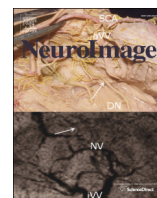




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Review

Theta rhythm and the encoding and retrieval of space and time

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ABSTRACT

Physiological data demonstrates theta frequency oscillations associated with memory function and spatial behavior. Modeling and data from animals provide a perspective on the functional role of theta rhythm, including correlations with behavioral performance and coding by timing of spikes relative to phase of oscillations. Data supports a theorized role of theta rhythm in setting the dynamics for encoding and retrieval within cortical circuits. Recent data also supports models showing how network and cellular theta rhythmicity allows neurons in the entorhinal cortex and hippocampus to code time and space as a possible substrate for encoding events in episodic memory. Here we discuss these models and relate them to current physiological and behavioral data.

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Introduction

Theta frequency oscillations appear in electroencephalographic (EEG) recordings from scalp electrodes and depth electrodes in human subjects, but controversy continues over the functional role of theta frequency oscillations (commonly referred to as theta rhythm). Understanding the functional role of theta rhythm will benefit from attention to data on the role of theta rhythm in animals. Here we will review data on theta rhythm in humans and animals and recent theories linking theta rhythm to mechanisms of memory and spatial navigation.

Experimental data on theta rhythm

Theta rhythm in humans and animals

In early EEG studies in humans (Niedermeyer, 1999), Hans Berger used the Greek letter *alpha* to designate 8–12 Hz frequencies observed first in resting participants, then used *beta* for 12–30 Hz frequencies in more attentive participants. Subsequently, *gamma* (30 to 100 Hz), and *delta* (below 4 Hz) were named. The 4 to 7 Hz band was designated *theta* (Walter and Dovey, 1944) to stand for thalamus (Niedermeyer, 1999) because thalamic lesions in monkeys shifted cortical dynamics from alpha (8–12 Hz) to theta (4–7 Hz). Early studies showed that theta in the cortical EEG correlates with developmental age and pathological conditions, but intracranial electrodes implanted to detect seizure activity also show cortical theta rhythm associated with performance of memory tasks in humans (Guderian et al., 2009; Kahana et al., 1999, 2001; Lega et al., 2011; Raghavachari et al., 2001, 2006; Rizzuto et al., 2006; Sederberg et al., 2003). The data in humans includes recordings during virtual navigation tasks showing increases in power of theta and delta frequency oscillations associated with spatial navigation and movement speed (Caplan et al., 2003; Ekstrom et al., 2005; Watrous et al., 2011, *in press*). Studies in humans also show a relationship of memory function to the theta rhythm in scalp EEG recordings (Jacobs et al., 2006; Klimesch, 1999; Klimesch et al., 1994, 1996), and in magnetoencephalographic (MEG) recordings (Jensen and Tesche, 2002; Osipova et al., 2006) that include effects of virtual movement on theta rhythm in MEG (Cornwell et al., 2008; de Araujo et al., 2002; Kaplan et al., 2012). Note that many of these studies show power changes in low theta and delta ranges, in contrast to higher theta frequencies found in animals. This article will focus on data from animals, as the topic of theta rhythm in humans is addressed in other reviews in this special issue by Ranganath, Ekstrom and Sederberg and Polyn.

Data from animals suggests functional roles of theta rhythm. Early studies of local field potentials (LFPs) in animals found prominent oscillations in the theta frequency range in the hippocampus (Green and Arduini, 1954). Fig. 1 shows theta rhythm recorded from the hippocampus. Theta rhythm refers to frequencies from 3 to 10 Hz in rodents because similar mechanisms appear to underlie this full range of frequencies (Buzsaki, 2002). Theta rhythm LFP oscillations also appear in rat entorhinal cortex (Alonso and Garcia-Austt, 1987; Brandon et al., 2011; Mitchell and Ranck, 1980) and medial prefrontal cortex (Jones and Wilson, 2005; Lee et al., 2005).

Behavioral correlates of theta rhythm

Theta rhythm power increases with a range of behaviors including attention to predators in rabbits (Green and Arduini, 1954; Sainsbury et al., 1987b), and voluntary movement in rats (Bland and Oddie, 2001; Kelemen et al., 2005; Lenck-Santini et al., 2008; Shin, 2011; Vanderwolf, 1969; Whishaw and Vanderwolf, 1973) including running on a track (Hinman et al., 2011; O'Keefe and Nadel, 1978; Skaggs et al., 1996), running wheel (Buzsaki et al., 1983; Hyman et al., 2003b), or treadmill (Brankack et al., 1993; Fox et al., 1986). Frequency and amplitude of rat theta increases with running speed (Hinman et al., 2011, 2013; Jeewajee et al., 2008; Maurer et al., 2005; Rivas et al., 1996;

Whishaw and Vanderwolf, 1973) and with jumping (Lenck-Santini et al., 2008; Vanderwolf, 1969), suggesting a role in coding of velocity and location.

Theta rhythm in the hippocampus correlates with learning and memory function (Berry and Thompson, 1978; Givens and Olton, 1990; Seager et al., 2002; Vertes and Kocsis, 1997; Winson, 1978). Conditioning of eye blink responses to air puff or jaw movements to reward occurs more rapidly in animals with greater power of pre-stimulus theta rhythm (Berry and Thompson, 1978), and when training occurs during periods of theta rhythm (Griffin et al., 2004; Seager et al., 2002). Theta rhythm also appears during conditioning of fear responses (Sainsbury et al., 1987a; Seidenbecher et al., 2003; Whishaw, 1972). In contrast, theta rhythm during passive rotation does not seem to increase with cognitive demands (Kelemen et al., 2005).

