

SECTION I. NEUROSCIENTIFIC DIMENSIONS OF SPATIAL COGNITION

Chapter 1. Hippocampus and Related Areas: What the Place Cell Literature Tells Us

About Cognitive Maps in Rats and Humans

A. David Redish and Arne Ekstrom

One of the most striking examples of how neurons code complex cognition is the place cell in the rodent hippocampus. Thus, any discussion of the hippocampal neurophysiology of spatial cognition needs to start from the fact that space is a primary driver of neural firing patterns in the rodent hippocampus (O'Keefe & Dostrovsky, 1971) and spatial firing is clearly the best first-order description of rodent hippocampal representations (for review see Redish, 1999). Non-spatial information is also represented in the rodent hippocampus, reliably modulating neural firing there, but arriving separately through distinct neuroanatomical pathways. Spatial information is also a key component of neural representations in the human hippocampus, as are non-spatial aspects. In this chapter, we present an integrated framework of rodent and human hippocampal function based on the idea that while space plays a primary role in hippocampal function, non-spatial variables overlap and share processing resources within the hippocampus as well.

We start with a quick review of the anatomy, and then turn to a review of the properties of place cells in the rodent hippocampus, identifying what is known about how spatial firing is achieved, how multiple maps are represented, and about the differences in representation across anatomical dimensions of hippocampus. From there, we turn to properties of place cells, identifying three phenomena that we connect to questions of human spatial cognition: (1) *phase precession*, in which sequences representing potential trajectories are played out during behavior,

(2) *replay*, in which sequences are played out during rest periods, and (3) *context sensitivity*, in which attention to task and environment plays an important role in determining which spatial representations are active at any time. Finally, we work backwards to discuss what is known about hippocampal inputs, including a discussion of the recently discovered *grid cells*, and the differences between lateral and medial entorhinal cortex, as well as perirhinal and postrhinal inputs into these structures. In the second section, we turn to the human hippocampus, reviewing what is known about spatial representations in human hippocampus, and the adjacent medial temporal lobe cortical structures. Our discussion focuses on evidence from lesion, fMRI, and invasive recording studies in humans and the role of the human hippocampus in representing multiple spatial routes and contexts, as well as the role of the human parahippocampal cortex in visual-spatial representation. We conclude with a discussion about a general role for the hippocampus in episodic memory, and how this relates to both future thinking and consolidation of past episodic information into general knowledge about the world.

Anatomy

Anatomically, both rodent and primate (including human) hippocampus can be subdivided into three primary subregions (dentate gyrus [DG], CA3, and CA1). These structures differ in connectivity, component interneurons, and projection neurons (Amaral & Lavenex, 2007; van Strien et al., 2009). In addition, hippocampus is anatomically differentiable along the dorsal-to-ventral (sometimes called the septal-to-temporal) axis and along the proximal-to-distal axis (Amaral & Lavenex, 2007). In the primate (including humans), the dorsal/ventral axis is transformed through development into a posterior-to-anterior axis, with the primate posterior hippocampus corresponding to the rodent dorsal hippocampus and the primate anterior hippocampus corresponding to the rodent ventral hippocampus. A simplified anatomical

diagram is shown in Figure 1.

-- Figure 1 about here --

Place Cells in the Rodent Hippocampus

The canonical place cell in the hippocampus is defined by a restricted firing field (or tuning curve) to a unimodal spatial area in an open environment. As a rat runs around the floor of a 1 m cylinder, foraging for food pellets thrown in at random intervals, a given place cell primarily fires its spikes in a single unimodal area, called a place field. Different place cells have different place fields. The population activity encodes the location of the animal in the cylinder. However, this description belies a host of complexity now known to exist.

