Chapter 10
20 Years of the Dynamics of Memory: The Long and Winding Road Linking Cellular Mechanisms to Behavior

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Abstract The first Computational Neuroscience meetings in the 1990s fostered an increasing focus on biologically realistic modeling of neurons to understand the function of neural circuits. This chapter reviews some of the developments over the past 20 years, relating papers presented at the early meetings to subsequent developments. The review addresses developments in research on associative memory function, hippocampal memory function, the functional role of theta rhythm oscillations, and the discovery and modeling of grid cells.

Impact of the Computational Neuroscience Meeting

I remember the feeling of excitement associated with the first Computational Neuroscience meetings in the early 1990s. I had a sense of a field coalescing from many different disciplines, building on research that had started decades earlier. I anticipated great accomplishments to take place over the subsequent 20 years from those first meetings. Now that the Computational Neuroscience meeting has taken place for 20 years, I can reflect on how far we have progressed since that time.

There were a number of changes in cultural styles from the 1980s to the 1990s. Neural modeling was dominated by connectionist models (Rumelhart et al. 1986; McClelland and Rumelhart 1988) and attractor dynamic models (Amit 1988; Amit and Treves 1989) in the 1980s. At the start of the 1990s, the excitement about connectionist models and attractor networks transitioned into a greater focus on biophysically detailed modeling of neural circuits. This type of work is essential to understanding the cellular and molecular mechanisms underlying behavior, which

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will be essential to guiding the development of treatments for disorders such as schizophrenia and depression. Much of the influential work on biophysically detailed modeling was performed by founders and early participants of the Computational Neuroscience meeting, including John Rinzel, Bard Ermentrout, Jim Bower, Nancy Kopell, Matt Wilson, Erik DeSchutter, Charlie Wilson, David Golomb, Eve Marder, Todd Troyer, Francis Skinner, Alain Destexhe, Ron Calabrese, Orjan Ekeberg, and Christian Linster. There are too many names to provide a complete list here.

The growth of the field was facilitated tremendously by the dedicated work of Dennis Glanzman, as the program chief of the Theoretical and Computational Neuroscience program at NIMH. His program provided guidance toward funding for many of the influential modelers in those early years. The work was also facilitated by a later collaborative funding venture between Dennis Glanzman at NIMH, Yuan Liu at NINDS, and Ken Whang at NSF in the program for Collaborative Research in Computational Neuroscience (CRCNS).

In describing progress over the past 20 years, I will focus on the biological dynamics of memory function, with a particular emphasis on understanding how episodic memories are encoded. I will address the progress in three general areas: (1) associative memory function, (2) hippocampal function, and (3) theta rhythm and grid cells.

Associative Memory Function

The early days of the Computational Neuroscience meeting included presentations addressing biological mechanisms for associative memory function. The theory of associations has a long history in research on human cognition. A review can be found in Schacter (1982). These models received a more detailed mathematical treatment in early linear associative memory models (Anderson 1972; Kohonen 1972, 1984). In these models, vectors represented patterns of neural activity in the brain. An association was encoded by modification of synapses, represented mathematically by computing the outer product matrix between a presynaptic activity vector and the associated postsynaptic activity vector. Retrieval of the association was performed by allowing the presynaptic activity cue to spread across the modified synapses, represented mathematically by matrix multiplication of the presynaptic vector by the pattern of synaptic connections.

An important early paper by Marr proposed that the excitatory recurrent connections in hippocampal region CA3 could underlie autoassociative memory function (Marr 1971). This was expanded upon in subsequent papers by hippocampal researchers (McNaughton and Morris 1987) as described in more detail in the next section of the chapter. In addition, the primary olfactory cortex was also proposed by Haberly and Bower to function as an autoassociative memory (Haberly and Bower 1989). This proved an interesting model system. Early Computational Neuroscience meetings included presentations of detailed biophysical simulations of the olfactory cortex developed in the Bower laboratory (Bower 1990; Wilson and Bower 1992)

and models of the olfactory cortex as an autoassociative memory (Hasselmo et al. 1990, 1994; Bergman et al. 1993). These biophysical simulations used the GENESIS simulation package initially written by Matt Wilson and developed further by many researchers within the Bower laboratory (Bower and Beeman 1995). The Bower laboratory provided an exciting environment where both biologically realistic modeling and intracellular recording experiments could be combined.

Excitatory recurrent connections will cause an explosion of activity unless the excitatory feedback is limited by the input–output function of individual neurons or by feedback inhibition. A dominant stream of research in the 1980s focused on fixed point attractor dynamics in associative memory function, in which activity converges to a stable fixed point. Mathematically, Lyapunov functions were used to show the stability of attractor states (Hopfield 1982, 1984; Cohen and Grossberg 1983). Many of these studies focused on relatively abstract representations of neurons and the computation of the storage capacity of attractor networks (Amit 1988). Initial models were highly unrealistic, for example, violating Dale's law by having both excitatory and inhibitory connections arise from the same neuron and driving neurons up to an asymptotic maximum activity. However, later studies addressed making these attractor networks more biologically realistic, for example, by modeling neurons with lower firing rates (Amit and Treves 1989; Amit et al. 1990).