Lesions of the medial septum and fornix that reduce theta power in the hippocampus (Rawlins et al., 1979) and entorhinal cortex (Mitchell et al., 1982) cause memory impairments in tasks including delayed spatial alternation (Aggleton et al., 1995; Givens and Olton, 1990), delayed non-match to position (Markowska et al., 1989), delayed response (Numan and Quaranta, 1990), spatial reversal (M'Harzi et al., 1987), the Morris water maze (Martin et al., 2007) and the 8-arm radial maze (Mitchell et al., 1982). Reduction in hippocampal theta rhythm correlates with impairments in memory (Winson, 1978) that are specific for recently experienced episodes but not for highly familiar memories (Givens and Olton, 1994; M'Harzi et al., 1987). Temporary inactivation of the medial septum impairs spatial memory and reduces theta rhythm in both the hippocampus (Brioni et al., 1990; Chrobak et al., 1989; Mizumori et al., 1990) and entorhinal cortex (Jeffery et al., 1995), and spatial memory performance after septal inactivation can be recovered by stimulation of the fornix at theta rhythm (McNaughton et al., 2006b), supporting a link between theta rhythm and behavioral encoding of space.

Functional coding by phase of theta rhythm

An ongoing controversy concerns whether neurons code information not just by the rate of spiking but also by the time of spiking (temporal coding, also known as phase coding). Support for temporal or phase coding comes from the spike timing relative to theta rhythm. Hippocampal place cells respond selectively when a rat visits a specific location (O'Keefe, 1976; O'Keefe and Dostrovsky, 1971; Skaggs et al., 1996). When a rat runs through a place cell firing field, the place cell initially spikes at late phases of the theta cycle, and then shifts to progressively earlier phases as the rat continues through the place field (O'Keefe and Recce, 1993). This phenomenon, termed theta phase precession, has been replicated in numerous recordings (e.g. Huxter et al., 2003, 2008; Lenck-Santini et al., 2008; Mehta et al., 2002; Mizuseki et al., 2009; Skaggs et al., 1996) showing that the phase of spikes relative to network oscillations codes space. This code could contribute to a cognitive map allowing association of items with locations (Arleo and Gerstner, 2000; Burgess et al., 1997; Erdem and Hasselmo, 2012; Hasselmo, 2012; Hasselmo and Eichenbaum, 2005; Jensen and Lisman, 2000; Redish and Touretzky, 1998). In humans, hippocampal place cells have been shown with depth electrodes in participants performing virtual navigation tasks (Ekstrom et al., 2003), but theta phase precession has not yet been shown in humans.

A phase code for space also appears in recordings of grid cells in the entorhinal cortex in rats (Hafting et al., 2008; Moser and Moser, 2008). Grid cells respond as a rat visits a regular array of locations in the environment described as falling on the vertices of tightly packed equilateral triangles (Fyhn et al., 2004; Hafting et al., 2005, 2008). Each time a rat passes through the firing field of a grid cell, the spiking starts at late phases of the LFP theta cycle, and shifts to earlier phases of the theta cycle (Climer et al., 2013; Hafting et al., 2008). Data supporting grid cells in humans comes from research based on a six-fold rotational symmetry of fMRI activation during

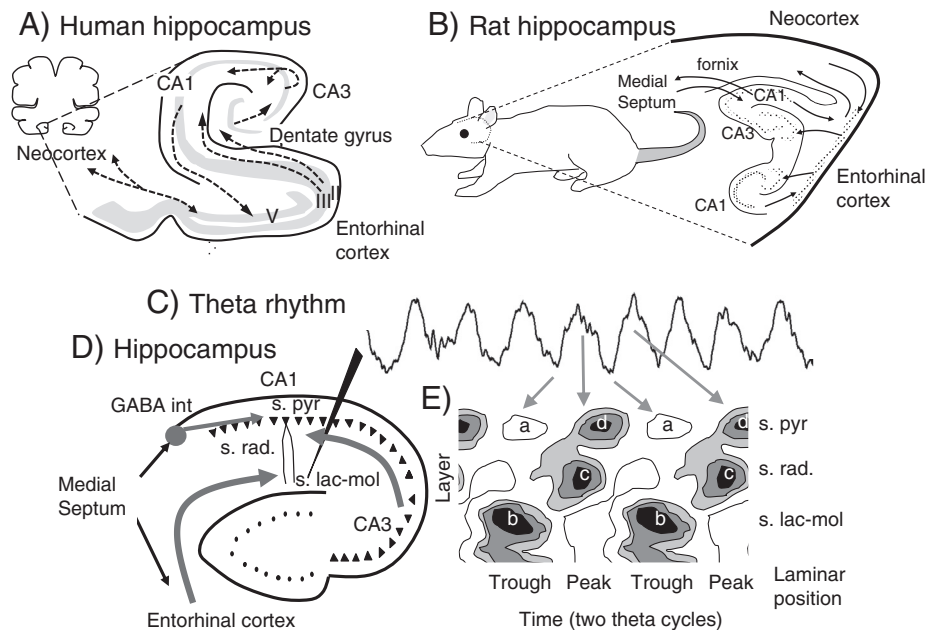


Fig. 1. Theta rhythm in the hippocampus. A. Location and anatomy of the hippocampus in the human brain. B. Anatomy of the hippocampus in the rat brain showing the input from the medial septum via the fornix. C. Theta rhythm in the EEG recorded in stratum lacunosum-moleculare (s. lac-mol) of hippocampal region CA1 of the rat. D. The medial septum input to GABA cells in the hippocampus paces theta rhythm (Buzsaki, 2002). Gray arrows show synaptic input from entorhinal cortex and CA3 causing synaptic currents in region CA1. E. Schematic based on current source density data (Buzsaki et al., 1986; Brankack et al., 1993) during two cycles of theta rhythm shows a source (“a” outward current) in the pyramidal layer (s. pyr) at the same phase as a sink (“b” inward current) appears due to entorhinal input in stratum lacunosum moleculare (s. lac-mol). At the opposite phase of theta rhythm, a current sink (“c”) occurs due to CA3 input in stratum radiatum (s. rad) and a sink (“d”) appears due to spiking in stratum pyramidale (s. pyr).

virtual navigation (Doeller et al., 2010) and unit recording from depth electrodes in human entorhinal cortex (Kahana, personal communication).

