

Theta phase precession beyond the hippocampus

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Abstract

The spike timing of spatially tuned cells throughout the rodent hippocampal formation displays a strikingly robust and precise organization. In individual place cells, spikes precess relative to the theta local field potential (6–10 Hz) as an animal traverses a place field. At the population level, theta cycles shape repeated, compressed place cell sequences that correspond to coherent paths. The theta phase precession phenomenon not only has afforded insights into how multiple processing elements in the hippocampal formation interact, but is also believed to facilitate hippocampal contributions to rapid learning, navigation, and lookahead. However, theta phase precession is not unique to the hippocampus, suggesting that insights derived from hippocampal phase precession could elucidate processing in other structures. In this review, we consider the implications of extrahippocampal phase precession in terms of mechanisms and functional relevance. We focus on phase precession in the ventral striatum (vStr), a prominent output structure of the hippocampus in which phase precession systematically appears in the firing of reward-anticipatory ‘ramp’ neurons. We outline how ventral striatal phase precession can advance our understanding of behaviors thought to depend on interactions between the hippocampus and the vStr, such as conditioned place preference and context-dependent reinstatement. More generally, we argue that phase precession can be a useful experimental tool in dissecting the functional connectivity between the hippocampus and its outputs.

Keywords: decoding; local field potential; medial prefrontal cortex; nucleus accumbens; phase coding; spike timing; temporal coding; ventral striatum.

Introduction

A prominent ~8-Hz thread runs through the hippocampal literature: pioneering electrophysiological studies in this area revealed a clear ‘theta’ rhythm (Green and Arduini, 1954; Vanderwolf, 1969), which has been at the center of numerous functional and mechanistic theories of hippocampal processing ever since (O’Keefe, 1993; Jensen and Lisman, 1996; Bland and Oddie, 2001; Buzsáki, 2002; Hasselmo, 2005). As a local field potential (LFP) phenomenon, hippocampal theta is susceptible to debate about how such an inherently ambiguous, population-level quantity is to be interpreted.¹ However, the power of the hippocampal theta rhythm as an experimental and theoretical touchstone is clearly illustrated by its relationships to (1) intrinsic membrane properties of individual neurons (Leung and Yim, 1986; Kamondi et al., 1998; Giocomo et al., 2007; Losonczy et al., 2010); (2) spiking and LFP activity within the hippocampus and anatomically related circuits (Klausberger et al., 2003; Siapas et al., 2005; Colgin et al., 2009; Mizuseki et al., 2009; Battaglia et al., 2011); (3) the efficacy of stimulation protocol timing, relative to theta, in evoking synaptic changes (Larson et al., 1986; Hölscher et al., 1997; Hyman et al., 2003); and (4) hippocampal function and behavior (Sederberg et al., 2003; Manns et al., 2007; Jeewajee et al., 2008). Thus, hippocampal theta links different levels of analysis, accessible with a variety of experimental techniques, across species and brain areas.

A particularly intriguing theta-related phenomenon is theta phase precession, originally observed in hippocampal ‘place cells’.² O’Keefe and Recce (1993) reported that as a rat traverses a place field, there is a systematic change in the phase of the theta LFP³ at which the cell fires (‘firing phase’): the firing phase advances, or precesses, with progress through the place field (Figure 1A,B). Theta phase precession is a robust and widespread phenomenon, typically observed in dorsal CA1 pyramidal neurons when rodents run along narrow tracks, but also apparent in less restricted environments (Skaggs et al., 1996; Huxter et al., 2008), hippocampal interneurons (Maurer et al., 2006; Ego-Stengel and Wilson, 2007), and other areas in the hippocampal formation (Skaggs et al., 1996; Johnson

¹In general, LFPs reflect summed contributions from synaptic input, membrane potentials, and synchronous spiking and is further influenced by neuronal morphology and geometrical arrangement of the population. For review, see, for example, Berens et al. (2008).

²For brevity, we use ‘hippocampal’ as referring to the hippocampal formation generally, which includes the entorhinal cortex and the subiculum; we will be more specific as required.

³The local field potential is typically recorded from the hippocampal fissure, where theta amplitude is largest, but the phase precession effect is also apparent relative to the LFP recorded from the cell layer.

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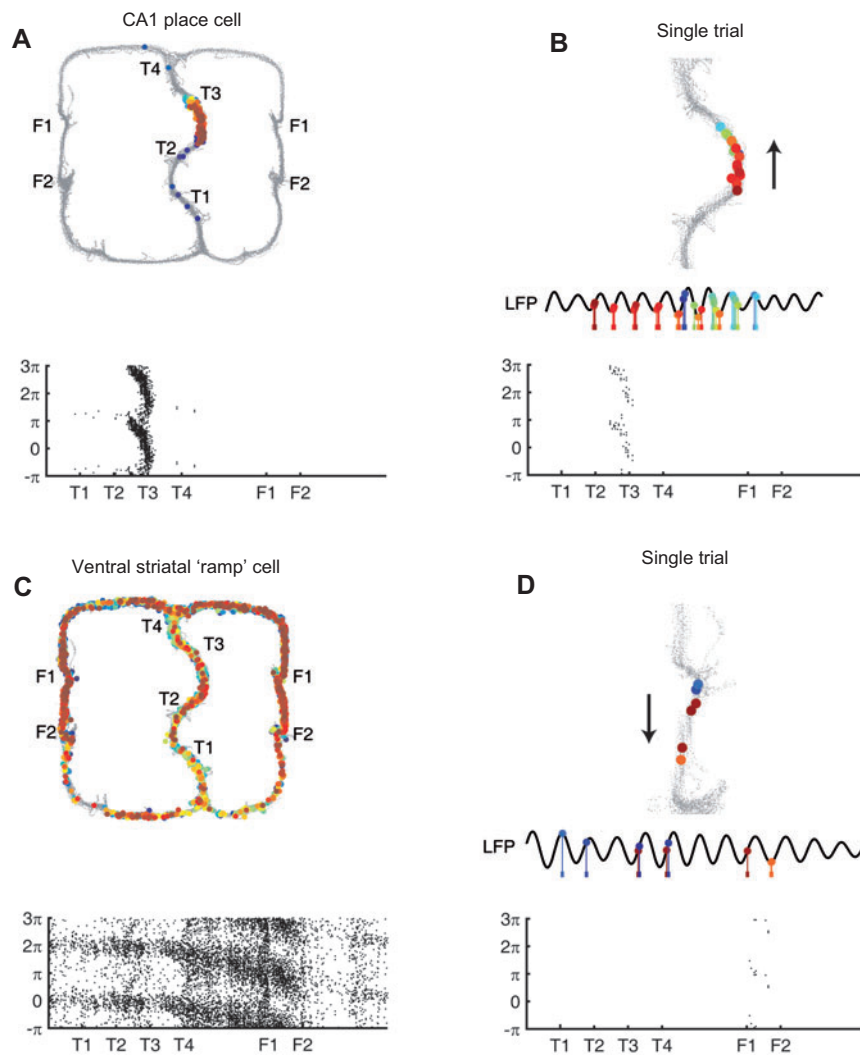


Figure 1 Examples of theta phase precession in a dorsal CA1 'place' cell (A,B, a putative pyramidal neuron) and a ventral striatal 'ramp' cell (C,D, a putative medium spiny neuron), recorded simultaneously from a rat running on an elevated track.

The left column shows the spikes of each neuron by position of the animal on the track, color coded by theta phase (top); phase is also shown along a linearized, one-dimensional view of the track (bottom). T1–T4 indicate turns on the track; F1 and F2 are reward sites. The right column shows a single pass through each neuron's firing field, with spikes shown alongside the theta-filtered local field potential (recorded from the hippocampal fissure in both cases), color coded on the same scale. The arrow indicates the animal's direction of travel. Phase precession is apparent both in the combined and single-trial plots, but note how phase precesses more rapidly in the hippocampal neuron. Data from van der Meer and Redish (2011a).

and Redish, 2007; Hafting et al., 2008; Kjelstrup et al., 2008; Royer et al., 2010).

Two main reasons can be discerned for ongoing interest in theta phase precession. The first is that the precise temporal coordination central to the phase precession effect is a useful tool in dissecting the underlying mechanisms of hippocampal processing. Phase precession inspires and constrains models, particularly when combined with experiments exploring the properties of theta phase precession under various conditions and manipulations (Harris et al., 2002; Mehta et al., 2002; Huxter et al., 2003; Cheng and Frank, 2008; Diba and Buzsáki, 2008; Lenck-Santini and Holmes, 2008; Harvey et al., 2009; Robbe and Buzsáki, 2009). Second, theta phase precession is thought to play a role in mediating hippocampus-specific

behaviors or functions, such as spatial navigation, planning or lookahead, and rapid encoding of sequences, including not just spatial trajectories but also episodic-like memories (Jensen and Lisman, 1996; Skaggs et al., 1996; Tsodyks et al., 1996; Yamaguchi, 2003; Shapiro et al., 2006; Leibold et al., 2008; Lisman and Redish, 2009). More generally, theta phase precession stands as one of the clearest examples of a timing (or phase) code in the brain and is therefore of substantial theoretical interest (Sejnowski and Paulsen, 2006; Masquelier et al., 2009; Nadasdy, 2009; Panzeri et al., 2010).

Given these different ways in which theta phase precession may be important, it is of interest to note that phase precession is also observed in structures outside the hippocampal formation. Jones and Wilson (2005a) found neurons in rat

medial prefrontal cortex (mPFC) that phase precess relative to hippocampal theta. Recently, van der Meer and Redish (2011a) reported theta phase precession in the rat ventral striatum (vStr).⁴ Both these structures receive prominent input projections from the hippocampal formation and are thought to mediate the translation of hippocampus-dependent forms of learning and memory into adaptive behavior (Mogenson and Yang, 1991; Mizumori et al., 1999; Poucet et al., 2004; Bast, 2007, 2011). The purpose of this review is to consider how insights about phase precession in the hippocampus can elucidate processing in downstream targets, such as the mPFC and the vStr.

In order to appreciate the potential relevance of theta phase precession for hippocampal output structures, we review current theories on mechanisms and functional relevance of phase precession in the hippocampus itself in the first half of the article. Readers familiar with these concepts may wish to skip ahead to the second half of the article (Phase Precession Outside the Hippocampus and subsequent sections) which deals with extrahippocampal phase precession. Thus, we start by highlighting the salient experimental data on hippocampal phase precession in the first section. In the Models of Phase Precession section, we consider current proposals of how phase precession may be generated. Next, we review the main ideas about the possible functional relevance of hippocampal phase precession (Functional Relevance of Phase Precession section). The following section moves to extrahippocampal phase precession, highlighting the key experimental findings alongside the relevant anatomy (Phase Precession Outside the Hippocampus section). We then focus on phase precession in the vStr, considering possible explanations for how it is generated. We situate the discussion in the context of behaviors thought to involve the hippocampus-vStr pathway, such as conditioned place preference (CPP) and context-dependent reinstatement (Functional Contributions of Hippocampal Inputs to the Ventral Striatum section). In the final section, we consider the functional relevance of ventral striatal phase precession, as well as ways to exploit it as an experimental and theoretical tool.

Theta phase precession in the hippocampal formation

Phase precession in single cells

The basic theta phase precession effect is readily apparent from observing the spike timing of a single hippocampal place cell relative to the extracellular LFP. In the seminal observations of O'Keefe and Recce (1993), as rats traverse a place field along a linear track, place cells spike at progressively earlier phases of the theta LFP. The range over which spike theta phase precesses during a single pass through the field is about 180° on average, but never exceeds a full cycle

(O'Keefe and Recce, 1993; Schmidt et al., 2009). Illustrative single trials and pooled data are shown in Figure 1 and simulated for a pair of adjacent place cells in Figure 4.

At the single-cell level, phase precession has a number of implications. Most obviously, it establishes a relationship between location and phase. As the animal first enters a place field, the corresponding place cell tends to fire at late phases of the theta LFP, but as the animal leaves the place field, the cell has precessed and now fires at early phases. This means that there is information about location in the theta phase of place cell spikes. Indeed, firing phase can correlate better with location than firing rate, particularly when there are variations in running speed (Jensen and Lisman, 2000; Huxter et al., 2003), an idea with potential functional implications discussed in the Functional Relevance of Phase Precession section.

Second, single-trial phase precession implies that an individual place cell must spike at a slightly faster frequency than the LFP.⁵ A cell that reliably spikes at the same frequency as a particular LFP frequency band is said to be phase *locked* (or entrained) rather than phase *precessing*. Phase precession refers to a smooth, gradual phase change over time.⁶ The relationship between theta modulation at the single neuron level being slightly faster than the theta LFP frequency is reliable enough that it is often used as a measure or even operational definition of a phase precessing cell (Lenck-Santini and Holmes, 2008; Royer et al., 2010; van der Meer and Redish, 2011a).