-- Figure 2 about here.--

Place cells can be found in all three components of hippocampus (DG, CA3, CA1), but dentate gyrus place fields tend to be sparser (Jung & McNaughton, 1993; Gothard et al., 2001) and more sensitive to subtle changes in an environment (Leutgeb et al., 2007). Current theories suggest that the sparse activity in dentate gyrus plays a primary role in pattern separation, a process of making similar representations more dissimilar, while recurrent connectivity in CA3 plays a role in pattern completion, a process of transitioning a partial instantiation into a stored complete representation (McNaughton & Morris, 1987; McClelland et al., 1995; Redish, 1999). Pattern separation allows for simpler storage because dissimilar patterns are less likely to interfere with each other (McNaughton & Morris, 1987; Hertz et al., 1991); pattern completion allows for content-addressable memories, retrieving complete memories by their partial content (Hebb, 1949; Hertz et al., 1991).

Supporting these hypotheses, manipulations of dentate gyrus affect the ability to recognize subtle spatial differences between tasks and environments (Gilbert et al., 2001). In

contrast, CA3 provides pattern completion processes, such as the presence of place fields after landmark removal (Pico et al., 1985; Nakazawa et al., 2002) and in the dark (Markus et al., 1994). CA3 place fields depend on dentate gyrus for pattern-separation (McHugh et al., 2007), but not for recall of place fields (McNaughton et al., 1989). CA1 place fields depend on CA3 for pattern completion (Nakazawa et al., 2002), but not for the existence of place fields (Mizumori et al., 1989).

Along the dorsal-to-ventral axis, place fields increase in size with smaller place fields in the dorsal region and broader place fields in ventral regions (Jung et al., 1994; Kjelstrup et al., 2008; Royer et al., 2010), suggesting a multi-scale representation of space (Maurer et al., 2005; Fiete et al., 2008). Very broad place fields could provide large-scale contextual cues and may be why ventral hippocampus is often associated with contextual and environmental-emotional associations (Bannerman et al., 2004), although the dorsal, intermediate, and ventral hippocampus each interact differently with other structures (van Strien et al., 2009). The spatial representations embodied in place fields are dependent on three factors: sensory cues (sometimes called the local view, even though those sensory cues are not necessarily visual), dead reckoning (sometimes called *path integration*¹), and non-spatial (contextual) cues. As we will see below, these non-spatial cues are fundamentally different from the spatial representations and are better understood as “map-selection”.

Several theories in the 1990s (see Redish, 1999, for review) suggested that the place fields in hippocampus are dependent on dead reckoning representations. Dead reckoning entails the maintenance of a position representation from self-motion information: if I know I am at location (x, y) and take a step $(\Delta x, \Delta y)$ then I know I am at location $(x + \Delta x, y + \Delta y)$. Of course, the updating calculation does not have to be done in Cartesian coordinates, but there are

computational reasons to expect it not to be done in polar coordinates (Gallistel, 1990). A few models of successful dead reckoning systems have been proposed (Müller & Wehner, 1988; Wittmann & Schwegler, 1995; Samsonovich & McNaughton, 1997; Conklin & Eliasmith, 2005; Burak & Fiete, 2008), but the actual mechanism underlying the dead reckoning system remains unknown.

While some early theories suggested that the hippocampus itself was the computational dead-reckoning component (Samsonovich & McNaughton, 1997), other theories suggested that the dead-reckoning component had to be an input to the system because of computational limitations due to the non-spatial representations in the hippocampus (Redish, 1999). Lesion studies have been unable to resolve this controversy, with some studies reporting that animals can perform dead reckoning without a hippocampus (Alyan & McNaughton, 1999) and others reporting that they cannot (Maaswinkel et al., 1999). Unfortunately, as with any lesion study, these studies are complicated by the availability of other mechanisms capable of solving the tasks without dead reckoning and behavioral components of the tasks that may require hippocampus but not dead reckoning. Nevertheless, the evidence that hippocampal representations are driven by dead reckoning components is incontrovertible. The cleanest demonstrations of this are the continued firing of place cells in the dark and after cue removal (O'Keefe & Conway, 1978; Markus et al., 1994; Nakazawa et al., 2002, as long as the animal is able to localize itself beforehand) and after manipulations were done that decoupled the hippocampus from the sensory representations (Knierim et al., 1998). Critically, the externally provided sensory cues are associated with internally-driven dead reckoning information, not the other way around. This means that (at least in rats) the internal coordinate system is primary and external cues are associated with it, not the other way around (Gallistel, 1990; Knierim et al.,

1995; Redish, 1999).

