Hippocampal Mechanisms for the Segmentation of Space by Goals and Boundaries

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Abstract In memory, the continuous flow of experience is punctuated at meaningful boundaries between one episode and the next. When salient events are separated by increasing amounts of space or time, memory systems can accommodate in two ways. One option is to increase the amount of neural resources devoted to longer event segments. The other is to maintain the same neural resources with sacrificed spatiotemporal resolution. Here we review how the spatial coding system is affected by the segmentation of space by goals and boundaries. We argue that the resolution of the place code is dictated by the amount of space encoded within periods of theta. Thus, the theta cycle is viewed as a 'neural word' that segregates segments of space and its cognitive equivalents (memory, planning). In support of this conclusion, we report that, as rats traverse a linear track, the beginning of a journey is represented at the falling phase of theta whereas the journey's end is represented on the ascending phase. The current location is represented in the temporal context of the past and future event boundaries. These results are discussed in relation to the changes in physiology observed across the longitudinal axis of the hippocampus, with a special consideration for how sequence information could be integrated by downstream 'reader' neurons.

Introduction

A typical morning is naturally described by a sequential list of events that are demarked by completion of sub-goals, like making a pot of coffee, leaving the apartment, and encounters with people during the subway commute. This discretization of experience has a profound influence on how information is learned and recalled (Kosslyn et al. 1974; Block 1982; Kahl et al. 1984; McNamara 1986;

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Mensink and Raaijmakers 1988; Montello 1991; Howard and Kahana 2002; Kurby and Zacks 2008; Unsworth 2008; Kiliç et al. 2013). Depending on the spacing of salient events, varying extents of space and time can be chunked together in memory. For instance, the start and end points of journeys of different length serve as salient boundaries that influence memory segmentation (Downs and Stea 1973; Golledge 1999; Bonasia et al. 2016).

Memory for events that unfold over space and time is known to depend upon the hippocampus (Tulving and Markowitsch 1998; Eichenbaum 2004; Buzsáki and Moser 2013). Recordings from hippocampal place fields have shown that salient locations and physical boundaries influence the neural representation of space. For example, when the physical size of a familiar space is extended, place field size shows a concomitant expansion (O'Keefe and Burgess 1996; Diba and Buzsáki 2008). Rescaling of the place field size has the effect of decreasing the resolution of the hippocampal code for that space. The critical role boundaries play in dictating the organization of memory may be due to an underlying influence on place field organization (Krupic et al. 2015).

Map-based spatial navigation has at least four requirements: first is the existence of a cognitive map (O'Keefe and Nadel 1978); second is self-localization on that map (O'Keefe and Nadel 1978); third is an appropriate orientation of the map assisted by the head-direction system (Ranck 1984); and fourth is the calibration of the distance scale of the map with the help of external landmarks. This latter requirement is essential for allocating neuronal resources for any journey and for an a priori determination of the place field size and their distances from each other. Currently, there is no agreed-upon mechanism to explain how the hippocampus or surrounding regions scale the representation of space.

The sequential firing of cell sequences bounded within the prominent hippocampal theta rhythm (Skaggs et al. 1996; Dragoi and Buzsáki 2006; Foster and Wilson 2007; Wang et al. 2014) may be essential for this scaling. As an extension to existing theories, we propose that the clustering of cells within theta periods defines event segmentation (Gupta et al. 2012; Wikenheiser and Redish 2015). In building this argument, we first discuss the influence that goals and landmarks have on the hippocampal representation of space. Then, we present recent electrophysiological evidence that the representations of the boundaries tend to bookend theta sequences. This observation suggests that the spatial scale of memory and the amount of allotted resources are dictated by the chunking of space within theta, which depends upon the distance between salient landmarks. Finally, we discuss outstanding challenges for sequence-based computations in the hippocampus and, potentially, other regions of the brain.

Goals and Other Boundaries Anchor and Alter the Hippocampal Place Code

Boundaries, goals and landmarks have been shown to anchor place fields (Muller et al. 1987; Knierim et al. 1995; Rivard et al. 2004). The importance of environmental geometry was clearly demonstrated in one study where rats explored a walled open arena and place fields were recorded. When rats were returned to the same space without walls, the place fields became much more diffuse and irregular (Barry et al. 2006). The walls were essential to the place field integrity. This same study found that cells that fire on one side of a boundary tend not to fire on the other, showing that spatial division causes segmentation of the hippocampal representation (Barry et al. 2006). Finally, in a study in which rats were trained to run down a linear track starting at different points, place fields tended to be anchored to either the start or end of journey (Gothard et al. 1996; Redish et al. 2000b). Fields closer to the moveable start location shifted to maintain a fixed spatial distance from the start box, whereas those fields closer to the track's end maintained their place field location even as the start box location was moved. A subset of neurons, typically with place fields in the center of the track, maintained their firing fields to the distal room cues.