A final implication is that the speed of phase precession is related to the size of the place field. Phase precession occurs over a limited range of the theta rhythm,⁷ but place fields can have different sizes. This means that for a small place field, this phase range is traversed quickly, whereas for a large place field, phase precesses more slowly. There is a dorsal-to-ventral⁸ gradient in the hippocampus proper (the DG-CA3-CA1 trisynaptic loop) with smaller field, fast phase precessing neurons in the dorsal part and larger field, slower phase precessing neurons in the ventral part (Jung et al., 1994; Kjelstrup et al., 2008; Royer et al., 2010; Figure 3). The limited theta range over which phase precession occurs

⁵This is not strictly true: in principle, the cell could spike at a frequency slightly faster than a multiple of the LFP frequency, skipping cycles but still precessing overall. However, this does not seem to happen systematically in hippocampal place cells (but see, e.g., Deshmukh et al., 2010, for an example of theta cycle skipping in the entorhinal cortex).

⁶There are observations of sudden shifts in theta phase (e.g., Hyman et al., 2011), which when averaged over many trials, could in principle create the appearance of a smooth precession effect. However, analysis of single trials shows that theta phase precession is gradual even on single trials (Schmidt et al., 2009; Figure 1).

⁷It is worth noting that in the original O'Keefe and Recce (1993) report, illustrative single trial examples were provided, but for analysis purposes, spikes from many passes through the place field were averaged. A recent study (Schmidt et al., 2009) showed that the range of phase precession on single trials is about 180°, significantly less than the range apparent after averaging.

⁸In the primate and human literature, the corresponding terminology is septal-to-temporal.

⁴We use this general term to refer non-specifically to the area encompassing the nucleus accumbens core, shell, and ventral caudate-putamen in the rat. As with the term 'hippocampal', we will be more specific where appropriate.

implies that a neuron with fast theta range interspike intervals (ISIs) will precess rapidly with respect to the LFP. This will cause it to reach the strong-inhibition phase of the theta cycle more rapidly, so it will have a small place field (Geisler et al., 2010). A neuron with a slow ISI (albeit still slightly faster than the period of the LFP) will precess more slowly and have a larger place field.⁹

Finally, we note that although phase precession at the single-cell level has to our knowledge not yet been demonstrated in the human or primate hippocampus, the extant data indicate compelling similarities between human/primate and rodent theta in terms of behavioral correlates and detailed electrophysiological signatures (O'Keefe and Burgess, 1999; Kahana et al., 2001; Ekstrom et al., 2005), suggesting that theta phase precession is of relevance beyond rodent species.

A temporal tapestry of theta sequences: phase precession at the population level

The most surprising and powerful aspects of phase precession are only apparent at the population level. Skaggs et al. (1996) first took the critical step of extending the analysis of hippocampal phase precession to more than one neuron. For two neurons with place fields in close proximity on the track, phase precession imposes a specific fine-timescale structure on the spike timing relationship between the two neurons – beyond what would be expected from the neurons' average firing fields (tuning curves) alone (Dragoi and Buzsáki, 2006; Foster and Wilson, 2007). To see this, consider two place cells A and B, whose fields partially overlap along a track: the subject encounters field A first, followed by field B (Figure 4A, top panel). Imagine first that phase precession is turned off¹⁰ and place cell spiking is generated stochastically from a spike density function in the shape of the cell's place field. In this case, for a single pass through A and B, cell A will tend to spike before cell B on a behavioral timescale (i.e., how long it actually takes the subject to reach the center of B from the center of A). But on a fine timescale (tens of milliseconds), there will be no discernible relationship between the spike timing from cells A and B (Figure 4A, top panel).

Contrast this with the situation where phase precession is turned on (Figure 4A, bottom panel). The theta phase of cell A's spikes precesses with progress through field A. Therefore, by the time the subject gets to field B, the spikes from A will be more advanced (precessed) than cell B's spikes, which have yet to start their precession. In fact, assuming that cells A and B will precess at similar speeds (as will be the case for similarly sized place fields), this implies that there will be a relatively fixed time interval between cells A and B's

spikes. This interval depends on the distance between their place fields: if the fields are very close, then cell B will start precessing only slightly later than cell A, so the time difference will be short. Conversely, if cell A has almost completely precessed before B begins firing, then the time difference will be long (although, of course, not longer than the period of a theta cycle). This effect can be clearly seen experimentally by inspecting the cross-correlograms between place cells with adjacent place fields (Skaggs et al., 1996; Dragoi and Buzsáki, 2006; 'CCG' plots in Figure 4, top right). Thus, theta phase precession generates a systematic, fine-timescale spike timing relationship between cells with nearby place fields. This observation is particularly notable in the light of experimental observations relating spike timing on this timescale to the direction and efficacy of synaptic plasticity in hippocampal slices (Bi and Poo, 1998); these and other functional implications of phase precession will be discussed in the Functional Relevance of Phase Precession section.

This analysis of phase precession in pairs of place cells extends to populations of place cells, which form sequences of successive locations within a theta cycle (Jensen and Lisman, 1996; Tsodyks et al., 1996; Dragoi and Buzsáki, 2006; Foster and Wilson, 2007; Maurer and McNaughton, 2007; Lisman and Redish, 2009; Maurer et al., 2011). Again, imagine a rat traveling along a track covered by place fields ABCDE from left to right. Within each theta cycle, a sequence of spikes appears, with each cell's spike(s) at a theta phase that reflects the rat's current location relative to that place cell's field. So, if the subject is at location A, cell A's spikes will have phase precessed to some extent, cell B's spikes will have phase precessed less so (because it is further away), and cell C may be just beginning to spike (at a late phase), giving rise to the sequence ABC. As the animal moves to location B, we would see sequence BCD, and so forth. As was the case with the pair of neurons considered previously, the relative distance between place fields translates into a particular spike timing relationship between the corresponding place cells within each theta cycle. Thus, 'theta sequences' of place cells appear repeatedly (one per theta cycle) and on a compressed timescale, even though behaviorally, the sequence is only traversed once.¹¹

As memorably put by Bruce McNaughton,¹² this effect is 'as a pigeon walks', that is, the represented location (signaled by the currently active place cells) appears to move forward, reset, and move forward again repeatedly (like the pigeon's head) around the subject's true location, which moves more gradually. More precisely, this implies that a decoder that

⁹For simplicity, the above assumed a constant speed; a further fineness is that place cells' firing frequency is modulated by speed to ensure that a comparable range of firing phases is covered regardless of speed (Burgess et al., 2007; Geisler et al., 2007; Diba and Buzsáki, 2008).

¹⁰A condition that can be experimentally approximated (Robbe and Buzsáki, 2009) as discussed in the Functional Relevance of Phase Precession section.

¹¹For the sake of simplicity, this description treated the cells participating in a theta sequence as phase precessing independently. However, there is evidence that the observed level of sequential organization exceeds that of what would be expected from such a scenario (Dragoi and Buzsáki, 2006; Foster and Wilson, 2007), suggesting that network mechanisms play a part.

¹²Kavli Institute for Theoretical Physics 'Dynamics of Neural Networks: From Biophysics to Behavior' series, UC Santa Barbara, 2001, online at <http://online.itp.ucsb.edu/online/neuro01/mcnaughton/>.

ignores theta phase will decode a location that oscillates at theta frequency around the subject's true location.¹³ Thus, although phase precession can be observed at the single-cell level, its true power arises from compressed-sequence organization at the population level.

Models of phase precession

There is complex literature detailing possible contributions to theta phase precession in the hippocampus. In general, these contributions include the passive and active conductance properties of single neurons, local microcircuits, synaptic and network effects, and external inputs. Attempts at integrated models thus face the challenge of accounting for the effects of a wide range of elements, their interactions, and variations between subregions and anatomical aspects of the hippocampal formation. Therefore, our aim in this section is not to compare the state of the art in phase precession models to the data, with the aim of establishing which (combination of) models are the current forerunners; for this, we refer the reader to the literature (most recently, Burgess and O'Keefe, 2011, but see also Maurer and McNaughton, 2007; Geisler et al., 2010; Losonczy et al., 2010; Leung, 2011; Navratilova et al., 2011). Rather, we will review the types of mechanisms that have been proposed, such that we are in a position to evaluate to what extent these mechanisms may apply to phase precession in areas outside the hippocampal formation.

In discussing possible mechanisms for phase precession, it is important to remember that even within the hippocampal formation, phase precession is found in several subregions. In particular, Hafting et al. (2008) demonstrated that phase precession in the entorhinal cortex (EC) persists after inactivation of the hippocampus proper. This suggests that although DG, CA1, and CA3 neurons have access to phase precessing input from the EC, such input is not required for EC neurons to phase precess. Thus, the mechanisms generating it in these regions need not be the same. In line with this view, we will discuss possible mechanisms for phase precession without attempting to map them onto specific subregions. Because the proposals are generally not mutually exclusive, we conceptualize phase precession in any given area as reflecting a particular mixture of different mechanisms. This view is conducive to considering which of these mechanisms may apply to explanations of phase precession beyond the hippocampus (Possible Mechanisms for Ventral Striatal Theta Phase Precession section).

At the root of explanations for single-cell phase precession lies the issue of how it is possible for single cells to oscillate faster than the population LFP. The hippocampal LFP, after all, is shaped by electrical currents ultimately arising from currents generated from those very same cells; more specifically, the LFP is thought to reflect a combination of synaptic currents and membrane potential oscillations (MPOs) (Buzsáki et al., 1983; Ylinen et al., 1995; Kamondi

et al., 1998; Leung, 1998). Synaptic contributions to the hippocampal theta LFP likely include inputs from the medial septum, afferent hippocampal subregions such as the EC, and local microcircuits between pyramidal neurons and various interneuron types (Amaral and Lavenex, 2006). MPOs can result from such oscillating inputs but may be additionally affected by the electrical properties of single neurons. These include passive properties as well as active conductances capable of generating intrinsic oscillations from non-oscillating input and resonance properties that selectively amplify and suppress particular input frequencies (e.g., Wang, 2010). Models of phase precession can be understood as proposals about how these different phenomena interact. We distinguish contributions to phase precession according to the proposed locus where such interaction is placed: (1) within individual phase precessing neurons, which implement some transformation of an input coherent with the LFP; (2) in the organization of a population of neurons assumed to shape the LFP; and (3) in synaptic and network interactions between neurons.

Phase precession arising from within-neuron interactions

Phase precession models of the first type identify the population LFP as corresponding to one of the inputs to a phase precessing cell. The cell then requires one or more additional mechanisms that cause it to oscillate faster than the LFP input, which forms the reference for the precession. This class of model has identified several different ways in which operations performed by a neuron may result in phase precession:

- *Asymmetric ramping.* Mehta et al. (2002) proposed that inhibition at the LFP frequency interacts with an excitatory asymmetric ramping input at the phase precessing neuron. As excitation increases, this will cause excitation to out-strip inhibition (leading to a spike) at progressively earlier phases of the extracellular LFP, resulting in phase precession (Figure 2C).
- *Interaction between oscillations of a different frequency.* If, in addition to an input at LFP frequency, a neuron either receives or generates a second oscillation at a different frequency, an interference or 'beat' pattern can result (O'Keefe and Recce, 1993; Bose and Recce, 2001; O'Keefe and Burgess, 2005). In such 'dual-oscillator' models, the frequency within each beat will be faster than the LFP, giving rise to phase precession (Figure 2A). A variation of this model occurs when one of the oscillations is frequency modulated; in this case, two oscillations can be out of phase outside the neuron's place field but in phase in the place field (Figure 2B). As long as both oscillations are faster than the LFP, the resulting spikes will phase precess (Lengyel et al., 2003; Yamaguchi et al., 2007).
- *Interaction between oscillations of the same frequency.* If two inputs to a neuron have the same frequency but differing phase, then a shift in the balance between these inputs can cause phase changes in a neuron that integrates these inputs (Kamondi et al., 1998; Leung, 2011; Figure 2F). A number of factors may contribute to an on-line modulation in this balance as to result in phase precession, such as

¹³Whether the decoded location is always forward of the subject, rather than symmetric or backward, is a topic of active investigation (Maurer et al., 2011).

