Mechanisms and Functions of Theta Rhythms

Laura Lee Colgin

Center for Learning and Memory, The University of Texas, Austin, Texas 78712-0805; email: colgin@mail.clm.utexas.edu

Annu. Rev. Neurosci. 2013. 36:295–312

First published online as a Review in Advance on May 29, 2013

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

This article's doi: 10.1146/annurev-neuro-062012-170330

Keywords

oscillations, memory, hippocampus, place cells, phase precession, CA1

Abstract

The theta rhythm is one of the largest and most sinusoidal activity patterns in the brain. Here I survey progress in the field of theta rhythms research. I present arguments supporting the hypothesis that theta rhythms emerge owing to intrinsic cellular properties yet can be entrained by several theta oscillators throughout the brain. I review behavioral correlates of theta rhythms and consider how these correlates inform our understanding of theta rhythms' functions. I discuss recent work suggesting that one function of theta is to package related information within individual theta cycles for more efficient spatial memory processing. Studies examining the role of theta phase precession in spatial memory, particularly sequence retrieval, are also summarized. Additionally, I discuss how interregional coupling of theta rhythms facilitates communication across brain regions. Finally, I conclude by summarizing how theta rhythms may support cognitive operations in the brain, including learning.

Contents

INTRODUCTION

Theta rhythms: ~4–12 Hz, nearly sinusoidal patterns of electrical activity that are associated with active behaviors and REM sleep

Execution of complex cognitive functions by the brain requires coordination across many neurons in multiple brain areas. Brain rhythms (or oscillations) provide a mechanism for such coordination by linking the activity of related ensembles of neurons. One of the most intriguing brain rhythms is the theta rhythm. The ~4–12-Hz theta rhythms were first discovered in the rabbit by Jung & Kornmuller (1938). Although researchers did not understand what theta rhythms signified, they did notice the large amplitude and nearly sinusoidal regularity of these rhythms (**Figure 1**). Scientific interest in theta rhythms continued to grow during the following decades, and investigators found that theta rhythms occurred in other species as well, including cats, rats, and monkeys (Green & Arduini 1954, Grastyan et al. 1959, Vanderwolf 1969).

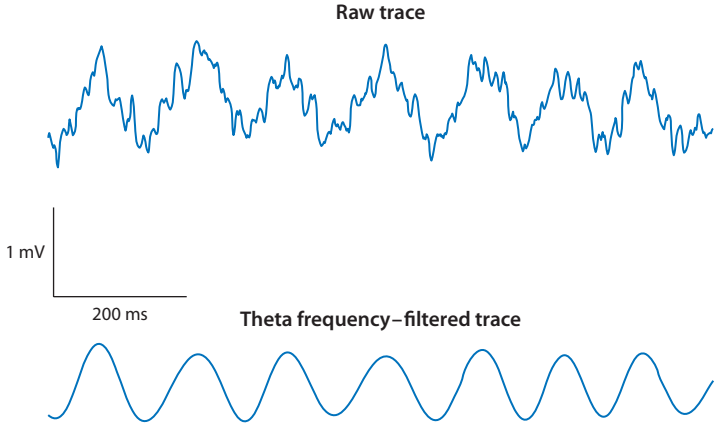

Figure 1

Theta recorded from hippocampal subfield CA1 of a freely exploring rat (L.L. Colgin, unpublished data). A raw trace (*top*) and a theta frequency (4–12 Hz) band-pass filtered trace (*bottom*) are shown.

In 1972, Landfield and colleagues reported that the degree to which rats remembered an aversive foot shock was correlated with the amount of theta recorded from screws implanted in the rats' skulls above the cortex (Landfield et al. 1972). The link between theta rhythms and memory was controversial at the time, but many studies have since supported the conclusion that theta rhythms are important for different types of learning and memory (Berry & Thompson 1978, Winson 1978, Macrides et al. 1982, Mitchell et al. 1982, Mizumori et al. 1990, M'Harzi & Jarrard 1992, Klimesch et al. 1996, Osipova et al. 2006, Robbe & Buzsáki 2009, Rutishauser et al. 2010, Liebe et al. 2012), as well as for synaptic plasticity (Larson et al. 1986, Staubli & Lynch 1987, Greenstein et al. 1988, Pavlides et al. 1988, Orr et al. 2001, Hyman et al. 2003). However, it remains unclear why theta rhythms influence memory processing. Do theta rhythms promote memory, as they promote other cognitive states such as anxiety (Adhikari et al. 2010), by facilitating interregional interactions (Seidenbecher et al. 2003, Jones & Wilson 2005, Kay 2005, Benchenane et al. 2010, Hyman et al. 2010, Kim et al. 2011, Liebe et al. 2012)? Do theta rhythms affect memory directly by providing the correct timing required to induce changes in synaptic strength (Larson et al. 1986, Greenstein et al. 1988)? Do theta rhythms affect cognitive operations in general by providing a way to chunk information (Buzsáki 2006, Kepecs et al. 2006, Gupta et al. 2012)?

Here, I review the current status of research on theta rhythms. I begin by discussing mechanisms that generate theta rhythms.

Understanding how theta rhythms are generated will provide clues regarding their function. I then review several proposed functions of theta rhythms. I discuss the effects of theta rhythms on the firing properties of hippocampal place cells, neurons that are activated in particular spatial locations (O'Keefe & Dostrovsky 1971). Functions of theta rhythms are also discussed with regard to cognition and behavior.

The question of whether theta rhythms exist in healthy humans was a subject of intense debate until fairly recently (Klimesch et al. 1994, Tesche & Karhu 2000). Consequently, research using animal models has established a longer-standing body of work on theta. This review focuses on studies of theta rhythms in lower mammals, primarily rats. I also place particular emphasis on theta rhythms in the hippocampus, a region that is critically involved in memory processing (Squire et al. 2004). Theta rhythms have been studied extensively in the hippocampus, and the hippocampal electroencephalogram displays prominent theta rhythms during active behaviors (**Figure 1**).

MECHANISMS OF THETA RHYTHMS

The Role of the Medial Septum in Theta Generation

Until recently, researchers generally agreed that the medial septum (MS) generates theta rhythms (see Vertes & Kocsis 1997 for a review) because lesioning or inactivating the MS disrupts theta (Green & Arduini 1954, Petsche et al. 1962, Mitchell et al. 1982, Mizumori et al. 1990). MS pacemaker cells are believed to be GABAergic inhibitory interneurons (Toth et al. 1997), which express hyperpolarization-activated and cyclic nucleotide-gated nonselective cation channels (HCN channels) (Varga et al. 2008). These HCN-expressing interneurons fire rhythmically at theta frequencies and are phase-locked to theta rhythms in the hippocampus (Hangya et al. 2009). Cholinergic neurons of the MS, on the other hand, do not fire rhythmically at theta frequencies (Simon et al. 2006) and are thus unlikely to act as theta pacemakers. Cholinergic neurons may instead modulate the excitability of other neurons in a way that promotes their theta rhythmic firing. Backprojections from the hippocampus to the MS may be important to keep the two regions coupled (Toth et al. 1993). The importance of other subcortical regions for theta generation has been addressed in another review (Vertes et al. 2004) and is not discussed here.

Recent work has brought into question the belief that the MS is responsible for theta generation. Goutagny and associates (2009) found that theta rhythms emerge in vitro in an intact hippocampus preparation lacking any connections with the MS (**Figure 2**). The in vitro theta rhythms appeared spontaneously (i.e., without application of any drugs). Also, theta activity persisted in hippocampal subfield CA1 after neighboring subfield CA3 was removed, indicating that an excitatory recurrent collateral network was not a required component of the theta-generating machinery. Local inactivation of an intermediate portion of the longitudinal axis did not eliminate theta from either the septal or the temporal pole. Instead, theta rhythms persisted in both septal and temporal regions but were no longer coherent. Theta in the septal hippocampus was faster than theta in the temporal hippocampus after the inactivation procedure. Whole-cell recordings of CA1 pyramidal cells revealed rhythmic inhibitory postsynaptic potentials, whereas rhythmic excitatory postsynaptic potentials were recorded in interneurons. These results suggest that theta rhythms are produced by local interactions between hippocampal interneurons and pyramidal cells.