These observations and others (O'Keefe and Burgess 1996) led to the hypothesis that place fields are formed by summation of input from boundary vector cells (BVCs) that fire maximally when the subject is at particular distance from a border at a preferred orientation. According to this model, hippocampal cells will fire in different locations according to the orientation and distance from a border coded by pre-synaptic neurons. In support of this model, cells that fire along boundaries have been found in the medial entorhinal cortex (mEC), the parasubiculum and the subiculum (Solstad et al. 2008; Lever et al. 2009). Importantly, if these cells fire in response to a border oriented north/south in one environment, for example, they will also fire, on the equivalent side of a parallel wall inserted in the same environment, in response to similarly oriented walls in other environments, and even to gaps that restrict movement instead of walls (Lever et al. 2009). The generality of the tuning curve suggests that the BVCs, and border cells, are truly sensitive to the edges of space.

Head direction cells that fire when subjects face a particular direction (Taube et al. 1990; Sargolini et al. 2006; Giocomo et al. 2014; Peyrache et al. 2015) may be crucial for anchoring place fields to the environmental boundaries. Consistent with this conclusion is the observation that head direction cells and place cells rotate in concert when landmarks are shifted (Knierim et al. 1995). Interestingly, head direction cells can align to different compass headings within connected regions of space (Taube and Burton 1995), further showing the critical role environmental boundaries have in segmenting the representation of space.

Another important component of the spatial coding system is the grid cells observed in mEC (Hafting et al. 2005). These cells tile the environment with multiple firing fields that are arranged in a hexagonal grid. Although the grid cell

representation was first assumed to be independent of environmental boundaries and the size of the testing arena (Fyhn et al. 2004; Hafting et al. 2005), recent grid cell studies have shown the critical role that boundaries play in dictating firing field location. In symmetrical environments, the grid appears to be aligned to the boundaries of the space (Stensola et al. 2015), whereas in non-symmetrical, open arenas grid spacing is strongly influenced by the angle at which the environmental walls meet (Krupic et al. 2015). Similarity analysis of the representation of contiguous regions of space reveals that sharp turns around corners in a zig-zag maze cause a de-correlation of the representation of neighboring spatial bins (Derdikman et al. 2009; Whitlock and Derdikman 2012). These low correlations were hypothesized to be the result of a reset of the integration of the distance travelled from the preceding wall (Derdikman et al. 2009). Similar resets have been observed in the hippocampus due to 180° turns on linear tracks (Redish et al. 2000a). Overall, these results show that the grid fields, like place fields and head direction tuning, are locked in the spatial boundaries.

In addition to walls and physical barriers, rewarded locations are also route boundaries that profoundly affect the hippocampal representation of space. Several studies have demonstrated that changing where an animal is rewarded causes cells to fire in different positions—to remap (Markus et al. 1995; Dupret et al. 2010; McKenzie et al. 2013). This remapping results in an accumulation of place fields at the goal locations (Dupret et al. 2010). Over-representation of goal locations depends upon NMDA receptor-dependent plasticity and correlates with learning (Dupret et al. 2010, 2013).

Many studies have emphasized the random nature in which place fields remap (Muller and Kubie 1987; Leutgeb et al. 2004; Vazdarjanova and Guzowski 2004; Rolls 2013; Alme et al. 2014; Rich et al. 2014). However, the remapping of place fields to goal locations can be predicted. In a recent study that addressed which cells became goal cells, rats were trained to find a new reward site in a maze in which several locations were already rewarded. Cells that began to fire at the new goal were those that had fired to other, previously learned goal locations (McKenzie et al. 2013). This distortion that reward plays on the spatial representation can be appreciated in Fig. 1. In this experiment, rats were trained to retrieve a cereal reward buried within pots that differed by how they were scented and what they were filled with (see McKenzie et al. 2014 for full details). To visualize these representations, a principal component analysis was conducted on the mean rate vectors as rats sampled each pot in each position. The first two principal components corresponded to two positions. Differences in reward potential scaled the representations along these dimensions, as if by causing a scalar increase in the firing rates of cells contributing to these components. Note that the rewarded events were associated with representations closer to the origin, due to cells that fired similarly to the rewarded item irrespective of its position (Lee et al. 2012; McKenzie et al. 2014). Therefore, the presence of reward caused some locations to be represented more similarly than others.