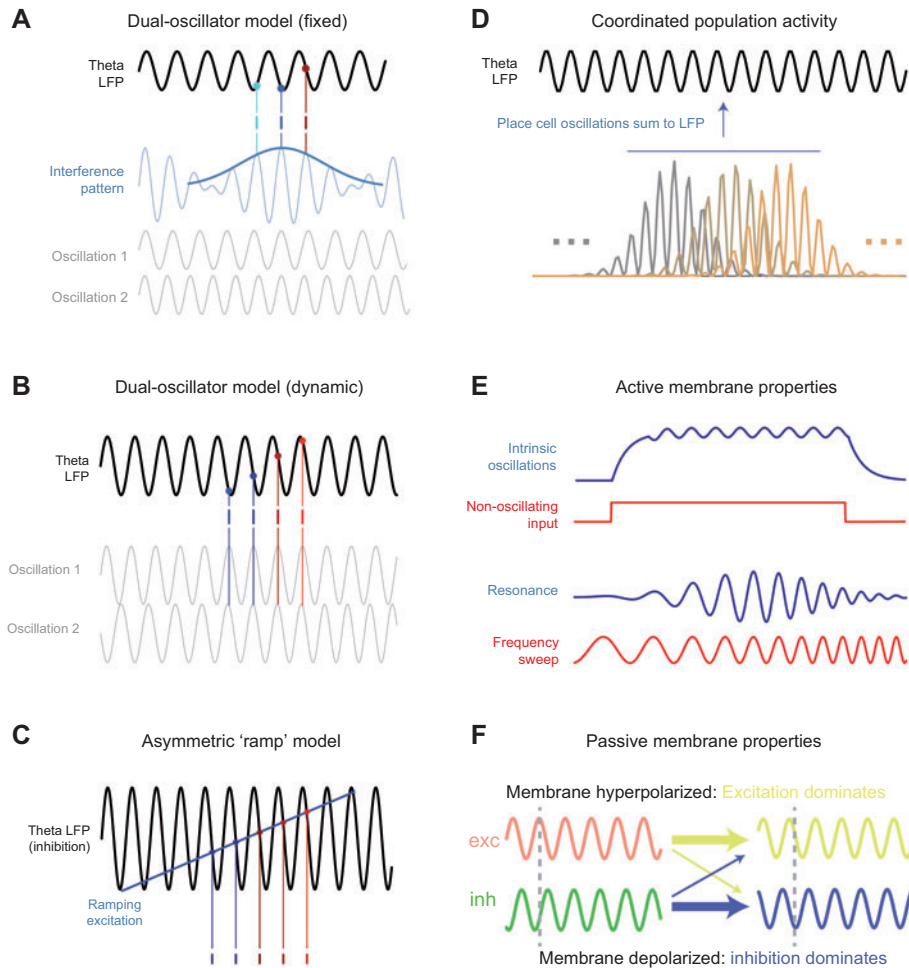


Figure 2 Possible contributions to the generation of theta phase precession.

In the classic dual oscillator model (A; O'Keefe and Recce, 1993), a phase precessing cell receives two oscillating input signals with fixed, but slightly different, frequencies; the slower one of these corresponds to the LFP frequency. When summed, these oscillations generate an interference or 'beat' pattern. Within a beat (indicated by the gaussian firing profile of a putative place cell), the frequency of the interference pattern is faster than that of the LFP, as indicated by the phase precessing spikes (color indicates phase). A variation of this model (B) occurs when one of the oscillations is frequency modulated; in this case, two oscillations can be out of phase outside the neuron's place field but in phase in the place field. As long as both oscillations are faster than the LFP, the resulting spikes will phase precess (Lengyel et al., 2003; Yamaguchi et al., 2007). (C) Asymmetric ramping excitation interacting with rhythmic inhibition at LFP frequency (Mehta et al., 2002). As excitation increases, the LFP phase of the point at which excitation exceeds inhibition precesses. (D) A different view, focusing on the relationship between membrane potential oscillations in place cells (bottom) and the resulting LFP (top). With appropriate offsets between cells, the LFP frequency can be lower than that in any single place cell (Geisler et al., 2010). (E) Active membrane properties can convert a non-oscillating input into an oscillation (top) or filter oscillating input through resonance (bottom). (F) The effectiveness of phase-shifted inhibitory and excitatory inputs depends on the membrane potential, leading to a phase shift as the membrane depolarizes (Leung, 2011).

externally imposed changes in the amplitudes of the input (Magee, 2001), synaptic adaptation (Thurley et al., 2008), or changes in the driving force of excitatory and inhibitory inputs due to depolarization (Kamondi et al., 1998; Leung, 2011). This type of interaction is sometimes referred to as 'somato-dendritic interference' (SDI), in reference to the likely origin of the two component oscillations. However, it is not to be confused with 'dual-oscillator' models in which two different frequencies interact to produce a true interference or 'beat' pattern.

- *Active properties.* Particular types and distributions of voltage-gated channel properties can endow a neuron with

the ability to generate MPOs in response to non-oscillating input and/or to selectively amplify and phase shift particular input frequencies (Leung and Yu, 1998; Hu et al., 2009; Figure 2E). These properties may modulate oscillations that participate in the mentioned models, thereby contributing to phase precession (Leung, 2011).

Phase precession arising from the neuron-to-LFP transformation A different view does not focus on the ways in which a single neuron comes to phase precess given an LFP input but instead asks how the population LFP can result from particular arrangements of individually precessing

neurons. Geisler et al. (2010) showed that the MPOs of a population of place cells can sum to a simulated LFP of a *slower* frequency than any of the individual cells (Figure 2D). This surprising possibility relies on a specific pattern of offsets (temporal delays) between the MPOs of individual place cells, for which there is experimental evidence (Geisler et al., 2010). Thus, this view highlights the fact that because the phase precession effect is about a relationship between spikes and the LFP, contributions to it can occur not just in the transformation from LFP to spikes (as in single neuron models) but also in the transformation from spikes to LFP.

Phase precession arising from network effects

Network-level explanations for theta phase precession do not require single neurons to have specific oscillatory properties but instead rely on synaptically mediated interactions between neurons. A prominent such class of model is based on the so-called attractor network, which conceptualizes hippocampal activity as an ‘activity packet’ that moves around on a two-dimensional surface of place cells (Samsonovich and McNaughton, 1997). This activity pattern represents the rat’s current location, tracking it as the rat moves location as it moves based on sensory input from visual, vestibular, and other systems. Critically, the network is not tied to these inputs but has internal dynamics that allow it to move by itself. For instance, recurrent connections in CA3 are thought to allow the spread of activity in the absence of external input. If these synaptic connections are structured to be asymmetric (i.e., favor a spread of activity corresponding to a forward direction), phase precession can result (Jensen and Lisman, 1996; Tsodyks et al., 1996; Wallenstein and Hasselmo, 1997). This occurs because for place fields corresponding to the rat’s current location, sensory input is largest leading to an early firing phase. Place fields ahead of the animal are less activated by sensory input but more by spreading activation, but because this is delayed by transmission through a chain of place cells, these will fire at a later phase. There is striking evidence that the required asymmetry can develop with experience, at least on one-dimensional tracks (Mehta et al., 1997).

Thus, in summary, a number of mechanisms have been proposed as contributing to phase precession. Following previous reviews (Maurer and McNaughton, 2007; Burgess and O’Keefe, 2011), we distinguish cell-intrinsic and network mechanisms, as well as the mapping from cells to LFP. These mechanisms are not mutually exclusive, and much ongoing experimental and theoretical work attempts to resolve the ways in which they interact (e.g., Navratilova et al., 2011). Here, discussion of these potential mechanisms forms a basis for exploring which of these apply to understanding phase precession beyond the hippocampus.

Functional relevance of phase precession

The possible mechanistic sources discussed in the previous section are agnostic about whether phase precession is *useful* or not. However, several authors have noted that phase precession may be functionally important for some of the known

contributions of the hippocampus to behavior. These ideas, reviewed in this section, are typically embedded in ‘learning and memory’ views of hippocampal function, including spatial navigation and episodic(-like) memory (Redish, 1999; Morris, 2006), rather than in affective processing and sensorimotor views (Gray and McNaughton, 2000; Bland and Oddie, 2001; Bast and Feldon, 2003; Bannerman et al., 2004). These different views of hippocampal function map onto anatomical dissociations between hippocampal aspects, with learning and memory functions primarily associated with the dorsal hippocampus and affective/sensorimotor processing primarily with the ventral aspect (Moser and Moser, 1998; Bast, 2007; Fanselow and Dong, 2010; Figure 3). The focus on learning and memory in functional ideas about phase precession may be justified given the parallel gradient observed in the distribution of theta phase precession, which is more prevalent in the dorsal hippocampus compared with the ventral hippocampus (Royer et al., 2010). However, phase precession is by no means absent from the ventral hippocampus (Kjelstrup et al., 2008; Royer et al., 2010), leaving open the possibility that phase precession may play a role in affective processing as well.

Phase coding

We distinguish three main ideas about how theta phase precession might support what the hippocampus does. The first – phase coding – builds directly on the observation that on the single-cell level, theta phase is related to the animal’s location within a place field (O’Keefe and Recce, 1993). This implies that a decoder receiving hippocampal place cell input could potentially exploit this phase information. In support of this idea, Jensen and Lisman (2000) showed, on the basis of actual recording data, that a decoder that takes the theta phase of each spike into account can obtain a more accurate read-out of the location of the animal compared with a decoder that ignores phase. Thus, in the context of the role of the hippocampus in tasks that require a representation of the animal’s current location (such as homing, shortcut, and allocentric goal finding), the accuracy boost provided by a phase-sensitive decoder could improve performance on navigation tasks.

A requirement for a downstream area to be able to read out the phase code is that it needs to have access to LFP phase (Jensen, 2001; Nadasdy, 2009). An extracellular theta rhythm coherent with hippocampal theta is present in both mPFC (Benchenane et al., 2010) and vStr (Berke et al., 2004), but it is not currently known if areas that receive input from the hippocampus in fact use phase information in this way. However, the idea of phase coding is not limited to improved spatial representation. Experimental demonstrations that rate and phase can be dissociated to a certain degree (Hirase et al., 1999; Huxter et al., 2003) raise the possibility that distinct messages may be coded by rate and phase, respectively (O’Keefe and Burgess, 2005). For instance, in two-dimensional environments, phase information can be used to extract the animal’s direction of travel (Huxter et al., 2008), and on nonspatial tasks, phase can distinguish between the encoding and recall of experience (Manns et al., 2007). Likewise, a number of

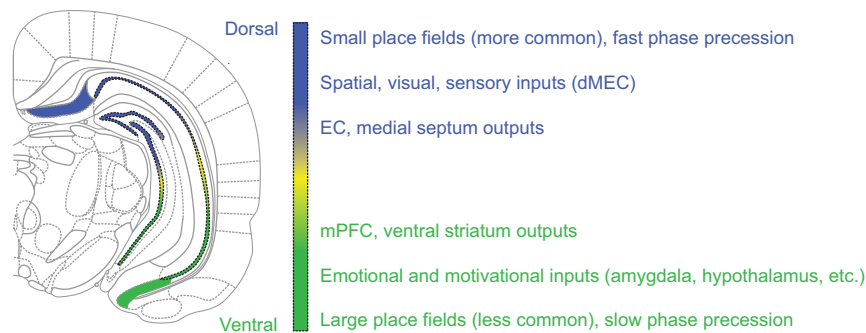


Figure 3 Different aspects of the hippocampus map onto distinct anatomical and functional subsystems.

Theta phase precession follows a gradient from dorsal to ventral in the hippocampus proper, with the proportion and strength of phase precessing cells decreasing toward the ventral aspect (Royer et al., 2010). This organization mirrors the gradual increase in place field size and degradation of the place representation toward the ventral aspect (Jung et al., 1994; Kjelstrup et al., 2008). [It is worth pointing out that the larger size of individual place cells, by itself, needs not imply a less ‘spatial’ code – at the population level, the optimal tuning width depends on factors such as the correlational structure and the time window available for decoding (Pouget et al., 1999; Zhang and Sejnowski, 1999; Berens et al., 2011); however, apart from the larger field size in the ventral hippocampus, there seem to be less neurons with place (and theta) modulation, supporting the notion that the code for place degrades along the dorsal-ventral axis.] In turn, hippocampal dorsal-ventral organization is thought to derive from a comparable gradient from dorsal to ventral medial entorhinal cortex, along which grid cells increase their spacing (Giocomo et al., 2007; Yamaguchi et al., 2007; Blair et al., 2008; de Almeida et al., 2009), as well as from different mixing of medial entorhinal and lateral entorhinal inputs (Amaral and Lavenex, 2006). Corresponding dissociations exist in the functional role of the dorsal, intermediate, and ventral aspects (see, e.g., Bast, 2007; Fanselow and Dong, 2010, for review). Less is known about the subiculum, which receives inputs from CA1 and is a major source of projections to the medial prefrontal cortex (mPFC) and the ventral striatum (vStr). The extent recording data indicate that the dorsal subiculum displays less context dependence than dorsal CA1/CA3 (Sharp, 2006), but to our knowledge, the coding properties of ventral subicular neurons are not known. Figure adapted from Paxinos and Watson (2007).

rate correlates have been identified, including running speed (McNaughton et al., 1983, but see Geisler et al., 2007), features of the environment (O’Keefe and Speakman, 1987; Leutgeb et al., 2005b), and sequential context (Eichenbaum et al., 1999).