Although the hippocampus may possess the machinery necessary to produce theta intrinsically in vitro, much evidence indicates that the MS is involved in theta generation in behaving animals. Lesioning or inactivating the MS disrupts theta in structures that receive MS projections, including the entorhinal cortex (EC) and the hippocampus (Green & Arduini 1954, Petsche et al. 1962, Mitchell et al. 1982, Mizumori et al. 1990, Brandon et al. 2011, Koenig et al. 2011). The MS transitions

Place cells: principal neurons of the hippocampus that fire selectively in specific spatial locations

Hippocampus: a region of the medial temporal lobe that is essential for spatial and episodic memory

Medial septum (MS): a subcortical region providing cholinergic and GABAergic inputs to cortical structures including the hippocampus and entorhinal cortex

HCN channels: hyperpolarization-activated and cyclic nucleotide-gated nonselective cation channels

EC: entorhinal cortex

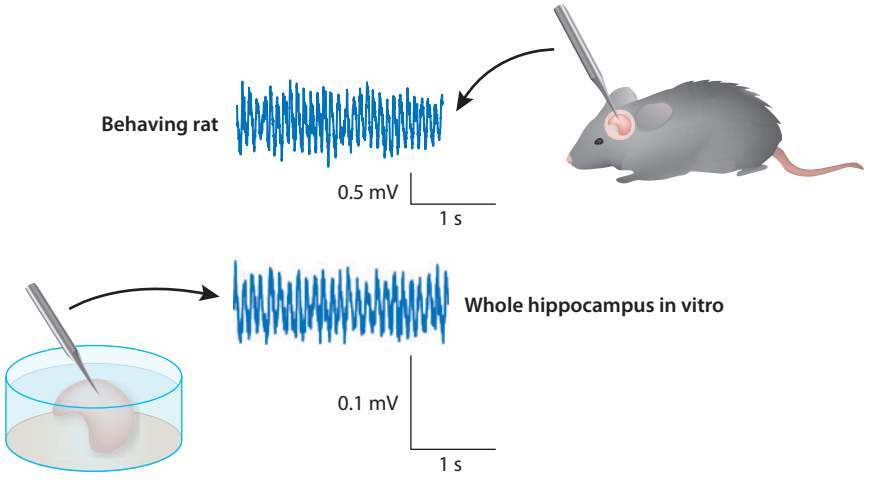

Figure 2

Theta rhythms recorded by Goutagny et al. (2009) in CA1 of a whole hippocampus in vitro preparation are highly similar to theta rhythms recorded from CA1 in vivo. Modified with permission from Colgin & Moser (2009).

to the theta state ~500 ms before theta appears in the hippocampus (Bland et al. 1999), supporting the idea that septohippocampal projections initiate theta rhythms. Spikes of MS pacemaker interneurons are maximally phase-locked to hippocampal theta occurring ~80 ms later (Hangya et al. 2009), supporting the idea that MS interneurons drive theta in the hippocampus (Toth et al. 1997), albeit with some delay. The substantial delay may reflect the time required to recruit a significant proportion of cells into a synchronized theta network (Hangya et al. 2009).

A Multitude of Theta Oscillators

Other mechanisms in addition to MS inputs appear to be involved in hippocampal theta rhythm generation in vivo. Current source density analyses of hippocampal local field potentials (LFPs) from freely exploring rats indicate that multiple current dipoles coexist during theta (Kamondi et al. 1998; see figure 4 in Buzsáki 2002). Presumably active current sinks are seen in stratum lacunosum-moleculare and stratum radiatum and are thought to reflect excitatory inputs from the EC and CA3, respectively. At the same time, a putative current source reflecting inhibitory inputs can be seen in stratum pyramidale. These inhibitory inputs are likely hippocampal interneurons firing rhythmically at theta frequencies during periods when they are released from theta inhibition imposed by MS interneurons (Toth et al. 1997). Following surgical removal of the EC, the stratum lacunosum-moleculare dipole disappears. Theta rhythms that remain after EC lesioning are suppressed by the cholinergic antagonist atropine, in contrast with atropine-resistant theta rhythms that normally occur during exploration (Kramis et al. 1975). Atropine-sensitive theta rhythms are normally observed during behavioral immobility and during anesthesia induced by urethane (Kramis et al. 1975), a drug that suppresses input from the EC (Ylinen et al. 1995). These findings suggest that the EC provides sufficient excitatory drive to entrain theta rhythms during active behaviors but that another source of excitatory drive is required in the absence of entorhinal inputs. This excitatory drive may come from MS cholinergic inputs, which produce slow depolarizations in hippocampal neurons (Madison et al. 1987).

A problem with this interpretation is that theta rhythms in the whole hippocampus in

LFP: local field potential

vitro are not blocked by atropine, yet the isolated hippocampus receives no input from the EC (Goutagny et al. 2009). Thus, it is unclear from where the excitatory drive originates in the isolated hippocampal preparation. One possibility is that neurons are more excitable in this preparation than in other in vitro preparations. The potassium concentration used in the artificial cerebrospinal fluid (aCSF) in the Goutagny et al. (2009) study (3.5–5 mM) was higher than the potassium concentration (2.5 mM) used in typical hippocampal slice studies (e.g., Frerking et al. 2001, Brager & Johnston 2007). Studies of spontaneous sharp-wave ripples in hippocampal slices used similarly high potassium concentrations in the aCSF (4.25–4.75 mM; Kubota et al. 2003, Colgin et al. 2004, Ellender et al. 2010). It is not obvious, however, why a relatively high concentration of potassium in the aCSF would lead to theta rhythms in an isolated whole hippocampal preparation and to sharp-wave ripples in hippocampal slices. One difference between preparations is a more intact CA3 recurrent collateral system in the isolated whole hippocampus. However, CA3 was essential for sharp waves in slices (Colgin et al. 2004) but not for theta rhythms in the isolated whole hippocampus (Goutagny et al. 2009), indicating that differences in spontaneous in vitro activity are not due to preservation of CA3 recurrent collaterals. One likely explanation is that a higher number of connections between interneurons and pyramidal neurons are preserved in the whole hippocampus preparation. A high degree of pyramidal cell-interneuron interconnectivity may be essential for theta generation but not for sharp-wave ripples. Of particular interest in this regard are horizontal interneurons (Maccaferri 2005, Goutagny et al. 2009). Horizontal interneurons are activated almost exclusively by CA1 axon collaterals (Blasco-Ibáñez & Freund 1995). Horizontal interneurons fire spontaneously, without requiring fast excitatory input (Maccaferri & McBain 1996), and thus would be likely to fire in the intact hippocampal preparation. Moreover, horizontal interneurons show resonance at theta frequencies (Pike et al. 2000). Thus, horizontal interneurons may be essential for generating theta rhythms intrinsically in the hippocampus.

MEC: medial entorhinal cortex

A common feature of horizontal interneurons in the hippocampus and pacemaker interneurons in the MS is the expression of HCN channels (Maccaferri & McBain 1996, Varga et al. 2008). HCN channels are nonselective cation channels that are activated by hyperpolarization (Robinson & Siegelbaum 2003). Activation of HCN channels leads to slow depolarizing currents (I_h currents) that can drive the membrane back to threshold and trigger action potentials. In neurons that express HCN channels, a repeating sequence of events can emerge that consists of an action potential, afterhyperpolarization, depolarization via HCN channels, and another action potential that starts the cycle again. In this way, HCN channels may facilitate rhythmic firing in neurons. Many neurons that exhibit theta rhythmic firing express HCN channels (Maccaferri & McBain 1996, Dickson et al. 2000, Hu et al. 2002, Varga et al. 2008). Theta frequency membrane-potential oscillations are disrupted by pharmacological blockade (Dickson et al. 2000) or genetic deletion (Giocomo & Hasselmo 2009) of HCN channels. Moreover, the time course of activation and deactivation of I_h currents may determine the particular theta frequency of membrane-potential oscillations in medial entorhinal cortex (MEC) neurons; that is, faster time constants correspond to higher-frequency theta rhythms (Giocomo et al. 2007, Giocomo & Hasselmo 2008). Together, these findings suggest that HCN channels may be a key cellular mechanism that contributes to theta rhythm generation.