Computationally, this result makes sense if one examines how animals make novel environments familiar. When an animal enters a new environment, it can maintain a representation of position relative to its starting point through dead reckoning systems; but dead reckoning systems have the intrinsic problem that systematic errors build up over time unless they are corrected (Gallistel, 1990). Once the animal knows the sensory cues for each position in the environment, it can correct those errors with the remembered sensory cues. Of course, knowing the cues at each position depends on the animal being familiar with the environment. To break this cycle, animals explore outward from a home base (Birke, 1983), associating the sensory cues with the dead reckoning coordinates. As the dead reckoning system drifts, the animal will have to return to the home base to reset its dead reckoning coordinate system (Redish, 1999). Consistent with this explanation, outbound journeys as animals explore environments are slow and meandering, while return journeys are fast and direct (Drai & Golani, 2001). What this means is that place cells fire initially on entry into an environment, but that they take time to tune up (Wilson & McNaughton, 1993).

Familiarizing oneself with an environment entails learning the relationship between locations within the environment sufficiently to be able to predict the effect of taking a path through the environment. Spatial cognition thus often critically involves spatial sequences, particularly in terms of navigating along those sequences. The dynamics of place cell firing show two important sequential representations when examined at fine time scales: (1) “phase precession” and (2) “replay”.

Phase precession. In addition to the single cell data, recording electrodes provide access to a slower signal, measured in the lower-frequencies (1–300 Hz), called *local field*

potentials (LFPs), which primarily reflect synaptic effects (Buzsaki, 2006; Katzner et al., 2009). In the hippocampus, LFPs reflect the information processing state of the system, identified primarily by either a slow 7 Hz rhythm (*theta*) seen during navigation, attentive behavior, and REM sleep or a broader-spectrum (*large amplitude irregular activity* or *LIA*) signal punctuated by 100 ms 200 Hz *sharp-wave ripple complexes* seen during non-attentive behaviors and slow-wave sleep (Vanderwolf, 1971; O'Keefe & Nadel, 1978; Ylinen et al., 1995; Bragin et al., 1995). During theta, the hippocampal system primarily processes information entering from the entorhinal cortex, while sharp-waves reflect information processing generated in the CA3 region (Hasselmo & Bower, 1993; Ylinen et al., 1995; Bragin et al., 1995; Buzsaki, 2006).

As animals run along a path, the phase-relationship between the firing of a given place cell and the 7 Hz LFP theta changes such that spiking precesses from late in the theta cycle on entry into a place field to earlier in the cycle on exit from the field (O'Keefe & Recce, 1993; Skaggs et al., 1996). This change in phase relationship as an animal passes through a place field is called *phase precession*. It is useful to think of the effect of phase precession on the neural ensemble: because place cells fire late in the theta rhythm on entry into place fields but early on exit from the place field, within each theta cycle, there is a sequence of firing along the path of the rat (Skaggs et al., 1996, see Figure 3). In fact, it is possible that phase precession is an epiphenomenon of an internal sequence and motion: within each theta cycle, some mechanism drives a sequence of activity along the path of the animal and that sequence precesses as the animal moves forward (Lisman & Redish, 2009).

-- Figure 3 about here. --

When first observed, it was suggested that phase precession could serve to improve the representation of location (O'Keefe & Recce, 1993; Skaggs et al., 1996), and that it does so on