Rapid storage of sequential experience

The second idea about the functional relevance of hippocampal phase precession is that it enables the rapid storage of experience. As discussed in the previous section, when viewed at the population level, theta phase precession implies that each theta cycle contains a coherent, compressed sequence of nearby place cells (Dragoi and Buzsáki, 2006; Foster and Wilson, 2007; Maurer et al., 2011). As originally noted by Skaggs and McNaughton (1996), this results in a cross-correlogram peak that depends on the distance between the place fields. This observation is potentially critical given the results on spike-timing-dependent plasticity in the hippocampus. These experiments show that the change in synaptic efficacy between neurons A and B depends on their relative spike timing, such that if A reliably spikes before B, their connection strength is increased, and if, conversely, B spikes before A, their connection strength is decreased (Hebb, 1949). Crucially, the time window for such changes to occur appears to be limited to about 40 ms at most, at least in slice preparations (Bi and Poo, 1998). As illustrated in Figure 4, without phase precession, there would not be much asymmetry in this 40-ms time range in the cross-correlogram between two sequentially arranged place cells, and thus, the resulting increase in synaptic efficacy would be weak. In contrast, with

phase precession, the precise temporal coordination between subsequently arranged place cells creates a large cross-correlogram asymmetry in the spike-timing-dependent plasticity (STDP) range. Thus, the resulting increase in synaptic strength is much larger. Several authors have noted that this combination of temporal coordination within a theta cycle and repeated sequential ordering across theta cycles is well suited to the rapid storage of experience (Yamaguchi, 2003; Buzsáki, 2005; Leibold et al., 2008). Given the well-documented role of the hippocampus in rapid learning in rodents and episodic memory in humans (O’Keefe and Nadel, 1978; Redish, 1999; Morris, 2006), this is a salient point.

The rapid storage view of hippocampal phase precession predicts a relationship between the fidelity or temporal precision of phase precession and subsequent memory. In support of this idea, there is a body of results showing that theta oscillations more generally are related to successful encoding (Sederberg et al., 2003; Rutishauser et al., 2010; Shirvalkar et al., 2010; Addante et al., 2011). To our knowledge, the only study to date to address the relationship between phase precession and memory-dependent performance specifically is that of Robbe and Buzsáki (2009). In this important study, the authors used a cannabinoid to disrupt hippocampal phase precession while leaving place fields stable and intact. Using a hippocampal-dependent delayed alternation task, it was found that the loss of phase precession was correlated with the magnitude of the performance impairment. A possible explanation in line with a role for phase precession in rapid encoding would be that without phase precession, the rats were not able to store the preceding trial for maintenance across the delay. Although other explanations may be consistent with the data also (e.g.,

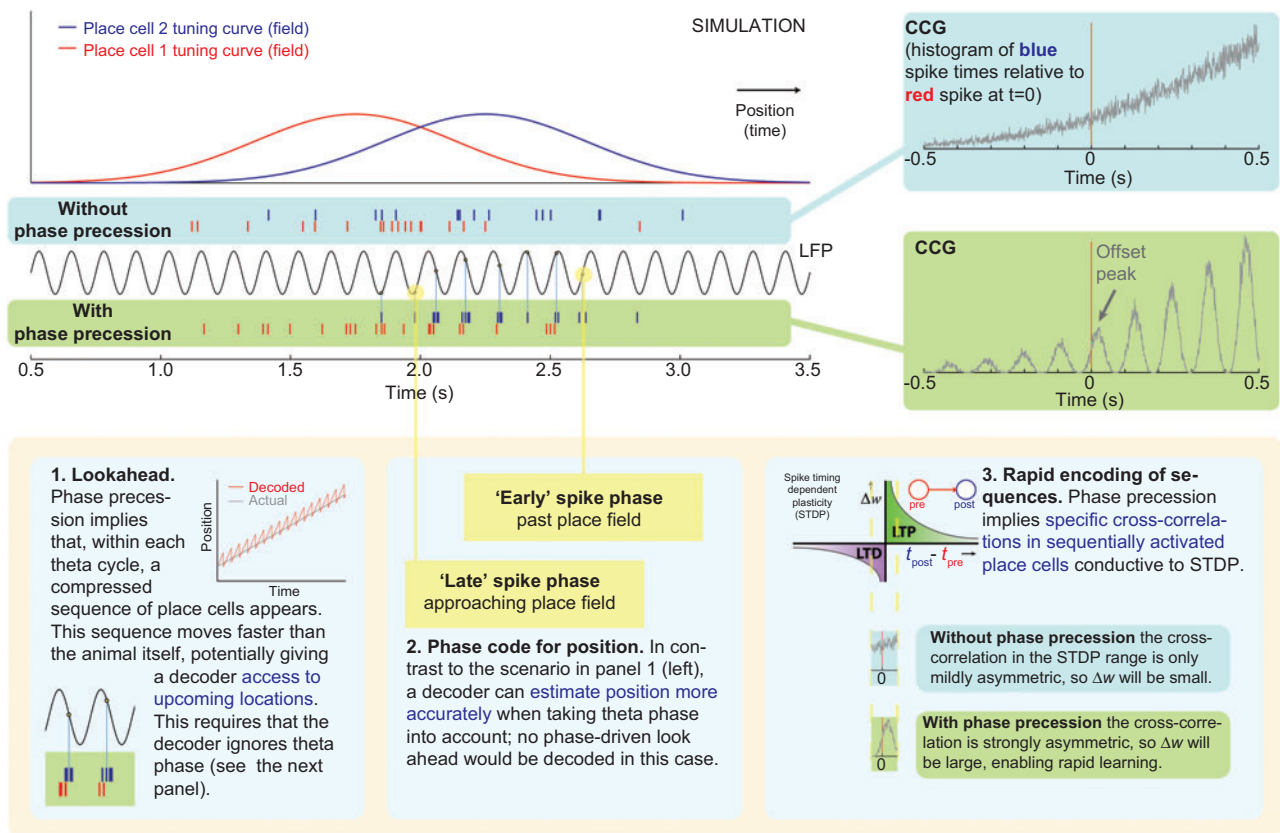


Figure 4 Schematic illustration of possible functional roles of phase precession in the hippocampus: (1) lookahead, (2) phase coding, and (3) rapid learning.

The top left panel shows a simulation of a single run through two adjacent, idealized place cells (from left to right: 'red' place cell followed by 'blue' place cell). In the hypothetical case of *no theta phase precession*, the pattern of spikes during the run would look like that in the blue panel ('without phase precession'). On average, the blue spikes appear later than the red spikes, reflecting the order of the place fields. However, little structure is apparent at a finer timescale: that is, sometimes a blue spike comes before, sometimes after a red spike. This is illustrated by the cross-correlogram (top right 'CCG' panel, computed across many runs), which shows a slow asymmetry of blue spikes relative to red spikes (aligned to $t=0$). This scenario contrasts with phase precession (green panel, 'with phase precession') where a systematic, fine-timescale pattern emerges: the blue spikes tend to come just after the red spikes within each theta cycle. As a result, the cross-correlogram exhibits a peak in the 20-ms range, conducive to spike-timing-dependent synaptic potentiation (green CCG panel). Thus, within a theta cycle, theta sequences form, consisting of a coherent sequence or path of place cells that enables the animal to represent upcoming locations ('lookahead'; lower left panel, Jensen and Lisman, 1996). The phase of each spike contains information about location, a phase code for position (lower center panel, Jensen and Lisman, 2000). Finally, the ordering of spikes within a theta cycle places them in the range of spike-timing-dependent plasticity (STDP; lower right panel, Skaggs et al., 1996).

phase precession may be important for the active maintenance of a previous-trial-dependent state through the delay period, or the rat's ability to recall the previous trial may be impaired, or the hippocampus's ability to synchronize with downstream structures may be affected), this is the first study to link disruption of phase precession to a behavioral deficit.

Despite these suggestive results, it is not immediately clear that the rapid storage of place cell sequences equates to a component of episodic memory. To help bridge this gap, we have noted that hippocampal neurons have nonspatial (or perhaps more accurately, supra-spatial) correlates as well, in line with O'Keefe and Nadel's (1978) original conception of the cognitive map (Leutgeb et al., 2005b; Manns et al., 2007). In humans, hippocampal neurons can have remarkably specific tuning, being activated by the viewing and recall of, for instance, particular features of TV show clips

(Gelbard-Sagiv et al., 2008). Thus, it is conceivable that the episodic encoding of attended experience – which may not be exclusively spatial – leads to sequential activation of hippocampal neurons, potentially subjected to the same phase precession rapid storage benefits as sequences of place cells. Studies examining the structure of nonspatial (Fortin et al., 2002; Ginther et al., 2011) or internally generated (Pastalkova et al., 2008) sequences in the rodent hippocampus, alongside high-resolution imaging and intracranial recording studies in humans (Jacobs et al., 2007; Doeller et al., 2010), have started to bridge this gap.

Lookahead

The final idea about functional relevance of theta phase precession – lookahead – is that it implements a forward-

looking mechanism that may be useful for decision making that relies on the explicit representation of upcoming places or outcomes, that is, planning.¹⁴ Again, this view is in principle agnostic about how this phenomenon is generated. It merely points out that a downstream structure receiving hippocampal inputs (a decoder) could extract position information that periodically (at theta frequency) sweeps ahead of the animal. As discussed in the Temporal Tapestry of Theta Sequences: Phase Precession at the Population Level section, when viewed at the population level, phase precession implies that within each theta sequence, a coherent sequence of place cells is activated. Thus, a simple decoder that does not use theta phase to improve its location estimate but is only sensitive to the identity of the spikes (representing location as the peak of each neuron's place field, for instance) would have access to past locations early in the theta cycle and upcoming locations late in the theta cycle (Jensen and Lisman, 1996; Jensen, 2001). As outlined by Lisman and colleagues, when the animal is at a location corresponding to the center of place cell C, a given theta cycle typically contains the sequence ABCDE, that is, starting some way behind the animal's current location and ending ahead of it.

The ability to represent upcoming locations is potentially useful for a number of behaviors that are known to require the hippocampus. A classic example is the ability to choose a path to an allocentrically defined goal from different starting locations ('locale navigation' in O'Keefe and Nadel, 1978), as occurs in certain Morris water maze protocols (Morris et al., 1982; Sutherland et al., 1987; Pearce et al., 1998) and plus maze probe trials (Tolman et al., 1946b). A related ability is the planning of shortcuts (Tolman et al., 1946a; Alvernhe et al., 2008), although phase precession has not yet been systematically studied in the context of not-yet experienced paths, which occur in the hippocampus during (p)replay events (Dragoi and Tonegawa, 2010; Gupta et al., 2010). As with the rapid sequence storage view, mentioned previously, the lookahead view is in principle not limited to spatial lookahead alone. To the extent that hippocampal neurons can represent nonspatial variables or outcomes, these could participate in lookahead also. In support of this idea, there is evidence from instrumental conditioning (lever pressing) tasks that the hippocampal formation is involved in representing outcome information required for sensitivity to devaluation of the outcome (Corbit et al., 2002), and that anticipatory representations in prefrontal areas depend on the hippocampus (Ramus et al., 2007; Burton et al., 2009). Thus, the known involvement of the hippocampus on tasks that require representations of upcoming paths or outcomes is congruent with the idea that phase precession enables such forward-looking representations.

An obvious limitation of this interpretation is that lookahead deriving from phase precession has a finite range: on

spatial tasks, typically not more than about 50 cm ahead of the animal in dorsal CA1 cells (Foster and Wilson, 2007; Maurer et al., 2011); it is presently unclear if the extended lookahead events observed during theta in dorsal CA3 by Johnson and Redish (2007) are a special case of phase precession. In any case, a well-established result in the reinforcement learning literature is that even limited lookahead is potentially useful, given access to a state value function that estimates the value of states that are not themselves rewarded (Dyna-Q: Sutton, 1990; Sutton and Barto, 1998). On T-mazes, a value function such as the one learned by typical temporal-difference reinforcement learning (TDRL) would back-propagate from the reward sites.¹⁵ Thus, for different reward values at either side of the maze, a limited lookahead would encounter a difference in values if they are sufficiently back-propagated by the TDRL algorithm. Furthermore, to the extent that ventral hippocampal neurons with their larger place fields form coherent theta sequences, the range of lookahead would be correspondingly extended.

Although there is currently little experimental evidence for this particular possible function of phase precession, the possibility of selectively disrupting phase precession (Robbe and Buzsáki, 2009) opens up approaches that could address this issue. For instance, a detailed analysis of behavior including pausing at the choice point (Blumenthal et al., 2011) or comparison of different reinforcement learning model variants to trial-by-trial choice (Samejima et al., 2005; O'Doherty et al., 2007; Huh et al., 2009; Ito and Doya, 2011) could potentially narrow down the precise nature of the behavioral impairment in the Robbe and Buzsáki (2009) study.

Phase precession outside the hippocampus

Given the insights theta phase precession has afforded into the mechanics of hippocampal processing and its potential for functional relevance, it is of interest that theta phase precession extends to at least two of the hippocampus (HC) major afferents: the mPFC and the vStr. It is worth noting from the outset that, because there are currently only two published experimental reports on extrahippocampal theta phase precession, many open questions are not yet explored, and even speculations based on those results will be preliminary because of the limited data. However, because both HC-mPFC and HC-vStr interactions are the subject of rich literature, which has recently benefited from simultaneous multistructure recording studies, even these initial reports on phase precession can be situated in a useful context. With this in mind, we turn first to the main experimental findings on extrahippocampal phase precession.