Grid cells, head direction cells and place cells are all anchored to boundaries and goals. In the hippocampus the presence of a goal location not only dictates where a

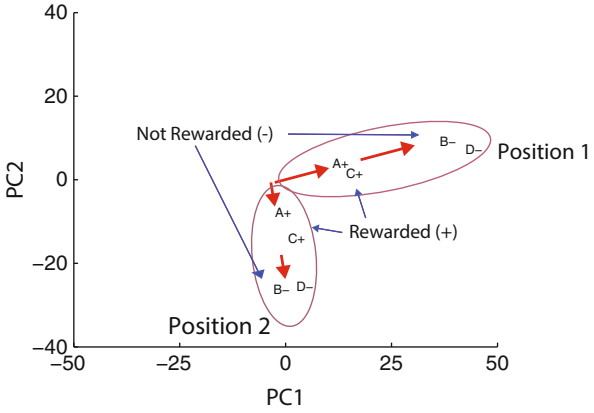

Fig. 1 Coding of rewards across different locations. CA1 and CA3 neurons (N = 438) were recorded as rats sampled rewarded (+) and not rewarded (−) pots (N = 4) that could appear in different positions (N = 4). Pots differed by odor and the material in which hidden reward was buried (labeled A, B, C, D). The mean firing rate during sampling of the 16 conditions (four pots, four positions) was calculated to generate a 438 × 16 firing rate matrix. The first two principal components (PC) of this matrix for eight item/place combinations are plotted. The PCA was computed over all 16 item and place combinations

cell fires, but also which cells are active. In the following sections, we will argue that these salient locations anchor and distort the hippocampal spatial map by biasing which cells initiate and finish cell sequences bounded by the periods of the theta rhythm.

The Hippocampus Organizes the Spatial Code into Temporal Sequences

In addition to spatial location, hippocampal firing is modulated by the theta rhythm, which, in the rat, is a 6- to 12-Hz oscillation that can be observed in the local field potential (LFP) throughout the hippocampal system (Grastyan et al. 1959; Vanderwolf 1969; Buzsáki 2002). Early models of the origin of theta posited that hippocampal cells oscillated at theta due to an external pacemaker drive from the medial septum (Petsche et al. 1962; Lewis and Shute 1967; Lee et al. 1994). It is now clear that theta-like activity can be induced in hippocampal slices (Konopacki et al. 1988; Goutagny et al. 2009) and that there are multiple theta generators (Buzsáki et al. 1986; Kamondi et al. 1998) driven by the entorhinal cortex (Mitchell and Ranck 1980; Alonso and Llinás 1989), CA3 (Konopacki et al. 1988; Kocsis et al. 1999), the subiculum (Jackson et al. 2014), and other areas within the hippocampal circuit (Konopacki et al. 1988). Even single cells show resonance at theta frequencies (Leung and Yu 1998; Stark et al. 2013; Vaidya and Johnston 2013). Modeling work has demonstrated that a network of resonant cells can

develop rhythmic firing activity (Traub et al. 1989; White et al. 2000; Thurley et al. 2013; Tchumatchenko and Clopath 2014). Regardless of the origin of theta, the strong rhythmic activity provides temporal windows in which presynaptic inputs can be integrated, other windows in which cells fire, and windows of refractoriness in which the network is relatively silent (Buzsaki 2006).

Hippocampal pyramidal cells fire maximally at the trough of local theta (Rudell et al. 1980; Csicsvari et al. 1999). Therefore, the actual firing rate profile as subjects run through a cell's place field is a series of rhythmic bursts on a skewed Gaussian place field envelope. In a purely rate-based coding scheme, the fact that both position and theta phase dictate spiking probability presents a fundamental problem for a downstream place decoder that relies on firing rate estimation. Low firing rates could be indicative of two scenarios: either the subject is far from the center of the cell's place field, or the rat was in the center of the place field but during a non-preferred phase of theta.

Resolving this ambiguity depends upon the time scale with which presynaptic input is integrated. A systematic relationship between spiking phase and position suggests that the hippocampus is capable of sub-theta period resolution. Upon entry to the place field, cells tend to spike at late phases of theta, after the activity of the majority of other cells. Moving through the place field, not only does the firing rate increase but there is also a systematic advance in the phase in which the cell fires. In the center of the field, where firing rate is the highest, cells spike just before the chorus of other neurons. Upon exiting the field, the cell's spikes occur at early theta phases, preceding the bulk of spikes from other cells. This systematic relationship between position and the theta phase in which a cell fires is known as theta phase precession (O'Keefe and Recce 1993; Skaggs et al. 1996).

