapidity with which a movement is initiated. This latter effect has been shown in experiments in which rats have been trained to jump up onto a ledge or to initiate running on a runway (Whishaw and Vanderwolf, 1973). The behavioral correlate of theta amplitude is less clear. Although Vanderwolf and colleagues failed to find a positive correlation between amplitude and speed, Rivas et al. (1996) reported a positive correlation between both the frequency and the amplitude of theta in the guinea pig and the speed of movement when movements are initiated in simple runways. Maurer et al. (this issue) report a correlation between the amplitude of theta recorded at the hippocampal fissure and running speed. It seems that there are many factors contributing to the amplitude of theta such that a consistent correlate of amplitude is not always seen. What is clear however is that the firing rate of hippocampal place cells does correlate with running speed (see later) and that the movement-related theta signal enters the hippocampus via the EC since the hippocampal theta that survives after large entorhinal cortical lesions is abolished by atropine (Kramis et al., 1975).

A second possible function of theta emerged from studies that looked at the relationship between the phase of theta and long-term potentiation (LTP). There is evidence that volleys arriving at different phases of the ongoing theta are differentially effective (Pavlides et al., 1988; Huerta and Lisman, 1995; Holscher et al., 1997; Hyman et al., 2003). Inputs arriving at the positive phase of theta result in synaptic potentiation, while those arriving at the negative phase yield depotentiation or depression.

A third function of the theta oscillations emerged from detailed observation of the phase correlate of the firing of the place cells. Previous work (Buzsaki et al., 1983; Fox et al., 1986) had looked at the average theta-phase relations of pyramidal cells under circumstances that were not ideal for looking at changes in phase at different locations within the place field, when the cell was firing at its highest rate. For example, Fox and colleagues examined the theta correlates while the animals ran on a treadmill which remained stationary relative to the room and probably did not contain the place fields for many of the pyramidal cells recorded. Furthermore, speculation about the role of interference patterns between two theta-like waves on information processing and storage in the hippocampus (O'Keefe, 1985) suggested that a detailed look at the place cell-theta phase correlate on a trial by a trial basis might prove instructive. This revealed the phase-precession phenomenon (O'Keefe and Recce, 1993) and has led to the idea that an important function of theta is to provide a periodic clocking system against which the timing of each hippocampal spike can be measured. The precession of the firing phase, combined with increasing then decreasing firing rate, of a place cell as the rat runs through its place field causes the average firing phase of the population of place cells to maintain a fixed phase relative to theta (Burgess et al., 1993), explaining the previous observations. Such a phase-coding system would have implications both for the effects of LTP (O'Keefe and Recce, 1993; Skaggs et al., 1996) and for the mechanisms by which the hippocampal representation of location might be updated by the animal's movement.

PHASE AND RATE CODING OF SPATIAL BEHAVIOR

Hippocampal pyramidal cells code for the animal's location by increasing their firing rates dramatically in one part of the environment (the place field), that is, different cells represent different patches of the environment. Within the place field, a finer-grained spatial localization is achieved by the temporal relationship between spike firing and the rhythmical EEG theta activity (O'Keefe and Recce, 1993).

Localization by Rate Code

The original discovery (O'Keefe and Dostrovsky, 1971) of the spatial correlates of hippocampal pyramidal-cell activity only took into account the differential firing rates between one part of an environment (the place field) and the remainder. Typically, the background rate outside the field is less than 1 Hz and that inside the field an order of magnitude higher. Figure 1 shows the firing fields of 32 neurons simultaneously recorded from the CA1 field of a rat as it moved around a square platform searching for food. It is clear that firing rates of even such a small number of cells can provide a reasonably good indication of the animal's location on the platform. Wilson and McNaughton (1993) estimated that the firing rates of 130 cells would be sufficient to localize the animal's position in an environment to an accuracy of 1 cm every second.

Localization by Phase

Movements that change the animal's location in an environment are accompanied by high frequency (7–11 Hz) theta activity in the hippocampal EEG. Many hippocampal pyramidal cells fire a series of bursts as the animal moves through the place field, with an interburst interval slightly shorter than the period of the concurrent EEG theta wave (Fig. 2A,B). The result of this is that the timing of the spikes relative to the EEG cycle changes as the animal progresses through the field, with each

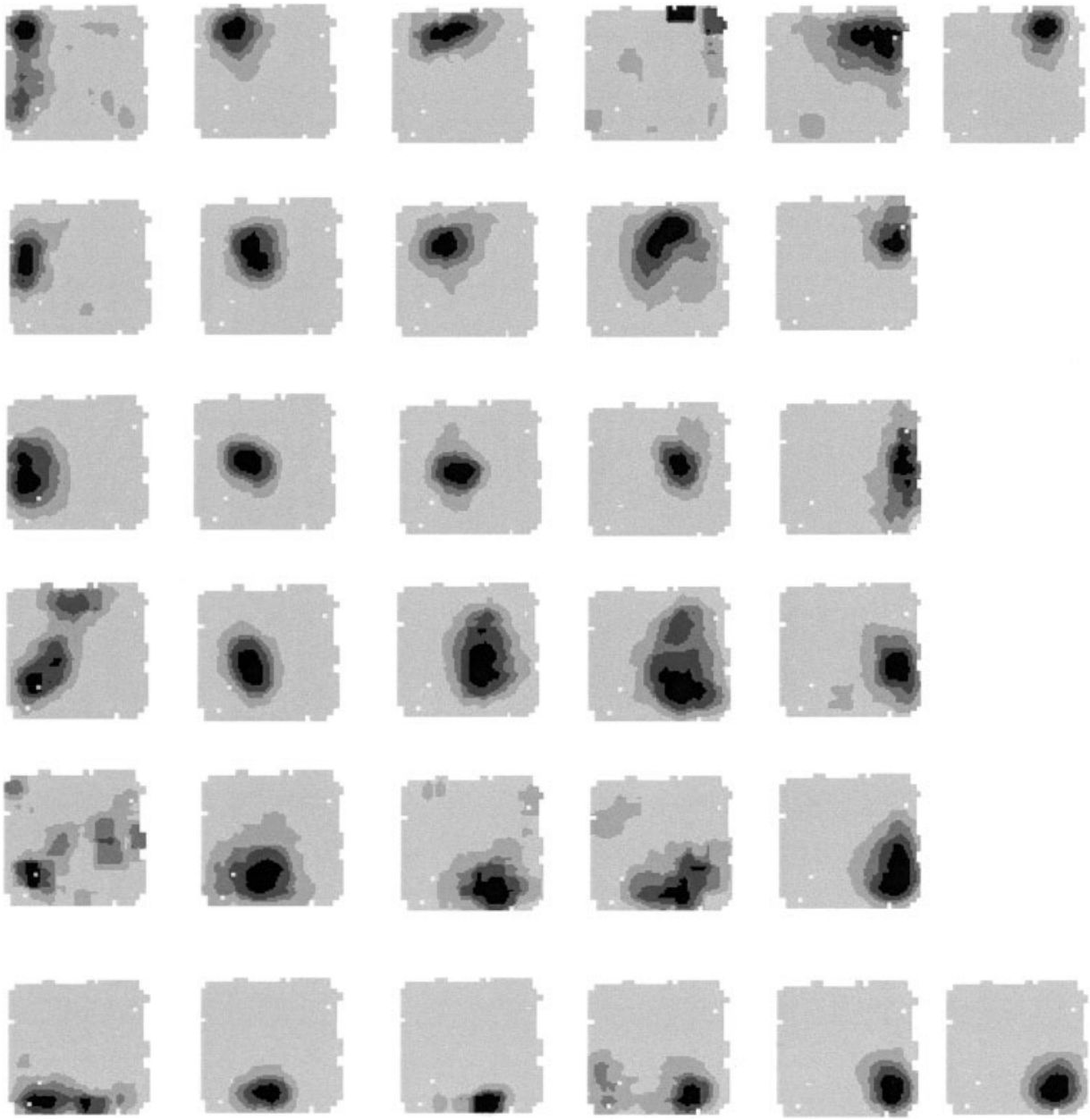

FIGURE 1. Firing rate maps for 35 place cells simultaneously recorded on multiple tetrodes (Recce and O'Keefe, 1989) in dorsal CA1. Each cell fires in well-localized portion of its environment. Firing rates (smoothed plots of number of spikes divided by time spent at each location) are shown in gray-scale plots with the darker shades signifying higher firing rates auto-scaled to the maximum for each cell. Adapted from Lever et al. (2002).

burst occurring at an earlier phase of the cycle (Fig. 2C). Phase correlates better with the animal's location than with temporal variables such as the time from the beginning of the run or the time since entering the place field (O'Keefe and Recce, 1993). The implication of this finding is that there is an adjustment of the time of spike firing and the frequency of the theta activity to take into account the variations in the speed of running on different trials. It has been suggested that the phase coding of location could be additional to the rate code, perhaps acting as a vernier to improve the localization of the animal. Using data from Skaggs et al. (1996), Jensen and Lisman (2000) showed that taking phase into account lead to an improvement in the ability to localize the rat by 43%.

