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A phase code for memory could arise from circuit mechanisms in entorhinal cortex

Michael E. Hasselmo *, Mark P. Brandon, Motoharu Yoshida, Lisa M. Giocomo, James G. Heys, Erik Fransen, Ehren L. Newman, Eric A. Zilli

Center for Memory and Brain, Department of Psychology and Program in Neuroscience, Boston University, 2 Cummington Street, Boston, MA 02215, United States

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ABSTRACT

Neurophysiological data reveals intrinsic cellular properties that suggest how entorhinal cortical neurons could code memory by the phase of their firing. Potential cellular mechanisms for this phase coding in models of entorhinal function are reviewed. This mechanism for phase coding provides a substrate for modeling the responses of entorhinal grid cells, as well as the replay of neural spiking activity during waking and sleep. Efforts to implement these abstract models in more detailed biophysical compartmental simulations raise specific issues that could be addressed in larger scale population models incorporating mechanisms of inhibition.

1. Introduction

The parahippocampal cortices play an important role in memory function. In humans, the severe anterograde amnesia seen in patient HM was associated with bilateral removal of both the hippocampus and the entire entorhinal cortex (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997). In monkeys, lesions of parahippocampal cortices without damage to the hippocampus cause severe memory impairments on delayed matching to sample tasks in both the visual and tactile modalities (Suzuki, Zola-Morgan, Squire, & Amaral, 1993; Zola-Morgan, Squire, Amaral, & Suzuki, 1989), and anterograde memory impairments caused by damage to the hippocampus are increased when accompanied by damage to parahippocampal cortices (Zola-Morgan, Squire, Clower, & Rempel, 1993). Damage to the entorhinal cortex alone causes a transient impairment in delayed match to sample at long delays (Leonard, Amaral, Squire, & Zola-Morgan, 1995), suggesting that it normally plays a crucial role in this task until other structures can compensate. In rats, lesions of the entorhinal cortex impair spatial memory in the water maze (Steffenach, Witter, Moser, & Moser, 2005) and in the 8-arm radial maze (Otto, Wolf, & Walsh, 1997) and cause impairments of memory for odors in delayed matching tasks (Otto & Eichenbaum, 1992; Staubli, Le, & Lynch, 1995; Young, Otto, Fox, & Eichenbaum, 1997). Note that a large number of these memory impairments involve impairments in delayed matching to sample tasks with delays on the order of seconds. This indicates a role for entorhinal cortex in the maintenance of memory representations.

2. Cellular mechanisms in entorhinal cortex

How do local circuits in the entorhinal cortex mediate this role in memory function? The connectivity of entorhinal cortex is summarized in Fig. 1A, showing that input from other neocortical areas arrives in the superficial layer II (Witter & Moser, 2006; Witter et al., 2000a; Witter, Wouterlood, Naber, & Van Haeften, 2000b). The recurrent connectivity between neurons in layer III and V appears to be stronger than in layer II (Dhillon & Jones, 2000), but recent studies have demonstrated excitatory recurrent connectivity in layer II as well (Kumar, Jin, Buckmaster, & Huguenard, 2007). There are strong interactions with both the hippocampus and the subiculum. Layer II projects to the dentate gyrus and region CA3, whereas layer III projects to region CA1 and subiculum in the rat (Witter, Griffioen, Jorritsma-Byham, & Krijnen, 1988), and layer V receives feedback from the hippocampal formation and subiculum (though layers II and III also receive input from subicular subregions).

Here we review data suggesting how cellular and circuit mechanisms might allow the relative phase of neural firing to code memories. These intrinsic cellular mechanisms have been

* Corresponding author. Tel.: +1 (617) 353 1397; fax: +1 (617) 358 3296.
E-mail addresses: hasselmo@bu.edu, hasselmo@gmail.com (M.E. Hasselmo).

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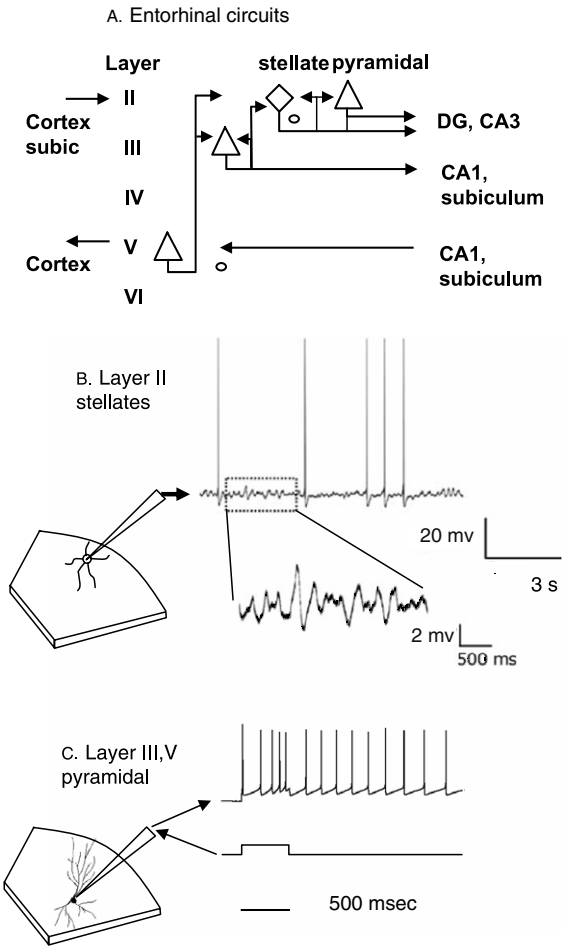

