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

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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

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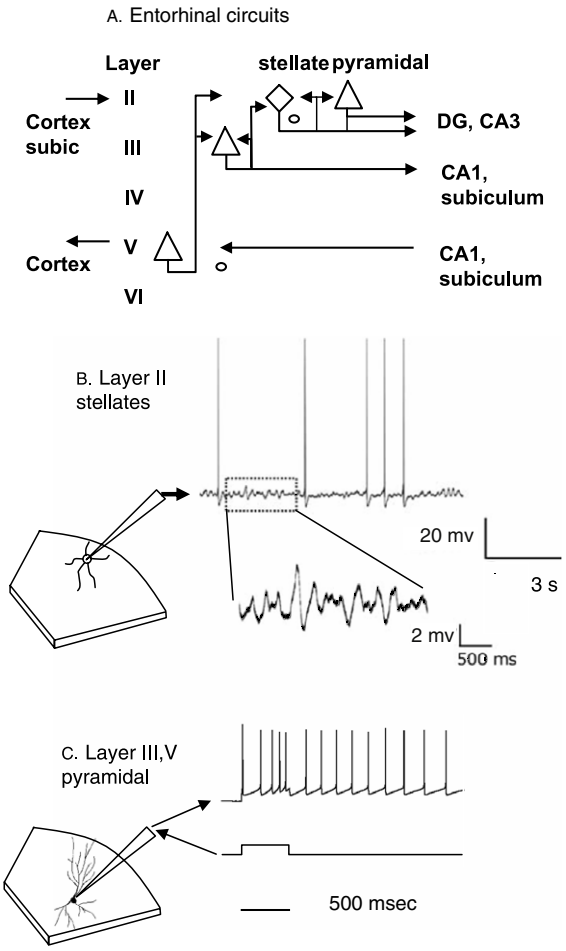

Fig. 1. A. Summary of the circuitry of medial entorhinal cortex. Input from other cortical areas (Cortex) and subiculum (sub) enters in layer II and III. Layer II contains both stellate and pyramidal cells, and these cells send recurrent connections to layer II and afferent connections to dentate gyrus 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.