Theta rhythm may provide separate phases of encoding and retrieval

The behavioral data indicates a role of theta rhythm in the encoding of new information, but the mechanisms for this role are not known. Modeling shows how specific physiological processes at different phases of theta rhythm could enhance encoding by separating the dynamics of encoding and retrieval on different phases of the theta rhythm (Hasselmo et al., 2002a).

Memory requires separation of information arriving from the external world, to be encoded as new, from the information retrieved from internal circuits, which must be treated as old. While speaking with a friend, you might remember something they said yesterday, but you must respond to what they said to you in the current moment, not your memory of what they said to you yesterday. Physiological data on theta rhythm inspired a model (Hasselmo et al., 2002a) in which the changes in synaptic current at different phases of theta rhythm mediate separate phases of encoding and retrieval that repeat on every cycle (Fig. 2), referred to here as the SPEAR model (Separate Phases of Encoding And Retrieval). This model has inspired further research described below.

In the SPEAR model, during the encoding phase of each theta cycle (Fig. 2A), external input from entorhinal cortex is strong (Hasselmo et al., 2002a), setting a new pattern of depolarization in the postsynaptic dendrites in region CA1 for encoding. During this encoding phase, synaptic input from region CA3 is weaker so that it does not drive the postsynaptic depolarization. However, synaptic modification at the synapses in region CA1 is strong during this phase, allowing synapses with NMDA receptors to strengthen, encoding associations between the presynaptic activity in CA3 and the postsynaptic activity induced in CA1 neurons by

input from entorhinal cortex. Physiological data shows that long-term potentiation is strongest at this phase of the EEG (Holscher et al., 1997; Huerta and Lisman, 1995; Hyman et al., 2003a).

During the retrieval phase of each theta cycle, external input from entorhinal cortex is weaker, but the excitatory input from region CA3 is stronger. The stronger input from CA3 means postsynaptic activity in region CA1 is driven by the spread of activity across previously modified synapses, retrieving previously stored associations. At this time, the cell body receives the least inhibition, allowing retrieval to drive the spiking output of the neurons. Long-term potentiation is reduced during this time, so that the retrieval activity is not stored as a new event.

Simulations show that separate phases of encoding and retrieval allow effective separation of new external input from prior retrieval (Hasselmo

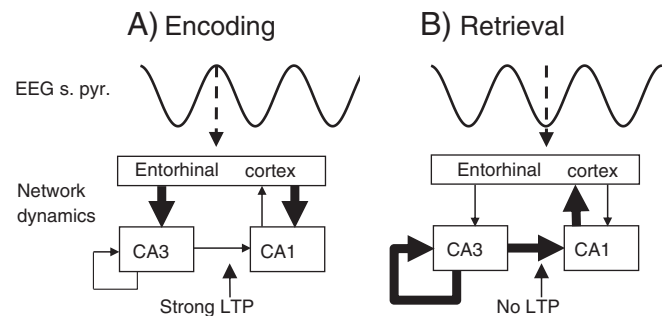


Fig. 2. Model of separate phases of encoding and retrieval (SPEAR) during different phases of hippocampal theta rhythm (Hasselmo et al., 2002a). A. Encoding. At the peak of the LFP in region CA1 stratum pyramidale (s. pyr), synaptic input from entorhinal cortex is strong (thick arrows), driving activity in CA3 and CA1. Synapses from CA3 to CA1 have weak transmission (thin arrows), causing less retrieval, but can undergo long-term potentiation (LTP) to encode new associations. B. Retrieval. At the trough of the LFP, synaptic input from entorhinal cortex is weaker (thin arrows), but synaptic transmission from CA3 is strong, allowing retrieval of previously stored associations to drive spiking in region CA1. LTP is weak (No LTP) to prevent encoding of retrieved activity as new.

et al., 2002a). Encoding and retrieval can overlap, but too much overlap could cause problems. If encoding dynamics happen during the retrieval phase, then you may mistake current sensory input for a retrieved memory (d  j   vu), or you might mistake your retrieved memory from yesterday as a new event happening today and new information may distort old memories. If retrieval is allowed during the encoding phase, the spread of retrieval activity causes postsynaptic spiking to occur during induction of long-term potentiation, resulting in formation of incorrect associations between old and new events, causing a breakdown in network function (Hasselmo et al., 2002b; Hasselmo, 2012).

Physiological data supporting the SPEAR model

Physiological data on theta rhythm are consistent with the encoding/retrieval model, including membrane potential dynamics, changes of inhibition, changes in synaptic transmission, and changes in LTP.

Phasic membrane potential dynamics

Hippocampal neurons fire at different rates on different phases of theta rhythm (Fox et al., 1986; O'Keefe and Recce, 1993; Skaggs et al., 1996), possibly due to phasic changes in membrane potential (Fox, 1989; Fujita and Sato, 1964; Kamondi et al., 1998). At one phase, the dendrites are depolarized (Kamondi et al., 1998) by entorhinal input, allowing encoding, while the cell body is hyperpolarized, preventing spiking due to interference from retrieval of previous associations (Hasselmo et al., 2002a). At the opposite phase, cell bodies are depolarized during input from region CA3, allowing spiking output for retrieval of previously stored associations. Consistent with this, spiking in region CA1 occurs at a phase following spiking in region CA3 and not during spiking in entorhinal layer III (Mizuseki et al., 2009).