Many of the early models used single neuron models that artificially limited the maximal output of neurons (i.e., using a step function or sigmoid function). This was justified as representing the maximal intrinsic firing rate of a neuron. However, recordings of cortical neurons in vivo almost never go above 100 Hz, whereas the maximal firing rate limited by intrinsic properties is usually higher. The intrinsic frequency–current (*f–I*) curve of a neuron is more accurately modeled with a threshold linear function. A more realistic way of limiting the maximal firing rate of modeled neurons is by use of feedback inhibition, for example as initially implemented by Wilson and Cowan (1972, 1973). In my own models, I used interactions of threshold linear excitatory and inhibitory neurons in attractor models of the hippocampus (Hasselmo et al. 1995; Kali and Dayan 2000). Carl van Vreeswijk wrote an unpublished paper with me on these types of models in my lab, and then went on to develop his model of balanced networks (van Vreeswijk and Sompolinsky 1996) in which chaotic activity involves a balance of excitatory and inhibitory activity.

Early associative memory models all used different dynamics during encoding and retrieval (Anderson 1972; Kohonen 1972, 1984; Hopfield 1982; Amit 1988). During encoding, activity in the network would be clamped to an external input pattern. The dynamics of retrieval were explicitly prevented during computation of an outer product for encoding of new input patterns. This was essential for the proper function of associative memory models, as retrieval during encoding would cause a build-up of interference between overlapping patterns (Hasselmo et al. 1992). However, there was no clear biological mechanism for this difference in dynamics during encoding and retrieval.

The effects of acetylcholine provide a potential biological mechanism for the difference in dynamics between encoding and retrieval in associative memory. Working on slices of the piriform cortex in the laboratory of Jim Bower, I studied differences between the properties of glutamatergic synaptic transmission at the afferent input

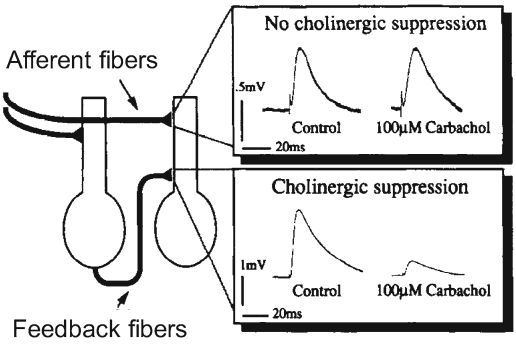

Fig. 10.1 Activation of acetylcholine receptors by the acetylcholine (ACh) agonist carbachol causes selective presynaptic inhibition of synaptic potentials evoked by stimulation of excitatory feedback synapses (*bottom*), with smaller change of synaptic potentials evoked by stimulation of excitatory afferent input (*top*) (Hasselmo and Bower 1992)

from the olfactory bulb in layer Ia and the glutamatergic excitatory recurrent connections in layer Ib arising from other piriform cortex pyramidal cells, extending previous work on the physiological properties of these synapses done by Jim Bower (Haberly and Bower 1984; Bower and Haberly 1986). I found a striking difference in the effects of acetylcholine on the glutamatergic transmission at these synapses (Fig. 10.1). Activation of muscarinic acetylcholine receptors caused much stronger presynaptic inhibition of glutamate release at excitatory recurrent synapses in layer Ib compared to afferent synapses in layer Ia (Hasselmo and Bower 1992, 1993).

The combined focus on modeling and physiology in the Bower lab gave me excellent tools for modeling the significance of this function. In the rooms on the top floor of the Beckman Behavioral Biology, I remember preparing piriform cortex slices, then starting simulations on a Sun workstation, then running a slice experiment, then checking on my simulation output and running a new batch file, in an interactive process throughout a 10 h experimental day. I found a clear effect of cholinergic modulation in abstract models of associative memory function in the piriform cortex. The selective suppression of excitatory recurrent connections clearly enhanced the encoding of new patterns by preventing interference from previously stored memories (Hasselmo et al. 1992; Hasselmo and Bower 1993). Later we simulated networks of piriform cortex neurons using the GENESIS simulation package for presentations at the Computational Neuroscience meeting (Bergman et al. 1993; Hasselmo et al. 1994), showing that encoding of new patterns was enhanced by these cholinergic effects. As shown in Fig. 10.2, interference from previously stored patterns was prevented by cholinergic suppression of synaptic transmission, and the rate of encoding was enhanced by cholinergic depolarization of pyramidal cells and the suppression of spike frequency accommodation (Barkai et al. 1994; Barkai and Hasselmo 1994).

These findings in the piriform cortex have been shown to generalize to other cortical structures in a wide range of subsequent studies. Research in my laboratory