¹⁴Thus, we distinguish lookahead as only one component of an integrated planning process. Planning requires not just the generation of potential outcomes (lookahead) but also their evaluation and translation to action (van der Meer and Redish, 2010).

¹⁵Briefly, TDRL is a reinforcement learning algorithm that learns which actions to take, based on how well these actions turned out in the past. In order to learn about actions that are not themselves rewarded but contribute to receiving reward later, it computes the values of intermediate (nonrewarded) states: the TDRL value function. For review, see Sutton and Barto (1998), van der Meer and Redish (2010).

Theta phase precession in medial prefrontal cortex

Jones and Wilson (2005a) were the first to report theta phase precession outside the hippocampus. Using a modified T-maze, they found that as animals approached the decision point, theta band coherence between HC and mPFC LFPs increased. Along with this increased coherence, theta phase precession was apparent in mPFC, both in single neuron examples and after averaging all recorded neurons within subjects.¹⁶ It was also possible for phase precession to occur at other points in the track, but the effect was clearest as animals approached the decision point. This decision-point-specific pattern is congruent with emerging literature that theta band coordination between HC and mPFC is important in the selection of appropriate location-specific actions or strategies (Floresco et al., 1997; Benchenane et al., 2010; Hyman et al., 2010; Sigurdsson et al., 2010; Womelsdorf et al., 2010), which would be preferentially manifested at decision points. Thus, given the prominent HC projection to the mPFC (Swanson, 1981; Jay and Witter, 1991; Thierry et al., 2000), a reasonable first explanation for how mPFC phase precession arises is to propose that it simply reflects increased hippocampal drive of mPFC neurons, which inherit the phase characteristics of the hippocampal afferents driving them. This ‘baseline’ account of extrahippocampal phase precession will be a recurring theme, and it suggests that a comparison of hippocampal phase precession with that in extrahippocampal structures is informative in evaluating this explanation.

For instance, as reviewed in the section on single-cell properties of theta phase precession, HC phase precession occurs over a limited range of the theta cycle, especially on a trial-by-trial basis (Figure 1). HC neurons also phase precess with a characteristic speed, which is inversely related to the size of their place field and which decreases along the dorsal to ventral axis. However, Jones and Wilson (2005a) noted that even in individual mPFC neurons, it was possible to observe phase precession that extended over more than a theta cycle (360°). Given the single-trial observations of Schmidt et al. (2009), an analysis of whether this large phase range in mPFC occurs on single trials, or arises because of averaging instead, would be of interest. In principle, however, this extended range would suggest that phase precessing mPFC neurons do not simply transmit ‘copies’ of a particular hippocampal firing pattern. Likewise, the phase precessing mPFC cells in the study of Jones and Wilson (2005a) precessed at a speed comparable with simultaneously recorded dorsal CA1 neurons. This would suggest the possibility that dorsal CA1 neurons

contribute to mPFC phase precession. However, in order to create the observed phase range and spatial distribution of phase precession in mPFC, it would not be sufficient to simply replicate CA1 firing patterns, which are more uniformly distributed over the track rather than focused around the decision point, and have a narrower theta range over which they precess. Although further studies beyond this initial report would be valuable, comparisons such as these illustrate how phase precession in neurons beyond the hippocampus could be used as a tool to infer possible inputs to such neurons; we will return to this point in the Possible Relevance of Ventral Striatal Phase Precession section.

Theta phase precession in the ventral striatum

Recording from the vStr as rats ran a spatial decision task, van der Meer and Redish (2011a) found clear theta phase precession in individual neurons as well as in the population. Strikingly, neurons with a characteristic ‘anticipatory ramping’ firing pattern up to the reward sites (commonly reported in the vStr across different tasks and species; Schultz et al., 1992; Carelli and Deadwyler, 1994; Lavoie and Mizumori, 1994; Hollerman et al., 1998; Miyazaki et al., 1998; Tremblay et al., 1998; Hassani et al., 2001; Cromwell and Schultz, 2003; Daw, 2003; Khamassi et al., 2008) tended to show the strongest phase precession. There were also a few neurons that phase precessed up to the decision point, reminiscent of the mPFC phase precession in Jones and Wilson (2005a). However, a population-level comparison with simultaneously recorded dorsal CA1 neurons revealed a contrast where the CA1 population showed precession throughout the task, but the ventral striatal population only precessed up to the decision point and the reward sites (see Figure 1 for illustrative examples). Thus, ventral striatal phase precession was restricted to a subset of neurons, and this population exhibited task-related firing patterns, apparently associated with the decision point and reward sites – unlike phase precession in dorsal CA1.

By analogy to the mPFC case, it is of interest to determine in what ways vStr phase precession is similar or different to that in the hippocampus. van der Meer and Redish (2011a) noted that the phase range over which vStr cells precessed was similar to that of hippocampal cells (close to 360° when averaged over multiple passes); however, this range was 180° out of phase with the simultaneously recorded dorsal CA1 population. Royer et al. (2010) recorded phase precessing cells in ventral hippocampus (CA3) and found that the phase range of these cells was similarly 180° out of the phase relative to dorsal hippocampal phase precession. Taken together, these results suggest that in accordance with the predominantly ventral hippocampal origin of the HC–vStr projection (for recent reviews, see Haber, 2009; Humphries and Prescott, 2010; Sesack and Grace, 2010), and the approximately 180° phase shift in dorsal and ventral theta (Lubenov and Siapas, 2009), theta phase precession in the ventral hippocampus and the vStr occurs over a similar range. As in the mPFC case, this similarity likely reflects the contribution of phase precessing hippocampal input to vStr.

¹⁶Note that in this study, as well as in the ventral striatal phase precession discussed in the next section, phase precession was typically considered relative to the hippocampal theta rhythm. Theta can be recorded locally from mPFC and vStr but is typically smaller in amplitude than the theta recorded from the hippocampal fissure, such that phase precession is clearer when the HC LFP is used. However, in line with the theta coherence observed between HC and the extrahippocampal phase precessing structures, van der Meer and Redish (2011a) showed that ventral striatal phase precession is also apparent relative to the ventral striatal theta rhythm.

A further notable property of the phase precessing ramp cells in the study of van der Meer and Redish (2011a) arose because of the structure of the task, which had multiple reward sites. The majority of ramp cells showed a larger (higher firing rate) ramp up to the first reward site and a smaller (lower firing rate) ramp up to the second reward site, even though the rewards delivered at these sites were similar (two 45-mg food pellets). Yet, in both ramps, phase precession occurred over a similar range of the theta cycle. Thus, theta phase was dissociable from firing rate, raising the possibility that temporal and rate codes in vStr can carry independent messages. In the context of hippocampal place cells, Huxter et al. (2003) proposed that theta phase could code for position (progress through the place field), leaving firing rate free to code for other variables such as running speed or more ‘episodic-like’ properties such as the presence or absence of particular objects or other features of the environment (O’Keefe and Speakman, 1987; Leutgeb et al., 2005b). Although at this time, we can only speculate, the observed rate/phase dissociation in ventral striatal ramp cells is consistent with a similar dual coding scheme: for instance, theta phase could indicate distance from a reward site, with firing rate indicating the expected value of the reward. This idea could be tested by recording the activity of phase precessing ramp neurons in a task that systematically varies distance to reward and reward value.

Thus, although the properties of single-cell theta phase precession in mPFC and vStr have similarities with that in hippocampal cells, at the population level, there are clear differences. In particular, extrahippocampal phase precession does not appear to be uniformly distributed over space on T-maze tasks but rather is specifically associated with decision points and reward sites. Hence, to the extent that hippocampal inputs to mPFC and vStr shape theta phase precession, some degree of selection or modulation of that input has to take place. We expand on this ‘selective inheritance’ interpretation in the Possible Mechanisms for Ventral Striatal Theta Phase Precession section.

Anticipatory ramp cells in the ventral striatum

The strong association of ventral striatal phase precession with a particular ‘anticipatory ramp’ firing pattern suggests that its mechanisms and functional relevance are somehow intertwined with the properties of these cells. What could these ventral striatal ramp cells be coding for? The intuitive interpretation that they reflect anticipation of aspects of reward has generally been upheld by the data, although many open questions remain. A series of studies by Schultz and colleagues using reaching tasks in monkeys revealed a variety of reward-related signals throughout the striatum, including ramp-like activity up to reward delivery in vStr (Apicella et al., 1991; Schultz et al., 1992; Hollerman et al., 1998; Tremblay et al., 1998; Hassani et al., 2001; Cromwell and Schultz, 2003; Cromwell et al., 2005; see Tremblay et al., 2009, for a recent review). Of course, these tasks are very different from the rodent T-maze where ventral striatal phase precession was originally found; thus, even quite apart from biological primate/rodent differences, the activity of ventral

striatal cells in primate reaching tasks may not be comparable with those in van der Meer and Redish (2011a). However, there are striking similarities between the ramping signals observed in primate and rodent vStr (Carelli and Deadwyler, 1994; Miyazaki et al., 1998; Carelli et al., 2000; Daw, 2003; Mulder et al., 2005; Khamassi et al., 2008; van der Meer and Redish, 2009). In particular, the properties of ventral striatal ramp cells can be summarized with a few key properties: (1) ramp cell activity can distinguish between the predicted amount; (2) the identity of reward outcomes; (3) this activity cannot be explained by potential covariates such as chewing or other anticipatory movements; and (4) there appears to be a distributed code for reward value, with some neurons ramping more (higher activity) as rewards get smaller. There are also examples of ramping up to instruction and trigger cues, which are not themselves rewarded but may function as conditioned reinforcers.

How might anticipatory ramp cells in vStr contribute to behavior?¹⁷ Not unlike current theories of ventral striatal function more generally, distinct contributions to learning and ongoing behavior can be discerned (van der Meer and Redish, 2011b). In particular, it has been suggested that ramping activity in vStr reflects a state value signal as would be expected from TDRL algorithms (Daw, 2003; Khamassi et al., 2008; van der Meer and Redish, 2011a). By assigning values to intermediate states (such as conditioned reinforcers), which are not themselves rewarded, agents can learn relationships between actions, which are temporally distant from resulting outcomes (i.e., solve the credit assignment problem). Placing this state value signal in vStr is consistent with a body of anatomical, lesion, and functional magnetic resonance imaging (fMRI) evidence (see Bornstein and Daw, 2011; Ito and Doya, 2011; van der Meer and Redish, 2011b, for recent reviews) and the known role of vStr modulating dopamine neuron activity in response to rewards (Tremblay et al., 2009; Sesack and Grace, 2010). The activity of ramp cells maps well onto the expected firing pattern of state value functions, including the higher firing rate up to the first reward compared with the second in van der Meer and Redish (2011a). However, when Khamassi et al. (2008) explicitly compared predictions of TDRL to ramp cell firing, they found significant deviations. For instance, when animals were scheduled to receive a number of rewards in sequence, anticipatory firing differed widely between identical rewards. A possible explanation advanced by Khamassi et al. (2008) was variability in the input state to the model algorithm, that is, the rats were uncertain about how many rewards they could expect. Other possibilities could include the idea that value in ramp cells is encoded in a distributed manner not just across values and outcomes, as reviewed in the preceding section, but also across states: in this scenario,

¹⁷ We note that anticipatory ramp-like signals have been observed in multiple other brain areas, often with anatomical links to the ventral striatum, such as the dorsomedial prefrontal cortex, the dorsal raphe, the ventral tegmental area, and even the ventral hippocampus. The issue of how the contributions of these areas within an interconnected network might be disentangled is beyond the scope of this review; for ideas, see, for example, Hare et al. (2008); Roesch et al. (2010); Salzman and Fusi (2010).

a given ramp cell would contribute to value coding only in a subset of states. Another idea is that the ramp cell signal does not exclusively reflect past, cached values as in TDRL, it also contains a contribution from current motivational (incentive) processes. Such a function is in line with the known role of vStr in invigorating or energizing ongoing behavior, either generally or directed toward specific cues or outcomes (Ikemoto and Panksepp, 1999; Cardinal et al., 2002; Wise, 2006; Berridge, 2007; Nicola, 2007; Salamone et al., 2007), the fact that anticipatory ramping appears to be observed toward specific outcomes, as well as more generally, suggests that ramp cells may instantiate a component of this vStr function. Although there have been few reports linking the activity of ramp cells specifically with behavior (but see Tremblay et al., 1998), in human fMRI studies, there is now a substantial body of work implicating reduced vStr reward anticipation in neurological disorders such as attention deficit hyperactivity disorder and addiction (Scheres et al., 2007; Beck et al., 2009; Peters et al., 2011).

Thus, a speculative function is emerging for ramp cells in supporting learning and performance functions in motivated behavior. In the Possible Relevance of Ventral Striatal Phase Precession section, we develop the idea that theta phase precession in these cells not only can be a useful tool in exploring this idea but may also be functionally important. To set the stage, we first turn to the possible mechanisms for ventral striatal phase precession.