Run-by-run analysis of the firing rates through the place field indicates a high degree of variability (Fenton and Muller, 1998). This leaves open the possibility that variations in firing rate, above the threshold rate needed to establish the place field, might convey additional information about other variables. For this to be true, however, the phase information and the rate information would need to be independent of each other. Although there has been some suggestion to the contrary (Harris et al., 2002; Mehta et al., 2002), our evidence supports the rela-

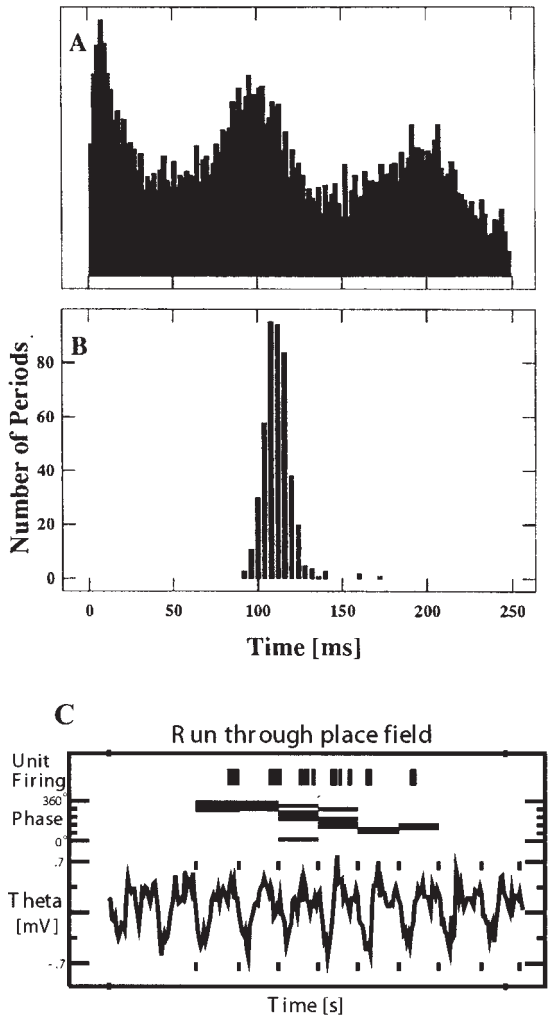

FIGURE 2. Many hippocampal pyramidal cells fire a series of bursts as the animal moves through the place field with an interburst interval (see autocorrelogram in A) slightly shorter than the period of the concurrent EEG theta wave (shown in B). C: The result of this is that the timing of the spikes relative to the EEG cycle changes as the animal progresses through the field with each burst of spikes occurring at an earlier phase of the cycle. Adapted from O'Keefe and Recce (1993).

tive independence of phase and rate. Huxter et al., 2003, showed that within the field the firing rate increases and decreases, while the phase continues to precess to earlier parts of the theta cycle throughout. Furthermore it is possible to find cells whose firing rate varies considerably from one trial to the next without any change in the phase correlate. Indeed, the phase correlate can be present in cells firing a single spike per run, ruling out mechanisms dependent on habituation or spike-frequency accommodation (see Fig. 3A).

Although the clearest data regarding phase precession, including that referred to above, comes from rats running along a narrow track, it is also possible to note a related behavioral correlate of firing phase in rats exploring in the open field. On a narrow track a place cell tends to fire only when the rat is running through the place field in one direction, and not when it runs through it in the other direction (McNaughton et al., 1983; but see Battaglia et al., 2004). In this situation, phase of firing correlates directly with position within the field, see earlier. In open field environments allowing free movement in two dimensions, place cells fire independently of direction (Muller et al., 1994). Now, although less clear, the phase of firing correlates with the distance the rat has passed through the place field *along the current direction of travel*, initial spikes being fired at a late phase of local theta and subsequent spikes being fired at successively earlier phases. Put the other way around, spikes from cells with fields centered ahead of the rat are fired at a late phase, while those from cells with fields centered behind the rat are fired at an early phase (Burgess et al., 1994; Skaggs et al., 1996).

Note that these observations of phase precession in the open field offer a potential explanation of how the preceding pattern of firing of the local "cell assembly" can enhance prediction of the timing of firing of a specific place cell (Harris, 2003): by signaling both the animal's location *and direction of travel* and thus indicating its likely phase of firing (the author controlled for the phase of firing predicted by location, but did not take direction into account).

Firing Rate Correlates With Speed of Running

If the firing rate can vary independently of the animal's location and the phase precession, what does it correlate with? Previous studies have reported a correlation between speed of running and place-cell firing rates (McNaughton et al., 1983; Czurko et al., 1999; Ekstrom et al., 2001). In our data (Huxter et al., 2003), fast runs through the place field are associated with higher firing rates than are slower runs. When we separated runs into the swiftest 25% and the slowest 25%, we found that the firing rates were systematically higher during the former. On average the correlation between runs and firing rate was 0.2, but within this average there was a wide variation with some cells yielding correlation coefficients of 0.5. The positive but low overall correlation suggests that speed of movement is only one of the variables that can be represented by firing rate. For example, Wiener et al. (1995) found that firing rate was also modulated by speed of turning within the place field. We have known for many years that the presence or absence of particular objects or stimuli in the place field can increase the firing rate (O'Keefe, 1976). Recently Wood et al. (1999) reported the existence of odour-in-place cells that fired maximally when a particular odour occurred in a particular location. It is not known whether the phase precession remained constant during these perceptual and behavioral variations or changed independently of the rate, but it is a reasonable working assumption that many variables occurring in the place field can be represented by firing rate independently of the phase. That is, simultaneous dual coding of information by the rate and timing of spikes may be a general coding strategy in hippocampal pyramidal cells.

Can We Be More Specific About the Spatial Variable Correlated With Pyramidal-Cell Firing Phase?

Firing phase shows a good correlation with the animal's location on the linear track. But is this with respect to the absolute

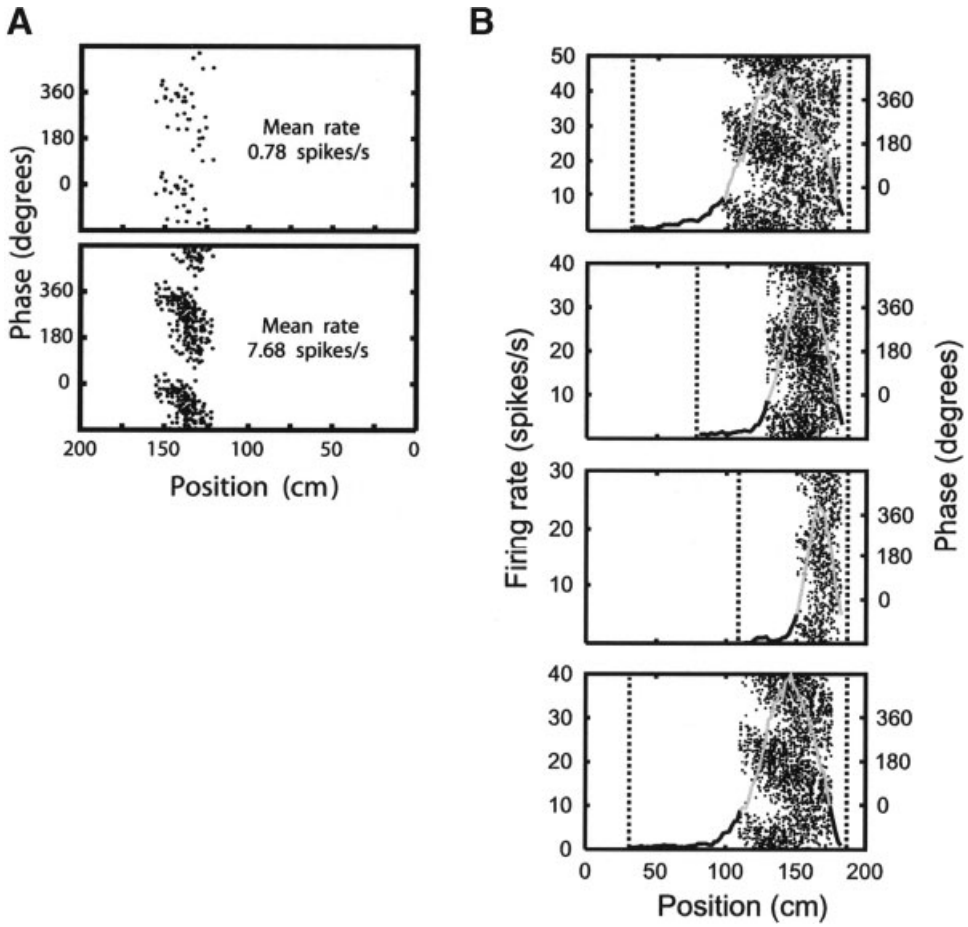

FIGURE 3. Phase precession, firing rate, and field size. A: Phase precession occurs similarly on low- and high-firing rate runs. Runs through the place field were divided into two equal groups according to the number of spikes fired. Data are shown for one low-firing rate cell. B: Rate of phase-precession scales with field size. Explorable portion of linear track shown by vertical dotted lines. Phase of spikes is shown by dots and scale on right, firing rate by black/gray line and scale on left. Central 90% of the firing field was analyzed, shown in gray. Adapted from Huxter et al. (2003).