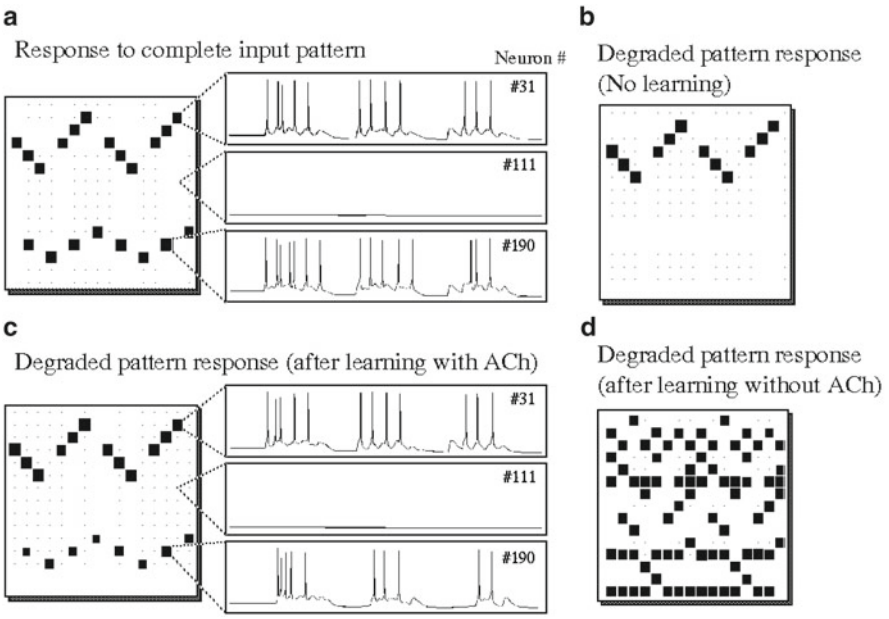

Fig. 10.2 (**a**) Biophysical simulation of spiking response to afferent input. Size of *black squares* indicates the amount of spiking activity (example membrane potential traces are shown). (**b**) With no synaptic modification (no learning), a degraded input pattern only activates a subset of neurons. (**c**) After learning with ACh, the network effectively completes missing components of the input pattern. (**d**) After learning without ACh, proactive interference results in retrieval of multiple different input patterns (Hasselmo et al. 1994; Barkai et al. 1994)

extended this work to subregions of the hippocampal formation. In region CA1 of the hippocampus, we showed that muscarinic presynaptic inhibition was stronger at excitatory connections arising from within the hippocampus (in region CA3) and terminating in stratum radiatum of region CA1 compared to afferent input from entorhinal cortex terminating in stratum lacunosum-moleculare (Hasselmo and Schnell 1994). Similarly, muscarinic presynaptic inhibition was stronger for synapses in stratum radiatum of region CA3 arising from CA3 pyramidal cells, compared to weaker presynaptic inhibition at afferent synapses in stratum lucidum, at synaptic input arising from the dentate gyrus (Hasselmo et al. 1995). This effect was later replicated in stratum lucidum (Vogt and Regehr 2001) and was extended to show less presynaptic inhibition in stratum lacunosum-moleculare of region CA3 (Kremin and Hasselmo 2007).

This principle of selective cholinergic suppression of excitatory feedback but not afferent input also proves to generalize to neocortical structures. In an early study, connections within somatosensory neocortex showed greater presynaptic inhibition than afferent input arising from the white matter (Hasselmo and Cekic 1996). This was subsequently shown in a study using thalamocortical slice preparations,

showing muscarinic presynaptic inhibition of excitatory recurrent connections in neocortex and also showing nicotinic enhancement of afferent input (Gil et al. 1997).

In the visual cortex, optical imaging was used to show cholinergic suppression of the internal spread of activity along excitatory recurrent connections compared to afferent input (Kimura and Baughman 1997; Kimura 2000). This indicated that acetylcholine should reduce the functional spread of activity on excitatory recurrent connections in visual cortex. This was supported by in vivo experimental data showing that iontophoretic application of acetylcholine decreases the extent of spatial integration, assessed by measuring a neuron's tuning to length of visual stimuli (Roberts et al. 2005). These effects appear to contribute to the influence of top-down attention on the dynamics of visual cortex processing (Herrero et al. 2008). This work has been extended to human subjects in a study showing that the acetylcholinesterase blocker donepezil reduces the extent of the spread of activity in visual cortical areas associated with foveal stimulation (Silver et al. 2008). Thus, the physiological effects of muscarinic activation modeled in these early papers in the Computational Neuroscience meeting have proved to be a general principle of cortical function in subsequent studies.

The hippocampal data and modeling generated the prediction that blockade of muscarinic receptors by the muscarinic antagonist scopolamine should enhance proactive interference in a paired associate memory task (Hasselmo and Wyble 1997; Wyble and Hasselmo 1997). This was supported by experimental data on scopolamine effects in human subjects (Atri et al. 2004). Enhancement of proactive interference was also shown in studies on discrimination of pairs of odors in rats administered scopolamine (De Rosa and Hasselmo 2000) or after receiving selective lesions of the cholinergic innervation of the olfactory cortex (De Rosa et al. 2001). In computational models, the build-up of proactive interference causes runaway synaptic modification within cortical networks that can spread from one region to another. This mechanism was proposed to underlie the early appearance of Alzheimer's disease neuropathology in the form of neurofibrillary tangles in lateral entorhinal cortex and the progressive spread from lateral entorhinal cortex to other regions (Hasselmo 1994, 1997). This provides a computational framework that would predict reductions in Alzheimer's pathology with loss of fast hippocampal learning (e.g., in the most extreme case, patient HM would be expected to show absence of Alzheimer's pathology in his remaining temporal lobe structures). This framework could account for the beneficial effects of the NMDA blocker memantine on Alzheimer's disease (Reisberg et al. 2003) and supports the use of selective activation of presynaptic muscarinic receptors with M4 agonists to enhance presynaptic inhibition of glutamate release in treatment of Alzheimer's disease (Shirey et al. 2008).