Phasic changes in inhibition

Membrane potential changes could arise due to different morphological classes of inhibitory interneurons that spike at different phases of theta rhythm (Klausberger and Somogyi, 2008; Klausberger et al., 2003). Modeling suggests functional roles for different phases of interneuron firing in separating encoding and retrieval (Cutsuridis and Hasselmo, 2012; Kunec et al., 2005). Inhibitory axo-axonic and basket cells could inhibit the cell bodies and axons of excitatory cells to reduce spiking output during encoding (Cutsuridis and Hasselmo, 2012). At the opposite, retrieval phase, oriens lacunosum-moleculare cell spiking inhibits the layer where entorhinal input contacts the distal dendrites, reducing external input during retrieval of associations at previously modified synapses in stratum radiatum (Hasselmo et al., 2002a; Kunec et al., 2005).

Phasic changes in synaptic input

Current source density analysis (Brankack et al., 1993; Buzsaki et al., 1986) shows systematic changes in synaptic currents during theta. During one phase, strong excitatory currents in stratum lacunosum-moleculare (Brankack et al., 1993; Buzsaki et al., 1986) could allow encoding by driving depolarization throughout the dendritic tree to form associations with coincident synaptic input from region CA3, even though spiking driven by retrieval is reduced by inhibition at the cell body (Kamondi et al., 1998). At the opposite phase, stronger excitatory currents in stratum radiatum (Brankack et al., 1993) could reflect previously strengthened synapses from region CA3 driving retrieval that causes spiking of CA1 pyramidal cells (Csicsvari et al., 1999; Fox et al., 1986; Skaggs et al., 1996) based on the pattern of previously encoded associations (Hasselmo et al., 2002a).

Phasic changes in synaptic input could also arise from differences in presynaptic inhibition of synaptic transmission (Wyble et al., 2000) causing changes in size of synaptic potentials (Villarreal et al., 2007; Wyble et al., 2000) and population spiking (Buzsaki et al., 1981; Rudell et al., 1980; Villarreal et al., 2007), possibly due to presynaptic inhibition

caused by GABA_B receptors (Hasselmo and Fehrlau, 2001; Molyneaux and Hasselmo, 2002). These phasic changes allow synaptic transmission in stratum radiatum to be weak when induction of long-term potentiation is strong during encoding (Hasselmo et al., 2002a).

Phasic changes in long-term potentiation

The separation of encoding and retrieval is consistent with phasic changes in long-term potentiation (LTP). LTP is stronger in dentate gyrus when a tetanus is delivered on positive phases of theta (Orr et al., 2001; Pavlides et al., 1988). In intracellular slice preparations of region CA1 in rat hippocampus showing theta rhythm, stimulation on the peak of theta causes LTP, while stimulation on the trough causes long-term depression (Huerta and Lisman, 1995). The phase change in LTP induction also occurs in anesthetized rats (Holscher et al., 1997), and awake, behaving animals (Hyman et al., 2003a) indicating that LTP can be induced at the synapses from region CA3 when synaptic transmission is weak at these CA3–CA1 synapses but postsynaptic dendrites are depolarized by entorhinal input. At this phase, the cell body is hyperpolarized, preventing spiking due to retrieval, but dendritic spikes can underlie LTP even when the soma is hyperpolarized (Golding et al., 2002). Thus, extensive physiological data are consistent with separation of encoding and retrieval on different phases of theta rhythm.

Network data relating to encoding and retrieval

The SPEAR model helps in understanding impairments of memory encoding during loss of theta rhythm (Givens and Olton, 1994; Winson, 1978). In rats, fornix lesions that reduce theta rhythm cause an increase in the number of erroneous visits to a previously rewarded arm in a T-maze task (M'Harzi et al., 1987). Without theta to separate encoding and retrieval, strong synaptic transmission may mediate retrieval of the memory for food at the now unrewarded location at the phase when long-term potentiation enhances synaptic strength, thereby slowing the extinction of the old food memory (Hasselmo et al., 2002a). The loss of the encoding phase could also underlie the impairments in memory tasks associated with inactivation of the medial septum (Chrobak et al., 1989).

The SPEAR model is consistent with data showing that the phase of theta rhythm correlates with sniffing (Macrides et al., 1982), that theta rhythm shows phase reset during stimulus encoding (Givens, 1996), and phase resetting enhances induction of long-term potentiation in rats (McCartney et al., 2004). EEG oscillations in human subjects show phase reset to different phases of theta rhythm during behavioral trials requiring item encoding versus response to a retrieval probe (Rizzuto et al., 2006). In rats performing a delayed non-match to sample task, spiking occurs at different phases of theta for match (retrieval) versus non-match (encoding) stimuli (Manns et al., 2007). Studies of gamma frequency oscillations in rats also support the model. Gamma appears on specific phases of theta in hippocampus (Bragin et al., 1995) and entorhinal cortex (Chrobak and Buzsaki, 1998; Tort et al., 2009). Consistent with the encoding phase of the model, high frequency gamma oscillations are coherent between entorhinal cortex and region CA1 at one phase of theta (Colgin et al., 2009). At a different phase of theta, region CA1 shows coherence of low frequency gamma with region CA3 (Colgin et al., 2009) consistent with a retrieval phase.

Because the retrieval phase is associated with long-term depression of synapses, the SPEAR model has the property of retrieval-induced forgetting, similar to another model using oscillations to strengthen target memories and weaken competing memories (Norman et al., 2006, 2007), consistent with EEG data in humans (Newman and Norman, 2010). Behavioral studies show that modulatory separation of encoding and retrieval may also occur over longer time courses, as indicated by data showing enhanced pattern completion that persists after periods of retrieval (Duncan et al., 2012).