Effects of HCN channels provide one potential explanation of the seemingly contradictory findings that theta rhythms depend on MS inputs yet can be generated intrinsically in the hippocampus. Perhaps any network of neurons that expresses HCN channels is primed to participate in theta rhythms, provided that the neurons are sufficiently depolarized to initiate the cycle described above. Depolarization

could come from a variety of sources, depending on experimental conditions. Rhythmically firing cells would recruit other cells, and theta rhythms would spread across the network. In this scenario, local neuronal ensembles would actually be separate oscillators; the range of synchronization would be determined by the extent of pacemaker projections. Although the simplicity of this explanation is attractive, theta rhythm generation appears to be more complicated, considering that theta rhythms in vivo are not decreased in HCN1 knockout mice (Nolan et al. 2004, Giocomo et al. 2011). Nevertheless, it seems likely that some combination of intrinsic conductances and network mechanisms allows theta oscillatory activity to originate from a variety of different sources.

Support for the idea of multiple theta oscillators comes from recent studies of theta oscillations in the hippocampus. In freely behaving rats, theta rhythms are not synchronized across the hippocampus. Instead, systematic phase shifts are observed across the septotemporal axis (Lubenov & Siapas 2009, Patel et al. 2012). That is, hippocampal theta rhythms are traveling waves that consistently propagate toward the temporal pole of the hippocampus. The mechanisms of traveling wave generation remain unknown, but investigators have proposed several possibilities (Lubenov & Siapas 2009, Patel et al. 2012). One possibility is that theta waves emerge first in the septal hippocampus because MS inputs reach the septal hippocampus first. This proposed mechanism is problematic for several reasons (Patel et al. 2012). A more likely mechanism is that traveling theta waves reflect interactions within a network of weakly coupled oscillators (Lubenov & Siapas 2009, Patel et al. 2012). Separate oscillators may relate to differences in intrinsic conductances between septal (also called dorsal) and temporal (also called ventral) hippocampi. Maurer et al. (2005) found that intrinsic theta oscillations have a lower frequency in the intermediate hippocampus than they do in the septal hippocampus in freely behaving rats. This finding is consistent with septal-to-temporal propagation of traveling waves (but see Marcelin et al. 2012 for contradictory in vitro results). Frequencies of intrinsic theta oscillations are lower in ventral MEC than in dorsal MEC (Giocomo et al. 2007, Giocomo & Hasselmo 2008), leading Lubenov & Siapas (2009) to predict that MEC theta is a traveling wave also.

Recordings of theta rhythms in the isolated whole hippocampus also provide support for the weakly coupled oscillators mechanism (Goutagny et al. 2009). Coherence between septal and temporal theta rhythms in CA1 decreased significantly when an intermediate CA1 location was inactivated. After the inactivation, septal and temporal theta rhythms became uncoupled, and the frequency of temporal theta rhythms decreased significantly. Prior to the inactivation, septal theta rhythms led temporal theta rhythms by ~50 ms. This finding suggests that the septal hippocampus entrains the temporal hippocampus during theta rhythms, an idea that is consistent with septotemporal propagation of traveling theta waves. These results suggest that theta oscillators are coupled by local interactions between pyramidal cells and interneurons, not by MS projections. However, different coupling mechanisms likely exist in behaving animals, including entrainment of hippocampal theta by MS and EC oscillators. Coupling of EC and hippocampal theta oscillators may involve excitatory inputs from the EC to the hippocampus (Buzsáki 2002) or long-range inhibitory connections between the EC and the hippocampus (Melzer et al. 2012).

Despite decades of research dedicated to uncovering the mechanisms of theta rhythm generation, new and surprising findings regarding theta mechanisms continue to be discovered. Achieving a deeper understanding of the mechanisms of theta rhythms is an essential step toward fully understanding the functions of this complex rhythm. Additionally, a thorough understanding of theta mechanisms will help investigators develop methods to block theta rhythm generation selectively, with minimal side effects (e.g., loss of neuromodulatory inputs, changes in mean firing rates). Such a selective blockade would allow researchers to assess how functions are altered when theta

rhythms are not present and to reveal causal links between theta and its functions.

FUNCTIONS OF THETA RHYTHMS

Behavioral Correlates of Theta Rhythms

Since the early days of theta rhythms research, scientists have looked for clues regarding theta functions by determining the behavioral correlates of theta rhythms (Buzsáki 2005). Theta rhythms arise during movement (Vanderwolf 1969) and exhibit higher amplitudes during active movement than during passive movement (Terrazas et al. 2005). Theta rhythms are also present during behaviors associated with intake of stimuli. The frequency of theta matches the frequency of whisking (Berg & Kleinfeld 2003) and sniffing (Macrides et al. 1982) in rats, as well as saccadic eye movements in humans (Otero-Millan et al. 2008). Theta rhythms selectively correlate with active, and not passive, sampling of stimuli. In rats sampling behaviorally relevant stimuli or stimuli associated with reward, theta rhythms were temporally correlated with rhythmic sniffing (Macrides et al. 1982) and whisking (Ganguly & Kleinfeld 2004). However, no relationship was observed between theta and whisking when rats were aimlessly whisking in air (Berg et al. 2006).

Curiously, theta rhythms also occur during rapid eye movement (REM) sleep (Vanderwolf 1969, Winson 1974), but the role of theta in REM sleep is less clear. One possibility is that theta rhythms play a role in memory consolidation during REM sleep (Louie & Wilson 2001, Montgomery et al. 2008), but this idea is controversial (Vertes 2004). This review does not cover functions of theta during REM sleep and instead focuses on functions of theta during waking states.

Information Packaging by Theta Rhythms

The hippocampus is at the end of an information-processing stream that begins when information is taken in from the environment. The hippocampus receives convergent information from multiple areas and thus requires a mechanism to coordinate related activity. The relationship between theta rhythms and rhythmic behaviors involved in stimuli intake suggests that each theta cycle contains a discrete sample of related sensory information (Kepecs et al. 2006). Theta rhythms may also link this information from different sensory modalities with information related to motivational or emotional states. Each theta cycle may thus represent a discrete processing entity that contains information about the current conditions at any given moment. This idea has recently received empirical support from two studies.

In the first study, Jezek and associates (2011) used an innovative behavioral task to investigate how CA3 neuronal ensembles respond to abrupt changes in environmental stimuli. In this task, rats were trained in two boxes that were distinguished by different sets of light cues. Initially, the two boxes were placed in different locations, connected by a corridor through which the rats could freely pass. This setup ensured that distinct ensembles of place cells were active in the two boxes, indicating that separate representations for the two environments had formed (Colgin et al. 2010). At a later stage of training, investigators presented an identical box that contained both sets of light cues in a common central location, midway between the two original locations. The light cues could be switched on and off to present one or the other environment, and separate representations for each environment were maintained. By switching the light cues, the authors could instantaneously "teleport" the rat from one environment to the other. After the switch, the network usually transitioned to the spatial representation that matched the new set of cues. In some cases, though, the network would flicker back and forth for a few seconds between the two representations, the one that matched the current set of cues and the one that matched the previous set of cues. During these episodes

Theta phase precession: a phenomenon in which spikes from an individual cell occur on progressively earlier theta phases across successive theta cycles

of instability, the different representations were separated by the period of a theta cycle, indicating that theta rhythms modulated the switching between distinct representations. In ~99% of cases, each theta cycle contained information related to only one of the memory representations, which suggests that theta rhythms link representations of sets of stimuli related to one environment and segregate them from representations of the other environment. Thus, these results support the hypothesis that theta cycles package related information.

Another study provided support for the hypothesis that theta cycles chunk information during spatial memory processing. In this study, Gupta and colleagues (2012) recorded CA1 place cells in rats running on a T-maze with two choice points. The maze contained several landmarks including two reward locations on the return arm. The authors analyzed theta cycles during which three or more place cells were active to find evidence of place cell sequences (i.e., sequences of spikes with a significant spatial and temporal structure related to the structure of behaviors on the maze). Place cell sequences within a theta cycle were found to represent particular paths on the maze. Longer theta cycles were associated with longer path lengths, suggesting that the theta cycle was the processing unit used to organize representations of discrete paths. Each theta cycle represented a path that began just behind the animal's current location and ended just in front of the animal. Theta sequences represented more space ahead of an animal leaving a landmark and more space behind an animal approaching a landmark, meaning that segments of the maze between landmarks were overrepresented. Thus, individual theta cycles contained representations of task-relevant maze segments, which suggests that a path containing different yet related spatial locations may be more efficiently encoded within a theta cycle as a coherent spatial concept (e.g., path between two feeders).