The levels of acetylcholine change dramatically during different stages of waking and sleep. Acetylcholine levels are high during active waking, show decreases during quiet waking, and decrease to less than 1/3 of waking levels during slow wave sleep (Marrosu et al. 1995). The decrease in acetylcholine levels during slow wave sleep has been proposed to decrease the presynaptic inhibition of glutamatergic transmission

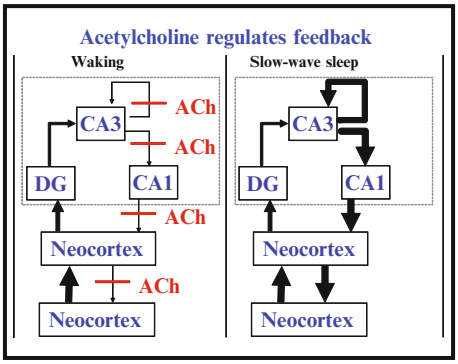

Fig. 10.3 (*Left*) During waking, high levels of ACh cause presynaptic inhibition of excitatory recurrent connections in CA3 as well as connections from region CA3 to region CA1 and feedback connections between neocortical structures. This allows a dominant influence of afferent input into the hippocampus during encoding. (*Right*) During slow wave sleep, lower levels of ACh allow stronger synaptic transmission at these connections. This results in a dominant influence of hippocampus on neocortex that could be appropriate for consolidation of previously encoded memories (Hasselmo 1999)

at connections from hippocampus back to neocortex, allowing activity based on recently formed associations in the hippocampus to spread back to the neocortex and drive consolidation of memories in the neocortex (for review see Hasselmo 1999). This proposal is consistent with the muscarinic cholinergic presynaptic inhibition shown at a number of stages of the feedback connections (Fig. 10.3), including the excitatory recurrent connections in region CA3 (Hasselmo et al. 1995; Vogt and Regehr 2001; Kremin and Hasselmo 2007), the connections from region CA3 to region CA1 (Hounsgaard 1978; Valentino and Dingledine 1981; Hasselmo and Schnell 1994; de Sevilla et al. 2002), and the feedback connections within neocortical structures (Hasselmo and Cekic 1996; Gil et al. 1997).

This model of the role of acetylcholine in consolidation led to some functional predictions that have been tested. If a reduction in cholinergic presynaptic inhibition enhances consolidation during slow wave sleep, then an increase in acetylcholine levels during slow wave sleep should impair consolidation. This was tested in a study in which subjects were administered physostigmine during slow wave sleep and showed reductions in subsequent tests of declarative memory consolidation performed after the subjects were awakened (Gais and Born 2004). On the other hand, the model predicts that reductions in acetylcholine modulation during waking should enhance consolidation. This was shown in a study in which scopolamine was administered to block muscarinic cholinergic receptors after encoding of information, and subjects showed an enhancement of consolidation on a later memory test (Rasch et al. 2006). Thus, computational modeling has provided an exciting link between cellular mechanisms of muscarinic presynaptic inhibition and behavioral studies in animals and humans.

This framework describes how the transitions between different levels of acetylcholine during waking and sleep can regulate the transition between encoding and consolidation. But this leaves the question of how more rapid transitions between encoding and retrieval could be regulated. Muscarinic presynaptic inhibition cannot change rapidly, as shown by studies in which 100 ms pressure pulse applications of acetylcholine cause changes in presynaptic inhibition that persist for 10–20 s (Hasselmo and Fehlau 2001). In contrast, rapid transitions between encoding and retrieval could be mediated by the change in dynamics during individual cycles of the theta rhythm oscillations in hippocampus (Hasselmo et al. 2002). These dynamical changes could be regulated by postsynaptic GABAA inhibition (Toth et al. 1997) and presynaptic GABAB inhibition (Molyneaux and Hasselmo 2002). Encoding could take place when entorhinal synaptic input is strongest at the trough of the EEG recorded at the hippocampal fissure (Hasselmo et al. 2002), and retrieval could be dominant when region CA3 input is strongest at the peak of fissure theta. The change in relative strength of synaptic input is supported by studies showing phasic changes in strength of evoked synaptic transmission on different pathways at different phases of the theta rhythm oscillation (Wyble et al. 2000; Villarreal et al. 2007). Consistent with the theorized role of these different phases in encoding and retrieval, the human EEG shows reset to different phases of theta rhythm during encoding versus during retrieval (Rizzuto et al. 2006), and spiking appears on different phases of hippocampal theta during match and nonmatch stimuli (Manns et al. 2007).

Hippocampus

In addition to these studies on associative memory in the piriform cortex, the early days of the Computational Neuroscience also included presentations of hippocampal models that have had a significant impact on subsequent research. These included papers on hippocampal models by Burgess, O'Keefe, and Recce; Idiart and Abbott; Redish and Touretzky; Holmes and Levy; Blum and Abbott; and Mehta and McNaughton. Modeling of the hippocampus has been very successful in guiding experimental work in this area. A number of experimental studies have tested specific predictions of computational models.