Fig. 1. A. Summary of the circuitry of medial entorhinal cortex. Input from other cortical areas (Cortex) and subiculum (sub) enters in layer II and III. Layer II contains both stellate and pyramidal cells, and these cells send recurrent connections to layer II and afferent connections to dentate gyrus and CA3. Layer III has recurrent connections to layer II and III and afferent connections to CA1 and subiculum. Region CA1 and subiculum send return connections to layer V which projects to other cortical regions. B. Whole cell patch recording in slice preparations shows that layer II entorhinal stellate cells generate subthreshold membrane potential oscillations in between the generation of action potentials (Giocomo & Hasselmo, 2008b). Blowup focuses on subthreshold oscillations. C. Whole cell patch recording in the presence of cholinergic or mGlulr agonists shows that layer III and V pyramidal cells exhibit persistent spiking that is maintained after the termination of a square pulse current injection (Yoshida et al., 2008).

demonstrated using intracellular sharp electrode or whole cell patch recording in entorhinal cortex neurons. Fig. 1B and C illustrate important intrinsic properties of entorhinal neurons that could contribute to the phase coding of memory.

2.1. Membrane potential oscillations

Entorhinal layer II stellate cells show subthreshold membrane potential oscillations when depolarized near firing threshold (Alonso & Klink, 1993; Alonso & Llinas, 1989; Giocomo, Zilli, Fransen, & Hasselmo, 2007). An example is shown in Fig. 1B (Giocomo & Hasselmo, 2008b). These are small oscillations of a few millivolts in amplitude that can influence the timing of action potentials (Fransen, Alonso, Dickson, Magistretti, & Hasselmo, 2004; Pervouchine et al., 2006; Rotstein, Oppermann, White, & Kopell, 2006) and may contribute to network theta frequency oscillations (Acker, Kopell, & White, 2003; Alonso & Garcia-Austt, 1987; Mitchell & Ranck, 1980). The frequency of membrane potential oscillations differs systematically along the dorsal to ventral axis of the medial entorhinal cortex (Giocomo et al., 2007). The oscillations appear to be due to a hyperpolarization activated cation current or *h*-current (Dickson et al., 2000), that differs in time constant along the dorsal to ventral axis (Giocomo & Hasselmo, 2008b). Membrane potential oscillations appear less frequently in layer II or layer III pyramidal cells (Alonso & Klink, 1993), but are observed in layer V pyramidal cells, where they may be caused by M-current (Yoshida & Alonso, 2007). The layer V membrane potential oscillations also show a gradient in frequency from dorsal to ventral medial entorhinal cortex (Giocomo & Hasselmo, 2008a). Membrane potential oscillations do not appear in neurons of the lateral entorhinal cortex (Tahvildari & Alonso, 2005).

2.2. Persistent spiking

In slices, pyramidal neurons in different layers of entorhinal cortex demonstrate the capacity to display persistent spiking activity after a depolarizing current injection or a period of repetitive synaptic input (Egorov, Hamam, Fransen, Hasselmo, & Alonso, 2002; Fransén, Tahvildari, Egorov, Hasselmo, & Alonso, 2006; Klink & Alonso, 1997; Tahvildari, Fransen, Alonso, & Hasselmo, 2007; Yoshida, Fransen, & Hasselmo, 2008), as illustrated in Fig. 1C. Some pyramidal neurons in layer II of medial entorhinal cortex show persistent spiking, whereas others show spiking that self-terminates over periods of many seconds (Klink & Alonso, 1997). Pyramidal cells in layer III show stable persistent spiking that can last for two minutes or more (Yoshida et al., 2008). Pyramidal neurons in deep layers of entorhinal cortex can maintain spiking at different graded frequencies for many minutes (Egorov et al., 2002). The persistent spiking appears to be due to muscarinic or metabotropic glutamate activation of a calcium-sensitive non-specific cation current (Fransén et al., 2006; Shalinsky, Magistretti, Ma, & Alonso, 2002; Yoshida et al., 2008). This graded persistent firing could allow these neurons to integrate synaptic input over extended periods. Persistent firing has also been shown in layer III of lateral entorhinal cortex (Tahvildari et al., 2007).

The mechanism of persistent spiking could code memories either in terms of the graded magnitude of firing rate (Egorov et al., 2002; Fransén et al., 2006), or in terms of the phase of spiking relative to the phase of a stable baseline frequency (Hasselmo, 2008a). Many models of cortex code memory in the form of the firing rate of individual neurons. For example, models of working memory based on recurrent connections code the previous presence of a specific stimulus by inducing and maintaining a different level of firing frequency in a population of neurons (Amit & Brunel, 1997; Lisman, Fellous, & Wang, 1998; Zipser, Kehoe, Littlewort, & Fuster, 1993). These types of models can also code and maintain the location of a simulus over time by maintaining a "bump" of activity in a set of neurons responding selectively to a particular location (Miller, 2006; Miller & Wang, 2006; Samsonovich & McNaughton, 1997). In contrast, other models have used phase to code the memory for a specific item. For example, sequences of spiking at different phases have been proposed to represent different items in a model of short term memory (Jensen & Lisman, 1996a, 1998, 2005), and the spiking phase arising from oscillatory interference has been proposed to code spatial location for path integration (Burgess, 2008; Burgess, Barry, & O'Keefe, 2007; O'Keefe & Burgess, 2005).

Here we focus on how the phase of rhythmic spiking activity relative to a reference phase could code memory, due to intrinsic cellular properties of neurons (Giocomo & Hasselmo, 2008a, 2009; Giocomo et al., 2007; Hasselmo, 2008a) or network dynamics. The mechanism can be used in models to encode the spatial location of a rat (Burgess, 2008; Burgess et al., 2007; O'Keefe & Burgess, 2005), or it could be extended to encode the spatial location of a stimulus, the magnitude of a stimulus or the temporal duration of a stimulus.