Gupta and colleagues (2012) also showed that some theta cycles heavily represented upcoming locations, whereas other theta cycles were biased toward locations in the recent past. The authors hypothesized that the theta sequences coding upcoming locations reflect a look-ahead mode, which signifies anticipation of an upcoming location. Sequences coding locations in the recent past may reflect a look-behind mode, which encodes recent experiences. The sequences studied by Gupta et al. (2012) may provide insights about place cell sequences during a phenomenon known as theta phase precession, as explained in the next section.

Theta Phase Precession

In theta phase precession, spikes from a place cell initially occur at late theta phases as the rat enters the cell's place field and then occur at progressively earlier phases on subsequent theta cycles (O'Keefe & Recce 1993, Skaggs et al. 1996) (**Figure 3*a***). Because each theta cycle is associated with spikes from multiple place cells with sequentially occurring place fields, individual theta cycles contain compressed representations of space (Skaggs et al. 1996; "theta sequences" in Foster & Wilson 2007). The compressed representation consists of a code for current location (represented by the most active place cells) preceded by representations of recently visited locations on earlier theta phases and succeeded by representations of upcoming locations on later theta phases (Dragoi & Buzsáki 2006). An alternative viewpoint is that spikes on early theta phases represent the current location, whereas spikes on later theta phases represent upcoming locations (Lisman & Redish 2009). The findings by Gupta et al. (2012), showing that some theta cycles contain sequences that largely represent space behind the rat, whereas sequences on other theta cycles represent more space ahead of the rat, seem to support the former interpretation of theta phase precession (for additional discussion of the predictive component of phase precession, see Lisman & Redish 2009). Here, the discussion of theta phase precession focuses on CA1 because the majority of phase precession studies have been conducted in

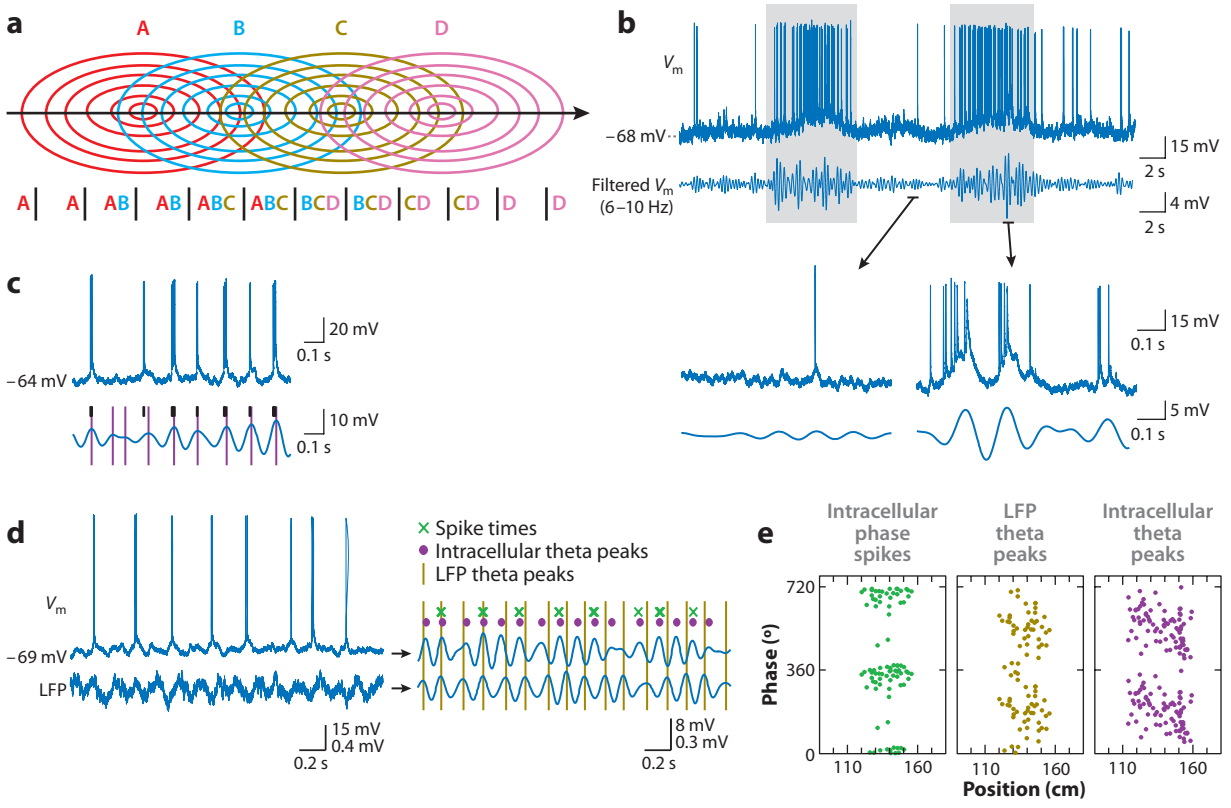

Figure 3

(*a*) Schematic of theta phase precession. Four partially overlapping place fields are shown for an animal running to the right. Repeated activation of place cell sequences on theta cycles (*vertical lines*) is depicted below. Reproduced with permission from Skaggs et al. (1996). (*b*) Example of unfiltered and theta-filtered (6–10 Hz) whole cell recordings from a mouse exploring a virtual environment during runs through the cell's place field (*gray*). Magnified recordings for the periods indicated with horizontal bars are shown below. (*c*) Example of raw (*top*) and theta-filtered membrane-potential recordings (*bottom*) illustrate phase-locking of spikes to intracellular theta. Black vertical lines indicate spike times. Peaks of filtered theta are indicated by purple vertical lines. (*d*) Raw (*left*) and theta-filtered (*right*) traces are shown for simultaneous whole cell (*top*) and local field potential (LFP) recordings (*bottom*). Note how spikes are locked to the peak of intracellular theta oscillations and show phase precession with respect to LFP theta. The top and bottom calibration bar labels indicate the scale for top and bottom traces, respectively. (*e*) Spikes' intracellular theta phases at positions along the virtual environment are plotted (*left*); note how theta phase-locking, but not theta phase precession, is seen. Spikes' phases with respect to LFP theta at positions in the virtual environment are plotted (*middle*); theta phase precession is apparent. The LFP theta phases associated with intracellularly detected theta peaks are plotted on the *y* axis, and corresponding positions are plotted on the *x* axis (*right*); note that intracellular theta shows phase precession with respect to LFP theta. Panels *b*, *c*, *d*, and *e* are modified with permission from Harvey et al. (2009).

CA1. However, it is important to note that theta phase precession has been reported in other regions as well, including the dentate gyrus (Yamaguchi et al. 2002, Mizuseki et al. 2009), CA3 (Mizuseki et al. 2009, 2012), the subiculum (Kim et al. 2012), the EC (Hafting et al. 2008, Mizuseki et al. 2009), and the ventral striatum (van der Meer & Redish 2011).

Many different models of theta phase precession propose various mechanisms for the phenomenon (O'Keefe & Recce 1993, Jensen & Lisman 1996, Tsodyks et al. 1996, Wallenstein & Hasselmo 1997, Kamondi et al. 1998, Magee 2001, Harris et al. 2002, Mehta et al. 2002, Maurer & McNaughton 2007, Navratilova et al. 2012). Thorough comparison

and contrast of the different models are beyond the scope of this review. I refer the reader to several other articles that discuss strengths and weaknesses of the various models (Maurer & McNaughton 2007, Lisman & Redish 2009, Burgess & O'Keefe 2011, Navratilova et al. 2012). Here, I instead discuss how recent whole-cell recordings of place cells in mice running in a virtual reality environment revealed mechanisms of phase precession that must be accounted for in future models (Harvey et al. 2009). First, depolarization of the place cell membrane potential during the first half of the place field ramped up asymmetrically (**Figure 3*b***), similar to asymmetric excitatory input proposed in the phase precession model of Mehta and colleagues (2002). Next, the power of membrane-potential theta oscillations was approximately two times higher within the cell's place field than that outside it. Last, spikes were phase-locked to intracellularly recorded theta and showed phase precession relative to LFP theta (**Figure 3*c–e***), consistent with predictions of "dual oscillator" models (Burgess & O'Keefe 2011).