There is a close relationship between the change in rate and the change in firing phase across different types of behavior. For example, during rapid eye movement sleep, when the subject is clearly not physically moving through space, phase analysis can be done on action potentials emitted early or late in spike trains. Like in the experiments with rats running through space, spikes initiating the train are observed on late phases whereas late spikes occur on early phases (Harris et al. 2002). This phase advance can be observed in other situations. In virtual reality, phase advancement is observed in cases when spiking is fixed to virtual positions (Harvey et al. 2009; Ravassard et al. 2013) and in cases where spiking seems to occur randomly in the virtual environment (Aghajan et al. 2014). When rats run on running wheels (Harris et al. 2002; Pastalkova et al. 2008; Wang et al. 2014) or treadmills (Kraus et al. 2013), cells can become tuned to specific time intervals into running, analogous to the place field sensitivity to space. As time spent running elapses through the 'time field,' firing rates increase and decrease and precession can be observed (Pastalkova et al. 2008; Wang et al. 2014). Intriguingly, in wheel running protocols that lack a memory demand, neurons tend to fire for seconds at a fixed phase (Hirase et al. 1999; Pastalkova et al. 2008). Phase precession seems to be linked to the waxing and waning of firing rates more so than the absolute firing rate observed on a trial-to-trial basis. Phase precession is therefore a fundamental organizing principal for *changes* in the hippocampal state.

Despite decades of debate and study, there is no agreed-upon biological mechanism for phase precession. One class of model posits that phase precession is a reflection of spikes being driven by an intracellular oscillation that is a higher frequency than the theta observed in the LFP (O'Keefe and Recce 1993; O'Keefe and Burgess 2005; Hasselmo et al. 2007). Intracellular recordings of place cells show that sub-threshold oscillations increase in frequency as rats traverse a place field and that action potentials lock to peaks on this intracellular rhythm. This frequency increase rides on top of a place-locked depolarization (Harvey et al. 2009). Several models predict that that depolarization directly drives the higher frequency oscillation which causes spikes to precess (Kamondi et al. 1998; Lengyel et al. 2003). A similar conversion of a rate code into a temporal code has been suggested for spatial tuning of entorhinal grid cells, where cells are thought to integrate head direction and velocity, rather than position, into changes in firing frequency (O'Keefe and Burgess 2005; Hasselmo et al. 2007). This class of model is challenged by the observation that silencing the hippocampus for $>$200 ms via hippocampal commissural stimulation does not cause a reset in spiking phase (Zugaro et al. 2005). Therefore spiking phase is likely determined on a cycle-to-cycle basis, a conclusion that is at odds with oscillatory interference models for hippocampal phase precession.

A single cell mechanism of phase precession has been proposed that focuses on the rhythmic dendritic excitation that is phase synchronized with somatic inhibition (Kamondi et al. 1998; Magee 2001; Losonczy et al. 2010). Moving to the place field center causes greater amplitude dendritic excitation that progressively overcomes somatic inhibition at early times, thus causing spikes early and often (Mehta et al. 1997; Kamondi et al. 1998). This type of model requires an additional mechanism—spike adaptation (Kamondi et al. 1998) or delayed inhibition (Losonczy et al. 2010) have been suggested—to prevent late phase spiking upon place field departure. Therefore, the decrease in the period between bursts of spikes, relative to the LFP, is driven directly by increases in depolarization. Importantly, tangential passes through place fields that miss crossing the field center result in a symmetric place by position relationship, one that roughly mirrors how rate varies across position (Huxter et al. 2008). This type of behavior is predicted if peak rates must be achieved to prevent late phase spiking upon place field exit.

There have also been network models of phase precession. In a simple version of the model, CA3 place cells are wired in a feedforward chain where the cells most strongly driven fire first and at the highest rate (Jensen and Lisman 1996; Tsodyks et al. 1996; Lengyel et al. 2005). These cells then excite, through recurrent connections in CA3 and perhaps the dentate, other cells with place fields in front of the animal. Cell spiking in this model is driven both by place-related excitation and from activation of other cells with place fields between the subject and the coded position. The synaptic activation causes a time (phase) delay proportional to the distance between the current position and the cell's place field due to greater numbers of intervening cells that must be chained for more distant locations. This type of model places a heavy onus on pre-existing wiring as phase precession can be observed for first time passes through a place field (Feng et al. 2015) and in unique

trajectories in two-dimensional environments (Harris et al. 2002; Huxter et al. 2008; Jeewajee et al. 2014). These results necessitate pre-existing chains for every running direction for every position, an unlikely scenario.

In another type of network model that is not mutually exclusive with those mentioned, the most excited cells fire first, which drives inhibitory cells to delay the activity of other place cells that code for more distant positions (Dragoi and Buzsáki 2006; Maurer et al. 2006; Geisler et al. 2007; Stark et al. 2013). Silencing of soma-targeting interneurons (Royer et al. 2012), or decoupling retrograde communication between pyramidal and inhibitory cells through endocannabinoid receptor antagonism (Robbe et al. 2006; Robbe and Buzsáki 2009; Losonczy et al. 2010), causes large disruptions in assembly coordination and a redistribution of spiking across theta phase. These findings show a clear role of inhibition in phase precession.