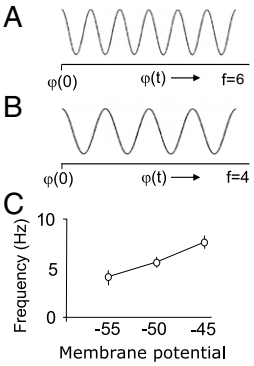

Fig. 2. Schematic representation of oscillations with different frequencies that could be regulated by neuronal input. A. Higher frequency oscillation ($f = 6$ Hz). B. Lower frequency oscillation ($f = 4$ Hz). C. Experimental data from different populations of stellate cells recorded at different membrane potentials shows a difference in mean oscillation frequencies (Giocomo & Hasselmo, 2008a).

3. Phase code for memory

The phase code of memory will first be illustrated in a simple example using an abstract representation of oscillations. These modelled oscillations can represent a range of different physiological phenomena. They could represent subthreshold membrane potential oscillations (MPO) arising from interactions of voltage-dependent membrane currents within single neurons. With a simple threshold function, trigonometric functions could represent rhythmic persistent spiking activity with a stable firing frequency regulated by calcium-sensitive membrane currents. These oscillations could also represent network level oscillations based on the interactions of sub-populations of stellate cells, pyramidal cells and inhibitory interneurons.

Consider a single oscillation with constant frequency over time:

$$V(t) = \cos(2\pi ft). \tag{1}$$

The number of cycles of the oscillation per unit time is determined by the frequency f, and the time duration of one cycle is the period $T = 1/f$. Examples of oscillations are shown in Figs. 2–4. Note that the oscillations can also be described by their instantaneous phase angle (the term "angle" is commonly dropped). The instantaneous phase corresponds to the angle being used at each point of time in the cosine function, as follows:

$$\varphi(t) = 2\pi ft. \tag{2}$$

Thus, for frequency $f = 1$ and time $t = 0.25$, the phase angle is $\varphi(t) = \pi/2$. Note that this description of instantaneous phase differs from the initial phase $\varphi(0)$ that would shift the entire oscillation from the starting time, as in $\cos(2\pi ft + \varphi(0))$.

The phase code described here focuses on the relative phase of one oscillation versus a baseline oscillation. The frequency of the baseline oscillation keeps a constant value f, as described by Eq. (2) above.

The memory mechanism described here can encode a new input through the influence of that input on the frequency of an oscillation holding the memory, thereby causing the oscillation holding the memory, labelled as $\varphi_m(t)$ in Figs. 2 and 3 to have a different relative phase. The instantaneous phase changes constantly, but the relative phase difference caused by a memory input can be quantified when compared to a reference phase. The new input will cause a change in frequency of the oscillation at different time points. The instantaneous phase $\varphi(t)$ at each new time step can be computed by adding the old phase angle at time t to the change in phase angle for each time interval Δt. When the frequency of an oscillation changes as a function of time $f(t)$, then the phase angle needs to be updated with different values of $f(t)$ for each time interval Δt, as follows: $\varphi(t+\Delta t) = \varphi(t) + 2\pi f(t)\Delta t$. Updated continuously, this results in the phase integrating the function of frequency over time $\varphi(t) = \int_0^t 2\pi f(\tau)\mathrm{d}\tau$. For the baseline oscillation with constant frequency f, this integration simply yields the baseline phase $\varphi(t) = 2\pi ft + \varphi(0)$.

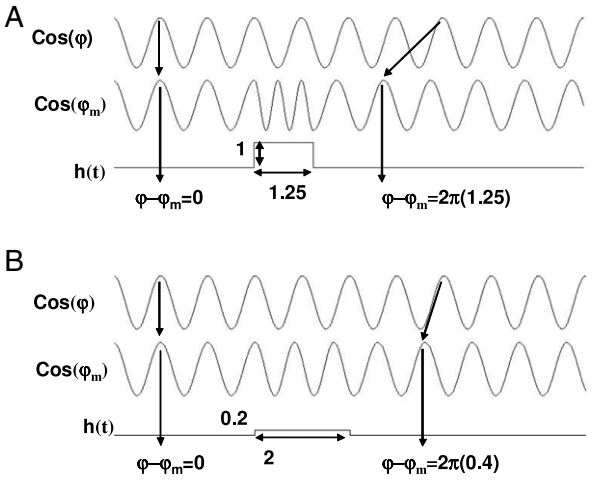

Fig. 3. Plot of the phase of membrane potential oscillations in a single cell $\cos(\varphi_m(t))$ interacting with the network theta rhythm oscillation $\cos(\varphi(t))$. A. Input $h(t)$ with magnitude 1.0 and duration 1.25, causes a shift in the frequency and phase of $\cos(\varphi_m(t))$ relative to $\cos(\varphi(t))$ that is proportional to the magnitude and duration of input. Thus, the input associated with a prior item input can alter the phase representation, providing memory for the item in the form of a shift in phase that is maintained over time. B. Example of the shift in frequency and phase caused by input $h(t)$ with magnitude 0.2 and duration 2.0.

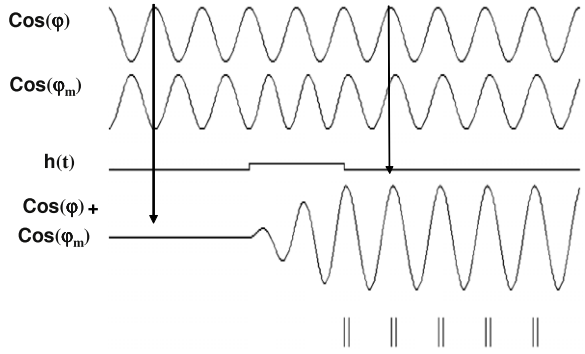

Fig. 4. The phase code of memory can be read out by spiking activity due to interference between oscillations. The top row shows two oscillations that start out in antiphase with each other. The depolarizing input $h(t)$ to $\cos(\varphi_m(t))$ causes the frequency of the oscillation to increase and the phase to shift relative to the reference oscillation $\cos(\varphi(t))$. The sum of the oscillations then shifts from showing destructive interference at the start to showing constructive interference. This constructive interference brings the summed oscillation over threshold, generating spiking activity.