Although this intracellular report provides extremely useful information regarding the mechanisms of theta phase precession, some questions remain. The intrinsic membrane-potential theta oscillations are thought to reflect rhythmic basket cell inhibition at the soma (Kamondi et al. 1998). Yet, Harvey and associates (2009) report that the frequency and amplitude of intracellular theta oscillations increase in the cell's place field, and it is not obvious how such increases would involve basket cell inhibition. Membrane-potential theta oscillations likely reflect basket cell inhibition in anesthetized animals (Kamondi et al. 1998) or at times when the animal is not in a cell's place field. When an animal enters a cell's place field, however, strong depolarization in the apical dendrites likely induces higher-frequency theta oscillations that result from intrinsic dendritic properties (Kamondi et al. 1998, Burgess & O'Keefe 2011). These faster dendritic oscillations may then entrain theta recorded at the soma, which would explain why spikes within the place field were so consistently phase-locked to the somatic oscillation (Harvey et al. 2009), even though inputs carrying spatial information arrive at the dendrites. Further support for this idea comes from recordings of theta under anesthesia (Kamondi et al. 1998), a condition in which excitatory dendritic inputs are suppressed (Ylinen et al. 1995). Under these conditions, intracellular and LFP theta oscillations share the same frequency (see figure 2*b* in Kamondi et al. 1998).

The question remains about how these proposed mechanisms of phase precession relate to the proposed sequence retrieval function of phase precession. One possibility is that gamma oscillations are involved in both theta phase precession and sequence retrieval. Gamma oscillations co-occur with theta oscillations (Buzsáki et al. 1983, Bragin et al. 1995) and may play a role in theta phase precession (Jensen & Lisman 1996, Dragoi & Buzsáki 2006). Spiking of some CA1 place cells is modulated by gamma oscillations during theta phase precession (Senior et al. 2008). Additionally, recent work indicates that theta-modulated gamma is the optimal pattern for dendritic signal propagation (Vaidya & Johnston 2012), raising the possibility that theta-modulated gamma inputs arriving in the dendrites (Bragin et al. 1995, Colgin et al. 2009) enhance membrane-potential oscillations during theta phase precession. Gamma oscillations have also been linked to sequence retrieval. Strong gamma rhythms occur when place cells represent upcoming sequences of locations as rats pause at decision points on a maze (Johnson & Redish 2007), and slow gamma rhythms promote sequence reactivation during nontheta states (Carr et al. 2012).

If gamma-mediated sequence retrieval occurs during theta phase precession, phase-phase coupling (Jensen & Colgin 2007) is expected between theta and gamma oscillations because spikes would be phase-locked to gamma while still maintaining phase precession relationships with theta. In support of this idea, Belluscio and colleagues (2012) recently reported phase-phase coupling between theta and gamma in the

hippocampus. When they subdivided gamma into different frequency bands, the slow gamma band displayed the strongest phase-phase coupling (see figure 7*a* in Belluscio et al. 2012). Sequence reactivation in the absence of theta involved slow gamma oscillations but no other gamma frequencies (Carr et al. 2012). Slow gamma rhythms couple CA3 and CA1 (Colgin et al. 2009), and CA3 is thought to be critical for retrieving representations of upcoming locations (Jensen & Lisman 1996, Dragoi & Buzsáki 2006). Thus, slow gamma rhythms may transmit retrieved sequences of upcoming locations from CA3 to CA1 during theta phase precession; in this scheme, representations of consecutive locations would be activated on successive gamma cycles (Jensen & Lisman 1996, Dragoi & Buzsáki 2006). Inputs from the EC provide information about current location (Hafting et al. 2005) and likely serve as a cue for CA3 recall of upcoming locations (Jensen & Lisman 1996, Dragoi & Buzsáki 2006). Layer III EC inputs to CA1 may contribute to phase precession in the second half of the place field because CA3 cells do not receive layer III input and do not show phase precession across the full extent of the theta cycle (Mizuseki et al. 2012).

Work described above demonstrates how intrinsic cellular properties may combine with synaptic interactions to facilitate hippocampal functions such as sequence retrieval. Thus far, most results discussed here involve effects within an individual region, mainly CA1. The next section discusses how theta rhythms affect interactions across different brain regions.

Theta Coupling between Regions

Theta oscillations are seen in structures involved in initial stages of sensory processing as well as in regions further down the processing stream (Jung & Kornmuller 1938, Vanderwolf 1969, Jones & Wilson 2005, Kay 2005). Much evidence suggests that theta rhythms are involved in facilitating the transfer of information from one brain region to another during sensory information processing. Theta-enhanced transmission across brain regions may be important for several different functions. Here, I focus on the role of interregional theta coupling in memory operations involving the hippocampus.

mPFC: medial prefrontal cortex

Consistent with the hippocampus's key role in spatial memory processing, several studies have demonstrated links between interregional theta coupling and performance on a variety of spatial memory tasks. In a spatial working-memory task, medial prefrontal cortex (mPFC) neurons were more strongly phase-locked to CA1 theta rhythms during correct-choice trials than during error trials (Jones & Wilson 2005). Additionally, Jones & Wilson (2005) observed theta coherence between CA1 and mPFC during choice trials but not during forced-turn trials. Similarly, in a delayed nonmatch to position task, Hyman and colleagues (2010) found that 94% of theta-modulated mPFC neurons were significantly more phase-locked to hippocampal theta during correct trials than during error trials. Moreover, theta coherence between CA1 and mPFC increased significantly after rule acquisition at the choice point in a Y-maze with periodically switching reward contingency rules (Benchenane et al. 2010). In another study involving the hippocampus and the mPFC, the proportion of mPFC neurons that were phase-locked to hippocampal theta oscillations increased after successful learning of an object-place association (Kim et al. 2011).

The mPFC is not the only region that exhibits theta coupling with the hippocampus during spatial memory processing. Theta coherence between the striatum and the hippocampus increased during the period between the tone and the selected turn in a tone-cued T-maze task, but only in rats that successfully learned the task (DeCoteau et al. 2007). In this same task, coupling between striatal theta phase and hippocampal gamma amplitude was observed during the tone onset period (Tort et al. 2008). The authors suggested that striatal theta phase-hippocampal gamma amplitude coupling may signify times during decision making when the striatum accesses spatial information from the hippocampus.

The studies described thus far in this section involve spatial memory, but interregional theta coupling appears to be involved in other types of memory processing as well. The results of one study indicate that theta coordination of the hippocampus and the amygdala is important for fear memory retrieval. Theta coupling between the lateral amygdala and CA1 was significantly increased when conditioned fear stimuli were presented, and significant correlations between CA1 and lateral amygdala theta were seen in animals that displayed behavioral signs of fear (i.e., freezing; Seidenbecher et al. 2003). Interregional theta coupling also affects memory processing of nonaversive stimuli. Kay (2005) found positive correlations between performance on a two-odor discrimination task and theta coherence of the olfactory bulb and the hippocampus, suggesting that theta coupling enhances communication between the olfactory bulb and the hippocampus during olfactory memory processing. In a trace conditioning task using a visual conditioned stimulus, theta synchronization across different mPFC sites increased after investigators presented the conditioned stimulus only after learning had occurred (Paz et al. 2008). Because CA1 and the subiculum project to the mPFC (Swanson 1981, Jay & Witter 1991), the authors hypothesized that enhanced theta coupling with hippocampal inputs was responsible for the increased synchronization across mPFC.

The above-described studies show theta coordination during memory processing involving the hippocampus. However, theta coupling across regions appears to be a more general mechanism that is useful for other cognitive operations and physiological states, including visual short-term memory (Liebe et al. 2012) and anxiety (Adhikari et al. 2010). Reductions in theta coupling across regions may also relate to behavioral deficits in diseases such as schizophrenia (Dickerson et al. 2010, Sigurdsson et al. 2010). Remarkably, a new study using a rat model of schizophrenia found that interventions that restore normal performance on a cognitive control task also reestablish healthy theta synchrony between left and right hippocampi (Lee et al. 2012).