Theta rhythm and models of the phase coding of space

The extensive data on theta phase precession (Huxter et al., 2003, 2008; Mehta et al., 2002; Mizuseki et al., 2009; O'Keefe and Recce, 1993; Skaggs et al., 1996) inspired a range of models addressing how the phase of spiking relative to theta rhythm codes the spatial location of an animal (Geisler et al., 2007; Jensen and Lisman, 1996; O'Keefe and Recce, 1993; Tsodyks et al., 1996; Wallenstein and Hasselmo, 1997; Samsonovich and McNaughton, 1997). The first paper on theta phase precession proposed that it arose from oscillatory interference (O'Keefe and Recce, 1993) between a baseline oscillation (e.g. network theta rhythm) and a velocity-controlled oscillator (e.g. single cell membrane potential) pushed to higher frequency by running speed. Consistent with this, data shows that average frequency of place cell spiking (detected by autocorrelation of spike trains) is higher than the frequency of network theta rhythm, which could cause the higher frequency spiking to systematically shift to earlier phases relative to the baseline.

The models of theta phase precession also address mechanisms of place cell generation. The oscillatory interference model (OIM) (O'Keefe and Recce, 1993) generates spatial firing fields because the sum of two oscillations shows a transition from zero amplitude when the oscillations are out of phase to a peak amplitude due to constructive interference when the oscillations are close in phase, followed by a decrease as they go back out of phase. As the oscillations continuously shift in and out of phase, this would produce multiple firing fields. This could be seen as the model of O'Keefe and Recce predicting the multiple firing fields of grid cells that were reported many years later in the entorhinal cortex (Hafting et al., 2005; Moser and Moser, 2008). When grid cells were discovered, Burgess, Barry and O'Keefe showed how the model could be extended to simulate the repeating array of grid cell firing fields as the rat moves through the environment due to interaction of multiple oscillators regulated by velocity relative to preferred directions of movement (Burgess, 2008; Burgess et al., 2005, 2007). In this model, velocity shifts the frequency of the oscillators, such that the relative phase of oscillations codes the spatial position of the animal, and summation of interfering oscillators generates grid cell firing fields as shown in Fig. 3. This model links the circuit dynamics of theta rhythm to the coding of space for behavior (Blair et al., 2007, 2008; Burgess, 2008; Burgess et al., 2005, 2007;

Hasselmo, 2008; Hasselmo and Brandon, 2012; Hasselmo et al., 2007; Welday et al., 2011). This model is referred to here as the OIM (Oscillatory Interference Model).

Despite the wealth of data, some researchers still argue that theta phase precession is an epiphenomenon not central to the cognitive function of cortical circuits, focusing on the role of attractor dynamics and rate coding in representation of space. However, recent models have shown that attractor dynamics and oscillatory interference are not incompatible, merging them to address experimental data on grid cells and place cells. This section will first address experimental data supporting the oscillatory interference model (OIM), and then will address data that presents a problem for this model.

Support for phase coding involving theta rhythm

Spiking frequency and theta phase precession

The OIM explicitly requires theta phase precession (Burgess et al., 2007) and predicted the experimental data showing theta phase precession of entorhinal grid cell spiking (Hafting et al., 2008), and the difference in slope of theta phase precession at different dorsal to ventral positions in entorhinal cortex and hippocampus (Hafting et al., 2008; Kjelstrup et al., 2008). This contrasts with models of grid cells using attractor dynamics, which do not automatically generate theta phase precession. The OIM also predicted the relationship of the intrinsic spiking frequency of grid cells tested by autocorrelograms (Burgess, 2008) to rat running speed and the spacing of grid cell firing fields (Jeewajee et al., 2008; Stensola et al., 2012). Consistent with the model, modulation of spiking frequency by the cosine of head direction has been shown in theta rhythmic neurons of the hippocampus and medial septum (Blair et al., 2008; Welday et al., 2011).

Dependence on oscillations

The OIM motivated tests of whether grid cells depend upon theta rhythm, using blockade of entorhinal theta rhythm via pharmacological inactivation of the medial septum (Brandon et al., 2011; Koenig et al., 2011). The blockade of theta rhythm was accompanied by loss of spatial periodicity of grid cells, without loss of head direction cell selectivity. Conjunctive grid cells that showed both grid cell spatial periodicity and head direction selectivity lost their grid cell spatial periodicity

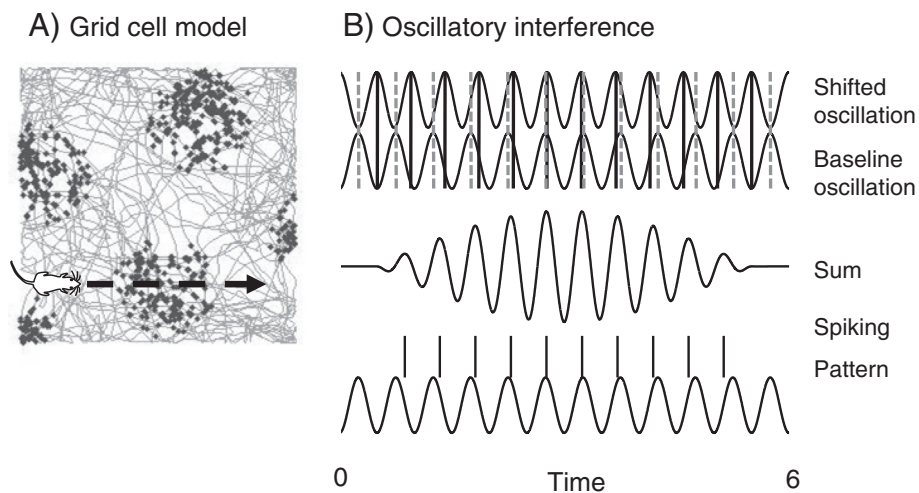


Fig. 3. Theta phase precession in the oscillatory interference model (OIM) of grid cells. A. This example shows the model as a rat runs straight through the firing field of a simulated grid cell at constant velocity. B. In the model (Burgess et al., 2007) the velocity alters the frequency of the Shifted oscillation relative to the Baseline oscillation, causing a shift in phase (solid lines) relative to baseline phase (dashed lines) that is proportional to the integral of velocity (location). The relative phase can be read out by spiking due to the Sum of the oscillations. The model replicates experimental data (Harvey et al., 2009) showing that spikes occur at the peak of membrane potential oscillations and spiking precesses (shifts backward in phase) relative to network field potential oscillations.

but not their head direction sensitivity during loss of theta rhythm (Brandon et al., 2011).