4. Memory as phase angle

Neural oscillations in single neurons have the potential capacity to hold memory for prior inputs in the form of the relative phase angle of the oscillation. In the simplest example, the memory being encoded would consist of some stimulus causing a shift in the frequency of an oscillation for the period of time that the stimulus is present. The change in frequency will shift the relative phase angle compared to the baseline oscillation. Thus, the stored memory takes the form of a difference in the phase angle of a neural oscillation relative to a reference phase angle. The shift in phase

angle will be proportional to the magnitude and duration of the encoded input.

Experimental data from stellate cells shows differences in the oscillation frequency observed in different individual cells recorded at different membrane potentials in dorsal entorhinal cortex (Giocomo & Hasselmo, 2008a), as summarized in Fig. 2. This suggests that oscillation frequencies may change with depolarization, though direct measures of changes in oscillation frequency with depolarization in single neurons do not always show clear frequency changes. The frequency is difficult to analyze across many membrane potential values in single neurons, because the amplitude of oscillations becomes small near resting potential, and the oscillations are obscured when cells are depolarized enough to generate spikes. In persistent spiking cells, additional depolarizing or hyperpolarizing current injection will increase or decrease the spiking frequency from the baseline persistent firing frequency (Yoshida and Hasselmo, unpublished data).

A potential difficulty for implementing a phase code with membrane potential oscillations concerns the tendency for oscillations within different parts of a single neuron to synchronize, as shown in computational studies (Remme, Lengyel, & Gutkin, 2007). Previous models have proposed that the relative phase of two oscillations could differ if one is an intrinsic oscillation in the dendrites of a neuron, and the other is a network oscillation altering the somatic membrane potential (Burgess et al., 2007; Lengyel, Szatmary, & Erdi, 2003; O'Keefe & Recce, 1993). As an alternative, persistent spiking of different individual neurons with the same baseline frequency could allow maintenance of separate phases (Hasselmo, 2008a), or the oscillation encoding the memory could also arise from network dynamics within a population of neurons.

Consider a neuron holding memory for the magnitude and duration of a previous movement. The shift in phase angle can be induced by changing the frequency of the oscillation for a period of time according to $h(t)$, representing some sensory input influencing frequency. For example, as shown in Fig. 3, imagine there is no initial movement until time $t = 3$, when movement occurs with magnitude 1 until time $t = 4.25$, at which time movement stops. This input causes a shift in the frequency of the oscillation that results in a shift in the phase of the oscillation as follows:

$$\varphi_m(t + \Delta t) = \varphi_m(t) + 2\pi(f + h(t))\Delta t. \quad (3)$$

This difference can be seen in Fig. 3 when comparing the phase φ_m of the oscillation holding the memory to the phase φ of the baseline oscillation. Before the movement occurs, the phase difference between the two oscillations is zero. During the movement, the phase difference increases by $2\pi h(t)\Delta t$, so that at the end of the movement the phase difference is $2\pi(1)(1.25)$. The total phase shift is proportional to the integral of $h(t)$ over the interval of input. In the absence of further input, this phase shift persists in the network over all of the subsequent cycles of oscillation.

The phase shift can integrate any function $h(t)$ over any interval. Another example is shown in the bottom of Fig. 3. In this case, $h(t)$ increases from zero to 0.2 for a period of 2 s, resulting in a phase shift of $2\pi(0.2)(2) = 2\pi(0.4)$. This is visible as a shift in the peak of φ_m to an earlier phase that precedes the peak of the baseline oscillation by about 4/10 of a full cycle. Thus, the figure illustrates how memory of a previous input can be maintained in the form of a shift in the phase of one oscillation relative to a baseline oscillation.

By integrating the magnitude and duration of previous input, the phase shifts described here encode a continuous representation of previous input and maintain this memory by holding the phase (in the absence of further input). However, this leaves open the problem of reading out the phase angle difference coding the memory.

5. Interference provides memory read-out

The memory encoded by phase shift in the previous section must be accessible for read-out. A potential mechanism for reading out the difference in phase is through the interference of oscillations (Burgess et al., 2007; O'Keefe & Recce, 1993). In the example in Fig. 4, the input causes a difference between the phase of the oscillation holding the memory and the phase of the baseline oscillation. This can be read out in the form of interference between these two oscillations.

As shown in Fig. 4, the sum of two oscillations that are out of phase with each other will undergo destructive interference so that the summed oscillation is a flat line. However, if one of the oscillations is shifted by input of magnitude 0.2 for 2 time steps, the integral of the shift is 0.4. Thus, the phase has shifted by about half a cycle. This brings the two oscillations closer in phase with each other. In this case, the sum of the oscillations now shows constructive interference, resulting in a large amplitude oscillation. If we consider a neuron that spikes whenever the oscillation crosses a threshold of 1.4, this results in regular spiking that indicates that a previous input of a particular magnitude was presented.