linear paths (Jensen & Lisman, 2000). However, on two dimensional paths, place cells are omnidirectional (Muller et al., 1994; Markus et al., 1995) and phase precess on the approach from any direction (Skaggs et al., 1996; Huxter et al., 2008). As originally noted by Skaggs et al. (1996), there are three possible relationships between phase precession and omnidirectionality: (1) The place fields in each direction can start from the same point and precess outward, suggesting that place fields receive a “kick” to start and reflect a memory of the recent past. This would imply identical locations of the entry into a place field in each direction, but varied exits. (2) The place fields in the two directions can cross, such that phase precession measures travel through the place field. This would imply that the center of the place field would be identical from any direction. (3) The place fields in the two directions could end at the same point, precessing inward, suggesting that place fields predict distance from a future goal. This would imply that the entry of the place field would differ between directions, but exits from the place field would coincide. This question was definitively settled by a pair of recent papers carefully examining bidirectional place fields (on the cue-rich linear track, Battaglia et al., 2004, and on the cylinder foraging task, Huxter et al., 2008). In both of these papers, place fields were found to shift between directions such that they ended at the same location, definitively confirming the third hypothesis: place fields predict distance to a goal (Lisman & Redish, 2009).

This hypothesis also suggests that phase precession should depend on forward motion of the animal. Unfortunately, when rats stop moving, the hippocampus no longer shows place fields or the theta rhythm. However, in a recent pair of experiments, Buzsaki and his colleagues examined animals running on a fixed wheel, so that the animals were in motion (thus showing theta) but not moving in space. Hirase et al. (1999) found that place cells of animals simply placed in the running wheel within their place fields showed continuous firing at a single phase

of theta. In contrast, Pastalkova et al. (2008) found that animals who had to run in the wheel for a set time (thus with a goal) showed clear phase precession. These data strongly suggest that phase precession is related to the presence of a goal. As shown in Figure 3, thinking of phase precession at the ensemble level provides a clear explanation for the differences between these processes. In a recent study of spatial decision-making, Johnson & Redish (2007) found that during deliberative pauses, spatial representations swept ahead of the animal, first down one potential path and then down the other. Although the animals were paused, the hippocampus remained in the theta-state, likely due to the presence of attentive theta (O'Keefe & Nadel, 1978), and the observed sequential firing was aligned to the theta rhythm, much like phase precession.

Phase precession entails sequential representations of paths towards a goal, and is likely related to planning, spatial navigation abilities, and goal-finding. It is possible to disrupt the sequential representations of phase precession without disrupting the place fields themselves (Robbe & Buzsaki, 2009). Disrupting these sequences has profound effects on an animal's ability to navigate, particularly on hippocampally-dependent spatial memory tasks (Robbe & Buzsaki, 2009; Pastalkova et al., 2008).

Replay. Although hippocampal place cells fire the vast majority of spikes in their place fields, they also occasionally fire spikes outside the place field, most notably at locations where the animals pause and rest at reward-delivery sites (O'Keefe & Nadel, 1978; Redish, 1999). If one decodes the spatial position represented at a given time by a recorded hippocampal ensemble, the position decoded reflects the position of the animal (Wilson & McNaughton, 1993; Zhang et al., 1998), particularly once the place fields have stabilized with experience (Wilson & McNaughton, 1993; Kentros et al., 1998; Frank et al., 2004). However, at reward

sites, decoded positions do not reflect the current position of the animal; instead, they reflect other positions in the environment and in previously experienced environments (Kudrimoti et al., 1999; Jensen & Lisman, 2000; Jackson et al., 2006; Karlsson & Frank, 2009). During these pause times, the hippocampus switches modes such that the local field potential no longer shows the 7 Hz theta rhythm, but rather shows a more broad spectrum local field potential termed LIA (“large amplitude irregular activity”), punctuated by 200 Hz bursts termed “ripples” or “sharp waves” (O’Keefe & Nadel, 1978; Buzsaki et al., 1983).

These representations not only entail firing of a coordinated set of out-of-field place cells, but also the lack of firing of in-field place cells. These phenomena were first discovered during sleep and were shown to entail a “reactivation” or “replay” of recently experienced spatial memories — the specific pattern of neural firing seen during behavior is repeated during the subsequent sleep (Wilson & McNaughton, 1994; Kudrimoti et al., 1999).