Possible mechanisms for ventral striatal theta phase precession

As reviewed in the Models of Phase Precession section, a number of mechanisms have been proposed for the *de novo* generation of theta phase precession in the hippocampus. Recall that these include (1) modification of LFP frequency input(s) by single neurons into a faster oscillation, (2) a population of oscillating neurons summing to a slower LFP, and (3) spread of activity through network mechanisms. In addition for extrahippocampal phase precession, there is potential for (4) selective inheritance of hippocampal phase precession patterns. We consider these possibilities in turn.

Single-neuron contributions Intracellular recordings from medium spiny neurons (MSNs, the striatal projection neuron making up ~90% of neurons) have reported theta oscillations in the membrane potential (Leung and Yim, 1993; O'Donnell and Grace, 1993) that persisted even after inactivation of hippocampal input (O'Donnell and Grace, 1995). However, the magnitude of low threshold spikes and after hyperpolarizations in MSNs (possible mechanisms for the intrinsic generation or sustaining of membrane oscillations; O'Donnell and Grace, 1993) were found to be (1) insufficient to sustain intrinsic oscillatory activity and (2) absent from those cells that showed theta oscillations. Thus, O'Donnell and Grace (1995) concluded there is little evidence for intrinsic generation of theta activity in MSNs. Similarly, intracellular recordings from striatal fast-spiking interneurons (FSIs) revealed no evidence for intrinsic membrane

properties conducive to theta generation, although clear gamma oscillations were found upon depolarization (Taverna et al., 2007). Thus, so far, there seems to be little positive evidence for the intrinsic generation of theta oscillations in ventral striatal neurons as required by some phase precession models.

In the absence of internally generated theta oscillations, single vStr neurons could contribute to phase precession by operating on theta-modulated inputs. Theta components are present in the ventral striatal LFP (likely reflecting contributions from hippocampal and prefrontal inputs, although the decisive experiments have not been done), as well as in MSN and FSI spiking (Berke et al., 2004; Berke, 2009; Gruber et al., 2009; Lansink et al., 2009; van der Meer and Redish, 2011a). This means that in principle, asymmetric ramping and SDI could contribute to ventral striatal phase precession. However, the asymmetric ramping model predicts a tight rate-phase relationship, incompatible with the clear dissociation in the data (van der Meer and Redish, 2011a). To our knowledge, the possibility of SDI in striatal MSNs, deriving from the conjunction of perisomatic FSI-MSN inhibition (Tepper et al., 2008) and dendritic excitation with different theta phases, has not yet been examined. Given the extensive differences in the physiology and morphology of neuronal, synaptic, and network organization between the hippocampus and the striatum, it seems unlikely that large, local contributions to theta phase precession exist in the vStr.

Population contributions to the LFP The idea that fast-oscillating phase precessing neurons can organize such that a slower LFP results could apply to vStr. It is currently unknown if vStr phase precessing cells display the required organization, but in any case, this contribution does not address how rhythmic spiking itself is generated.

Network effects Striatal MSNs send relatively sparse GABAergic collaterals to other MSNs, as well as to FSIs, which in turn broadly and powerfully inhibit nearby MSNs (Taverna et al., 2007; Tepper et al., 2008; Berke, 2011). Network explanations of phase precession rely on a coherent ensemble representation (e.g., of space, as in the hippocampus) with internal dynamics. Studies of ventral striatal ensemble recordings revealed little support for a coherent representation of space (van der Meer et al., 2010a), although this does not exclude the existence of a representation for other motivationally related variables. The degree to which ventral striatal representations exhibit internal dynamics is an issue of interest for future work.

Selective inheritance Thus, noting that certain ventral striatal contributions to 'locally generated' phase precession appear possible in principle, there is currently little evidence that this in fact occurs. Given that vStr receives prominent input from the hippocampus, of which at least some proportion of cells likely already displays phase precession, the most straightforward explanation of ventral striatal phase precession appears to be 'selective inheritance'. In fact, as a site of convergence, the ventral striatum receives projections

from multiple areas known to exhibit theta oscillations, including the hippocampus (Buzsáki, 2002), the prefrontal cortical areas (Jones and Wilson, 2005b; van Wingerden et al., 2010), the amygdala (Paré, 2002; Seidenbecher et al., 2003), the ventral tegmental area (Kocsis et al., 2001), and the dorsal raphe (Kocsis and Vertes, 1992). It is also notable that the medial septum, a structure known to provide an important theta input to the hippocampus (Petsche et al., 1962; Brandon et al., 2011; Koenig et al., 2011), is physically adjacent to the vStr, and thus, volume conduction from this area could contribute to ventral striatal theta. Although it is possible that theta-modulated inputs from all these sources contribute to ventral striatal theta, there are several indications that the hippocampal input in particular is a major contributor. In line with the prominent projections from multiple hippocampal subfields (CA1, subiculum, and EC; Groenewegen et al., 1987, 1999; Brog et al., 1993; Finch, 1996; Voorn et al., 2004; Haber, 2009; Humphries and Prescott, 2010; Sesack and Grace, 2010), theta LFP oscillations and spiking activity in the vStr cohere with simultaneously recorded hippocampal activity in a task-related manner (Martin and Ono, 2000; Tabuchi et al., 2000; Goto and O'Donnell, 2001; Martin, 2001; Gruber et al., 2009; Lansink et al., 2009; van der Meer and Redish, 2011a). Furthermore, ventral striatal neurons participate in off-line 'replay' events generated by the hippocampus (Pennartz et al., 2004; Lansink et al., 2008, 2009), and stimulation of the (ventral) hippocampus results in vStr-mediated dopamine release (Blaha et al., 1997; Floresco et al., 2001). Thus, it is no surprise that vStr would 'inherit' phase precessing activity from hippocampal inputs.

In line with this inheritance scenario, van der Meer and Redish (2011a) found that theta phase precession in single ventral striatal neurons had striking similarities to phase precession in ventral CA3 neurons (Royer et al., 2010). In particular, ventral hippocampal cells start and end their phase precession 180° out of phase relative to dorsal hippocampal cells (Lubenov and Siapas, 2009; Royer et al., 2010); although van der Meer and Redish (2011a) did not record in ventral hippocampus, the phase precessing cells in vStr precessed over the same theta phase range as ventral hippocampal cells (Supplementary Information in Royer et al., 2010). However, the strongly nonuniform distribution of ventral striatal phase precession across the track (van der Meer and Redish, 2011a) suggests that it may not be a verbatim copy of (ventral) hippocampal input.¹⁸ Instead, the projection from hippocampus to vStr may selectively emphasize or de-emphasize particular phase precessing inputs in a flexible manner, driven by dopaminergic modulation of synaptic plasticity; we discuss this 'selective inheritance' idea in more detail in Possible Relevance of Ventral Striatal Phase Precession section. First, however, we situate it in the context of current thinking about the role of the hippocampal-ventral striatal projection in behavior.

¹⁸It is notable that the subiculum, and especially its ventral aspect, is a major hippocampal source of ventral striatal inputs (Haber, 2009; Humphries and Prescott, 2010; Sesack and Grace, 2010); yet, it is relatively understudied in comparison with other hippocampal subfields.

Functional contributions of hippocampal inputs to the ventral striatum

Context and place in the hippocampus

The prevailing view on the role of hippocampal inputs to the vStr is that information about place and context from the hippocampus modulates or gates ventral striatal contributions to behavior (Whishaw and Mittleman, 1991; Mizumori et al., 1999; Johnson et al., 2007; Gruber et al., 2009; Grace, 2010). Recording studies have demonstrated in rich detail that the hippocampus represents both location within a context and the context itself (Figure 5). This idea is congruent with abundant, although not always straightforward to interpret, behavioral evidence that inactivations of the hippocampus (1) impair the ability to discriminate between contexts (Jeffery et al., 2004; Maren, 2008; Nadel, 2008) and (2) interfere with tasks that rely on location information, such as navigating to an allocentrically defined goal or home base (Redish and Touretzky, 1998; Whishaw et al., 2001; Jeffery and Etienne, 2004).

The debate about what exactly constitutes a context and under what conditions context vs. discrete cues dominate (e.g. Holland and Bouton, 1999; Nadel, 2008) is beyond the scope of this review. However, it is important to point out that recent converging evidence indicates context representations in the hippocampus are complex and dynamic – even changing while an animal is in a given environment. The hippocampus can treat two contexts as the same or different depending on training history (Leutgeb et al., 2005a; Fuhs and Touretzky, 2007; Colgin et al., 2010), currently active strategy (Rosenzweig et al., 2003; Eschenko and Mizumori, 2007; Jackson and Redish, 2007), and motivational state (Kennedy and Shapiro, 2009). Hippocampal context representations can switch after unsignaled changes in reinforcement contingencies (Smith and Mizumori, 2006; Fenton et al., 2010; Kelemen and Fenton, 2010) or perhaps, most simply, between left and right runs on a linear track (McNaughton et al., 1983; Figure 5B). To the extent that these hippocampal representations affect ventral striatal processing (an issue discussed in latter part of this article), it will be important to take into account an expanded notion of 'context' as suggested by these hippocampal ensemble dynamics.

Context and place gate ventral striatal processing

The two distinct but related views of hippocampal information representation – place and context – have resulted in similarly distinct, not mutually incompatible, views of how this information may be used by the vStr. The first view relies on representation of specific places within an environment. This is thought to be important in foraging settings, where animals need to learn and recall associations between particular places in an environment and rewards. Experimentally, a popular task that relies on this kind of association is CPP. In a representative setup, animals learn that a particular chamber within an environment is associated with reward, as exhibited by an

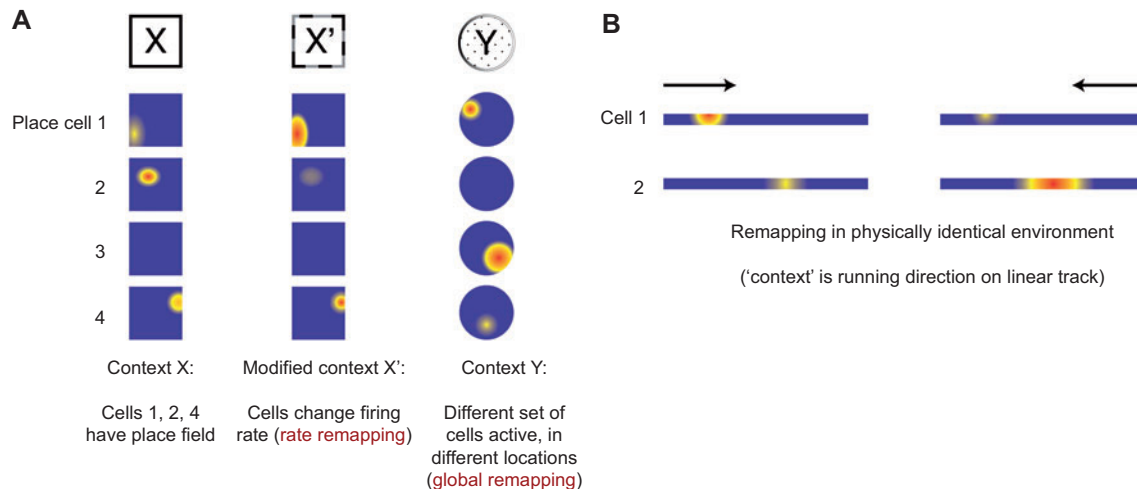


Figure 5 Representations of place and context in the hippocampus.

(A) The hippocampal code for place recruits a specific set of neurons for a given context or environment, such as a square box (context X). Each neuron that participates in the 'map' for this context has a spatially tuned receptive field ('place field', red indicates elevated firing rate, blue indicates zero), such that together, these place cells represent the organism's location within this context. (For instance, if place cells 1 and 2 were simultaneously active, this would indicate the animal is likely to be at the location where the two cells' fields overlap.) When the organism is returned to this environment at some later time, the same set of place cells will be active at the same locations in the environment: the hippocampus recalls the same 'map'. Minor changes in the environment (context X') can result in changes in firing rate ('rate remapping', Leutgeb et al., 2005b). Major changes in the environment (context Y) results in a different set of place cells being active ('global remapping'). Thus, the hippocampus represents context, as well as the animal's place within it, using the same population of neurons. In decoding which context an animal is in based on hippocampal firing patterns alone, no single place cell provides sufficient information. Rather, the combination of which place cells are active together for a given location distinguishes the context (Jeffery et al., 2004). (B) Remapping can also occur without changes in the environment, but as a function of the animal's internal segmentation of it. Here, left and right runs on a linear track result in remapping (McNaughton et al., 1983).

increased amount of time spent at the rewarded location (the place preference). Using this type of setup, Ito et al. (2008) showed that a functional connection between the hippocampal formation and the vStr (specifically, the nucleus accumbens shell) is required for CPP.¹⁹ Rats with disconnection lesions showed reduced preference for the rewarded chamber of a multicompartament apparatus. Similarly, Floresco et al. (1997) found that disconnection of the ventral subiculum (vSub) and vStr impaired rats' ability to collect rewards on the radial arm maze.²⁰ Thus, these studies offer direct support for a role of the HC-vStr projection in behavior requiring associations between places and rewards.