This read out specifically indicates the integral of prior input, giving the same response for a magnitude of 0.8 for 0.5 time steps or a magnitude of 0.1 for 4 time steps. In addition, it codes magnitude in a repeating manner, responding the same for 0.4 and 1.4. However, the readout can be made more specific by utilizing oscillations with different sensitivity to input that shifts them by different amounts. For example, consider a second pair of oscillations in which the input is scaled by 2/7. This second pair of units will respond to 0.4 and 1.4 with 0.11 and 0.4, thereby distinguishing the two states. The interaction of different coding scales can effectively code very large ranges according to the least common denominator of interactions (Gorchetchnikov & Grossberg, 2007). Different scales could arise from the differences in intrinsic frequency in neurons at different anatomical positions in medial entorhinal cortex (Giocomo & Hasselmo, 2008a, 2008b, 2009; Giocomo et al., 2007) that may underlie differences along the dorsal to ventral axis in the size and spacing of grid cell firing fields as well as the size of place cell firing fields in the hippocampus (Hasselmo, 2008b; Kjelstrup et al., 2008). This raises the intriguing possibility that anatomical differences in intrinsic frequencies in other structures such as prefrontal cortex and piriform cortex could underlie differences in the scale of coding for different behaviours (Hasselmo, 2008b).

This section described how a shift in phase of oscillations can provide a memory for prior input, and shows how interference between shifted phases can provide read-out of the prior memory. This process could code memory for the temporal duration and magnitude of a stimulus or stimulus feature. For example, neurons responding to different stimulus features could create a phase code for individual sample stimuli that would be maintained over a delay period by maintenance of the relative phases of oscillations.

Alternately, this process could code memory for the velocity of self-motion in an environment, providing a mechanism for path-integration (Burgess, 2008; Burgess et al., 2007). Velocity can be coded by head direction cells (Taube, Muller, & Ranck, 1990b) combined with cells responding to speed of translational motion (O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998). Starting from an initial relative phase, input coding the direction and speed of movement will shift the phase of firing in proportion to velocity. The shift in phase integrates velocity, so that at the end of the movement, the relative phase codes the relative difference in position between the starting location and the end location. The interference of different oscillations will show repeated patterns of spiking dependent upon the movement. This phenomenon forms

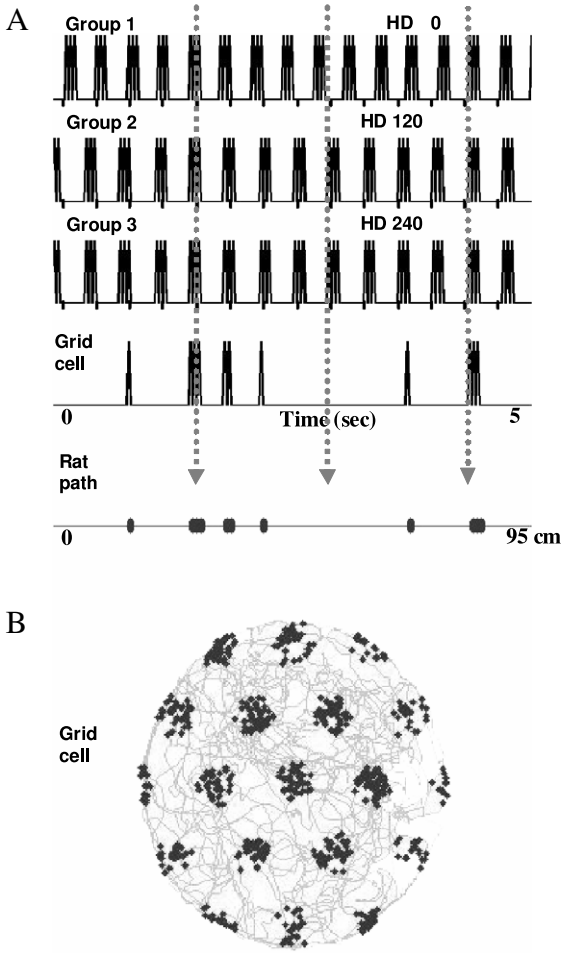

Fig. 5. Mechanism for interaction of persistent firing cells to cause grid cell firing. A. Spiking activity over time of three different groups of persistent firing neurons. Here, each group consists of three persistent spiking cells firing with a baseline frequency of 3 Hz with different phases. Cells receive input from head direction (HD) cells with 0 degree preferred angle for Group 1, 120 degree angle for Group 2, and 240 degree angle for Group 3. Grid cell firing arises from the convergent spiking of the three groups of persistent firing neurons. When all three persistent firing groups fire in synchrony, the grid cell will fire (dots). B. Grid cell spiking (dots) occurs only when all of the persistent firing neurons fire at the same phase, resulting in a typical grid cell firing pattern. Gray line indicates rat trajectory from experimental data (Hafting et al., 2005).

the basis for a model of the grid cell responses of medial entorhinal neurons (Burgess, 2008; Burgess et al., 2007; Giocomo et al., 2007; Hasselmo, Giocomo, & Zilli, 2007). An example of how this phase code can result in grid cell firing is shown in Fig. 5.

6. Alternate mechanisms for phase coding

There could be many possible mechanisms for the maintenance of the phase code. The phase code could depend upon intrinsic membrane potential oscillations (Giocomo & Hasselmo, 2008a; Giocomo et al., 2007; Hasselmo et al., 2007), but the same framework can be used to describe a phase code using stable persistent spiking (Hasselmo, 2008a). An example using stable persistent spiking is shown in Fig. 5. In this example, a population of neurons all have the same baseline level of stable persistent spiking. Within this population, different neurons receive input coding the velocity of movement relative to different directions. In Fig. 5A, the response of the network to movement in one direction is shown, demonstrating how the velocity input systematically shifts the phase of spiking of one group of cells relative to the other groups. In Fig. 5B, the response of the circuit during random movements within a circular open field environment is shown. The relative phase shift caused by the different velocity signals cause patterns of interference resulting in grid cell firing properties. The pattern of activity represented by grid cells can be read out as a purely spatial code by grid cell activation of spiking in a population of hippocampal place cells, as shown in a number of models (Gorchetchnikov & Grossberg, 2007; Hasselmo, 2008c; Rolls, Stringer, & Elliot, 2006; Solstad, Moser, & Einevoll, 2006).