location relative to the room or to the relative location within the field (i.e., relative to the size of the field)? What would happen if we shrank or lengthened the field? We know from previous work (Muller and Kubie, 1997; O'Keefe and Burgess, 1996) that changing the dimensions of the testing apparatus alters the size of some place fields; for example, changing a square environment into a rectangular one by stretching one of its two dimensions leads to an elongation of some place fields in that dimension. This is because some cells try to maintain a fixed distance to large landmarks such as the box walls in opposite directions, and moving those walls relative to each other causes the field shape to change (Hartley et al., 2000). We tried a similar manipulation on the linear track (Huxter et al., 2003). After baseline trials on the standard 1.5-m track to establish the field sizes, peak firing rates, and phase-precession characteristics, the end walls were moved closer together compressing the track length to 1.0 or 0.75 m and the changes in the fields recorded. A typical example of the field changes is shown in Figure 3B. The field shrinks, the peak firing rate decreases, and the slope of the phase precession increases. The decrease in firing rate coupled with an increase in the slope of the phase precession is another example of the uncoupling of these variables. In a related finding, Ekstrom et al. (2001) blocked LTP by administration of the NMDA receptor blocker CCP. They observed normal phase precession in the absence of the experience-dependent asymmetric place-field expansion, again emphasizing the ability of these processes to occur independently. In Huxter et al.'s shortened-track data, the increased rate of phase precession with position correlated with the reduction in field size, and had no relationship to the change in firing rate. There was insufficient data to decide whether the relationship between rate of phase precession and field size is linear or an inverse one. If it turns out to be the latter, then the increase in rate of phase precession would be exactly compensating for the reduction in field size so that the phase would be a good measure of the proportion of the field traversed regardless of its absolute size, as would be predicted by an interference model of phase precession, see below.

Reading the Rate and Phase Codes

These results indicate that the same spike train can code for two variables at the same time, and that the two variables can vary independently of each other. Firing rates can vary by as much as an order of magnitude without changes in the slope of the phase precession. Altering the size of the place field by compressing the track results in a compensatory increase in the angle of the phase precession, independently of any changes in the firing rate. One question that arises is whether circuitry exists within the hippocampus itself or in downstream structures capable of reading these two codes. One way this could be accomplished would involve the existence of two filters, one selectively tuned to the timing of spikes, and the other, to the number of spikes in a train. Pouille and Scanziani (2004) have recently identified two different types of CA1 hippocampal interneurons that are ideally suited to carry out this task. One type ("onset-transient") has a high probability of responding to the first stimulus in a train but ignores the rest; the second type ("late-persistent") rarely responds to the first stimulus but increases its probability of spiking as a function of the number of stimuli in the train, up to about four. The onset-transient cells preferentially target the somata of the pyramidal cells and might be any of the interneurons, including basket cells, which target this region, while the late-persistent cells target the apical dendrites of the CA1 pyramidal cells and may be O-LM cells (Klausberger et al., 2003). It seems reasonable to assume that the same train of action potentials impinging on these two different interneuronal types would initially lead to an IPSP in the soma of the pyramidal cells timed with reference to the first spike in the train, and subsequently to an IPSP in the apical dendrites whose magnitude depended on the number of spikes in the train. The separation of function is strengthened by the O-LM cells being active later in the theta cycle (19°, or the negative trough of CA1 theta), while the basket cells tend to fire on the descending ± phase (271°) (Klausberger et al., 2003).

WHAT CAUSES THE PHASE PRECESSION?

It is reasonable to suppose that most or all of the hippocampal pyramidal cells are undergoing subthreshold oscillations in membrane potential at the EEG theta frequency when the cells are not firing. In vitro experiments in hippocampal slices have shown that intracellular potentials in CA1 cells are 180° out of phase with the population EEG theta. Furthermore, many of the theta-cell interneurons fire in phase with the EEG theta and do not show strong indications of phase precession. The synchronous IPSPs in the target pyramidal cells account for at least part of the global EEG theta signal (Buzsaki, 2002). The question then is what causes the bursting frequency of individual pyramidal cells to increase above the theta frequency when they begin to fire in the field.

The simplest model for the shift of the spike bursts relative to the population EEG theta is an increasing level of depolarization causing the EPSP to reach the firing threshold earlier on each successive cycle (Harris et al., 2002; Mehta et al., 2002). To produce the observed monotonic phase precession under this simple model requires a monotonically increasing input to the cell over the spatial extent of the place field. Mehta and colleagues (2002) reported evidence supporting this model: both place field asymmetry (i.e., resemblance to a monotonic increasing shape) and the strength of the phase-precession effect increase together over the course of the first few trials of each session. Equally, the simple model would predict a negative correlation between the number of spikes per theta cycle and their mean phase, as both respond to the cell's increasing input. Harris et al. (2000) reported such a correlation between phase and rate. However, as we noted earlier, the firing rate typically increases until the animal reaches the center of the field, after which it decreases, resulting in a roughly Gaussian firing field profile, whereas the phase precession continues throughout the field. Furthermore it is pos-

FIGURE 4. The relationship between the phase and instantaneous rate of place-cell firing on a linear track may derive from the relationship of both firing phase and firing rate to the rat's position. A: Scatter plots showing the relationship between phase and position, instantaneous rate (i. rate) and position, and phase and instantaneous rate for six CA1 place fields. Correlation coefficients (r) and associated regression lines, taking account of the circular nature of phase, show the greater range and strength of the variation of phase with position than with rate. See Huxter et al. (2003) for details and for population summary statistics. B: Analysis of spikes pooled across cells, as in Harris et al. (2002), showing the relationship between phase and position, rate and position, and phase and rate (25,158 spikes, 77 fields). Points show the appropriate (circular or linear) mean, error bars show the appropriate (circular or linear) standard error. Rat position data was scaled to reflect the proportion of the distance traveled through each field. These analyses combine the absolute phases of spikes from different cells relative to the theta rhythm in the EEG local to the cell, irrespective of cells' different locations and overall firing rates. They replicate the relationship between phase and rate found by Harris et al. (2002) (right), but suggest that it derives from the stronger and steeper correlation between phase and position (left), and the relationship between rate and position (middle). C: Simulation showing how a weaker and shallower regression of phase on rate can result from a stronger and steeper regression of phase on position. Note (right plot) that the late-field firing (light gray) influences the regression line less than the early-field firing (black) because of the increasing variation in phase with position. The reliability of this subsidiary phase–rate correlation increases with the number of data points, explaining the stronger correlation for the pooled data ($r = -0.37$, see B) than the average correlation for the individual cells (mean $r = -0.07$, Huxter et al., 2003). Data for phase φ and instantaneous rate r were simulated as functions of position in the place field x according to:

$$\{\varphi, r\} = \{350 - 250x/L + 75\mu_1 x/L, 15(1 - (2x/L - 1)^2) \times (\mu_2 + 2.5\ (1 - (2x/L - 1)^2))\},$$

where μ_1 and μ_2 are drawn from a unit Normal distribution and L is the length of the place field (shown as 40 cm). Adapted from Huxter et al. (2003, supplementary Fig. 1).