The phenomenon later described as spike-timing dependent plasticity was initially discovered by William B. "Chip" Levy (Levy and Steward 1983) and modeled extensively by Holmes and Levy (1990). The temporal asymmetry of synaptic modification modeled by Holmes and Levy was incorporated in a circuit model by Abbott and Blum (Abbott and Blum 1996; Blum and Abbott 1996). This model predicted that the potentiation of excitatory connections should cause a backward expansion of hippocampal place fields. An experimental test of the model was performed by Mayank Mehta in Bruce McNaughton's laboratory (Mehta and McNaughton 1997). They presented the experimental data from this test at the Computational Neuroscience meeting, showing the predicted backward expansion

of the size of place fields of hippocampal place cells (Mehta et al. 1997; Mehta and McNaughton 1997). This phenomenon has been replicated extensively in subsequent studies (Mehta et al. 2000, 2002).

Some of the theories of hippocampal function had a slower time constant for their influence on experimental work in the field. For example, the early paper by Marr (1971) is extensively credited with proposing the principle of pattern completion on excitatory recurrent connections in region CA3 of hippocampus. Marr also proposed that interference between patterns stored in CA3 could be reduced by the process of pattern separation (orthogonalization) in the dentate gyrus (the codon hypothesis of Marr). Several papers in the late 1980s and early 1990s reviewed these basic ideas of pattern separation in the dentate gyrus (McNaughton and Morris 1987; McNaughton 1991; O'Reilly and McClelland 1994; Hasselmo and Wyble 1997) and pattern completion by autoassociative memory function in hippocampal region CA3 (McNaughton and Morris 1987; Treves and Rolls 1994; Hasselmo et al. 1995). These principles were also combined together in a simulation of the role of the hippocampus in human episodic memory function presented at the Computational Neuroscience meeting (Hasselmo and Wyble 1997; Wyble and Hasselmo 1997).

The basic principles proposed by Marr had an impact on experimental work over 20 years later. Selective genetic manipulations in mice allowed selective knockout of the NMDA receptor in hippocampal region CA3, and these mice showed an impairment of pattern completion based on learning a spatial response in an environment with multiple cues and being tested for their response in an environment with a single cue (Nakazawa et al. 2002). Similarly, selective expression of tetanus toxin in mouse region CA3 to block synaptic transmission from these neurons also impairs pattern completion in that task (Nakashiba et al. 2008). In contrast, selective knockout of NMDA receptors in the dentate gyrus caused impairment of responses that required distinguishing two separate but similar contextual environments (McHugh et al. 2007). In addition, selective lesions of the dentate gyrus impair the capacity of rats to encode and selectively respond to spatial locations that are close to each other (Gilbert et al. 2001).

Unit recording studies have also analyzed the response properties of the dentate gyrus versus other hippocampal subregions. Neurons in the dentate gyrus show sparser coding of the environment, with fewer responsive cells and smaller response fields for dentate place cells (Barnes et al. 1990). Minimal changes in the spatial environment can cause distinct responses of dentate gyrus granule cells (Leutgeb et al. 2007). Other unit recording studies have tested for the effect of partial shifts in the environment on neural responses in region CA3. In one study, the partial shift caused less change of neural response in CA3 compared to CA1 suggesting pattern completion (Lee et al. 2004), whereas in another study, region CA3 responded with distinct representations to partial changes in the environment (Leutgeb et al. 2004). These apparently conflicting results were unified by demonstration of a nonlinear transformation in region CA3 (Vazdarjanova and Guzowski 2004). Input patterns that are somewhat similar to each other induce very similar response patterns, whereas input patterns that are more different evoke more strongly differentiated patterns of neural activity (Guzowski et al. 2004; Vazdarjanova and Guzowski 2004).

Theta Rhythm, Theta Phase Precession, and Grid Cells

Another important body of modeling research has focused on the role of oscillations in cortical function. Here I will focus on models of the role of theta rhythm in hippocampal function. An early paper presented at the Computational Neuroscience meeting presented a model of goal-directed behavior in the hippocampus that used the phenomenon of theta phase precession to provide a more accurate spatial code (Burgess et al. 1994).

Theta phase precession was first discovered by O'Keefe and Recce (1993) and then replicated extensively in other studies (Skaggs et al. 1996; Huxter et al. 2003). In theta phase precession, the spiking response of hippocampal place cells changes relative to theta rhythm oscillations recorded simultaneously in the hippocampal EEG. When a rat first enters the place field of an individual place cell, the spikes occur predominantly at a relatively late phase of the theta rhythm. The spikes shift to progressively earlier phases as the rat traverses the field. In the original paper describing theta phase precession, the phenomenon was proposed to arise from a progressive phase shift between the network EEG oscillation frequency and the intrinsic spiking frequency of the neuron which was shown to have a higher frequency based on the autocorrelation of spiking activity (O'Keefe and Recce 1993). That paper presents a simple figure showing how the interaction of two oscillations of slightly different frequency will cause a precession of the summed oscillation relative to the lower frequency oscillation. This model makes an interesting additional prediction that there should be multiple firing fields, each showing the same precession. Since most place cells had a single firing field, this was perceived as a problem of the model, and later implementations kept the oscillations out of phase with each other until one was shifted to a higher frequency in the firing field (Lengyel et al. 2003). However, the later discovery of grid cells casts a different light on the original model, fulfilling the prediction of the model for multiple firing fields that was initially perceived as a problem of the model. Thus, the model by O'Keefe and Recce essentially predicted the existence of grid cells.