How does theta coupling enhance communication across brain areas? Theta synchronization of neurons in a given brain area likely leads to a more effective activation of downstream targets. Interregional theta coupling likely also ensures that downstream neurons will be excitable when inputs arrive. Theta's relatively slow time scale permits long synaptic delays and thus can feasibly sustain coupling across distributed brain regions. These points, taken together with the results reviewed above, support the conclusion that theta rhythms promote coordination across distributed brain areas during different types of information processing.

CONCLUDING REMARKS

Studies in recent years have provided breakthroughs in our understanding of the mechanisms and functions of theta rhythms. Theta-modulated neurons likely express intrinsic properties that prime them to produce theta oscillations in response to a variety of extrinsic inputs. Projections from interneurons in the MS are thought to pace theta in most neurons in the hippocampus at a given time. However, when an animal is in a cell's place field, excitatory CA3 and entorhinal inputs in the dendrites may produce stronger and faster theta oscillations that entrain the cell's firing. This flexibility in theta entrainment likely allows inputs to select the appropriate cell ensembles during particular cognitive tasks. Theta synchronization of related cell ensembles may then promote effective activation of target structures and thereby facilitate cognitive operations such as learning.

Although much progress has been made, many questions remain regarding the mechanisms and functions of theta rhythms. How important are intrinsic neuronal mechanisms for theta generation? It would be interesting to determine how theta rhythms in vivo are affected by manipulations that selectively and reversibly inhibit conductances that are tuned to theta. Regarding theta functions, major questions persist about how results from rodents pertain

to other species. Theta rhythms are continuous in rodents during active behaviors (Buzsáki et al. 1983, Buzsáki 2002) but occur only in short bouts in humans (Kahana et al. 1999), bats (Yartsev et al. 2011), and monkeys (Killian et al. 2012). It seems unlikely that complex functions such as learning could be achieved by short theta bouts in bats and primates and yet require continuous theta in rats. One possibility is that the conditions used in typical primate experiments are not optimal for engaging theta machinery. Rodents in experimental settings often engage in behaviors that are similar to their natural behaviors (e.g., foraging for food). Human studies of theta often involve virtual-reality environments. These uncommon behaviors may not readily activate circuits involved in theta rhythm generation. Moreover, foraging tasks require rodents to use a combination of sensory cues (e.g., olfactory, tactile, visual) and thus would be expected to engage a mechanism that packages related information from different sensory modalities. In contrast, investigations of theta in primates typically employ tasks requiring only one sensory modality, vision. Perhaps theta-generating machinery is less easily triggered in such tasks. Wireless monitoring devices implanted in patients undergoing deep brain stimulation may provide a way for researchers to measure theta rhythms during ordinary human behaviors. However, a recent study has shown that the activity of hippocampal place cells in bats is not modulated by theta rhythms during flying, bats' natural exploratory behavior (Yartsev & Ulanovsky 2013). Moreover, bat MEC neurons, unlike rat MEC neurons, do not exhibit membrane-potential resonance at theta frequencies (Heys et al. 2013). The puzzles that remain regarding theta functions across species underscore the importance of ongoing theta research in humans and in animal models.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

I thank the Klingenstein Fund and the Sloan Foundation for their support.

LITERATURE CITED

Adhikari A, Topiwala MA, Gordon JA. 2010. Synchronized activity between the ventral hippocampus and the medial prefrontal cortex during anxiety. *Neuron* 65:257–69

Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsáki G. 2012. Cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus. *J. Neurosci.* 32:423–35

Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, et al. 2010. Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron* 66:921–36

Berg RW, Kleinfeld D. 2003. Rhythmic whisking by rat: retraction as well as protraction of the vibrissae is under active muscular control. *J. Neurophysiol.* 89:104–17

Berg RW, Whitmer D, Kleinfeld D. 2006. Exploratory whisking by rat is not phase locked to the hippocampal theta rhythm. *J. Neurosci.* 26:6518–22

Berry SD, Thompson RF. 1978. Prediction of learning rate from the hippocampal electroencephalogram. *Science* 200:1298–300

Bland BH, Oddie SD, Colom LV. 1999. Mechanisms of neural synchrony in the septohippocampal pathways underlying hippocampal theta generation. *J. Neurosci.* 19:3223–37

Blasco-Ibáñez JM, Freund TF. 1995. Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. *Eur. J. Neurosci.* 7:2170–80
Brager DH, Johnston D. 2007. Plasticity of intrinsic excitability during long-term depression is mediated through mGluR-dependent changes in I(h) in hippocampal CA1 pyramidal neurons. *J. Neurosci.* 27:13926–37
Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsáki G. 1995. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* 15:47–60
Brandon MP, Bogaard AR, Libby CP, Connerney MA, Gupta K, Hasselmo ME. 2011. Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science* 332:595–99
Burgess N, O'Keefe J. 2011. Models of place and grid cell firing and theta rhythmicity. *Curr. Opin. Neurobiol.* 21:734–44
Buzsáki G. 2002. Theta oscillations in the hippocampus. *Neuron* 33:325–40
Buzsáki G. 2005. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* 15:827–40
Buzsáki G. 2006. *Rhythms of the Brain*. New York: Oxford Univ. Press. 448 pp.
Buzsáki G, Leung LW, Vanderwolf CH. 1983. Cellular bases of hippocampal EEG in the behaving rat. *Brain Res.* 287:139–71
Carr MF, Karlsson MP, Frank LM. 2012. Transient slow gamma synchrony underlies hippocampal memory replay. *Neuron* 75:700–13
Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, et al. 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 462:353–57
Colgin LL, Kubota D, Jia Y, Rex CS, Lynch G. 2004. Long-term potentiation is impaired in rat hippocampal slices that produce spontaneous sharp waves. *J. Physiol.* 558:953–61
Colgin LL, Leutgeb S, Jezek K, Leutgeb JK, Moser EI, et al. 2010. Attractor-map versus autoassociation based attractor dynamics in the hippocampal network. *J. Neurophysiol.* 104:35–50
Colgin LL, Moser EI. 2009. Hippocampal theta rhythms follow the beat of their own drum. *Nat. Neurosci.* 12:1483–84
DeCoteau WE, Thorn C, Gibson DJ, Courtemanche R, Mitra P, et al. 2007. Learning-related coordination of striatal and hippocampal theta rhythms during acquisition of a procedural maze task. *Proc. Natl. Acad. Sci. USA* 104:5644–49
Dickerson DD, Wolff AR, Bilkey DK. 2010. Abnormal long-range neural synchrony in a maternal immune activation animal model of schizophrenia. *J. Neurosci.* 30:12424–31
Dickson CT, Magistretti J, Shalinsky MH, Fransén E, Hasselmo ME, Alonso A. 2000. Properties and role of I(h) in the pacing of subthreshold oscillations in entorhinal cortex layer II neurons. *J. Neurophysiol.* 83:2562–79
Dragoi G, Buzsáki G. 2006. Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron* 50:145–57
Ellender TJ, Nissen W, Colgin LL, Mann EO, Paulsen O. 2010. Priming of hippocampal population bursts by individual perisomatic-targeting interneurons. *J. Neurosci.* 30:5979–91
Foster DJ, Wilson MA. 2007. Hippocampal theta sequences. *Hippocampus* 17:1093–99
Frerking M, Schmitz D, Zhou Q, Johansen J, Nicoll RA. 2001. Kainate receptors depress excitatory synaptic transmission at CA3–>CA1 synapses in the hippocampus via a direct presynaptic action. *J. Neurosci.* 21:2958–66
Ganguly K, Kleinfeld D. 2004. Goal-directed whisking increases phase-locking between vibrissa movement and electrical activity in primary sensory cortex in rat. *Proc. Natl. Acad. Sci. USA* 101:12348–53
Giocomo LM, Hasselmo ME. 2008. Time constants of h current in layer II stellate cells differ along the dorsal to ventral axis of medial entorhinal cortex. *J. Neurosci.* 28:9414–25
Giocomo LM, Hasselmo ME. 2009. Knock-out of HCN1 subunit flattens dorsal-ventral frequency gradient of medial entorhinal neurons in adult mice. *J. Neurosci.* 29:7625–30
Giocomo LM, Hussaini SA, Zheng F, Kandel ER, Moser MB, Moser EI. 2011. Grid cells use HCN1 channels for spatial scaling. *Cell* 147:1159–70
Giocomo LM, Zilli EA, Fransén E, Hasselmo ME. 2007. Temporal frequency of subthreshold oscillations scales with entorhinal grid cell field spacing. *Science* 315:1719–22