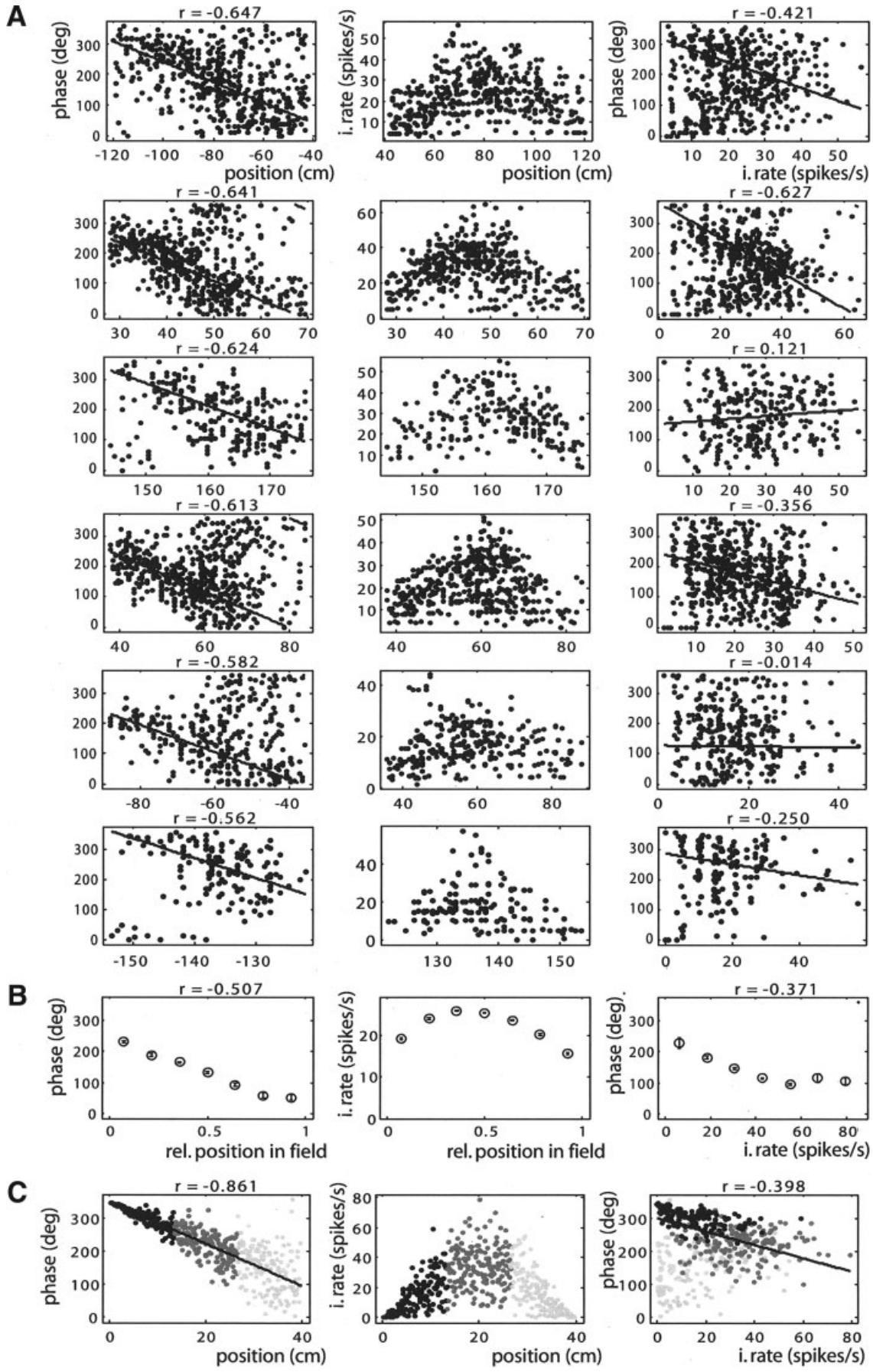
A
r = -0.647
phase (deg)
position (cm)
i. rate (spikes/s)
r = -0.421
i. rate (spikes/s)
r = -0.641
r = -0.627
r = -0.624
r = 0.121
r = -0.613
r = -0.356
r = -0.582
r = -0.014
r = -0.562
r = -0.250
B
r = -0.507
rel. position in field
r = -0.371
C
r = -0.861
r = -0.398

FIGURE 4

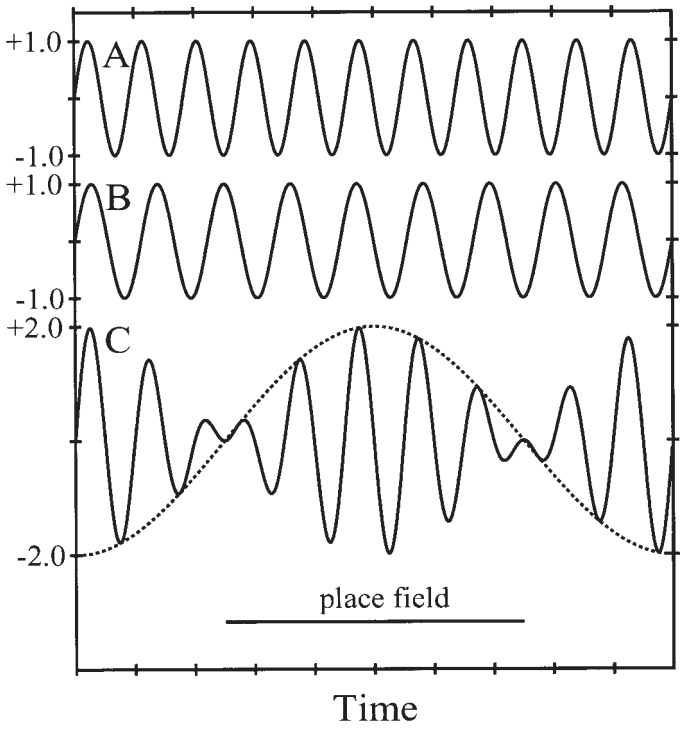

FIGURE 5. Interference pattern formed by the summation of two sinusoids of different frequencies. The wavelets will repeat at regular intervals. (Taken from O'Keefe and Recce (1993)).

sible to see that faster runs through the place field in which the firing rate is high show the same phase precession as the ones in which the rate is much lower. Thus we do not think the simple model provides a good explanation for the phase-precession effect (see Huxter et al., 2003).

The apparent discrepancy between the results of Huxter et al. (2003) and Harris et al. (2002) and Mehta et al. (2002) demands further explanation. It now seems likely that the results of Mehta et al. (2002) are due to the appearance, over the first few runs through the field, of a small number of spikes at fixed (late) phase prior to the entry to the place field, which provide an extended initial tail to the bulk of the distribution. Although they fall outside the main body of the field considered by Huxter et al. (2003) (i.e., the 90% of spikes closest to the field peak), and do not show phase precession themselves, the sometimes large distances by which they precede the field results in both a change in the overall asymmetry of the field and in the strength of the correlation between phase and position. We believe that the correlation between phase and rate reported by Harris et al. was caused by the twin relationships of firing rate to position (first rising, then falling) and of phase to position (phase decreasing with position, but also increasing in variance) (See Fig. 4).

Interference Models of Phase Precession

The combination of an inverted U-shaped firing rate profile with a monotonically changing phase correlate suggested to O'Keefe and Recce that it would be difficult to explain the latter in terms of the former. By contrast, the addition of two waves of slightly differing frequency would produce such a pattern (see Fig. 5). It was known from the work of Vanderwolf, and Bland and others (e.g., Lawson and Bland, 1993) that the cholinergic theta and noncholinergic movement-related theta had slightly different frequencies, and it was not unreasonable to assume that both impinged on the same cells producing the wavelet pattern of activation. A physiologically plausible model that assumes that the two theta-like waves impinge on the hippocampal pyramidal cell has been presented by Lengyel et al. (2003; see also Huhn et al., this issue). They also noted that the 180° of phase precession in one lobe of the standard interference pattern could be increased to nearly 360° if the higher frequency oscillation has higher amplitude than the theta oscillation.

One problem for interference models is that they predict a repeating series of firing fields rather than a single one. However, as we discuss later, this type of regular pattern of firing fields has recently been observed in the medial EC (mEC; Hafting et al., 2005). (See Fig. 6.)