Intracellular membrane properties

The OIM predicted (Burgess et al., 2007) that the difference in spacing between firing fields of grid cells at different dorsal to ventral positions in the medial entorhinal cortex (Hafting et al., 2005; Sargolini et al., 2006) should be associated with a difference in intrinsic frequency of neurons (Fig. 4). Intracellular recordings in stellate cells showed a corresponding difference in frequency of resonance and subthreshold membrane potential oscillations at different anatomical positions in medial entorhinal cortex (Giocomo et al., 2007) that has been extensively replicated (Boehlen et al., 2010; Dodson et al., 2011; Giocomo and Hasselmo, 2008a, 2008b, 2009; Heys et al., 2010; Pastoll et al., 2012; Shay et al., 2012), building on the initial work showing resonance (Erchova et al., 2004; Haas and White, 2002). The OIM also accounts for the appearance of grid cells in medial but not lateral entorhinal cortex (Hargreaves et al., 2005) in correlation with membrane potential resonance appearing in medial but not entorhinal cortex neurons (Canto and Witter, 2012; Shay et al., 2012). Physiologically, resonance is tested by intracellular injection of oscillatory current that increases in frequency. The frequency that causes a maximal voltage change in the neuron is the resonance frequency, which also reflects the time course of depolarizing rebound from hyperpolarization.

These resonance properties correlated with grid field spacing can arise from the hyperpolarization-activated cation current (h current) that causes a depolarizing rebound from hyperpolarization (Dickson et al., 2000; Fransén et al., 2004). Mice with knockout of the HCN1 subunit of the h current channel show a decrease in resonance frequency (Giocomo and Hasselmo, 2009) and an increase in spacing of grid cell firing fields (Giocomo et al., 2011), supporting the link to molecular mechanisms. However, grid cell firing patterns were not abolished by HCN1 knockout, indicating the role of other mechanisms (e.g. HCN2 subunits). Activation of muscarinic acetylcholine receptors decreases the magnitude of h current (Heys and Hasselmo, 2012), and the frequency of resonance (Heys et al., 2010). The OIM shows how this could underlie the increase of grid cell spacing in novel environments (Barry et al., 2012b, 2012c), because acetylcholine levels increase in novel environments (Acquas et al., 1996). The h current has also been implicated in generation of theta rhythm in the hippocampus (Rotstein et al., 2005).

Current issues for phase coding models

Some data do not support the OIM. Aspects of the data support complementary models of grid cells that involve attractor dynamics

(Burak and Fiete, 2009; Fuhs and Touretzky, 2006; Guanella et al., 2007; McNaughton et al., 2006a, 2006b), or self-organization of afferent input (Kropff and Treves, 2008; Mhatre et al., 2010; Si et al., 2012). These points of discussion include the following areas of experimental data.

Intracellular membrane potential properties

The OIM correctly predicts differences in intrinsic frequency, but an OIM involving interactions of membrane potential within a single neuron cannot function. Oscillations of different phase within a neuron will synchronize (Remme et al., 2010). An alternate OIM used the influence of velocity on spiking frequency of neurons (Hasselmo, 2008; Hasselmo and Brandon, 2008). Single neuron persistent spiking is too variable in phase (Zilli et al., 2009), but this problem was overcome by using populations of spiking neurons (Zilli and Hasselmo, 2010).

The OIM requires a linear change in oscillation frequency with depolarization driven by running speed. Recordings from neurons in slices of entorhinal cortex show that depolarization does not cause a linear shift in membrane potential oscillations (Yoshida et al., 2011), but membrane potential resonance does show a systematic linear change in resonance frequency with depolarization (Shay et al., 2012). The properties of resonance motivated development of a newer variant of the oscillatory interference model (Fig. 5) in which the rebound depolarization correlated with resonance regulates the movement of grid cell spiking, and which can replicate theta cycle skipping properties of entorhinal neurons (Brandon et al., 2013).

Recently, the use of virtual visual worlds allowed intracellular recordings from grid cells in head fixed mice. Consistent with the OIM, these recordings show oscillations in membrane potential during running that shift in phase relative to network theta rhythm (Schmidt-Hieber and Häusser, 2013). These recordings also show a depolarizing shift in membrane potential that correlates with the firing field of a neuron (Domnisoru et al., 2013; Schmidt-Hieber and Häusser, 2013) that could arise from attractor dynamics that could occur at the same time as OIM mechanisms.

Spiking properties of neurons

Data supports the need for network attractor dynamics to generate modules of grid cells with shared orientation (Hafting et al., 2005; Stensola et al., 2012) and shared size and spacing of firing fields (Barry et al., 2007; Stensola et al., 2012). Consistent with the OIM, the Moser lab showed that grid cells share intrinsic frequency within modules (Stensola et al., 2012), but argued that the predicted correlation of intrinsic frequency with grid cell spacing does not occur in all rats. However, the correlation does appear when all cells are pooled, and the inconsistent examples usually involve smaller numbers of cells.