The second view of HC-vStr interactions is that representation of context in the hippocampus allows the vStr to respond differentially to context itself and to discrete cues with context-specific motivational relevance. This process

¹⁹It is important to note that the hippocampal dependence of CPP is not universal but a function of the types of cues (discrete, contextual, internal) that can be used to define the preferred location; see, for example, Ferbinteanu and McDonald (2001).

²⁰A surprising result in this study is that on a delayed version of the task, HC-vStr disconnections no longer impaired performance, even though both bilateral HC and bilateral vStr lesions separately did result in impairments. As noted by the authors, a possibility is that the recruitment of mPFC in the delayed task allows for an indirect functional connection between HC and vStr through the mPFC.

does not use information about specific locations within an environment but instead uses the identity of the context as a modulator or gate on ventral striatal processing. This type of arrangement is thought to underlie the role of hippocampal-ventral striatal interactions in context-specific drug sensitization and reinstatement (Crombag et al., 2008; Lodge and Grace, 2008), an important translationally relevant model to which we will return in more detail in the latter part of this article. This role is conceptually similar to the role of the hippocampus in contextual fear conditioning, which is thought to rely on context representations in the hippocampus to modulate processing in the amygdala (Anagnostaras et al., 2001); a major difference is that the HC-vStr projection connects context representations to the mesolimbic dopamine pathway (Floresco et al., 2001; Grace, 2010; Sesack and Grace, 2010), a possible avenue for hippocampal context representations to powerfully modulate learning and behavior. Studies documenting the 'gating' or 'switching' effects of hippocampal inputs on individual ventral striatal neurons (O'Donnell and Grace, 1995; Mulder et al., 1998; Goto and Grace, 2008) provide elements of a physiological implementation of this idea.

Most relevant to context-dependent interactions between the hippocampus and the vStr is the phenomenon of context-dependent reinstatement or relapse (Crombag et al., 2008). In an illustrative setup, the subject (typically a rodent) learns

to lever press for an appetitive reward in context A. Upon transferring the animal to a novel and distinct context B, some nonzero amount of lever pressing is observed; however, in context B, lever presses are not rewarded, and lever pressing will extinguish. When the animal is returned to context A, lever pressing is reinstated or renewed. This scenario is similar to what in the addiction literature is referred to as 'relapse', which represents a serious limitation to many current treatments of substance dependence. These may initially appear successful – mirroring the extinction phase in context-dependent reinstatement – but, in general, there is substantial incidence of relapse, to which contextual cues are thought to be a contributing factor (Conklin, 2006). The role of the vStr in driving the reinstatement for drug rewards is well established in a number of settings, including relapse driven by context (Crombag et al., 2002; Bossert et al., 2007; Chaudhri et al., 2010). Given the context dependence of reinstatement and relapse, a likely source of contextual information is the hippocampus. In support of this idea, lesions of the dorsal hippocampus interfere with the context-dependent reinstatement of cocaine seeking (Fuchs et al., 2005). The ventral hippocampus, including the ventral subiculum, is also implicated in reinstatement for drug rewards (Vorel et al., 2001; Rogers and See, 2007), an effect that may be context dependent (Lasseter et al., 2010). Thus, noting caveats that testing for effects of context is not always straightforward (Holland and Bouton, 1999; Maren, 2008; Nadel, 2008), there is evidence that context-dependent reinstatement and relapse depends on an interaction between the hippocampus and the vStr.

The given view conceptualizes the HC-vStr interaction as a conditioned association between places (in HC) and rewards (in vStr) or context (in HC) and rewards. There is, however, also evidence that the HC-vStr projection plays a role in unconditioned behaviors. Given the connectivity of the ventral hippocampus with brain areas involved in unconditioned defensive behaviors and discrete cue associations, the effects of ventral hippocampal inactivation or stimulation are likely not exclusively context specific (Bannerman et al., 2004). For instance, stimulation of the ventral hippocampus leads to a general increase in locomotor activity, an effect that can be prevented by inactivation of the vStr (Lodge and Grace, 2008). Thus, the known role of the ventral hippocampus in mediating general, rather than context- or place-specific affective states, suggests that hippocampal inputs to vStr likely include not only context or place information but also information reflecting the animal's current motivational state. This view raises an interesting disconnect: almost without exception, the recording work on which the 'place/context' view of the hippocampus is based has been done in the dorsal hippocampus. Compared with ventral hippocampal areas, the dorsal hippocampus sends relatively minor projections to the vStr; future work in this direction is required to establish if the hippocampally centered view that the ventral areas are less spatial/contextual, and the subcortically centered view that hippocampal inputs are a source of spatial/contextual information, are compatible.

Possible relevance of ventral striatal phase precession

Leaving aside the gaps in our understanding of representation in ventral hippocampal areas, we are in a position to speculate about the possible relevance of ventral striatal phase precession. The discussion mirrors that of the earlier section outlining the reasons for interest in hippocampal phase precession, with its two broad answers: (1) ventral striatal phase precession is a useful tool, particularly for revealing cross-structure connectivity, and (2) it may be functionally important for coding, rapid learning, and/or planning.

Ventral striatal phase precession as an experimental and theoretical tool

With respect to phase precession as a tool, to the extent that phase precession is hippocampally derived (as argued in the Possible Mechanisms for Ventral Striatal Theta Phase Precession section), ventral striatal phase precession effectively 'tags' ventral striatal neurons as receiving hippocampal input. Furthermore, because the properties of phase precession in the hippocampus – the subiculum excepted – are relatively well known, the specific pattern of phase precession in vStr allows inferences about the likely source of the hippocampal input. For instance, imagine a random set of hippocampal neurons, with place fields and phase precession distributed over the task, were to provide input to a ventral striatal neuron (Figure 6A,B). In this scenario, the resulting phase precession pattern in the vStr neuron would look relatively disorganized (Figure 6B). Systematic phase precession up to the reward sites (van der Meer and Redish, 2011a) could not result from such a collection of random hippocampal inputs with distributed fields and phase precession; instead, such organization suggests inputs from a highly specific set of hippocampal neurons, perhaps as a result of reward-driven learning (Figure 6C). This is the 'selective inheritance' idea (see the Possible Mechanisms for Ventral Striatal Theta Phase Precession section). Thus, it would be of interest to track the development of ramping activity and phase precession in ventral striatal neurons on a spatial task, because this example illustrates that it might be possible to infer some properties of learning in hippocampal-ventral striatal synapses, which are known to exhibit long-term potentiation (LTP) (Boeijinga et al., 1993).

Because the speed and range of phase precession in hippocampal place cells are readily extracted from the data, it seems possible to incorporate phase precession into a network model of hippocampal-ventral striatal projection. Such models could make quantitative predictions of what output patterns of phase precession would result from particular input distributions; especially when inputs from multiple areas are combined, which may be precessing at different rates and phases (Lubenov and Siapas, 2009; Royer et al., 2010), the output may not be intuitive. From a functional perspective, such models could test how particular learning rules (such as spike-timing- and/or dopamine-dependent rules proposed for the striatum; Houk et al., 1995; Izhikevich, 2007) might support the proposed reinforcement learning functions of the

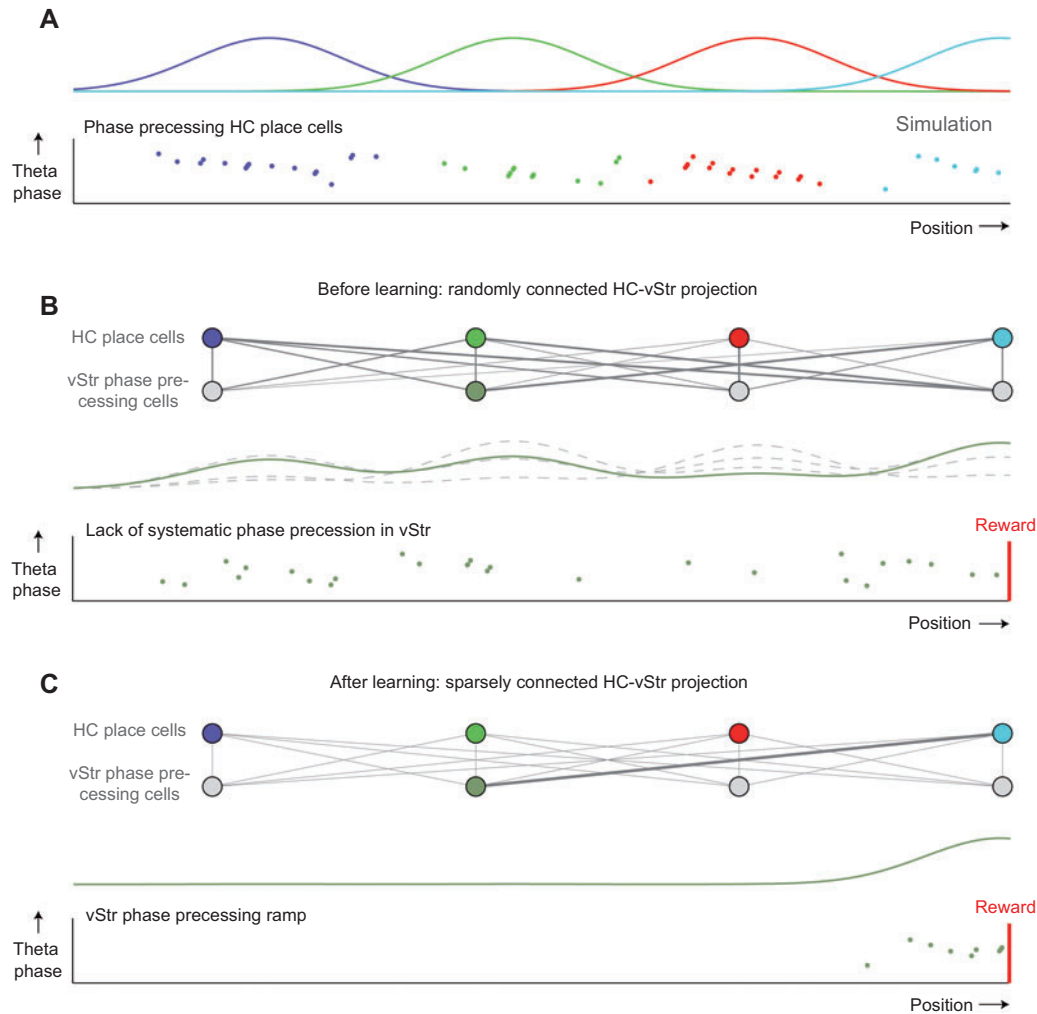


Figure 6 Schematic of hypothesized hippocampus (HC)-ventral striatum (vStr) interactions during learning, illustrating how ventral striatal phase precession can reveal the pattern of hippocampal inputs to a ventral striatal neuron.

(A) Spatial tuning curves ('place fields') of four hippocampal place cells arranged on a linear track, along with a sample phase precession pattern as the animal runs along the track from left to right. (B) Model network with randomly weighted, all-to-all connectivity between the four place cells in panel (top row) and putative ventral striatal cells (bottom row). Random connectivity results in diffuse ventral striatal activity along the track; highlighted is the tuning curve of a single vStr neuron (dark green line and spike phase plot). Because this neuron's activity is driven by a combination of different phase precessing place cells, its spatial tuning curve is relatively nonspecific and its pattern of phase precession erratic. This scenario may correspond to a naive animal first introduced to an environment. (C) As the animal learns about reward locations, a three-factor learning rule that depends on hippocampal, ventral striatal, and dopamine activity may strengthen specific HC-vStr synapses. As a result, after learning, the vStr neuron's firing and phase precession pattern over the track changes from spatially diffuse to systematic ramping: it selectively inherits a particular phase precession pattern.

vStr. By using spatial tasks, the phase precession effect can be exploited to reveal the dynamic relationship between place and context signals in the hippocampus and reward-related signals in the vStr.

Rapid learning and ventral striatal phase precession

With respect to the possible functional importance of ventral striatal phase precession, we consider the same three possibilities supported by hippocampal phase precession: rapid sequence learning, phase coding, and planning or lookahead. A translation of the rapid learning view applied to vStr would

hold that vStr phase precession contributes to changes in the efficacy of HC synapses onto that particular neuron.²¹ As with intrahippocampal phase precession, in this scenario, cross-

²¹By analogy to hippocampal subfield CA3 and its recurrent connections, we might entertain the possibility that phase precession contributes to intra-vStr plasticity; however, given the very different nature of MSN-MSN and FSI-MSN interactions (see, e.g., Berke, 2011, for a recent review) compared with the hippocampus, this seems far-fetched at this time. A first step in this direction would be to establish whether ventral striatal phase precessing neurons form coherent theta sequences.

structure phase precession, by virtue of sequence compression and repetition with theta cycles, would lead to rapid encoding of experience. In other words, those HC neurons that phase precess with the appropriate time delay and speed will increase their synaptic strength onto the vStr neuron more rapidly than without phase precession. This would require the existence of an appropriately spike-timing-dependent modulation of synaptic strength; it is known that the HC-vStr pathway exhibits NMDA receptor-dependent LTP (Boeijinga et al., 1993), but to our knowledge, there has been no demonstration of STDP.