A number of other models have also simulated theta phase precession. For example, the oscillatory interference model has been presented in a variant involving inhibitory influences on pyramidal cells (Bose et al. 2000; Bose and Recce 2001). In another class of models, the replication of phase precession in the McNaughton laboratory was accompanied by a model of phase precession based on slow retrieval of a learned sequence of spatial locations during each theta cycle (Tsodyks et al. 1996). A similar sequence read-out model was presented that year by Jensen and Lisman (1996a). In the Jensen and Lisman model, the phase precession during encoding arose from a working memory buffer in which afterdepolarization allowed neurons to be played out in a sequence on each theta cycle (Jensen and Lisman 1996b). Both of these models required relatively slow read-out of the sequence across the full theta cycle, at a rate slower than the time constants of glutamatergic AMPA conductances. The following year a different model was presented (Wallenstein and Hasselmo 1997) in which read-out had the faster time course of

AMPA conductances, but the length of the read-out would shift across the theta cycle based on the level of presynaptic inhibition or the level of postsynaptic depolarization. This model was extended later to include the context-dependent retrieval of sequences, accounting for the reappearance of theta phase precession over initial trials on each new day (Hasselmo and Eichenbaum 2005).

Another class of models proposed that phase precession arose from progressive shifts in the postsynaptic depolarization of neurons, causing spikes to occur at different phases relative to network inhibitory oscillations (Kamondi et al. 1998; Magee 2001; Mehta et al. 2002). These different models have motivated a number of different experimental studies. The sequence retrieval models were supported by an initial study showing that reset of theta phase oscillations did not shift phase, spiking after reset would commence at the same phase as before the reset (Zugaro et al. 2005). However, a more recent study strongly supported the oscillatory interference model by showing that intracellularly recorded oscillations in membrane potential also show phase precession relative to network oscillations (Harvey et al. 2009), an effect not predicted by the sequence read-out model. The postsynaptic depolarization model did not predict this shift in phase of intracellular oscillations (Kamondi et al. 1998). In addition, the postsynaptic depolarization models predicted an asymmetrical sawtooth waveform for a depolarizing shift in the place field, whereas the data showed a symmetrical depolarization in the place field (Harvey et al. 2009).

As noted above, the original presentation of the oscillatory interference model of theta phase precession predicted the existence of neurons with multiple, regularly spaced firing fields (O'Keefe and Recce 1993). Though the authors initially saw this as a problem for the model, the generation of multiple firing fields by the model is explicitly shown in Fig. 10 of the O'Keefe and Recce (1993) paper. This initially undesired prediction of the model was validated by the later discovery of grid cells in the medial entorhinal cortex in the Moser laboratory. In the data from the Moser lab, the existence of repeating firing fields was first noted in the dorsal portion of medial entorhinal cortex (Fyhn et al. 2004), and subsequently the regular hexagonal arrangement of firing fields was noted and found to extend to more ventral regions of medial entorhinal cortex with larger spacing between the firing fields (Hafting et al. 2005). The systematic increase in spacing between firing fields for neurons in more ventral locations has been shown in great detail in subsequent papers (Sargolini et al. 2006), including very large and widely spaced firing fields in more ventral medial entorhinal cortex (Brun et al. 2008).

When the first paper on grid cells appeared, O'Keefe and Burgess immediately recognized the significance of the repeating nature of grid cell firing, as this had been a strong feature of the theta phase precession model. They rapidly pointed out how oscillatory interference could underlie the properties of grid cell firing (O'Keefe and Burgess 2005). In the Computational Cognitive Neuroscience meeting in Washington in 2005, Neil Burgess presented a poster with a detailed model using velocity modulation of firing frequency to generate realistic grid cell firing fields (Burgess et al. 2005). The oscillatory interference model of grid cells immediately generated a prediction about the mechanism for the difference in spacing of grid

cells along the dorsal to ventral axis of medial entorhinal cortex (O'Keefe and Burgess 2005). To quote that paper directly: "The increasing spatial scale of the grid-like firing as you move from the postrhinal border of the medial entorhinal cortex would result from a gradually decreasing intrinsic frequency …" I saw Neil Burgess's poster in Washington and with graduate student Lisa Giocomo set out to test this explicit prediction of the model. Neil kindly sent us a copy of his poster with the model that he presented later in a full paper (Burgess et al. 2007).

To test the prediction, Lisa performed intracellular whole cell patch recording from stellate cells in slice preparations of medial entorhinal cortex (Giocomo et al. 2007). She used horizontal slices of entorhinal cortex and kept track of the dorsal to ventral position of the individual horizontal slices, so she could plot differences in intrinsic properties relative to anatomical position. We found a clear difference in the resonant frequency and the frequency of subthreshold membrane potential oscillations (Giocomo et al. 2007), with a gradual decrease in these intrinsic frequencies for slices more ventral relative to the postrhinal border. Thus, the prediction of the model was clearly supported by the data. The data on frequency membrane potential oscillations and resonance has been replicated by other groups (Boehlen et al. 2010) and by other researchers working in my laboratory (Heys et al. 2010).