It is still unclear how much these replays and reactivations drive an improvement of representation within the hippocampus itself (Buzsaki, 1989), a coordination of memory across cortical structures (Teyler & DiScenna, 1985; Alvarez & Squire, 1994), or actual information transferred to cortical structures (Marr, 1971; McClelland et al., 1995). These issues are still unresolved (see Sutherland & McNaughton, 2000, and Nadel & Moscovitch, 1997, for reviews). Nevertheless, there is clear evidence for a role of sharp waves in learning (Girardeau et al., 2009; Ego-Stengel & Wilson, 2010), as well as an interaction between hippocampus and downstream structures. Several cortical areas show reactivation of representations after behavior, including visual cortex (Ji & Wilson, 2007), prefrontal cortex (Euston et al., 2007), and coordinated activity across cortical ensembles (Hoffmann & McNaughton, 2002). However, it is not yet known whether cortical representations can reactivate without hippocampal input. Sharp wave

events in hippocampus also have effects on non-cortical structures: they trigger reactivation of reward-related activity in the portions of nucleus accumbens known to receive hippocampal input (Lansink et al., 2008).

As noted above, in addition to reactivation during subsequent sleep, hippocampal ensembles also reactivate during awake, rest behaviors when the hippocampus transitions from the theta to LIA states (Jackson et al., 2006; Karlsson & Frank, 2009). Just as reactivation is higher during sleep after behavior than before (Wilson & McNaughton, 1994; Kudrimoti et al., 1999), reactivation increases throughout experience on a task (Jackson et al., 2006; O'Neill et al., 2006) and preferentially represents other tasks after a behavior rather than before (Jackson et al., 2006; Karlsson & Frank, 2009).

-- Figure 4 about here. --

While replay during sleep has so far only been shown to be forward in order (that is, to be a replay of the recent paths, Skaggs & McNaughton, 1996; Nadasdy et al., 1999), “replay” during awake, rest behaviors has now been shown to include both forward, backward, and even novel sequences (Foster & Wilson, 2006; Davidson et al., 2009; Gupta et al., 2010). The presence of novel sequences never experienced by the rat implies that there may be a second role for hippocampal replay: that of mental exploration, possibly linking together separate components of a cognitive map.

Context sensitivity. Remapping of place fields seems to be primarily random between environments, that is, the probability of a cell having a place field in one environment and the location of the field in that environment is independent of whether the cell has a field in another environment or the location of the field in the other environment (Muller & Kubie, 1987; Barnes et al., 1997; Guzowski et al., 1999; Redish, 1999). Some studies have, however, also reported

partial remapping, in which some cells show similar representations between two visually-similar environments (e.g. Skaggs & McNaughton, 1998). These similarities, however, may be due to realignments of the dead reckoning coordinate system in each box (Redish & Touretzky, 1998b); separating the dead reckoning coordinate systems between the two boxes increases remapping (Fuhs et al., 2005; Colgin et al., 2010).

Map-selection occurs via a categorization process (likely involving pattern separation in DG and pattern completion CA3). Bistability in map recall ability should produce bimodality in water maze performance on a trial by trial basis — recall of the correct map would allow proper navigation to the goal, while recall of the incorrect map would leave the animals lost. This is exactly what was found (Barnes et al., 1997): proper navigation requires not only locating oneself correctly, but also locating oneself on the correct map.

If different tasks or subtasks within an environment were represented by different maps, place cells switching place fields would appear to be sensitive to non-spatial signals (Redish & Touretzky, 1997). If the animal divided its attention between two maps, repetitive map switching would appear as noise in the activity of place cells as the animal traverses the place field (Olypher et al., 2002). Both of these phenomena occur.

As noted above, under certain conditions, place cells are sensitive to other factors beyond the spatial location of the animal. (See Redish, 1999, for a review of the primary literature on this topic.) The multiple-map hypothesis suggests that these non-spatial sensitivities are due to changes in the underlying active map. Directional sensitivity depends on regularity of the traversals of the paths (Markus et al., 1995); sensitivity to subtask components depends on the different goal orientations rather than the cues provided (Eichenbaum et al., 1987); sensitivity to episodic events develops with experience and depends on the salience of the event (Moita et al.,

2004). For example, place fields remapped after being exposed to a fear-conditioning experiment (Moita et al., 2004).