Several observations support network models of precession. Place cells show trial-to-trial variance in their firing rates that cannot be explained by changes in position or theta phase alone (Lánský et al. 2001). Statistical models have shown that the precise trial-to-trial timing can be predicted by the spiking activity of other neurons, as would be expected if sequencing was brought about through a chaining of co-active ensembles oscillating faster than the baseline LFP (Harris et al. 2002; Dragoi and Buzsáki 2006; Geisler et al. 2007). However, principal cells respond to many environment stimuli and therefore a misspecification of the model may mistake common external modulation for a causal network interaction (Chadwick et al. 2015). Therefore further experimentation is needed to resolve whether theta sequences truly reflect network level synchronization.

Theta Sequences Code for Behaviorally Relevant Spatial Segments

Early investigators realized that phase precession could reflect cell sequences chunked into theta periods (Skaggs et al. 1996; Dragoi and Buzsáki 2006; Foster and Wilson 2007). Theta periods tend to begin with cells that have mean firing fields behind the present location and end with cells with mean fields slightly ahead. Accordingly, decoding of position on sub-theta time scales reveals spatial sequences that begin behind the animal and sweep in front (Itskov et al. 2008; Maurer et al. 2012).

Theta sequences reflect about a ten-times compression of the timing of events in the real world to time lags observed during theta (Skaggs et al. 1996) that increases with the size of the environment (Diba and Buzsáki 2008). The compression ratio can be reached by taking the cross correlation of pairs of spike trains and considering the lag in the peak at different time scales. For two place cells, the cross correlation will have a global maximum at a lag that is proportional to the distance between the place fields (Dragoi and Buzsáki 2006). These experiments are typically conducted on linear tracks with stereotyped velocity to allow a rough

equivalence between space and time. In addition, the cross correlation is strongly modulated by theta. The lags of the local maximum, on theta time scales, correlate with the time taken to traverse between the place fields. The ratio of these lags reflects the degree of compression.

A recent study explicitly tested the link between theta phase precession and theta sequencing as rats explored a novel linear track (Feng et al. 2015). This study found that phase precession was observed on the first trial, though theta sequences were not. The sequencing emerged rapidly, by the second trial, and this development coincided with a decrease in the phase variability in which cells fired upon place field entry. Therefore, theta sequencing seems to be a natural consequence of a group of cells that phase precess at the same rate (slope) and begin firing at the same phase (Dragoi and Buzsáki 2006). It is unknown what causes cells to fire at more reliable theta phases. The known importance of inhibitory cells in dictating firing phase (Royer et al. 2012) and the hypothesized role of inhibition in phase precession (Kamondi et al. 1998; Geisler et al. 2010; Losonczy et al. 2010; Stark et al. 2013) suggest a potential candidate for this phase alignment may be plasticity between excitatory and inhibitory cells. Interestingly, cells recorded at the same site tended to have more uniform phases upon place field entry (Feng et al. 2015), consistent with models in which interneurons coordinated place cells within the range of their axonal arbor.

There is growing evidence that theta sequences represent a meaningful segmentation of space. In one experiment that addressed this issue, rats were habituated to a linear track and the place field order and theta sequences were identified. Then, the track was expanded, a manipulation known to cause concomitant increases in place field size (O'Keefe and Burgess 1996). Remarkably, the theta time-scale lag remained fixed, thereby causing an increase in the compression of the amount of behavioral time represented within a theta cycle (Diba and Buzsáki 2008).

A recent experiment found that the magnitude of compression observed within each theta sequence varied significantly according to where the rat was on the maze. The amount of space represented ahead of, or behind, the rat varied systematically according to where the rat was relative to the experimentally defined landmarks (Gupta et al. 2012). This heterogeneity of theta sequence content suggests that one role of theta could be to divide space into meaningful segments.

In the aforementioned study, theta sequences could have chunked space according to the physical geometry or due to some process related to route planning. To dissociate these two possibilities, rats were trained to traverse around a circular track, collecting rewards by waiting a variable amount of time at each of three locations (Wikenheiser and Redish 2015). Rats had a choice to stay and wait for a reward or run to the next location, which was the optimal strategy if the wait time for reward at the more distant site was shorter (Wikenheiser et al. 2013). When activity on the late phases of theta was analyzed, there was a strong correlation between the distance the rat was about to run and the places represented by the active cells. Different cells spiked in the same location depending on where the rat would run next. Importantly, there was no relationship between the distance the rat had just run and the distances represented in these late theta phases. These data

showed that hippocampal activity during theta could reflect more than a representation of current state and may reflect a vicarious trial-and-error important for planning (Schmidt et al. 2013).