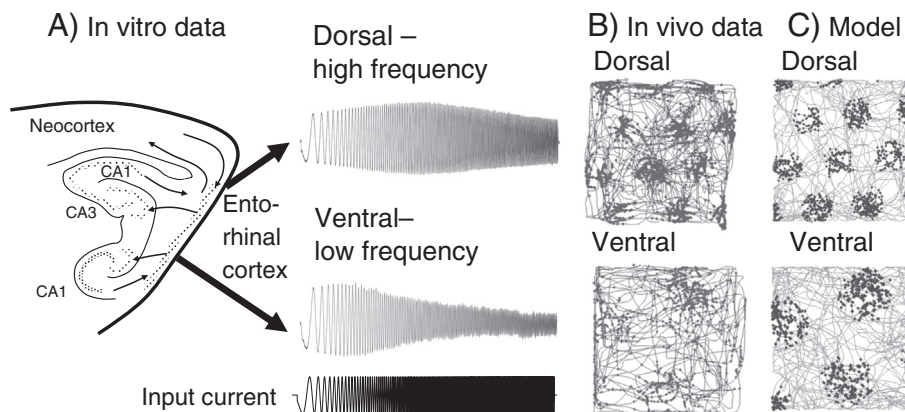


Fig. 4. Intrinsic resonance frequency of neurons and spacing of grid cell firing fields. A. Experimental data shows that the intrinsic membrane potential resonance of layer II stellate cells in response to an input current sweeping through increasing frequencies (bottom trace) shows a peak amplitude at a higher frequency in dorsal cells and lower frequency in ventral cells (Giocomo and Hasselmo, 2008b; Giocomo et al., 2007; Shay et al., 2012). B. This decrease in frequency scales with the increase in spacing between grid cell firing fields in data from awake behaving rats (Hafting et al., 2005). C. The oscillatory interference model can link the in vitro data in A to the in vivo data on grid cell firing fields in B.

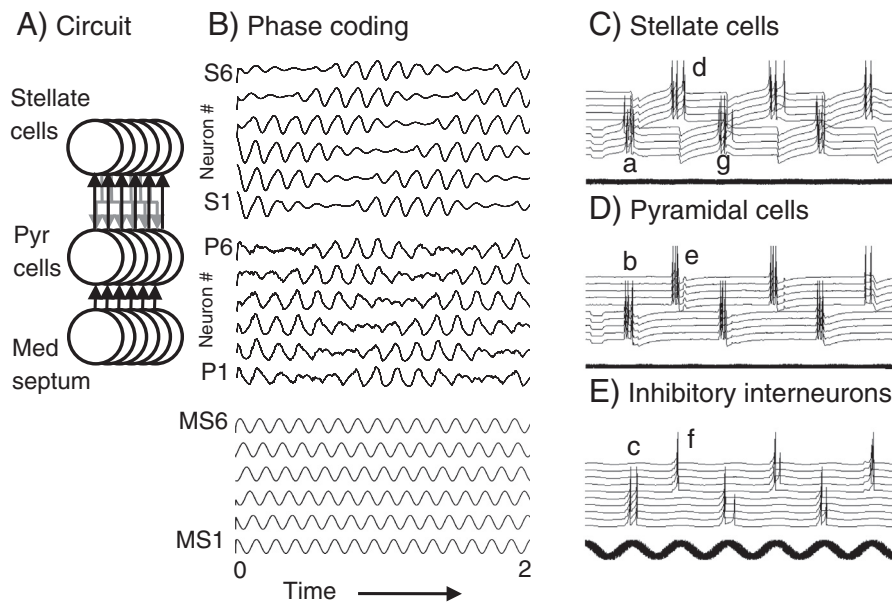


Fig. 5. A–E. Neurons with resonance properties can interact in oscillatory attractor dynamics to generate coding of spatial location by relative phase similar to the OIM. A. The circuit involves a population of resonant stellate cells with excitatory connections with pyramidal cells (Pyr Cells) that receive phase-specific oscillatory input from medial septal neurons (Med Septum). B. Stellate cell numbers S1–S3 start out active and then show rebound activity that activates pyramidal cells P1–P4 according to the phase of Medial Septum (MS) input to pyramidal cells, and engages excitatory feedback between the stellates and pyramidals. Stellate cells rebound slightly faster than the frequency of MS input, activating pyramidal cells at earlier phases, causing a progressive shift in attractor dynamics to different populations. C–E. A similar model uses resonance to generate the theta cycle skipping properties of entorhinal neurons. A set of five stellate cells (C) respond to a hyperpolarizing pulse with rebound spikes (Ca) that excites a set of pyramidal cells (D) causing spiking (Db) that activates a set of inhibitory interneurons (E). The spiking of the interneurons (Ec) causes hyperpolarization in another set of stellate cells to cause rebound spiking (Cd) that induces spiking in a different group of pyramidal cells (De) and interneurons (Ef). These interneurons cause inhibition that induces rebound spiking in the first set of stellate cells (Cg) to start the cycle again. The firing on alternate cycles of theta rhythm resembles theta cycle skipping observed in unit recording from entorhinal cortex (Brandon et al., 2013; Deshmukh et al., 2010).

Attractor models do not require theta phase precession, but precession can be generated in attractor models by adding rhythmic rebound properties (Navratilova et al., 2012). Attractor dynamics and oscillatory dynamics are compatible and can be combined in many ways (Hasselmo and Brandon, 2012). For example, a shift in intrinsic resonance frequency can shift an attractor due to the interaction between neurons with different oscillation phases as shown in Fig. 5B.

Oscillations in rats and bats

As noted above, grid cell spatial periodicity disappears during the blockade of theta rhythm in rats (Brandon et al., 2011; Koenig et al., 2011). However, the role of theta rhythm may be species specific, as grid cells have been demonstrated in crawling bats that show only brief bouts of theta rhythmicity in the field potential and do not show theta rhythm in the spiking autocorrelograms (Yartsev et al., 2011). The absence of theta rhythmicity in autocorrelograms could be due to the low firing rate of grid cells recorded in crawling bats (Barry et al., 2012a). Recordings in slices show that bat medial entorhinal cortex neurons do not reveal the same distribution of theta frequency resonance that appears in rodents (Heys et al., 2013), though bat cells do show lower frequency resonance that could still underlie oscillatory interference.