The second problem is the need for a correspondence between the temporal interference pattern and the animal's spatial location. The location of the firing field within the environment is usually thought to be determined by sensory input to the place cell somehow gating its activity (Lengyel et al., 2003). Beyond this, the frequency of the higher oscillator may be thought to increase with running speed so as to maintain a better relationship between phase and location than between phase

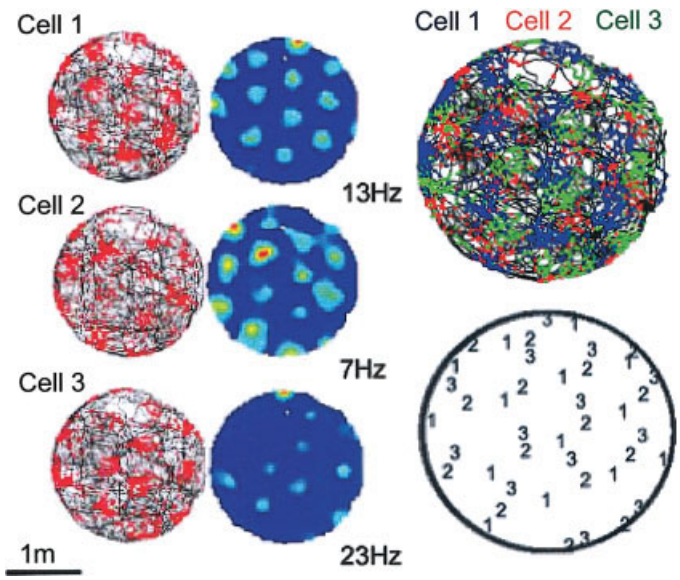

FIGURE 6. Three grid cells recorded in the dorsocaudal mEC. Left: scatter plots of spike locations (black) on the path of the rat (gray) of three nearby and simultaneously recorded grid cells. Middle: firing rate maps of the three grid cells. Right: the spike locations (above, in different colors: black, gray, light gray) and locations of peak firing rate (below) for the three cells shown together (labeled numerically). Nearby grid cells show aligned but slightly translated triangular grid-like firing patterns. Adapted from Hafting et al. (2005) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

and time (e.g. Lengyel et al., 2003), at least for movements in a straight line.

Evidence for Oscillators of Differing Frequencies

The idea that the phase-precession effect is due to two oscillators of differing frequencies would be greatly strengthened if they could be found. A search for cells in the two major input into the hippocampus, the medial septum and the EC, has failed to reveal cells with frequencies different from the hippocampal theta rhythm (Jeffery et al., 1995; King et al., 1998). This leaves open the possibility that the second oscillator is actually intrinsic to the place cells themselves, possibly located in the dendrites (Kamondi et al., 1998; Lengyel et al., 2003). The paper by Maurer et al. (this issue) provides some evidence for this view. In their experiment, place cells in the dorsal hippocampus had a higher (intrinsic) frequency of oscillation than those located more ventrally despite no differences in the frequency of the EEG theta or the theta cells in the two regions. It is suggested that, consistent with an interference model, the dorso-ventral gradient in intrinsic frequency (higher in the dorsal hippocampus) causes the gradient in the spatial extent of the firing fields (smaller fields in the dorsal hippocampus). More specifically, the interference of two sinusoidal oscillations corresponding to a global theta input (frequency f_θ) and a slight higher intrinsic oscillation (frequency f_I) would lead to an oscillation frequency of $(f_I + f_\theta)/2$ and amplitude modulation of $\cos[(f_I - f_\theta)t/2]$. Thus, if the rat is running in a straight line at constant speed(s), the field size would be proportional to (and the distance between successive peaks would be equal to) $2\pi s/(f_I - f_\theta)$.

Does Firing Phase Reflect Internal Hippocampal Dynamics or Representation of an External Variable?

Many models of phase precession suggest that it is due to the internal dynamics of the hippocampal network. For example, one particularly popular model (Tsodyks et al., 1996; Mehta et al., 2002; Lisman and Hasselmo, this issue) holds that the temporal advance of spikes is due to initial (late-phase) firing being driven by input from cells with place fields earlier on the track, while (early-phase) firing toward the end of the place field is driven by external input from the environment. The delay in conduction of activity from the cells with fields earlier on the track causes the later phase of the initial spikes. An alternative type of model is that the phase of place-cell firing directly reflects some aspects of the environment (O'Keefe, 1991) or reflects an already phase-coded entorhinal input (Burgess et al., 1994).

A recent study by Zugaro et al. (2005) suggests that phase precession is indeed determined by the input to the hippocampus rather than to its internal dynamics. They delivered a single 0.1-μs duration electric shock to the fibers of the ventral hippocampal commissure, which had the effect of resetting the phase of the hippocampal theta and inhibiting all recorded cells for ~200–250 ms. They found that when the cells began firing again they did so at the appropriate phase of the (reset) theta to correctly code for the animal's location at that point. This finding appears to be incompatible with a view that the internal dynamics of the hippocampal formation determines the phase precession and suggests that firing phase is determined by inputs external to the hippocampus that were not affected by the intervention. The most likely source of this positional information is the EC, which has direct projections to the CA3 and CA1 pyramidal cells as well as to the dentate granule cells. Zugaro et al. provided indirect evidence that their stimulation did not markedly affect the entorhinal–hippocampal pathways since they did not observe a rebound evoked-potential characteristic of synchronous stimulation of these via the feedback CA1-to-entorhinal pathway. As we shall see in the next section, the mEC contains grid cells that are theta-modulated and could identify changes in the animal's location in the environment independent of the hippocampus.

RELATIONSHIP OF PLACE CELLS TO MEDIAL ENTORHINAL "GRID" CELLS

In a recent paper, Hafting and colleagues (2005) have identified a group of cells in the mEC that provide a grid structure that could form the basis of the Euclidean distance and direction metric postulated by the cognitive map theory of hippocampal function (O'Keefe and Nadel, 1978). Each cell fires in several locations in an environment, with the locations forming a regular pattern as though they were nodes on a triangular grid (Fig. 6). Different cells recorded at the same location have the same grid spacing and orientation relative to the environment. They differ however in the location of the nodes such that the firing peaks of one cell are slightly shifted from those of its neighbor. The multiple fields of several such cells together cover the environment. For each cell, the size of the grid appears to be independent of the size or shape of the environment. The orientation of the grid relative to the environment, however, is dependent on the location of a polarizing visual cue on the wall of the enclosure in much the same way as the postsubicular head direction (Taube et al., 1990b) and the hippocampal place cells (Muller and Kubie, 1987). Cells located at increasing depths from the postrhinal border form grids whose nodes have fields of increasing size and spacings.

Grid cells are theta-modulated although the phase relationships of their firing to each other, to other cell types, and to EEG theta are not known, nor is it known whether or not they show phase precession. It does however mean that they are part of the theta system. Grid-cell firing seems to parallel hippocampal place-cell firing in terms of a progression from smaller to larger spatial extent of firing fields moving away from the postrhinal border within the mEC—corresponding to the dorso–ventral (septo-temporal) axis of the hippocampus and consonant with the topography of projections between the two regions (Dolorfo and Amaral, 1998).

How Might the Grids Be Formed?

The regular pattern of firing on the linear track (Hafting et al., 2005) is strikingly reminiscent of the multipeaked inter-

ference pattern suggested by the interference model shown in Figure 5. This would imply that mEC grid cells have an intrinsic oscillation slightly higher than theta frequency, and that their firing results from interference between the two frequencies, as discussed earlier for hippocampal place cells.

Alonso and colleagues have identified a theta generator in the mEC layer II, which is independent of hippocampal theta. Stellate cells in layer II of mEC slices exhibit subthreshold oscillations in the theta range (8–9 Hz, Alonso and Llinas, 1989) in response to depolarization. Interestingly, the action of the cholinomimetic carbachol is to not only depolarize the cells, and to facilitate the appearance of the subthreshold oscillations, but to reduce their frequency from 8–9 Hz to 6 Hz (Klink and Alonso, 1997). This latter effect is reminiscent of the lower frequency of atropine-sensitive theta found in the hippocampus and suggests that there are two thetas with different frequencies present in the medial entorhinal layer II cells as well.

The increasing spatial scale of the grid-like firing as you move from the postrhinal border of the mEC would result from a gradually decreasing intrinsic frequency, as suggested for the hippocampus by Maurer and colleagues (this issue). Experimentally, the intrinsic oscillation frequency and phase-precession effects should be observable in the grid cells. However, any mechanism based on temporal interference patterns, or on path integration (see later), would need to be anchored to the sensory input from the environment to produce a reliable spatial organization, such as that seen in the grid cells. Indeed it is noticeable (Hafting et al., 2005) that the two spatial patterns of a grid cell's firing as the rat runs in both directions on a linear track seem to align with each other when visual cues are present but not when they are absent.

What Might the Grids Be Used For?

We first make one suggestion regarding their direct use for spatial computations, and then go on to consider their potential role in a wider network, including place cells, for combining path integration and environmental inputs in the representation of spatial location.