In our initial presentation of the data on differences in intrinsic frequency (Giocomo et al. 2007), we illustrated the functional significance of the data by incorporating the difference in intrinsic frequency into the oscillatory interference model by Burgess (Fig. 10.4). Using a multiplicative version of the model, we showed that higher intrinsic frequency in dorsal cells could generate the narrower spacing between firing fields of grid cells recording in dorsal entorhinal cortex and the lower frequency in ventral cells could generate the wider spacing in more ventral cells. In a later paper, we showed that the data was more consistent with an additive model that could account for very wide spacings by having a shallower slope of change in frequency with velocity (Giocomo and Hasselmo 2008a).

The dorsal to ventral difference in intrinsic frequency was accompanied by a gradual slowing of the time constant of the depolarizing sag in stellate cells caused by hyperpolarizing current injections activating the H current and causing a depolarizing rebound (Giocomo et al. 2007). This suggested a role for H current in the dorsal to ventral difference in intrinsic frequency, which was supported by voltage clamp data suggesting a difference in the time constant of the H current as well as a trend toward differences in the magnitude of the H current (Giocomo and Hasselmo 2008b). Testing of intrinsic frequencies in mice with knockout of the H current showed a flattening of the gradients of intrinsic frequencies (Giocomo and Hasselmo 2009). These results were consistent with recordings in oocytes showing that homomeric H current channels using just HCN1 subunit had faster time constant than homomeric HCN2 channels, with an intermediate time constant for heteromeric channels combining HCN1 and HCN2 subunits (Chen et al. 2001). Thus, this model provided an exciting link between molecular and cellular properties of neurons in medial entorhinal cortex, and the functional coding of space by the grid cell firing properties of these neurons. This was beyond anything that I had dreamed of accomplishing when the Computational Neuroscience meeting started in the early 1990s.

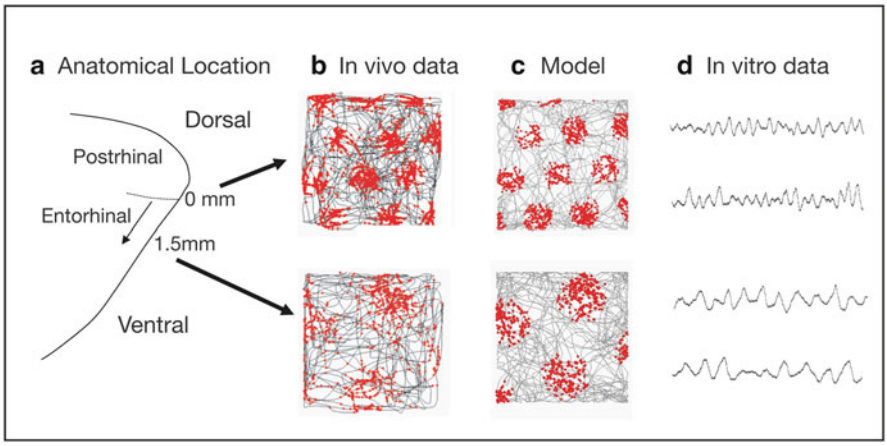

Fig. 10.4 (**a**) Anatomical location of grid cells with different spacing. (**b**) Dorsal cells near the postrhinal border have spacing between firing fields of about 40 cm (*top*). Cells recorded about 1.5 mm more ventral from the postrhinal border have spacing between firing fields of about 80 cm (*bottom*) (from Hafting et al. 2005). (**c**) The oscillatory interference model of grid cells can replicate these spacing properties based on a steeper slope of oscillation frequency to velocity in dorsal compared to ventral cells (Burgess et al. 2007; Hasselmo et al. 2007). (**d**) The prediction of the model for different intrinsic oscillation frequencies during depolarization is supported by whole cell patch recordings of stellate cells in slice preparations of medial entorhinal cortex from dorsal (*top*) versus ventral (*bottom*) anatomical locations (Giocomo et al. 2007)

After we published the Science paper, I felt that the next step would be simple. The model in the Science paper used interference of cosine functions. The next step would be to implement the model within a compartmental simulation of an entorhinal stellate cell as implemented in GENESIS by Fransén et al. (2004). I believed we could simulate subthreshold oscillations on different dendrites within a compartmental simulation (Hasselmo et al. 2007). However, in simulations run by Jim Heys in my laboratory, subthreshold oscillations on different dendrites tended to synchronize. The same result was obtained in work by Michiel Remme with Boris Gutkin and Mate Lengyel in extensive simulations and computational analysis (Remme et al. 2009, 2010). In addition, analysis of the variability of oscillation period showed that the membrane potential oscillations were too noisy to allow stable coding of location by phase (Giocomo and Hasselmo 2008a; Zilli et al. 2009). These points argued against a single cell implementation of the model and argued for a network implementation.