Movement direction input

An important problem for all of these models concerns the consistent use of velocity to shift grid cell firing in both oscillatory interference models and attractor models. These models cite data on changes in firing rate with running speed in hippocampus (Maurer et al., 2005; O'Keefe et al., 1998) and entorhinal cortex (Sargolini et al., 2006; Wills et al., 2012), and neurons that change firing rate with head direction relative to the preferred head direction of a neuron, as if responding to the compass direction of the head (Sargolini et al., 2006; Taube et al., 1990). However, recent data (Raudies, Brandon, Chapman, Hasselmo, unpublished) shows that the spiking response of most head direction cells and conjunctive grid by head direction cells

does not correlate with the actual movement direction of the animal when it differs from head direction. As an alternative to current models, head direction may allow tracking of the direction and speed of change in the spherical angle of sensory stimuli for updating of grid cell firing, with grid cells of different spacing responding to features at different vertical positions or distances within the visual field.

Theta rhythm and episodic memory

Theta rhythm may contribute to encoding the where and when of episodic memory. In addition to coding spatial location, neurons in the hippocampus and entorhinal cortex also respond selectively at consistent time points within the trials of a behavioral task (Kraus et al., in press; MacDonald et al., 2011; Pastalkova et al., 2008). These responses have been referred to as “time cells” (MacDonald et al., 2011). The firing of time cells could allow events or items to be associated with a specific time point coded by neural activity as well as a specific location coded by place cells. Previous modeling shows that the same framework used for modeling grid cells with theta rhythm could contribute to coding of time intervals (Hasselmo, 2009, 2012) consistent with phase precession relative to jumping time (Lenck-Santini et al., 2008). This use of oscillations to code time intervals resembles previous models of coding of time intervals (Brown et al., 2000; Miall, 1989). Fig. 6A shows how neurons rhythmically spiking near theta frequency could generate the response of a time cell.

Models of episodic memory show how the coding of time and space by theta rhythm could account for episodic retrieval (Hasselmo, 2009, 2012) that could underlie the hippocampal activity found in functional magnetic resonance imaging studies of navigation (Brown and Stern, 2013; Brown et al., 2010). In this framework, an episodic memory involves continuous movement through time and space along a spatio-temporal trajectory that induces a continuous shift in relative phase in different populations of neurons in the entorhinal cortex (Hasselmo, 2009, 2012). Neurons that shift frequency based on velocity can generate grid cell firing responses that code location, whereas neurons that

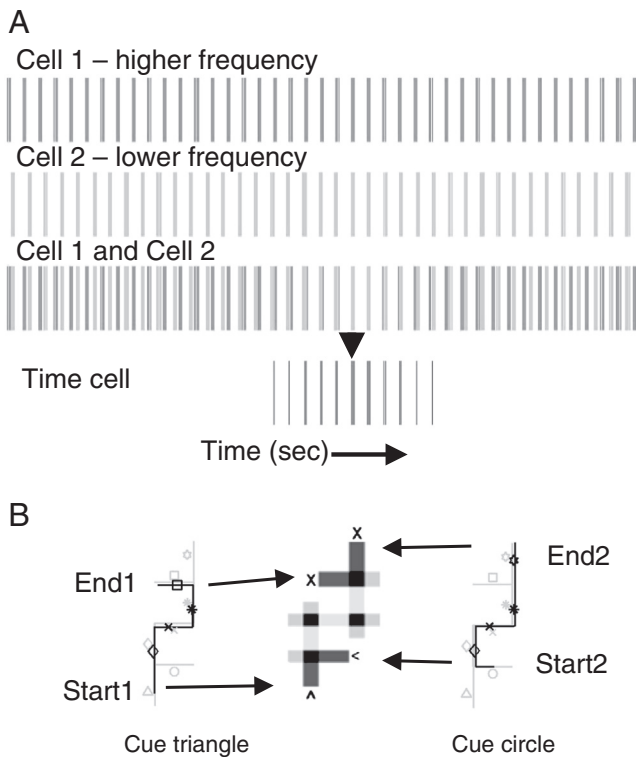


Fig. 6. A. Model of generation of time cell firing by interaction of two theta rhythmic neurons. Cell 1 (top) fires at a slightly higher fixed difference in frequency relative to the theta rhythmic firing of Cell 2 (middle). The two cells start out of phase with each other and gradually approach the same phase of firing (Cell 1 and Cell 2). When they fire at the same phase, they drive the spiking of a Time Cell (arrow), that codes the time from the onset of firing. B. Time cells allow disambiguation of different memories involving overlapping spatial trajectories in a simulation of a behavioral task using virtual hallways with items in each hallway (Brown et al., 2010). In a simulation (Hasselmo, 2012), items are represented by different icons. One item (cue triangle) in a start hallway (Start1) can cue retrieval of a full spatiotemporal trajectory that ends with the correct turn into the final hallway (End1). A different item (cue circle) in a different start hallway (Start2) can cue retrieval of a different spatiotemporal trajectory that shares spatial locations, but uses different time cells to code the different trajectory, allowing the correct turn into the correct final hallway (End2).

maintain a fixed difference in frequency that starts at a specific phase at the start of a trial can code time intervals (Fig. 6A). The phase coding of space and time in entorhinal cortex could drive hippocampal place cells and time cells that allow the spatiotemporal trajectory to be associated with specific items and events occurring at specific positions along the spatiotemporal trajectory (Hasselmo, 2012).

Fig. 6B shows an example of how the coding of a spatiotemporal trajectory allows bidirectional associations of positions along the trajectory with items in the environment. This allows individual items to cue episodic retrieval of trajectories through the environment, with coding by time cells allowing disambiguation of spatially overlapping trajectories (Hasselmo, 2009, 2012). In this framework, the theta rhythm observed in depth electrodes in humans could provide the phase coding of space and time for encoding of episodic memories (Kahana et al., 1999, 2001; Lega et al., 2011; Raghavachari et al., 2001, 2006; Rizzuto et al., 2006; Sederberg et al., 2003). The simulation of spatiotemporal trajectories using phase coding provides an explicit model linking the cellular mechanisms for coding space and time to the elements of episodic memory.

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Conflict of interest

The authors have no conflicts of interest.

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