The amazingly regular structure of the firing patterns of grid cells suggests that they be used directly to calculate spatial translations. We note that some entorhinal cells can directly integrate their input over long timescales (Egorov et al., 2002), although these were recorded in layer V rather than layer II (where the grid cells were reported). If grid cells, head-direction cells, and these integrator cells could be connected so that a given integrator cell receives input from a given grid cell (or a set of grid cells covering the environment, see Fig. 7B) cosine-modulated by the animal's direction of movement, then it would be possible for the firing of different integrator cells to directly reflect the distance traveled by the animal in a given direction. In addition, the input would also need to be proportional to running speed, either because grid-cell firing rate increases with speed of movement (this is not known, although place-cell firing rates do—see above), or because of the modulation of the input by "speed cells" (O'Keefe et al., 1998) or possibly by the modulation of the head-direction input by speed (Sharp, 1996). Two such integrator cells tuned to perpendicular directions would provide a direct Euclidean encoding of the geodesic between the start and end of the movement. Such a path-integration device would need to be related to the environment to calculate trajectories to useful places other than the start of the previous trajectory (e.g., to perform more general "spatial updating" of locations in the environment). To this end, we consider a model of the grid cells' interaction with place cells.

Grid Cells as the Path Integration Input to Place Cells

Because different grid cells differ in terms of the orientation and spatial scale of the corresponding grid-like firing pattern, it is easy to imagine how the firing of grid cells could support the firing of place cells. All that is required is that all the grid cells with peak firing rates at a given location be connected to the place cell (or cells) whose place fields are centered at that location. (Whether this is arranged developmentally or on first exposure to an environment is not clear. Some type of Hebbian synaptic modification would suffice either way.) The summed input from these cells will be maximal at the center of the place field and will fall off with increasing distance from it as the grids of different orientation and scale no longer align. The firing of place cells allows navigation to specific previously visited locations (Burgess et al., 1994), which would not be directly possible from grid-cell firing itself.[1] In the model of place-cell firing outlined here, the number and spatial scale of the grid cells driving each place cell should relate to the number of multiple fields seen in place cells (corresponding to locations where enough grids coincide to exceed the place cell's firing threshold). Further, the small shifts in grid-cell firing observed when the rat is placed in a new environment (Hafting et al., 2005) are consistent with the "remapping" observed in simultaneously recorded place cells as the firing patterns of the grid-cell inputs will no longer align as before.

The first suggestion regarding the relationship of the grid cells to environmental input and to place cells (and the two may be related, see later) is that they might provide the path integration input for place cells. As pointed out by Hafting et al. (2005; see also Hargreaves et al., 2005), the fact that nearby grid cells vary only by translation of their grid suggests that they provide a natural substrate for a path-integration mechanism by means of local recurrent connections. We outline such a mechanism below (see Fig. 7). By analogy with the continuous attractor models of CA3 (McNaughton et al., 1996; Zhang, 1996; Samsonovich and McNaughton, 1997), a path-integration system would result from learning asymmetric

[1]The model's use of a set of goal cells (Burgess et al., 1994), each with firing slightly shifted in specific allocentric directions so that their relative firing rates provide the direction to the goal as a population vector, may relate to the slightly shifted patterns of nearby grid cells' firing.

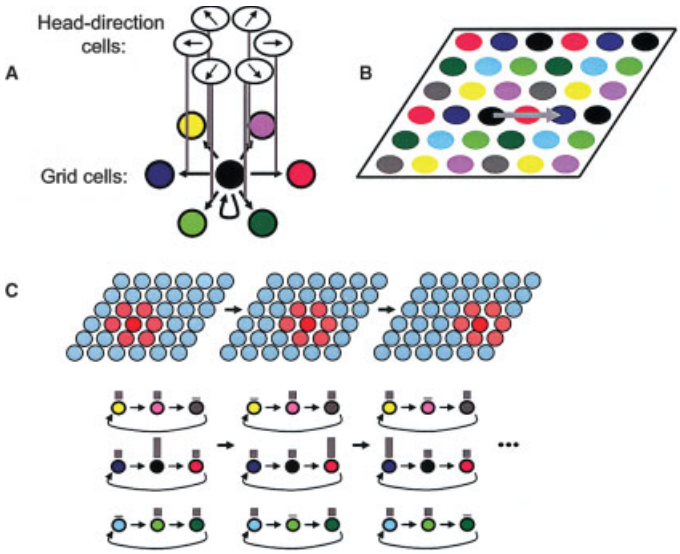

FIGURE 7. Schematic of medial entorhinal grid cells as a substrate for path integration. A: Connections between grid cells with aligned but shifted grid-like firing patterns (see B) suitable for supporting path integration. The connections from one cell (the central, black cell) are shown (black arrows). It has connections to each neighbor that are modulated by input from head-direction cells (gray lines) tuned to the direction in which that cell's firing pattern is shifted. This modulation might occur via interactions in the dendrite of the target cell, or via an expanded grid *x* direction representation elsewhere (modulation via running speed is also required). B: Locations of peak firing of the grid cells in part A (plus two more, gray and turquoise, for complete coverage). The gray arrow shows the movement corresponding to activation patterns shown in C). C: The changing pattern of activation (shown in red) when the rat moves as shown in a population of place cells (above: each one represented by a circle in the location corresponding to the location of its firing field), and in the nine grid cells whose firing patterns are shown in B) (below: firing rates shown by a bar above each cell). The nine East-modulated connection weights shown are sufficient to support continued path integration of ongoing Eastward movement of the rat. The connections between these 9 grid cells are repeatedly used to support path integration along any trajectory in any environment, allowing continual fine-tuning. Many more, much less frequently used, connections and cells would be required for path integration to be calculated in the CA3 place cell layer.

(and head-direction mediated) connection weights between grid cells with grids that are shifted relative to each other along the corresponding direction.[2] In fact the rate of shift of activity (Zhang, 1996) should be proportional to running speed, perhaps involving mediation of connections by "speed cells" (Sharp, 1996; O'Keefe et al., 1998) as well as by head direction cells.[3] Thus, when the rat is moving East, activity can spread from one grid cell to the neighboring cell with an East-shifted grid (see Fig. 7). If it applies to grid cells, the property of phase precession of place cells in the open field of cells with fields centered ahead of the rat firing after those with fields centered behind it, but both firing within the same theta cycle (Burgess et al., 1994; Skaggs et al., 1996) means that these connections could result naturally from spike-time dependent plasticity (associating the field behind to the field in front). Thus this view predicts that phase precession occurs in each node of a grid as it does in place cells, and that place cells' phase precession may be sustained by their mEC inputs independently from the internal dynamics of the hippocampus itself.

The above scheme has already been proposed for place cells (McNaughton et al., 1996; Zhang, 1996; Samsonovich and McNaughton, 1997), so what advantages do grid cells offer? The cyclically repeated firing pattern of grid cells means that a small connected set of nearby grid cells (whose firing patterns are offset relative to each other but have the same orientation and scale) can support path integration throughout an environment. Figure 7 shows the firing of a set of nine grid cells that cover the environment. Learning asymmetric connections between these cells is sufficient to support path integration across the whole environment (grid cells would be too few otherwise the connections will be symmetric: the "asymmetric" connections from *A* to *B* equalling those from *B* to *A*). Thus the learning of suitable connection strengths can continue unperturbed by the animal moving to a different part of the environment. (See Fig. 7.) The learning of such connections among place cells would require every location in the environment to be traversed

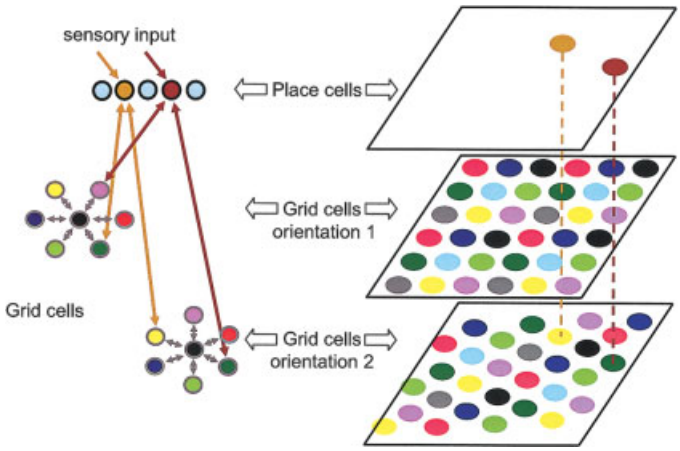

FIGURE 8. Relationship of grid cells to place cells and sensory input. Place cells are needed to read-out grid-cell firing corresponding to a single location; to allow association of grid cell firing with the sensory input in a given location, so as to give a reliable correspondence between grid cells and the environment; to allow different grids to support each other (as connections between them are only valid at given places, connections between different grids need to be mediated by place cells). By associating place cells with the grid cells that happen to fire at the same location, place cells can serve both to read-out the result of path integration by sets of connected grid cells, and via feed back connections, to enable it to be maintained in register with sensory input and with other sets of connected grid cells.