The same model could describe oscillatory dynamics involving feedback interactions between excitatory neurons and inhibitory cortical interneurons. Numerous studies have shown that circuits of excitatory neurons interacting with inhibitory interneurons can cause oscillatory dynamics at gamma frequency (Chow, White, Ritt, & Kopell, 1998; White, Chow, Ritt, Soto-Trevino, & Kopell, 1998). More complex dynamical interactions can cause oscillatory dynamics at theta frequency (Cutsuridis, Cobb, & Graham, 2008, 2009; Denham & Borisyuk, 2000; Kunec, Hasselmo, & Kopell, 2005; Pervouchine et al., 2006; Rotstein et al., 2005). Circuits that generate synchronous rhythmic activity of neurons have the potential for generating phasic firing of neurons at different phase relationships. Different groups of neurons with the same internal connectivity but lesser cross-connectivity could show different phases of firing. If external depolarizing input causes even a small magnitude linear shift in frequency of one oscillation, then this will cause systematic shifts in relative phase of spiking in different groups of neurons. In this case, the framework described here can be used for coding memory in these types of networks.

One problem that confronts the models of grid cells based on intrinsic mechanisms concerns the effect of phase noise. As seen in Fig. 1B, membrane potential oscillations show high variability in oscillation period, and persistent spiking activity shows variability in spiking phase. Simulations with this level of variability show a rapid loss of coding accuracy (Giocomo & Hasselmo, 2008a; Welinder, Burak, & Fiete, 2008; Zilli, Yoshida, Tahvildari, Giocomo, & Hasselmo, in review). However, these effects of noise could be reduced by network interactions. For example, analysis of the spike time response curves (STRC) in entorhinal stellate cells shows that the *h* current results in excitatory synaptic potentials causing phase shifts that drive neurons toward synchrony (Acker et al., 2003; Pervouchine et al., 2006). Experimental data shows that individual stellate cells receiving input from a dynamic clamp replicating excitatory interactions with other stellate cells will synchronize (Netoff, Acker, Bettencourt, & White, 2005a; Netoff et al., 2005b). Thus, stellate cells firing rhythmically in response to external input will shift into phase with each other due to recurrent excitatory coupling. This synchronization on the population level should be able to overcome the independent variability of the intrinsic mechanisms for membrane potential oscillations or persistent spiking. Simulations have demonstrated that network dynamics can maintain synchrony despite noise within individual neurons (Zilli and Hasselmo, unpublished work).

Thus, the grid cell firing properties of entorhinal cortex could involve the interaction of different populations of neurons. There are a number of different possible configurations. One possible network configuration could involve an interaction of persistent firing cells and cells showing membrane potential oscillations. Persistent firing cells can change frequency with depolarization and maintain activity without synaptic input. Studies of synchronization due to membrane potential oscillations commonly use a steady applied current to ensure a stable background firing frequency (Acker et al., 2003; Rotstein et al., 2006). However, excitatory recurrent connectivity sufficient to maintain spiking activity would tend to drive the neurons to higher frequencies. In contrast, intrinsic persistent spiking cells in medial entorhinal cortex layer III (Yoshida et al., 2008) or postsubiculum (Yoshida & Hasselmo, 2009) can maintain stable

low frequency firing. This could then drive the stellate cells in layer II that would have weak excitatory interactions sufficient for synchronization but not strong enough to change the overall frequency of the circuit (Acker et al., 2003; Netoff et al., 2005b; Rotstein et al., 2006). A similar interaction could occur between persistent spiking cells in layer III of entorhinal cortex and local circuits in region CA1 that generate synchronization through interactions of pyramidal cells, and two types of interneurons: fast spiking cells (FS) and oriens-lacunosum-moleculare (OLM) cells (Netoff et al., 2005b; Rotstein et al., 2005). These CA1 circuits could interact with entorhinal circuits because of the topographic relationship between entorhinal projections to CA1 and the return projections from CA1 to deep layers of entorhinal cortex (Tamamaki & Nojyo, 1995).

The cholinergic modulation of intrinsic properties could influence the generation of oscillations. Cholinergic modulation has been shown to enhance theta rhythm oscillations in the hippocampus (Bland, 1986; Konopacki, MacIver, Bland, & Roth, 1987). On a single cell level, cholinergic modulation lowers the resonance frequency of entorhinal stellate cells (Heys, Giocomo, & Hasselmo, in review). By reducing neuronal intrinsic frequencies, acetylcholine could cause an increase in the size and spacing of grid cell firing fields observed in novel environments (Barry, Fleming, Jeewajee, O'Keefe, & Burgess, 2008). Microdialysis shows increases in cortical acetylcholine levels in novel environments (Acquas, Wilson, & Fibiger, 1996).

7. Phase code substrate for episodic memory

The phase code of memory described here provides an effective means of representing continuous changes in a range of different dimensions, including spatial location, time and features of stimuli (such as size, color, or stimulus motion). This phase code could provide a substrate for encoding and retrieval of complex spatiotemporal trajectories relevant to episodic memory function (Hasselmo, 2008c; Hasselmo & Brandon, 2008), as well as individual features of encountered items.

The circuit mediating episodic memory function (Hasselmo, 2008c; Hasselmo & Brandon, 2008) could involve an interaction of grid cells in entorhinal cortex layer II and III (Hafting, Fyhn, Bonnevie, Moser, & Moser, 2008; Moser & Moser, 2008) with place cells in the hippocampus (Burgess, Barry, Jeffery, & O'Keefe, 2005; Fyhn, Hafting, Treves, Moser, & Moser, 2007; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006) and with head direction cells in postsubiculum (Boccara et al., 2008; Taube, Muller, & Ranck, 1990a) and entorhinal cortex layer V (Sargolini et al., 2006). As described above, the head direction cells coupled with cells responding to translational speed could provide a velocity signal at each point on a trajectory. This velocity signal could drive a phase code for continuous space based on intrinsic cellular properties that drive the spiking activity of grid cells. The grid cells could then drive spiking activity in a population of hippocampal place cells, as shown in a number of models (Hasselmo, 2008c; Rolls et al., 2006; Solstad et al., 2006). The encoding of a trajectory would involve strengthening either direct or indirect synaptic connections between hippocampal place cells in region CA1 and cells coding velocity in the postsubiculum or entorhinal cortex layer V (Hasselmo, 2008c). As shown in Fig. 6, the model effectively encodes and retrieves a range of different spatiotemporal trajectories, with explicit representation of both the spatial location and the time duration at specific locations.