A rapid learning role for ventral striatal phase precession is of relevance to acquisition of place-reward and context-reward associations. Recall that the hippocampus appears to code both contexts and locations within it by activating a unique combination of place cells to each location (Context and Place in the Hippocampus section and Figure 5). As an animal moves through a particular environment (spatial context), phase precession ensures that place cells representing nearby locations are bound together through STDP (see the Temporal Tapestry of Theta Sequences: Phase Precession at the Population Level section). Ventral striatal phase precession suggests that anticipatory ‘ramp’ neurons participate in these sequences, and thus, that hippocampal place and context representations become associated with ventral striatal ramp neurons. For this scenario to work, the ventral striatal neuron would have to be appropriately theta modulated already, even before learning has taken place. A possibility for realizing this is that some vStr neurons receive a baseline amount of input sufficient to generate theta modulation and/or phase precession, leaving room to modulate synaptic strength up and down in an experience-dependent manner. As discussed in the Possible mechanisms for Ventral Striatal Theta Phase Precession section, there are a number of possible inputs that could provide such a signal; however, the real test would be to ask whether ventral striatal neurons are theta modulated or even phase precessing before learning of place- or context-reward associations has taken place.

How might this rapid learning role for ventral striatal phase precession elucidate the mechanisms underlying context-dependent reinstatement? Notably, a single pairing of context and drug reward is sufficient to evoke long-lasting context-dependent relapse (Ciccocioppo et al., 2004). This is suggestive of a rapid encoding and storage process of the kind that phase precession has been proposed to enable (Functional Relevance of Phase Precession section). Furthermore, using a procedure similar to context-dependent relapse, context-dependent sensitization to cocaine. Koya et al. (2009) demonstrated that sensitization in a particular context is mediated by a sparse population of ventral striatal neurons: selectively inactivating those neurons that were activated in a specific context abolished sensitization in that context. Thus, context-specific neural ensembles linked to particular behaviors form in the vStr; given the role of the hippocampus in mediating such context-specific behavior in related settings, it is tempting to speculate that these ventral striatal ensembles reflect a conjunction of context-specific hippocampal input and the action of cocaine. Thus, the effects of cocaine (and other drugs susceptible to contextual reinstatement) on phase precessing ventral striatal neurons will

be informative; in addition, how the hippocampus represents contexts under different conditions will likely impact vStr and context-dependent reinstatement in particular.

Rate and phase codes in the ventral striatum

Phase precession in vStr raises the possibility that distinct neural codes may be carried by firing rate and phase. The data in van der Meer and Redish (2011a) are consistent with a *phase code* for distance to a reward site and a parallel *rate code* for expected (discounted) reward value. Recording studies observing rate and theta phase in the ventral striatal neurons as reward value is manipulated could test this idea. As noted by theoretical studies of phase coding (e.g., Jensen, 2001; Nadasdy, 2009, in a hippocampal context), phase codes can only be read out with access to the LFP that was used for encoding. Thus, in the case of a ventral striatal ramp cell, a decoder would only know whether a given spike indicated a short or long distance to reward if it also knew the phase of that spike. Because a theta LFP is present in the vStr and is typically coherent with the hippocampal LFP (see the Possible Mechanisms for Ventral Striatal Theta Phase Precession section), this information is locally available in principle. Evidence that ventral striatal neurons, or downstream targets of the vStr, can use this information is not yet available; future work along the lines of showing that the probability of a post-synaptic spike depends on the theta phase of input or stimulation (as has been demonstrated in the hippocampus) would be proof of principle, constituting a phase-sensitive decoder.

Interestingly, there is independent evidence from human studies that the theta phase of ventral striatal activity contains information. Cohen et al. (2009a) recorded LFPs from the human nucleus accumbens with 8–12 Hz of oscillations as well as bursts of gamma oscillations (40–80 Hz, as occurs in the rat vStr; see van der Meer et al., 2010b, for review). It was found that the 8–12 Hz of phase at which these gamma oscillations occurred was different between rewarded and unrewarded trials, and that breakdown in this phase relationship predicted strategy changes (Cohen et al., 2009b). Thus, although the mechanism by which theta phase coding in the vStr might contribute to behavior is unclear, the data indicate that across species and experimental settings, theta phase coding is relevant to ventral striatal information processing.

Phase precession and lookahead

Phase precession implies sequence compression within a theta cycle that can be interpreted as retrospective or prospective activity, potentially useful for decision making. It is currently not known whether ventral striatal phase precessing cells participate in coherent theta sequences, either within multiple simultaneously recorded ventral striatal cells or in concert with hippocampal inputs. In support of the possibility that they might, however, Lansink et al. (2009) found that during off-line replay, theta-modulated neurons in vStr were activated at the expected time based on their firing field relative to hippocampal place cells. If this sequential structure is preserved during ongoing behavior, it would mean that theta

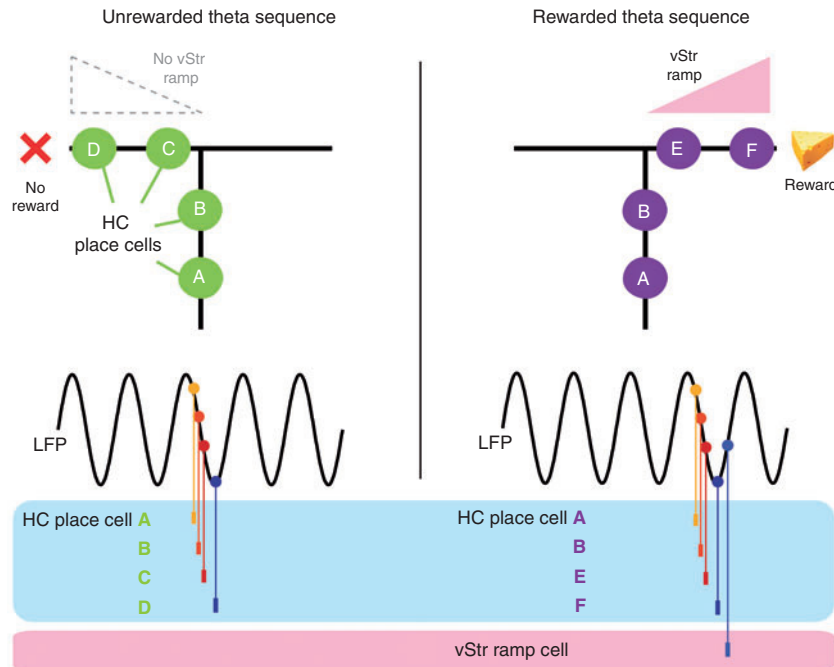


Figure 7 Schematic of hypothesized hippocampus-ventral striatum interaction during behavior (theta sequences).

As the animal faces a left/right choice at a T-maze, subsequent theta sequences traverse different parts of the maze, first to the unrewarded left side (left panel) and then to the rewarded right side (right panel). Shown schematically are the place field centers of hippocampal place cells (labeled A–F, top panels). In other words, the animal is paused – but attentive – at location A, such that a theta sequence extends first to the unrewarded side of the maze (place cells ABCD). This sequence is ineffective in triggering ventral striatal ramp cell activity (no ‘vStr’ spike in the bottom panel). On the next theta cycle, a different theta sequence (place cells ABEF) occurs to the rewarded side of the maze. Based on previous association with a ventral striatal ramp cell (pink ramp), this sequence triggers a ramp cell spike (‘vStr’ spike at the late theta phase in the bottom panel). The conjunction of activity in the choice-specific place cells EF and the ventral striatal neuron at a late phase of theta constitutes a potentially informative cue for biasing behavioral choice (van der Meer and Redish, 2010).

sequences consist of not just place information alone but are enriched with a reward-related representation, well positioned to modulate behavior.²²

To illustrate this idea, Figure 7 shows two schematic hippocampal place cell sequences straddling a T-maze choice point. The first sequence, ABCD, leads to the unrewarded side of the maze and does not activate the ventral striatal ramp neuron. The second sequence, ABEF, leads to the rewarded side, activating the ventral striatal ramp neuron. Downstream structures that can relate the activity of this neuron to the upcoming place that generated it could then bias behavior in this direction. Of course, for this type of mechanism to work, a previous association between the ABEF sequence and the ramp cell would have to have been established. However, this does not mean that lookahead is not useful: for instance, to the extent that ventral striatal ramp neurons reflect current (rather than past) motivational state, ramp neurons could provide an on-line evaluation of a potential outcome, as required in so-called ‘model-based’ decision making that is not tied to cached values reflecting past reward values (Dayan and

Balleine, 2002; Daw et al., 2005; Niv et al., 2006). Moreover, this conception of vStr mediating the influence of internally generated potential outcomes (‘internal cues’; O’Reilly and Frank, 2006; Zilli and Hasselmo, 2008) is congruent with its known role in energizing and directing behavior in response to motivationally relevant external (discrete) cues (van der Meer and Redish, 2010).

Conclusion

In our review of the hippocampal literature on phase precession, we have distinguished three main proposals about its functional relevance: phase coding, lookahead, and rapid learning. The fact that phase precession occurs robustly in the mPFC and the vStr suggests that these ideas have relevance beyond the hippocampus. In particular, the vStr is a major output pathway through which the hippocampus can influence learning and ongoing behavior. Behaviors such as CPP and context-dependent relapse depend on interactions between the hippocampus and vStr; in these settings, we have shown that the necessary ingredients are in place for phase precession to have an impact. Furthermore, using the idea of selective inheritance, phase precession can be a useful tool to reveal informative details about the inputs to particular phase

²²Lansink et al. also found non-theta-modulated neurons in the ventral striatum that exhibited coordinated reactivation with the hippocampus; we predict that such relationships are formed more slowly than those with theta-modulated neurons.

Table 1 Some open questions about extrahippocampal phase precession.

Generality of extrahippocampal theta phase precession	
1.	Does theta phase precession occur in other structures known to be theta-modulated and anatomically related to the hippocampus and/or the ventral striatum, such as the amygdala, orbitofrontal cortex, and dorsal raphe?
2.	Does ventral striatal phase precession occur on nonspatial tasks, such as during a delayed-reward waiting period (e.g., Khamassi et al., 2008)?
Source of ventral striatal phase precession	
3.	Does the development and maintenance of ventral striatal phase precession depend on hippocampal input?
4.	Are ventral striatal phase precessing cells 'copies' of ventral hippocampal cells with similar firing patterns (Royer et al., 2010)?
Role of the subiculum	
5.	Do (ventral) subicular cells phase precess and form theta sequences?
6.	How does the ventral subiculum represent places, contexts, and rewards?
Properties of ventral striatal phase precessing cells	
7.	Do ventral striatal phase precessing cells participate in theta sequences, within ventral striatum and with hippocampal place cells?
8.	Do ventral striatal phase precessing cells carry independent rate and phase codes, such as for distance to and magnitude of expected reward?
Ventral striatal phase precession and decision making	
9.	To what extent do phase precessing cells reflect past vs. current reward values?
10.	What is the impact of ventral striatal firing phase on interneurons and downstream targets?
Learning of place-reward associations	
11.	How does ventral striatal phase precession develop? Are ventral striatal phase precessing cells theta modulated or phase precessing when an animal is first exposed to a novel environment?
12.	How do ventral striatal phase precessing cells, as a population, respond to hippocampal remapping and context changes more generally?

precessing neurons, opening the door for the targeted investigation of how place-reward and context-reward associations are formed and used during behavior.

Given that it is still early days for experimental reports on extrahippocampal phase precession, many of the ideas outlined in the second half of this article are necessarily speculative. However, we believe these ideas illustrate the potential for phase precession to elucidate the mechanistic basis of how the hippocampal formation interacts with downstream structures. Our hope is that this collection of ideas will stimulate future work in this area; to this end, we present a summary of major open questions in Table 1.

Acknowledgments

The authors are indebted to Tobias Bast, Anoopum Gupta, Nathan Insel, Rutsuko Ito, Carien Lansink, A. David Redish, and Thilo Womelsdorf for their insightful comments on an earlier draft of the manuscript, and thank Chris Eliasmith, Kari Hoffman, L. Stan Leung, Tiago Maia, Yan Wu, and John Yeomans for discussion. MvdM is supported by the Canada Research Chairs program through the National Science and Engineering Research Council (NSERC, Tier II), VENI award 863.10.013 from the Netherlands Organisation for Scientific Research (NWO) and the University of Waterloo.

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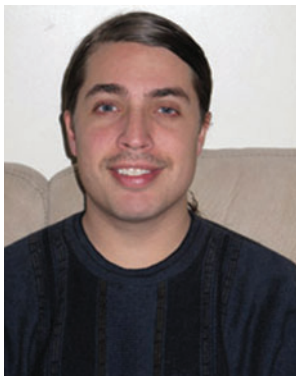
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Received August 12, 2011; accepted November 23, 2011



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