Goutagny R, Jackson J, Williams S. 2009. Self-generated theta oscillations in the hippocampus. *Nat. Neurosci.* 12:1491–93

Grastyan E, Lissak K, Madarasz I, Donhoffer H. 1959. Hippocampal electrical activity during the development of conditioned reflexes. *Electroencephalogr. Clin. Neurophysiol.* 11:409–30

Green JD, Arduini AA. 1954. Hippocampal electrical activity in arousal. *J. Neurophysiol.* 17:533–57

Greenstein YJ, Pavlides C, Winson J. 1988. Long-term potentiation in the dentate gyrus is preferentially induced at theta rhythm periodicity. *Brain Res.* 438:331–34

Gupta AS, van der Meer MA, Touretzky DS, Redish AD. 2012. Segmentation of spatial experience by hippocampal theta sequences. *Nat. Neurosci.* 15:1032–39

Hafting T, Fyhn M, Bonnevie T, Moser MB, Moser EI. 2008. Hippocampus-independent phase precession in entorhinal grid cells. *Nature* 453:1248–52

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. *Nature* 436:801–6

Hangya B, Borhegyi Z, Szilagyi N, Freund TF, Varga V. 2009. GABAergic neurons of the medial septum lead the hippocampal network during theta activity. *J. Neurosci.* 29:8094–102

Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, et al. 2002. Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells. *Nature* 417:738–41

Harvey CD, Collman F, Dombeck DA, Tank DW. 2009. Intracellular dynamics of hippocampal place cells during virtual navigation. *Nature* 461:941–46

Heys JG, MacLeod KM, Moss CF, Hasselmo ME. 2013. Bat and rat neurons differ in theta-frequency resonance despite similar coding of space. *Science* 340:363–67

Hu H, Vervaeke K, Storm JF. 2002. Two forms of electrical resonance at theta frequencies, generated by M-current, h-current and persistent Na+ current in rat hippocampal pyramidal cells. *J. Physiol.* 545:783–805

Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME. 2003. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. *J. Neurosci.* 23:11725–31

Hyman JM, Zilli EA, Paley AM, Hasselmo ME. 2010. Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Front. Integr. Neurosci.* 4:2

Jay TM, Witter MP. 1991. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. *J. Comp. Neurol.* 313:574–86

Jensen O, Colgin LL. 2007. Cross-frequency coupling between neuronal oscillations. *Trends Cogn. Sci.* 11:267–69

Jensen O, Lisman JE. 1996. Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. *Learn. Mem.* 3:279–87

Jezek K, Henriksen EJ, Treves A, Moser EI, Moser MB. 2011. Theta-paced flickering between place-cell maps in the hippocampus. *Nature* 478:246–49

Johnson A, Redish AD. 2007. Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. *J. Neurosci.* 27:12176–89

Jones MW, Wilson MA. 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 3(12):e402

Jung R, Kornmuller AE. 1938. Eine Methodik der ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. *Arch. Psychiat. Nervenkrankh.* 109:1–30

Kahana MJ, Sekuler R, Caplan JB, Kirschen M, Madsen JR. 1999. Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature* 399:781–84

Kamondi A, Acsády L, Wang XJ, Buzsáki G. 1998. Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. *Hippocampus* 8:244–61

Kay LM. 2005. Theta oscillations and sensorimotor performance. *Proc. Natl. Acad. Sci. USA* 102:3863–68

Kepecs A, Uchida N, Mainen ZF. 2006. The sniff as a unit of olfactory processing. *Chem. Senses* 31:167–79

Killian NJ, Jutras MJ, Buffalo EA. 2012. A map of visual space in the primate entorhinal cortex. *Nature* 491:761–64

Kim J, Delcasso S, Lee I. 2011. Neural correlates of object-in-place learning in hippocampus and prefrontal cortex. *J. Neurosci.* 31:16991–7006

Kim SM, Ganguli S, Frank LM. 2012. Spatial information outflow from the hippocampal circuit: distributed spatial coding and phase precession in the subiculum. *J. Neurosci.* 32:11539–58

Klimesch W, Doppelmayr M, Russegger H, Pachinger T. 1996. Theta band power in the human scalp EEG and the encoding of new information. *NeuroReport* 7:1235–40

Klimesch W, Schimke H, Schwaiger J. 1994. Episodic and semantic memory: an analysis in the EEG theta and alpha band. *Electroencephalogr. Clin. Neurophysiol.* 91:428–41

Koenig J, Linder AN, Leutgeb JK, Leutgeb S. 2011. The spatial periodicity of grid cells is not sustained during reduced theta oscillations. *Science* 332:592–95

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

Kubota D, Colgin LL, Casale M, Brucher FA, Lynch G. 2003. Endogenous waves in hippocampal slices. *J. Neurophysiol.* 89:81–89

Landfield PW, McGaugh JL, Tusa RJ. 1972. Theta rhythm: a temporal correlate of memory storage processes in the rat. *Science* 175:87–89

Larson J, Wong D, Lynch G. 1986. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res.* 368:347–50

Lee H, Dvorak D, Kao HY, Duffy AM, Scharfman HE, Fenton AA. 2012. Early cognitive experience prevents adult deficits in a neurodevelopmental schizophrenia model. *Neuron* 75:714–24

Liebe S, Hoerzer GM, Logothetis NK, Rainer G. 2012. Theta coupling between V4 and prefrontal cortex predicts visual short-term memory performance. *Nat. Neurosci.* 15:456–62

Lisman J, Redish AD. 2009. Prediction, sequences and the hippocampus. *Philos. Trans. R. Soc. Lond. B* 364: 1193–201

Louie K, Wilson MA. 2001. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29:145–56

Lubenov EV, Siapas AG. 2009. Hippocampal theta oscillations are travelling waves. *Nature* 459:534–39

Maccaferri G. 2005. Stratum oriens horizontal interneurone diversity and hippocampal network dynamics. *J. Physiol.* 562:73–80

Maccaferri G, McBain CJ. 1996. The hyperpolarization-activated current (Ih) and its contribution to pacemaker activity in rat CA1 hippocampal stratum oriens-alveus interneurones. *J. Physiol.* 497(Pt. 1):119–30

Macrides F, Eichenbaum HB, Forbes WB. 1982. Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. *J. Neurosci.* 2:1705–17

Madison DV, Lancaster B, Nicoll RA. 1987. Voltage clamp analysis of cholinergic action in the hippocampus. *J. Neurosci.* 7:733–41

Magee JC. 2001. Dendritic mechanisms of phase precession in hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* 86:528–32

Marcelin B, Lugo JN, Brewster AL, Liu Z, Lewis AS, et al. 2012. Differential dorso-ventral distributions of Kv4.2 and HCN proteins confer distinct integrative properties to hippocampal CA1 pyramidal cell distal dendrites. *J. Biol. Chem.* 287:17656–61

Maurer AP, McNaughton BL. 2007. Network and intrinsic cellular mechanisms underlying theta phase precession of hippocampal neurons. *Trends Neurosci.* 30:325–33

Maurer AP, Vanrhoads SR, Sutherland GR, Lipa P, McNaughton BL. 2005. Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* 15:841–52

Mehta MR, Lee AK, Wilson MA. 2002. Role of experience and oscillations in transforming a rate code into a temporal code. *Nature* 417:741–46

Melzer S, Michael M, Caputi A, Eliava M, Fuchs EC, et al. 2012. Long-range-projecting GABAergic neurons modulate inhibition in hippocampus and entorhinal cortex. *Science* 335:1506–10

M'Harzi M, Jarrard LE. 1992. Effects of medial and lateral septal lesions on acquisition of a place and cue radial maze task. *Behav. Brain Res.* 49:159–65

Mitchell SJ, Rawlins JN, Steward O, Olton DS. 1982. Medial septal area lesions disrupt theta rhythm and cholinergic staining in medial entorhinal cortex and produce impaired radial arm maze behavior in rats. *J. Neurosci.* 2:292–302