In this particular model, the representation of the continuous time scale for movements in continuous space is provided by velocity. During encoding, this velocity signal arises from behavior, which drives the cells coding velocity, and thereby update the phase code in entorhinal grid cells, and the place

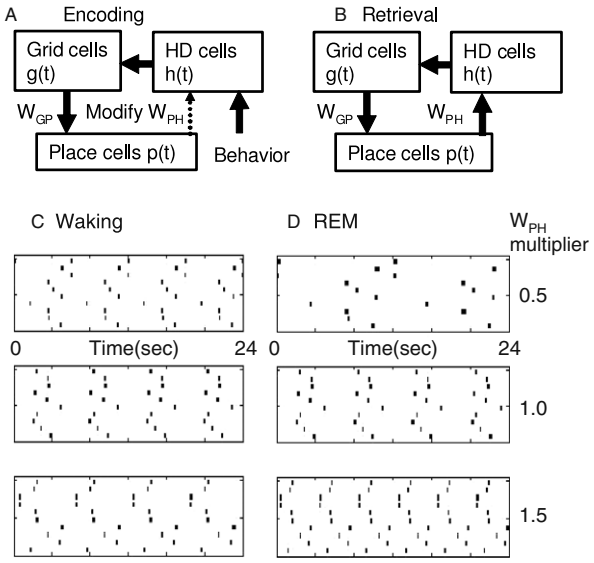

Fig. 6. Model of encoding and replay of trajectories. A. During encoding, behavior drives the activity of head direction cells $h(t)$ that drive the activity of grid cells in entorhinal cortex layers II and III. The grid cells drive place cell firing $p(t)$ in the hippocampus. Links between state (place) and action (speed and head direction) are made by strengthening synapses between place cells and head direction cells W_{PH}. B. During retrieval, the activity of place cells activates head direction cells coding the velocity from that state which then activates the next encoded location. **C-D.** The model simulates temporally structured replay of spiking activity of place cells during REM sleep. The speed of replay depends on the strength of connections W_{PH}. Column C shows place cell activity during waking, with the same speed of movement. Column D shows spiking during simulated REM replay. In each row of Column D, the connections W_{PH} are multiplied by a different value (0.5, 1.0 or 1.5) to change overall strength and thereby speed of REM replay.

code of hippocampal place cells. Hebbian synaptic modification of connections from place cells to cells coding velocity encodes the velocity association with individual locations, effectively encoding the rate of movement through continuous time. During retrieval, the activity of cells coding velocity is not driven by behavioral input, but instead by the spread of activity across previously modified synapses from hippocampal place cells. The retrieval of velocity drives grid cells which drives a new pattern of place cell activity which drives different cells coding a different magnitude of velocity in a recurrent loop that can progressively retrieve trajectories with an explicit representation of changes in speed at different locations (Hasselmo, 2008c, in press; Hasselmo & Brandon, 2008). Thus, a circuit involving entorhinal cortex and hippocampus results in the retrieval of a previously experienced high resolution trajectory through continuous dimensions of space and time.

In contrast to this coding of velocity, the representation of continuous time could arise from other sources such as running speed, or simple time duration. The mechanism described above using velocity has difficulty with the coding of overlapping trajectories, and with coding of the temporal duration of stationary periods. These properties can be provided by the additional role of cells in which the membrane potential oscillations or persistent spiking do not depend on velocity, but respond only to speed, thereby coding the arc length of the trajectory (Hasselmo, 2007). Alternately, the coding of time can be provided by oscillatory interference of cells that keep the same frequency over time, thereby directly coding continuous time instead of continuous space (Hasselmo et al., 2007). This provides a temporal code that differentiates trajectories that overlap in the same spatial location at different times, as well as allowing coding of the temporal duration spent stationary at a single location (Hasselmo, 2008c, in press; Hasselmo et al., 2007). Alternately, the phase reset of temporal oscillations regulated by velocity can provide

context-dependent activity in the grid cell model driven by velocity (Hasselmo, 2008a).

8. Continuous versus discrete models

This model contrasts with most previous models in which individual mental states are coded as discrete patterns of spiking activity (Hopfield, 1982; Jensen & Lisman, 1996b; Lisman & Idiart, 1995), and transitions between these states are coded by synaptic connections between populations of units (Kleinfeld, 1986; Lisman, 1999). Most previous models focus on forming associations between sequential states encountered during behavior, resulting in a discrete stepwise sequence (like a series of static images of individual instants). If a series of states are encountered during an episode, formation of synaptic associations between these states alone will result in a rapid transition through the states at a speed much higher than the original experience. In contrast, the new framework presented here forms associations between the continuous state and a continuous quantitative representation of actions or transitions, allowing a continuous dimension of action magnitude to determine the rate of transition between different states in the memory (Hasselmo, 2008c, in press).