In simple foraging tasks, place cells show unexpectedly high variability in spiking on different traverses through a place field (Fenton & Muller, 1998). On goal-directed tasks, the variability in spatial firing of place fields drops (Olypher et al., 2002), such that at times when animals are approaching a single goal the variability closes in on the expected inherent variability due to other factors (Jackson & Redish, 2007; Keleman & Fenton, 2010). When forced to avoid shock in two different reference frames, hippocampal representations switch between those reference frames, but tend to be in the relevant reference frame when the animal was close to the shock zone in a given reference frame (Keleman & Fenton, 2010).

Analogously, in experiments that place dead-reckoning in conflict with external cues (Gothard et al., 1996, 2001; Redish et al., 2000), animals were unable to find a reward unless the hippocampus had reset to the correct coordinate frame (Rosenzweig et al., 2003).

Inputs to hippocampus. The primary informational input into the hippocampus comes from entorhinal cortex, which is divided into the medial and lateral entorhinal cortex (MEC and LEC, respectively). Early studies of MEC found that MEC cells contained spatial information (Quirk et al., 1992) However, our understanding of representations in medial entorhinal cortex took a quantum leap forward with the discovery of grid cells by Fyhn et al. (2004): these cells show multi-peaked tuning curves to spatial location in a triangle tessellated pattern. (See Figure 5.) Grid cells cover the space, and contain sufficient spatial information to decode position (Hafting et al., 2005). The spacing of the triangular tessellation (the “grid”) increases from dorsal to ventral MEC, paralleling the increased place field sizes seen in hippocampus (Hafting et al., 2005; Kjelstrup et al., 2008).

-- Figure 5 about here --

As noted above, the hippocampus seems to be an association between spatial coordinates (the dead reckoning or “path integration” system) and external cues (the “local view”). This means that when the internal spatial coordinate system shifts, the external cues will be misaligned, suggesting to the animal that it is in a different environment, which should drive a remapping process (Redish & Touretzky, 1998b; Redish, 1999). Fyhn et al. (2007) explicitly tested this by examining the changes in grid cell firing under conditions in which place fields shifted or remained constant. In cases in which there was only limited remapping (rate remapping), the grid cell population remained constant, but in cases in which there was total remapping (map shifting), the grid cell population shifted and/or rotated its grid fields (Fyhn et al., 2007). Interestingly, the grid cells themselves translated or rotated as a group, like head direction cells², but unlike the hippocampal place cells, which remapped.

The multiple-map theory of hippocampal spatial representations suggests that spatial and non-spatial information should enter the hippocampus through different pathways (Redish, 1999; Manns & Eichenbaum, 2006; Henriksen et al., 2010). Early studies found spatial representations in medial entorhinal cortex (Quirk et al., 1992), but there were no reports of spatial representations in lateral entorhinal cortex. This question was settled by Hargreaves et al. (2005), who found that medial entorhinal cells showed more spatial information than lateral entorhinal cells. Similarly, recordings of postrhinal cells showed spatial firing, while perirhinal cells did not. In general, the postrhinal cortex tends to receive spatial input, predominantly from the cingulate, parietal, and occipital cortices, while the perirhinal cortex tends to receive polymodal, less spatial input, predominantly from piriform, frontal, and insular cortices (Furtak et al., 2007).

These data suggest that two pathways converge on the hippocampal formation: a spatial

pathway (parietal, postrhinal cortex, and medial entorhinal) combined with a contextual, object-recognition, less-spatial pathway (polymodal sensory, perirhinal cortex, and lateral entorhinal). However, current detailed anatomical studies of the entorhinal/hippocampal interaction suggest that the detailed connectivity may be both more complete and more segregated than these earlier studies imply (see van Strien et al., 2009).