A similar observation has been made by decoding position using CA3 firing rates at the choice points. This analysis reveals transient moments in which CA3 represented positions ahead of the rat, sweeping down the potential paths before the rat made its decision (Johnson and Redish 2007). These findings are closely related to the fact that the phase of spiking contains information about heading direction in two-dimensional environments (Huxter et al. 2008), as would be expected if theta sequences code for upcoming positions.

Overall, studies to date have demonstrated that theta sequences always begin with place representations behind the subject and end with representations of the future. However, the exact span coded by theta sequences has not been addressed carefully. If the cells that are active at the trough of the CA1 theta cycle code for the current position in the context of past and future locations, how is the span of the past and future determined at the physiological level? One possibility is that theta sequences code for a fixed amount of time or distance around the current location. Alternatively, each geometric segment (e.g., individual corridors) and event along the journey could be represented separately as a 'neural word' and such words would be concatenated, perhaps via sharp wave ripples (Foster and Wilson 2006; Davidson et al. 2009; Wu and Foster 2014), to represent the entire journey from the beginning to the end. Yet another possibility is that the start and end (reward) locations of a complex trajectory through a maze are coded in a given cycle. This final option raises the question of just how much space could be segmented within a theta cycle.

Data collected in our lab demonstrate that theta periods segment the environment either according to goals or to environmental geometry. As a rat ran down the track, the probability that it occupied any given position given the observed CA1 spiking pattern was computed by comparing the instantaneous rates to a template of the session averages, the cells' place fields. When these posterior probability distributions were calculated at every theta phase (Zhang et al. 1998), we observed theta sequences that started at one end of the track and finished at the other (Fig. 2). Thus, in addition to the goal being represented at late theta phases (Wikenheiser and Redish 2015), our findings show that the start location is represented at early phases. Combining these observations, the phase code is defined by the current location in the context of a past bounded by a journey's beginning and a future bounded by the journey's end. Separation of the future and past boundaries is assured by the strongest inhibition at the peak of the theta cycle (Buzsáki 2002).

Recall the studies in which place fields expanded when familiar environments were stretched. How do place fields expand with the environment? An answer begins to emerge when one considers that the theta sequences are anchored to the boundaries. The amount of space represented within the sequence, the compression, dictates the resolution of the spatial code. When boundaries are moved apart, either in the stretched environments or for journeys of different lengths, theta sequences that are bookended by those boundaries necessarily represent more space which, in

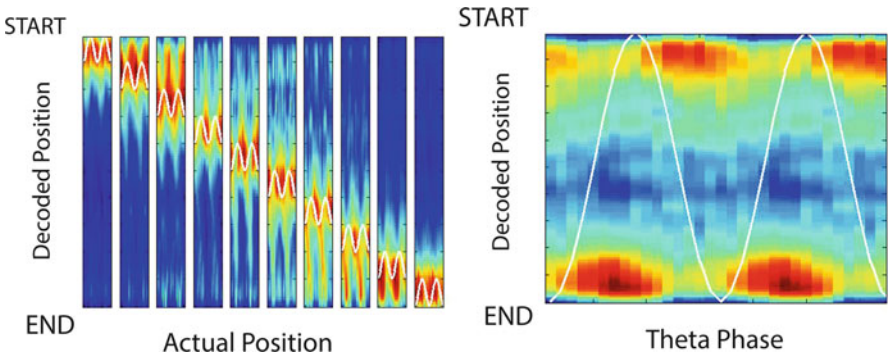

Fig. 2 *Left*, as rats run on a 1.2-m linear track, the decoded probability (high probability = *red*) of the rat occupying each track position (y-axis) is calculated at each phase of theta (x-axis, *white* sine wave). In each subplot, the range of the white sine wave demarks the rat's actual position. Generally, there is a high probability of the rat occupying its actual position. However, within a subplot, theta sequencing can be visualized by diagonal streaks of high probability that begin at the START position on the falling phase of theta and finish at the END position at the rising phase. *Right*, the same data averaged across all positions actually occupied by the rat. Note that theta sequences are bookended by representations of the linear track START and END positions at the falling and rising phases, respectively. Note that decoding was done on simultaneous ensembles measured across 4 mm of the hippocampus

turn, causes place fields to expand (Diba and Buzsáki 2008). As Redish and colleagues have shown, subjects can, on a moment-to-moment basis, allocate computational resources as a function of the planned trajectory length. Long trajectories were associated with larger place fields, and thus the resolution of the spatial code for these trials was coarser (Wikenheiser and Redish 2015). Our findings expand on these observations by demonstrating that it is not only the goal but both the beginning and end of a continuous stretch (such as a linear track) that are simultaneously represented by the theta assemblies. In our linear track experiments, the environmental boundaries and the goal locations were the same, and therefore further studies are needed to determine whether the route boundaries or the environmental geometry dictated the reliable phase coding of the start and stop locations.