The effect of single cell resonance on spike timing is a topic of ongoing research. It is clear that resonance does not result in rhythmic spiking only at the resonant frequency, but allows a range of frequencies with only a small deflection at the resonant frequency (Giocomo and Hasselmo 2008a). In contrast, recordings of intrinsic persistent spiking mechanisms in medial entorhinal pyramidal cells show that cells tend to spike rhythmically at steady frequencies around theta rhythm (Egorov et al. 2002; Fransén et al. 2006; Tahvildari et al. 2007). Therefore, I developed a model of

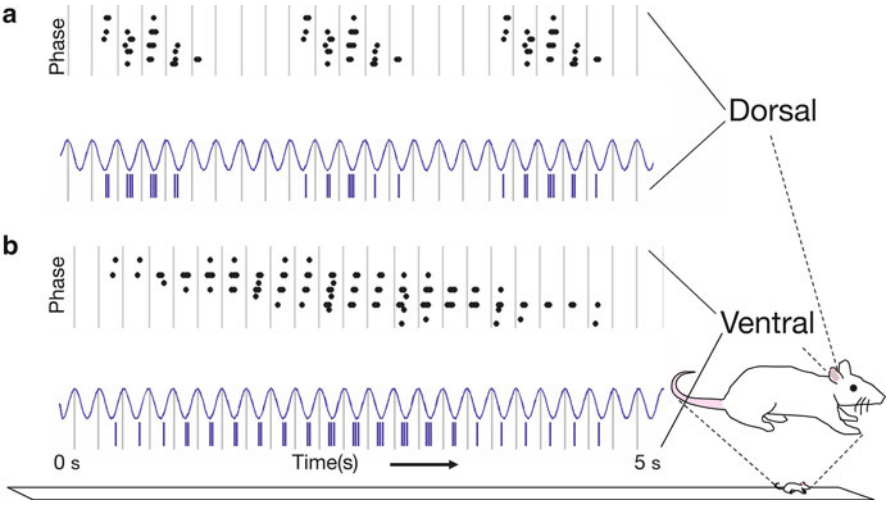

Fig. 10.5 Theta phase precession using the persistent spiking neuron model. (**a**) Simulation of neuron in dorsal entorhinal cortex with higher persistent firing frequency for a given velocity. *Black dots* show phase of spiking versus location during multiple passes through firing fields. *Blue trace* shows simulated EEG with *dashes* indicating spike times. (**b**) Ventral entorhinal cortex neuron with lower persistent spiking frequency for a given velocity, showing slower shift in phase with position in a larger grid cell firing field (Hasselmo 2008)

grid cells based on persistent spiking cells that could hold a steady baseline frequency. Cells with stable baseline frequencies have been shown in deep layers of medial entorhinal cortex (Egorov et al. 2002; Fransén et al. 2006; Tahvildari et al. 2007), in layer III of lateral entorhinal cortex (Tahvildari et al. 2007), and in the postsubiculum (Yoshida and Hasselmo 2009). These neurons tend to fire at the same stable baseline frequency regardless of the duration of the stimulation causing persistent spiking (Yoshida and Hasselmo 2009). A computational model of grid cells based on persistent spiking was developed using grid cells responding to the convergent input from different groups of persistent spiking cells that receive input from different sets of head direction cells (Hasselmo 2008). This effectively simulated grid cells based on shifts in the frequency of persistent spiking input (Hasselmo 2008), and as shown in Fig. 10.5, simulates theta phase precession in grid cells (Hasselmo 2008) consistent with experimental data showing theta phase precession in grid cells (Hafting et al. 2008).

Persistent spiking also shows variability in firing frequency that could interfere with the stability of phase coding. However, network level dynamics may overcome this variability, allowing cells that are intrinsically noisy and irregular in their firing to still participate in a network oscillation with frequency and phase sufficiently stable to generate grid cell firing (Zilli and Hasselmo 2010). This model can respond with different frequencies for different depolarizing inputs depending on the magnitude of the H current in individual neurons, though it is difficult to maintain a linear relationship between depolarizing input and magnitude of frequency change.

This model indicates the ongoing validity of the oscillatory interference model as a theory of the generation of grid cell firing responses and provides a framework for explaining the relationship between intrinsic resonance and the spacing of grid cell firing fields.

A number of alternate mechanisms have been proposed for the generation of grid cell firing properties, including attractor dynamics due to structured excitatory recurrent connectivity (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009) and self-organization of afferent input (Kropff and Treves 2008). The attractor dynamics models do not account for some data as well as oscillatory interference models, but they are better at accounting for the consistent orientation and spacing of grid cells within local regions of the medial entorhinal cortex (Hafting et al. 2005) and the apparent quantal transitions in the spacing between firing fields (Barry et al. 2007). However, most attractor dynamic models do not utilize theta frequency oscillations in spiking activity and do not account for theta phase precession. However, a recent model used attractor dynamics and simulated grid cell theta phase precession, while generating differences in spacing based on the time course of medium afterhyperpolarization (Navratilova et al. 2012). The importance of theta rhythm oscillations for grid cell generation has been demonstrated by local infusions into the medial septum that block network theta rhythm oscillations in the entorhinal cortex. Grid cell firing patterns do not appear during pharmacological blockade of theta rhythm oscillations (Brandon et al. 2011), whereas head direction responses are spared.

As described here, the discovery of grid cells and their relationship to the intrinsic resonance properties of entorhinal neurons provides fascinating clues to the function of the entorhinal cortex and hippocampus in human episodic memory. A theoretical framework based on the oscillatory interference model can perform the encoding and retrieval of complex trajectories as episodic memories. The data have not yet converged on a final model of the mechanism for generation of grid cells, but the ongoing interaction of computational modeling guiding experimental neurophysiology has provided insights beyond any that I imagined 20 years ago at the Computational Neuroscience meeting.

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