[2]See Conklin and Eliasmith (2005) for an equivalent CA3 path integrator model that avoids using multiplicative synapses, or Hausser and Mel (2003) for processes that might effectively multiply inputs occurring locally on a dendrite.

[3]We note that the breadth of tuning of head-direction cells (full width half maximum is roughly 60°) is appropriate to mediate connections along the six directions of the triangular grids.

in each direction at least once. Different sets of nearby grid cells can independently learn connections appropriate to the orientation and scale of their grid-like firing pattern. If entry to a new environment (see earlier) only causes relative shifts in the firing patterns of different connected sets of cells, but not of different cells within a set, then each set can continue to learn path-integrating connections unperturbed even by environmental changes that cause remapping of place cells. Hafting et al. (2005) and Hargreaves et al. (2005) also point out that the mEC is anatomically well placed—receiving direct input from the head-direction cells of the postsubiculum which the place cells do not.

How is the firing of grid cells related to environmental inputs and place-cell firing? The grid cells acting alone as a path-integration device lack three properties: (i) a read-out mechanism; (ii) association to sensory inputs to maintain a stable relationship between grid locations and environment over time; (iii) association between different connected sets of grid cells to maintain a stable relationship between grids at different orientations and scales (and thus also provide additional stability, robustness to noise, local damage, cue removal etc). The read-out mechanism could operate via the place-cell code, as described earlier. However, we argue below that properties (ii) and (iii) probably also depend on the place cells (see Fig. 8).

Relating the Grids to the Environment and to Each Other

Because grid cells fire in multiple locations, they are inappropriate for associating the sensory input specific to a single place, which would be the simplest way to fix the grid to the environment. By contrast, a given place cell is caused to fire in a given location in response to some particular sensory input (O'Keefe and Burgess, 1996; Hartley et al., 2000). Thus feedback from a place cell to the grid cells that happen to fire in the same location as the place cell does on the first trial in an environment will serve to ensure that they both continue to fire in that location in future (see Fig. 8). Similarly other grid cells will be associated to the locations of other place cells, fixing the grids to the environment. Finally, we note that remapping might be initiated in the place cells in response to environmental input; rather than simply reflecting relative shifts of mEC grids, the altered pattern of place-cell firing might cause relative shifts in the firing of different local sets of grid cells, as their altered pattern of firing feeds back onto different sets of grid cells, fixing them to different locations in the environment. Thus producing environmentally-appropriate remapping might be the role of the recurrent connections in CA3 via point-attractor-like dynamics (Wills et al., 2005), rather than providing a continuous attractor path integration device.

The grid cells in connected sets supporting grids at different orientations and scales cannot be directly connected to each other: even if their firing overlaps at a given location, nearly all of the other locations at which one of them fires will not coincide with firing in the other. Different pairs of grid cells need to be associated to each other at different locations in the environment. Again, this can be done via connections from grid cells to place cell and feedback from place cells to grid cells, as described earlier (see Fig. 8). The connection between pairs of grid cells whose firing happens to overlap at a given location can be mediated by the place cell that fires at that location and is connected to both of them. One of these grid cells will overlap with a different partner in another location and can be connected to that grid cell at that location via the place cell that fires at that location.[4]

We have proposed a system of local sets of grid cells that can act as a continuous attractor supporting path integration and are connected to environmental input and to each other via the place cells. The overall structure of a path-integration system, including EC and hippocampus, follows Hafting et al. (2005) and Hawley et al. (2002), and is not inconsistent with an earlier proposal by Redish and Touretzky (1997). The proposed mechanism resembles some models of CA3 as a path integrator (McNaughton et al., 1996; Zhang, 1996; Samsonovich and McNaughton, 1997), but we argue that the cyclic firing patterns of grid cells make them a more efficient substrate for forming the connections necessary for path integration than CA3. The proposed relationship between grid cells and place cells is consistent with the effects of hippocampal lesions on grid-cell firing (Fyhn et al., 2004), namely spatial firing patterns becoming less stable from trial to trial and less evenly distributed over directions.

CONCLUSION

The theta system appears to play a crucial role in the organization of spatial information throughout the hippocampal formation. It unifies the various anatomical structures into an organized whole to allow cooperative behavior across a large number of principal cells and interneurons. Within the hippocampus, the theta system provides a basic clock cycle against which the time of spikes can be measured to provide a fine-grained spatial localization via the phase coding of place cells. This appears to leave variations in overall firing rate free to code for nonspatial variables such as the speed of running and, perhaps, the nature of objects or actions occurring in a given location.

It also seems possible that the spatial firing of medial entorhinal grid cells and hippocampal place cells results from the interference pattern generated by theta interacting with intrinsic oscillations in the cells concerned. Such a model may explain

[4]An alternative to the earlier description of path integration via asymmetric connections between grid cells would be for grid cells to connect to other grid cells with slightly shifted firing patterns via ''place by direction'' cells in the presubiculum (Sharp, 1996; Cacucci et al., 2004). These cells could provide the appropriate modulation by head direction and, possibly, running speed, but would again require large numbers of connections—as with the CA3 path integration models, unlike the efficiency of the proposed use of small numbers of connections within local sets of grid cells.

the physical distribution of the spatial scales of these firing patterns and also the phase-precession effect observed in place-cell firing. In addition, the observed spatial pattern of firing in EC may provide the basic distance metric, which, when combined with the head-direction input from the dorsal presubiculum, may underpin a path-integration system. Such a system corresponds to the metric posited by the cognitive map theory of hippocampal function (O'Keefe and Nadel, 1978). A model is proposed for the operation of such a system, as independent sets of highly efficient path integrators are associated to environmental sensory input, and to each other, via place cells.

Acknowledgments

We gratefully acknowledge useful conversations with Caswell Barry, Tom Hartley, John Huxter, Kate Jeffery, Peter Latham, and Colin Lever.

REFERENCES

Alonso A, Llinas RR. 1989. Subthreshold Na^+-dependent theta-like rhythmicity in stellate cells of entorhinal cortex layer II. Nature 342:175–177.

Battaglia FP, Sutherland GR, McNaughton BL. 2004. Local sensory cues and place cell directionality: additional evidence of prospective coding in the hippocampus. J Neurosci 24:4541–4550.

Bullock TH, Buzsaki G, McClune MC. 1990. Coherence of compound field potentials reveals discontinuities in the CA1-subiculum of the hippocampus in freely-moving rats. Neuroscience 38:609–619.

Burgess N, O'Keefe J, Recce M. 1993. Using hippocampal "place cells" for navigation, exploratory phase coding. In: Hanson SJ, Cowan JD, Miles CL, editors. Neural information processing systems 5. San Mateo: Morgan Kaufmann p 929–936.

Burgess N, Recce M, O'Keefe J. 1994. A model of hippocampal function. Neural Networks 7:1065–1081.

Buzsaki G. 2002. Theta oscillations in the hippocampus. Neuron 33: 325–340.

Buzsaki G, Leung LW, Vanderwolf CH. 1983. Cellular bases of hippocampal EEG in the behaving rat. Brain Res 287:139–171.

Cacucci F, Lever C, Wills TJ, Burgess N, O'Keefe J. 2004. Theta-modulated place-by-direction cells in the hippocampal formation in the rat. J Neurosci 24:8265–8277.

Conklin J, Eliasmith C. 2005. A controlled attractor network model of path integration in the rat. J Comput Neurosci 18:183–203.

Czurko A, Hirase H, Csicsvari J, Buzsaki G. 1999. Sustained activation of hippocampal pyramidal cells by "space clamping" in a running wheel. Eur J Neurosci 11:344–352.

Dolorfo CL, Amaral DG. 1998. Entorhinal cortex of the rat: topographic organization of the cells of origin of the perforant path projection to the dentate gyrus. J Comp Neurol 398:25–48.

Egorov AV, Hamam BN, Fransen E, Hasselmo ME, Alonso AA. 2002. Graded persistent activity in entorhinal cortex neurons. Nature 420:173–178.

Ekstrom AD, Meltzer J, McNaughton BL, Barnes CA. 2001. NMDA receptor antagonism blocks experience-dependent expansion of hippocampal "place fields." Neuron 31:631–638.