Given the rapid formation of place fields upon entry into a new environment (Frank 2004; Dragoi and Tonegawa 2011; Feng et al. 2015), there must be some mechanism that estimates the spatiotemporal extent of the event segment to allocate resources appropriately. The fact that nearby neurons exhibit similarly sized place fields (Jung et al. 1994; Kjelstrup et al. 2008) suggests that there is a characteristic segment size for a species that moves through space at a particular rate. It is possible that salient events tend to happen at regular temporal or spatial intervals (Sreekumar et al. 2014). Alternatively, the segment size may depend upon internal limitations of hippocampal processing, for example, the limited amount of time in which information can be held across a delay or a limited amount of time a cell can fire at a faster rate than the overall population (Geisler et al. 2010). It is telling that,

even in large stretches of 'open space,' rodents choose certain spots as 'home bases' (Eilam and Golani 1989), perhaps to subdivide the space into spatial segments tailored for hippocampal processing. A recent study of neurons in the ventral hippocampus showed that, with learning, place fields shrank to encompass the space that equivalently predicted which objects contained a hidden reward (Komorowski et al. 2013). In this study, the default place field size was a poor predictor of the spatial extent of the context boundaries and therefore the system was modified to resolve the mismatch.

In an intriguing parallel to the organization of theta sequences, firing of cells in the ventral striatum has been shown to phase precess relative to hippocampal theta (van der Meer and Redish 2011; Malhotra et al. 2012). Cells in the ventral striatum showed ramped firing as subjects ran towards goals. Remarkably, striatal phase precession occurred over a long spatial extent for distant goals and over much shorter spatial segments when goals were close together. The phase precession appeared to be bookended by experimentally defined boundaries—the goal sites. Striatal activity might be driven by cells in the ventral hippocampus, which showed precession (Kjelstrup et al. 2008), ramped firing towards goals (Royer et al. 2010) and connectivity with the ventral striatum (Groenewegen et al. 1987). These results suggest that downstream areas may be sensitive to how space is segmented by hippocampal theta sequences (Pezzulo et al. 2014), though future studies in which both regions are recorded simultaneously are needed to assure the link between these two observations.

How Could Theta Sequences Be Integrated by Post-synaptic Readers?

Aside from the distance between place fields, there are other factors that influence the temporal lags in cell activity. The mutual dependency of the distance between place fields and anything else in determining spiking phase lag seriously complicates the aforementioned models for the computation role of cell sequences.

Cells recorded in different regions of the hippocampus have different properties. Septal CA1 cells tend to have smaller, unimodal place fields whereas more temporal cells have larger, multi-modal fields (Jung et al. 1994; Kjelstrup et al. 2008; Royer et al. 2010; Komorowski et al. 2013). Hippocampal place cells have been shown to phase precess, with spikes initiating the spike train emitted on the late phases of local theta (Maurer et al. 2005; Kjelstrup et al. 2008). Therefore, considering a pair of cells with their place fields centered at the same location, the timing difference between spikes will change in sign as the rat crosses the place fields' common center. A range of place field sizes will cause a range in timing offsets, all of which equivalently code for the same position.

The situation is complicated further by the systematic shift in theta phase across the longitudinal axis of the hippocampus. Simultaneous recording of the LFP or

current source density analysis has shown that theta is a traveling wave (Lubenov and Siapas 2009; Patel et al. 2012) that begins at the most septal end of the hippocampus closest to the subiculum and moves temporally and proximally, resulting in a 180° phase shift at the two poles of the hippocampus (Patel et al. 2012). The speed of the travelling wave and, therefore, the maximal phase offset also change between waking and REM sleep (Patel et al. 2012). Importantly, the phase preference for spiking, with respect to local theta, does not change across the longitudinal axis (Patel et al. 2012) and, as mentioned, the phase onset and offset of precession are the same regardless of cell location (Maurer et al. 2005; Kjelstrup et al. 2008; Patel et al. 2012). Therefore, every instant in time is associated with cells at different parts of their phase precession cycle.