Mizumori SJ, Perez GM, Alvarado MC, Barnes CA, McNaughton BL. 1990. Reversible inactivation of the medial septum differentially affects two forms of learning in rats. *Brain Res.* 528:12–20

Mizuseki K, Royer S, Diba K, Buzsáki G. 2012. Activity dynamics and behavioral correlates of CA3 and CA1 hippocampal pyramidal neurons. *Hippocampus* 22:1659–80

Mizuseki K, Sirota A, Pastalkova E, Buzsáki G. 2009. Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. *Neuron* 64:267–80

Montgomery SM, Sirota A, Buzsáki G. 2008. Theta and gamma coordination of hippocampal networks during waking and rapid eye movement sleep. *J. Neurosci.* 28:6731–41

Navratilova Z, Giocomo LM, Fellous JM, Hasselmo ME, McNaughton BL. 2012. Phase precession and variable spatial scaling in a periodic attractor map model of medial entorhinal grid cells with realistic after-spike dynamics. *Hippocampus* 22:772–89

Nolan MF, Malleret G, Dudman JT, Buhl DL, Santoro B, et al. 2004. A behavioral role for dendritic integration: HCN1 channels constrain spatial memory and plasticity at inputs to distal dendrites of CA1 pyramidal neurons. *Cell* 119:719–32

O'Keefe J, Dostrovsky J. 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res.* 34:171–75

O'Keefe J, Recce ML. 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3:317–30

Orr G, Rao G, Houston FP, McNaughton BL, Barnes CA. 2001. Hippocampal synaptic plasticity is modulated by theta rhythm in the fascia dentata of adult and aged freely behaving rats. *Hippocampus* 11:647–54

Osipova D, Takashima A, Oostenveld R, Fernández G, Maris E, Jensen O. 2006. Theta and gamma oscillations predict encoding and retrieval of declarative memory. *J. Neurosci.* 26:7523–31

Otero-Millan J, Troncoso XG, Macknik SL, Serrano-Pedraza I, Martinez-Conde S. 2008. Saccades and microsaccades during visual fixation, exploration, and search: foundations for a common saccadic generator. *J. Vis.* 8:1–18

Patel J, Fujisawa S, Berenyi A, Royer S, Buzsáki G. 2012. Traveling theta waves along the entire septotemporal axis of the hippocampus. *Neuron* 75:410–17

Pavlides C, Greenstein YJ, Grudman M, Winson J. 1988. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Res.* 439:383–87

Paz R, Bauer EP, Pare D. 2008. Theta synchronizes the activity of medial prefrontal neurons during learning. *Learn. Mem.* 15:524–31

Petsche H, Stumpf C, Gogolak G. 1962. The significance of the rabbit's septum as a relay station between the midbrain and the hippocampus. I. The control of hippocampus arousal activity by the septum cells. *Electroencephalogr. Clin. Neurophysiol.* 14:202–11

Pike FG, Goddard RS, Suckling JM, Ganter P, Kasthuri N, Paulsen O. 2000. Distinct frequency preferences of different types of rat hippocampal neurones in response to oscillatory input currents. *J. Physiol.* 529 (Pt. 1):205–13

Robbe D, Buzsáki G. 2009. Alteration of theta timescale dynamics of hippocampal place cells by a cannabinoid is associated with memory impairment. *J. Neurosci.* 29:12597–605

Robinson RB, Siegelbaum SA. 2003. Hyperpolarization-activated cation currents: from molecules to physiological function. *Annu. Rev. Physiol.* 65:453–80

Rutishauser U, Ross IB, Mamelak AN, Schuman EM. 2010. Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature* 464:903–7

Seidenbecher T, Laxmi TR, Stork O, Pape HC. 2003. Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science* 301:846–50

Senior TJ, Huxter JR, Allen K, O'Neill J, Csicsvari J. 2008. Gamma oscillatory firing reveals distinct populations of pyramidal cells in the CA1 region of the hippocampus. *J. Neurosci.* 28:2274–86

Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. 2010. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature* 464:763–67

Simon AP, Poindessous-Jazat F, Dutar P, Epelbaum J, Bassant MH. 2006. Firing properties of anatomically identified neurons in the medial septum of anesthetized and unanesthetized restrained rats. *J. Neurosci.* 26:9038–46

Skaggs WE, McNaughton BL, Wilson MA, Barnes CA. 1996. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6:149–72

Squire LR, Stark CE, Clark RE. 2004. The medial temporal lobe. *Annu. Rev. Neurosci.* 27:279–306

Staubli U, Lynch G. 1987. Stable hippocampal long-term potentiation elicited by 'theta' pattern stimulation. *Brain Res.* 435:227–34

Swanson LW. 1981. A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Res.* 217:150–54

Terrazas A, Krause M, Lipa P, Gothard KM, Barnes CA, McNaughton BL. 2005. Self-motion and the hippocampal spatial metric. *J. Neurosci.* 25:8085–96

Tesche CD, Karhu J. 2000. Theta oscillations index human hippocampal activation during a working memory task. *Proc. Natl. Acad. Sci. USA* 97:919–24

Tort AB, Kramer MA, Thorn C, Gibson DJ, Kubota Y, et al. 2008. Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proc. Natl. Acad. Sci. USA* 105:20517–22

Toth K, Borhegyi Z, Freund TF. 1993. Postsynaptic targets of GABAergic hippocampal neurons in the medial septum-diagonal band of Broca complex. *J. Neurosci.* 13:3712–24

Toth K, Freund TF, Miles R. 1997. Disinhibition of rat hippocampal pyramidal cells by GABAergic afferents from the septum. *J. Physiol.* 500(Pt. 2):463–74

Tsodyks MV, Skaggs WE, Sejnowski TJ, McNaughton BL. 1996. Population dynamics and theta rhythm phase precession of hippocampal place cell firing: a spiking neuron model. *Hippocampus* 6:271–80

Vaidya SP, Johnston D. 2012. HCN channels contribute to the spatial synchrony of theta frequency synaptic inputs in CA1 pyramidal neurons. *Soc. Neurosci. Annu. Meet. Abstr.* 435.15 (Abstr.)

van der Meer MA, Redish AD. 2011. Theta phase precession in rat ventral striatum links place and reward information. *J. Neurosci.* 31:2843–54

Vanderwolf CH. 1969. Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr. Clin. Neurophysiol.* 26:407–18

Varga V, Hangya B, Kranitz K, Ludanyi A, Zemankovics R, et al. 2008. The presence of pacemaker HCN channels identifies theta rhythmic GABAergic neurons in the medial septum. *J. Physiol.* 586:3893–915

Vertes RP. 2004. Memory consolidation in sleep: dream or reality. *Neuron* 44:135–48

Vertes RP, Hoover WB, Viana Di Prisco G. 2004. Theta rhythm of the hippocampus: subcortical control and functional significance. *Behav. Cogn. Neurosci. Rev.* 3:173–200

Vertes RP, Kocsis B. 1997. Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. *Neuroscience* 81:893–926

Wallenstein GV, Hasselmo ME. 1997. GABAergic modulation of hippocampal population activity: sequence learning, place field development, and the phase precession effect. *J. Neurophysiol.* 78:393–408

Winson J. 1974. Patterns of hippocampal theta rhythm in the freely moving rat. *Electroencephalogr. Clin. Neurophysiol.* 36:291–301

Winson J. 1978. Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. *Science* 201:160–63

Yamaguchi Y, Aota Y, McNaughton BL, Lipa P. 2002. Bimodality of theta phase precession in hippocampal place cells in freely running rats. *J. Neurophysiol.* 87:2629–42

Yartsev MM, Ulanovsky N. 2013. Representation of three-dimensional space in the hippocampus of flying bats. *Science* 340:367–72

Yartsev MM, Witter MP, Ulanovsky N. 2011. Grid cells without theta oscillations in the entorhinal cortex of bats. *Nature* 479:103–7

Ylinen A, Soltesz I, Bragin A, Penttonen M, Sik A, Buzsáki G. 1995. Intracellular correlates of hippocampal theta rhythm in identified pyramidal cells, granule cells, and basket cells. *Hippocampus* 5:78–90

Annual Review of Neuroscience

Volume 36, 2013

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Neuroscience* articles may be found at http://neuro.annualreviews.org/