Spatial Representations in the Human Medial Temporal Lobe

Similar to rats, experimental lesion work suggests that damage to the human hippocampus impairs several forms of spatial cognition. These include memory for the spatial relations of multiple objects in an arena (Bohbot et al., 1998), the spatial relations of objects within a scene (Hartley et al., 2007), learning spatial information from a shifted view-point (King et al., 2002), drawing maps of recently learned virtual environments (Spiers et al., 2001), and learning virtual analogues of the Morris Water Maze and the 8-arm maze (Goodrich-Hunsaker et al., 2010). Hippocampal contributions appear particularly pronounced when patients with hippocampal lesions have to remember multiple spatial routes to different locations or several different spatial environments with distinct routes (Corkin, 2002; Bohbot et al., 2007). For example, patients with hippocampal lesions did not show deficits when retrieving a single route to a hidden location but were impaired when retrieving the location of multiple hidden objects within a spatial environment (Bohbot et al., 1998, 2007). These findings suggest that the human spatial memory system may be similar to the rodent, with computations involving multiple routes and environments largely dependent on an intact hippocampus.

The neural basis of human spatial memory relies on more than hippocampus alone. Additionally, the human hippocampus likely plays a role in more than just spatial cognition. As with rodents, there is reason to believe that some of this "extra-spatial" hippocampal function

may relate to a more general role in episodic memory (Cohen & Eichenbaum, 1993), which we will discuss in more detail later in this chapter. It is clear that other brain systems, such as the parahippocampal cortex and retrosplenial cortex, also support spatial memory in humans. As we shall see, these include visual-spatial scene processing and survey representation.

Human spatial navigation: Role of the parahippocampal cortex in spatial processing. Several studies suggest that some forms of spatial memory remain intact following hippocampal damage. This includes the ability of hippocampally-damaged patients to find the location of a recently learned hidden object within a room (Bohbot et al., 1998) and to perform eye-movements to the locations of recently learned spatial cues (Ploner et al., 2000). Along these lines, the classic patient H.M., one of the first studied patients with medial temporal lobe damage, did not show deficits in many aspects of spatial memory, including knowledge of the layout of his apartment (Corkin, 2002; Bohbot & Corkin, 2007). However, the posterior parts of H.M.'s hippocampus, which other studies have suggested might be important for spatial processing (Hartley et al., 2003), were largely intact (Corkin et al., 1997). H.M., however, was deficient on learning new spatial routes, particularly storing and retrieving multiple new spatial routes, suggesting that the parts of his hippocampus damaged were at least relevant for some forms of spatial processing (Bohbot & Corkin, 2007).

Consistent with a role for extra-hippocampal regions in spatial processing, several findings suggest that the posterior parahippocampal cortex, an area in humans that receives strong input from visual areas (Witter, 2002), provides some "simple" allocentric processing of visual-spatial information (Burgess et al., 2002; Bohbot & Corkin, 2007). Consistent with this argument, some of the same lesion studies cited above showed that patients with parahippocampal lesions³ had profound deficits in the same spatial tasks on which patients with

more exclusive hippocampal damage did not show deficits (Habib & Sirigu, 1987; Bohbot et al., 1998; Ploner et al., 2000). Together, these data suggest a critical role for the parahippocampal cortex in spatial memory, particularly in visual-spatial processing.

fMRI studies of visual-spatial processing in medial temporal lobe. Although fMRI is based on an indirect measure of neural activity using the blood oxygen-level dependent (BOLD) signal (Ogawa & Lee, 1990), it remains one of the few techniques for observing neural activity in deep brain structures such as the hippocampus. However, fMRI is not a direct measure of neural activity and its exact relation to underlying neural activity remains an area of active research (Logothetis, 2008). Several studies suggest that the BOLD signal in the visual cortex and other neocortical areas such as the parahippocampal cortex reflect synaptic activity (Logothetis, 2008; Ekstrom et al., 2009), similar to what might be observed with invasive electroencephalography (iEEG, equivalent to the local field potentials [LFP] in the rat). However, the exact relation between the BOLD signal and neural activity in the hippocampus remains unclear (Ekstrom, 2010). Even at the highest resolutions, it is unlikely that fMRI can provide a window into the activity of single neurons, particularly in areas such as the hippocampus that utilize sparse coding (Logothetis, 2008; Ekstrom et al., 2009). The fact that fMRI is unlikely to reflect the activity of single neurons in an area such as the hippocampus under most behavioral conditions puts obvious limitations on using fMRI as a means to measure things like place cell activity. However, fMRI is also one of the few methods available that can be used with individuals free of any neurological impairment. While invasive recordings and lesion studies provide direct information about a structure such as the hippocampus, they are limited to patients with clinical conditions such as epilepsy. Thus, while not a direct measure, assuming the appropriate caution, fMRI provides valuable evidence about the functions of areas