This observation led to the realization that moments in time do not represent points in space but could instead represent line segments (Lubenov and Siapas 2009). Since there are a range of phases that can be observed in any snapshot of time, there could theoretically be a range of represented positions, if spike phase codes for a point in space. Unless cells had equivalent place fields and were located at the same transverse lamellae along the longitudinal axis, the time delays between cells would not convey any reliable information about the distance between the place fields. The reports for this correlation in the literature are likely due to the sampling from ensembles that conform to these restrictions (Dragoi and Buzsáki 2006; Feng et al. 2015).

It is unknown whether the hippocampus acts as a single computational unit or whether transverse lamellae have different, and independent, computational roles (Andersen et al. 2000; Strange et al. 2014). If lamellae have a relative degree of independence, then the conditions could be met for phase lags to represent place field separation. Early track tracing studies showed mainly parallel fibers along transverse lamellae, implying that the trisynaptic loop is the fundamental processing module that repeats across the longitudinal axis (Andersen et al. 1969, 2000; Tamamaki and Nojyo 1991). Subsequent cell tracing studies revealed that the Schaffer collateral fans broadly from CA3 to CA1, thus allowing for substantial integration across the longitudinal axis (Amaral and Witter 1989; Ishizuka et al. 1990; Li et al. 1994), in addition to the well-known CA3 recurrent collaterals (Lorente De Nó 1934; Wittner et al. 2007). Furthermore, the axonal arborization of GABAergic cells can innervate as much 800 μm of the longitudinal axis, allowing for considerable inter-laminar crosstalk (Sik et al. 1995; see also Sloviter and Lømo 2012).

Despite this newer anatomical evidence, others have argued for relative independence of the transverse lamellae (Sloviter and Lømo 2012). Stimulation of a small region of CA3 causes maximal axonal volleys in CA1 regions in the same transverse plane (Andersen et al. 2000). Lesion and inactivation studies have also shown dissociations in the function of the septal and temporal hippocampus. Lesions to the septal hippocampus cause spatial memory deficits whereas those to the temporal hippocampus are often associated with anxiolytic measures and motivation (Moser et al. 1995; Kjelstrup et al. 2002; Pentkowski et al. 2006; Bast et al. 2009; Jarrard et al. 2012; Kheirbek et al. 2013; Wu and Hen 2014). There are

also large differences in efferent and afferent connections as well as sharp genetic variations that delineate regions across the longitudinal axis (reviewed in Strange et al. 2014). In further support of anatomical segregation is the finding that place cells in the septal versus the temporal hippocampus have been shown to remap at different rates (Komorowski et al. 2013) and to possess different place field properties on the radial arm maze, linear track, and zig-zag maze (Royer et al. 2010).

The anatomy and physiology of CA1 projections to the subiculum strongly suggest that single subicular cells have access to a large range of the longitudinal axis of CA1. Cell reconstruction studies have shown that CA1 cells project to "slabs" of the subiculum that span a narrow range of the transverse axis but up to 2 mm along the longitudinal axis (Tamamaki and Nojyo 1990, 1991). Those subicular cells would integrate across a broad range of hippocampal theta phases (~60°). *In vitro* comparisons of physiology in hippocampal slices versus that in an intact preparation showed large differences in the theta phase offsets between CA3 and the subiculum and in the theta frequency, suggesting that the slice preparation severed processes necessary for communication across lamellae (Jackson et al. 2014). Physiological studies, like those done between CA3 and CA1 (Andersen et al. 2000), are needed to determine the strength of these cross-laminar projections.

If cross-laminar communication is substantial, the compression that had been hypothesized to occur over time may occur instead over co-active neurons firing at different local phases (Lubenov and Siapas 2009). In this scheme, information is communicated by which neurons are co-active and not by their inter-spike intervals (Harris 2005). Segmentation of the environment would still be evidenced by which regions of space were represented by the ensemble at each phase, though these segments may not change within a theta period (for a different perspective see Shankar and Howard 2015).

Conclusion

Goal locations have been shown to discretize memory and to segment the hippocampal representation of space. Here we have presented evidence that salient boundaries play an important role in defining how theta sequences begin and end. We propose that this segmentation anchors place cell firing and consequently the organization of memory. However, basic questions remain as to how the hippocampal spatial code becomes coordinated during theta. What causes different areas of space to be chunked within a theta sequence and consequently the resolution of the spatial code? How do certain locations become over-represented? Are these phenomena related? How does a planning-related signal shift the represented position further ahead (or behind) the rat with the expected (or realized) journey length? Simultaneous recordings from across the longitudinal axis of the hippocampus and between the hippocampus and its output regions will help resolve the

spatial and temporal scale in which information is integrated. Finally, behavioral tests combined with recordings are required to establish whether segmentation of space into theta sequences is linked to how subjects behaviorally segment experience. Future experiments that address these questions may reveal important evidence as to how the continuous nature of experience becomes discretized in our memory.

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