Many models of memory function in neural circuits use a discrete representation of experience. Traditional memory models in mathematical psychology use discrete vectors to represent items, without explicitly representing their spatial relationships (Gillund & Shiffrin, 1984). Many models of hippocampal memory function focus on fixed point attractor dynamics (Hasselmo, Schnell, & Barkai, 1995; Treves & Rolls, 1992, 1994) in which neural activity evolves toward encoded memories that are discrete stable patterns of activity. Networks with two time scales of connectivity have been used to store sequences, but these still have the nature of discrete representations, with fast dynamics leading to fixed-point attractors, and slow dynamics terminating each discrete fixed-point attractor to allow a dynamical transition toward another discrete fixed point attractor (Kleinfeld, 1986; Lisman, 1999). In contrast, episodic memories appear to involve representations of continuous space and time. The continuous representation of time presented here more closely resembles the oscillatory codes for encoding word order in immediate serial recall used in the OSCAR model (Brown, Preece, & Hulme, 2000), or the temporal context model used to model conditional response probability in free recall (Howard, Fotedar, Datey, & Hasselmo, 2005; Howard & Kahana, 2002). In addition, this use of oscillations resembles the use of oscillations for encoding temporal intervals in models of the timing of behavioral responses (Matell & Meck, 2004; Miall, 1989).

9. Mechanism of episodic memory and mental time travel

The framework described above has the specific property that it effectively encodes not only the individual states during an episode, but it encodes the temporal duration of transitions between these individual states, and the duration of individual states (Hasselmo, in press). Thus, it effectively maintains the timing properties of the episode. This can be considered as an element of the property of mental time travel, which has been described as an essential element of episodic memory (Eichenbaum & Cohen, 2001; Tulving, 1983, 2002), as well as an element of future planning (Clayton, Bussey, & Dickinson, 2003; Suddendorf & Corballis, 1997). In fact, studies of patients with damage to the entorhinal cortex and hippocampus have demonstrated impairments of mental time travel into future or imaginary events, showing up as a deficit in the richness of description of both past and future events (Hassabis, Kumaran, Vann, & Maguire, 2007; Hassabis & Maguire, 2007; Kirwan, Bayley, Galvan, & Squire, 2008; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Schacter, Addis, & Buckner, 2007).

The travel along future trajectories through familiar environments could utilize the same machinery as episodic retrieval, but instead of a recurrent loop driving the retrieval of a previous trajectory, the actions along the trajectory would be determined by prefrontal input to the cells coding velocity. For example, if you wanted to go forward along a familiar hallway and then turn right at a particular door, the prefrontal commands could drive head direction cells coding the initial allocentric velocity. These cells could then drive the phase code of grid cells to progressively update place cell populations representing different locations. When the desired location is reached, prefrontal input could drive a different set of head direction cells to change the direction of the velocity vector to the right.

The theoretical framework presented here (Hasselmo, 2008c, in press) is supported by neurophysiological data on the replay of previously experienced neurophysiological activity in animals. Early studies showed reactivation of previously experienced neural ensembles during slow wave sleep (Pavlides & Winson, 1989; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). In particular, recording during REM sleep shows temporally structured replay of neurophysiological activity of place cells, that is, replay of place cell activity with the same timing intervals observed during waking behavior (Louie & Wilson, 2001). The model presented here effectively simulates the temporally structured replay during REM sleep (Hasselmo, 2008c), as shown in Fig. 6. In contrast, previous models of replay used strengthening of excitatory synapses between place cell populations activated at different locations on a trajectory (Hasselmo & Eichenbaum, 2005; Jensen & Lisman, 1996a, 1996c; Levy, 1996; McNaughton & Morris, 1987; Minai & Levy, 1993; Treves & Rolls, 1994; Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996; Wallenstein & Hasselmo, 1997). This allowed retrieval of sequences, but at a much faster speed than during initial encoding, failing to maintain the original timing relationships.

The evidence for temporally structured replay during REM sleep indicates that neural circuits in animals can replay episodes with an explicit representation of the explicit relative time the rat spent in a previously experienced location (Louie & Wilson, 2001). The model presented here predicts that this replay should involve replay of activity in cells coding rat head direction, and this effect has been tested by simultaneous unit recording data from an array of head direction cells, during waking and REM sleep. The necessary machinery for mental time travel may be present in rats. Other data has shown that replay type phenomena appear to occur during waking at points when a rat might be performing vicarious trial and error, using retrieval of prior episodes to choose between different possible future actions (Johnson & Redish, 2007). Thus, neurophysiological data on replay supports this model of mental time travel for episodic memory.

10. Interaction of memory systems

Previous work has shown how specific behavioral tasks can be solved with different types of memory strategies (Zilli & Hasselmo, 2008b, 2008c), or the interaction of memory systems (Zilli & Hasselmo, 2008a). Human imaging data shows that active maintenance of activity in the absence of a stimulus is correlated with the subsequent memory for that stimulus at a later time (Schon et al., 2005; Schon, Hasselmo, Lopresti, Tricarico, & Stern, 2004). The new modeling framework presented here provides potential mechanisms for simultaneously modeling the interaction of memory systems such as working memory and

episodic memory (Hasselmo & Stern, 2006). For example, the active maintenance of a phase representation can be considered to be a working memory for current spatial location (or the working memory for the presence of an item). However, once the phase code activates the loop through hippocampal place cells and head direction cells to alter the current phase, this can be considered to be retrieval of episodic memory. Thus, this framework allows the interaction of working memory with episodic memory for solution of the task, consistent with mathematical analysis showing how different types of memory can disambiguate individual states in a behavioral tasks (Zilli & Hasselmo, 2008a).

Previous work on memory guided behavior in a spatial alternation task (Hasselmo & Eichenbaum, 2005) used episodic retrieval of sequences of discrete states (locations), due to associations between cells representing individual places. That model used retrieval at each location, but was extended with a model using selection of memory actions such as "encode" and "retrieve" to perform memory functions only when necessary for task performance (Zilli & Hasselmo, 2008c). The selection of memory actions could guide the selection of activity to initiate retrieval, and similar mechanisms could be used to drive mental time travel in imaginary or future locations.

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