Fenton AA, Muller RU. 1998. Place cell discharge is extremely variable during individual passes of the rat through the firing field. Proc Natl Acad Sci USA 95:3182–3187.

Fox SE, Wolfson S, Ranck JB Jr. 1986. Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats. Exp Brain Res 62:495–508.

Fyhn M, Molden S, Witter MP, Moser EI, Moser MB. 2004. Spatial representation in the entorhinal cortex. Science 305:1258–1264.

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. Nature (Epub ahead of print).

Hargreaves EL, Rao G, Lee I, Knierim JJ. 2005. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. Science 308:1792–1794.

Harris KD, Csicsvari J, Hirase H, Dragoi G, Buzsaki G. Organization of cell assemblies in the hippocampus. Nature 424:552–556.

Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, Czurko A, Buzsaki G. 2002. Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells. Nature 417:738–741.

Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J. 2000. Modeling place fields in terms of the cortical inputs to the hippocampus. Hippocampus 10:369–379.

Hausser M, Mel B. 2003. Dendrites: bug or feature? Curr Opin Neurobiol 13:372–383.

Hawley ES, Hargreaves EL, Kubie JL, Rivard B, Muller RU. 2002. Telemetry system for reliable recording of action potentials from freely moving rats. Hippocampus 12:505–513.

Holscher C, Anwyl R, Rowan MJ. 1997. Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. J Neurosci 17:6470–6477.

Huerta PT, Lisman JE. 1995. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 15:1053–1063.

Huxter J, Burgess N, O'Keefe J. 2003. Independent rate and temporal coding in hippocampal pyramidal cells. Nature 425:828–832.

Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME. 2003. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J Neurosci 23: 11725–11731.

Jeffery KJ, Donnett JG, O'Keefe J. 1995. Medial septal control of theta-correlated unit firing in the entorhinal cortex of awake rats. NeuroReport 6:2166–2170.

Jensen O, Lisman JE. 2000. Position reconstruction from an ensemble of hippocampal place cells: contribution of theta phase coding. J Neurophysiol 83:2602–2609.

Kamondi A, Acsady L, Wang XJ, Buzsaki G. 1998. Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. Hippocampus 8:244–261.

King C, Recce M, O'Keefe J. 1998. The rhythmicity of cells of the medial septum/diagonal band of Broca in the awake freely moving rat: relationships with behaviour and hippocampal theta. Eur J Neurosci 10:464–477.

Klausberger T, Magill PJ, Marton LF, Roberts JD, Cobden PM, Buzsaki G, Somogyi P. 2003. Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. Nature 421:844–848.

Klink R, Alonso A. 1997. Muscarinic modulation of the oscillatory and repetitive firing properties of entorhinal cortex layer II neurons. J Neurophysiol 77:1813–1828.

Kramis R, Vanderwolf CH, Bland BH. 1975. Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbital. Exp Neurol 49:58–85.

Lawson VH, Bland BH. 1993. The role of the septohippocampal pathway in the regulation of hippocampal field activity and behavior: analysis by the intraseptal microinfusion of carbachol, atropine, and procaine. Exp Neurol 120:132–144.

Lengyel M, Szatmary Z, Erdi P. 2003. Dynamically detuned oscillations account for the coupled rate and temporal code of place cell firing. Hippocampus 13:700–714.

Lever C, Wills T, Cacucci F, Burgess N, O'Keefe J. 2002. Long-term plasticity in hippocampal place-cell representation of environmental geometry. Nature 416:90–94.

McNaughton BL, Barnes CA, O'Keefe J. 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp Brain Res 52:41–49.

McNaughton BL, Barnes CA, Gerrard JL, Gothard K, Jung MW, Knierim JJ, Kudrimoti H, Qin Y, Skaggs WE, Suster M, Weaver KL. 1996. Deciphering the hippocampal polyglot: the hippocampus as a path integration system. J Exp Biol 199(Pt 1):173–185.

Mehta MR, Lee AK, Wilson MA. 2002. Role of experience and oscillations in transforming a rate code into a temporal code. Nature 417:741–746.

Mitchell SJ, Ranck JB Jr. 1980. Generation of theta rhythm in medial entorhinal cortex of freely moving rats. Brain Res 189:49–66.

Muller RU, Kubie JL. 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci 7:1951–1968.

Muller RU, Bostock E, Taube JS, Kubie JL. 1994. On the directional firing properties of hippocampal place cells. J Neurosci 14:7235–7251.

O'Keefe J. 1976. Place units in the hippocampus of the freely moving rat. Exp Neurol 51:78–109.

O'Keefe J. 1985. Is consciousness the gateway to the hippocampal cognitive map? A speculative essay on the neural basis of mind. In: Oakley DA, editor. Brain and mind. London: Methuen. p 59–98.

O'Keefe J. 1991. The hippocampal cognitive map and navigational strategies. In: Paillard J, editor. Brain and space. Oxford: Oxford University Press. p 273–295.

O'Keefe J, Burgess N. 1996. Geometric determinants of the place fields of hippocampal neurons. Nature 381:425–428.

O'Keefe J, Dostrovsky J. 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171–175.

O'Keefe J, Nadel L. 1978. The hippocampus as a cognitive map. Oxford: Oxford University Press.

O'Keefe J, Recce ML. 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3: 317–330.

O'Keefe J, Burgess N, Donnett JG, Jeffery KJ, Maguire EA. 1998. Place cells, navigational accuracy, and the human hippocampus. Phil Trans Roy Soc Lond B Biol Sci 353:1333–1340.

Pavlides C, Greenstein YJ, Grudman M, Winson J. 1988. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. Brain Res 439:383–387.

Pouille F, Scanziani M. 2004. Routing of spike series by dynamic circuits in the hippocampus. Nature 429:717–723.

Ranck JB Jr. 1984. Head-direction cells in the deep cell layers of the dorsal presubiculum in freely moving rats. Soc Neurosci Abstr 10: 599.

Recce M, O'Keefe J. 1989. The tetrode: a new technique for multiunit extracellular recording. Soc Neurosci Abstr 15:1250.

Redish AD, Touretzky DS. 1997. Cognitive maps beyond the hippocampus. Hippocampus 7:15–35.

Rivas J, Gaztelu JM, Garcia-Austt E. 1996. Changes in hippocampal cell discharge patterns and theta rhythm spectral properties as a function of walking velocity in the guinea pig. Exp Brain Res 108: 113–118.

Samsonovich A, McNaughton BL. 1997. Path integration and cognitive mapping in a continuous attractor neural network model. J Neurosci 17:5900–5920.

Sharp PE. 1996. Multiple spatial/behavioral correlates for cells in the rat postsubiculum: multiple regression analysis and comparison to other hippocampal areas. Cerebr Cortex 6:238–259.

Skaggs WE, McNaughton BL, Wilson MA, Barnes CA. 1996. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus 6:149–172.

Slawinska U, Kasicki S. 1998. The frequency of rat's hippocampal theta rhythm is related to the speed of locomotion. Brain Res 796: 327–331.

Taube JS, Muller RU, Ranck JB Jr. 1990a. Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis J Neurosci 10:420–435.

Taube JS, Muller RU, Ranck JB Jr. 1990b. Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations J Neurosci 10:436–447.

Tsodyks MV, Skaggs WE, Sejnowski TJ, McNaughton BL. 1996. Population dynamics and theta rhythm phase precession of hippocampal place cell firing: a spiking neuron model. Hippocampus 6: 271–280.

Vanderwolf CH. 1969. Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr Clin Neurophysiol 26: 407–418.

Whishaw IQ, Vanderwolf CH. 1973. Hippocampal EEG, behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learned movement patterns in rats and cats. Behav Biol 8:461–484.

Wiener SI, Korshunov VA, Garcia R, Berthoz A. 1995. Inertial, substratal and landmark cue control of hippocampal CA1 place cell activity. Eur J Neurosci 7:2206–2219.

Wills T, Lever C, Cacucci F, Burgess N, O'Keefe J. 2005. Attractor dynamics in the hippocampal representation of the local environment. Science 308:873–876.

Wilson MA, McNaughton BL. 1993. Dynamics of the hippocampal ensemble code for space. Science 261:1055–1058.

Wood ER, Dudchenko PA, Eichenbaum H. 1999. The global record of memory in hippocampal neuronal activity. Nature 397:613–616.

Zhang K. 1996. Representation of spatial orientation by the intrinsic dynamics of the head-direction cell ensemble: a theory. J Neurosci 16:2112–2126.

Zugaro MB, Monconduit L, Buzsaki G. 2005. Spike phase precession persists after transient intrahippocampal perturbation. Nat Neurosci 8:67–71.