such as the hippocampus and parahippocampal cortex during navigation. Because fMRI is a non-invasive tool and can thus be conducted routinely with healthy subjects, its convergence with lesion and invasive studies is particularly informative to our current considerations.

Several fMRI studies support a role for the parahippocampal cortex in allocentric spatial scene processing. The parahippocampal cortex typically activates during scene processing and virtual navigation (Aguirre et al., 1996; Epstein & Kanwisher, 1998; Epstein, 2008; Ekstrom et al., 2009) and shows less activation in blind subjects who imagine navigating compared to sighted controls (Deutschlander et al., 2009). Committeri et al. (2004) further showed that when subjects viewed two objects in a visual scene and made judgments about which of the two objects is closer to a third landmark, the parahippocampal cortex showed greater activation than when they made judgments about which object was located closer to them. Janzen & van Turennout (2004) demonstrated greater parahippocampal activation when subjects viewed landmarks that they used to successfully locate targets compared to viewing landmarks without navigational relevance to which they nonetheless attended. These findings then suggest that the parahippocampal cortex plays a role in simple scene processing, allocentric processing of visual-spatial information, and processing of landmarks during navigation.

Invasive recordings in humans implicate hippocampus and parahippocampal cortex in distinct aspects of spatial navigation. Ekstrom et al. (2003) recorded directly from 317 neurons in the hippocampus, parahippocampal cortex, and other areas (frontal lobes and amygdala) of epileptic patients while they performed a virtual navigation experiment. In the task, patients freely explored a two-dimensional virtual environment, searching for passengers and delivering them to salient landmarks. Ekstrom et al. (2003) found cells in the hippocampus that responded robustly to spatial location (Figure 6); these neurons did not show changes in firing

rate for viewing landmarks. Many of these neurons also showed modulations according to the patient's goal, changing firing rate depending on the store that a patient searched for, reminiscent of findings in the rodent (Ferbinteanu & Shapiro, 2003; Ainge et al., 2007). In addition to neurons responsive to spatial location, Ekstrom et al. also found cells that increased firing dependent on what landmark a subject viewed. These neurons were active from a variety of spatial positions, consistent with previous studies in the monkey that have also noted view-responsive neurons within the hippocampus and parahippocampus gyrus (Rolls & O'Mara, 1995). Together, these data support a possible division of labor within the hippocampus and parahippocampal cortex — while neurons in the human hippocampus increased firing rate at specific locations, neurons in the parahippocampal cortex increased firing rate during viewing landmarks.

-- Figure 6 about here --

A second study by Jacobs et al. (2010) investigated epilepsy patients undergoing seizure monitoring, and found place responsive neurons in a virtual circular environment, replicating the findings of Ekstrom et al. (2003). Jacobs et al. (2010) found that these place-responsive neurons tended to be directionally tuned on the circular track such that they only fired when the patient navigated one way around the track and not the other, similar to findings in the rodent. Jacobs et al. also examined the firing rate of entorhinal neurons in the same task. They did not find evidence for grid-cell like firing, instead reporting that entorhinal neurons increased firing non-specifically for one direction around the circular track compared to another. One issue when considering whether this study provides evidence against grid-cells in humans is that it is not currently clear where and if the human homologue of medial entorhinal cortex exists (Insausti et al., 1995; Doeller et al., 2010). Given the differences between lateral and medial entorhinal

representations in rodents (reviewed above), the Jacobs et al. (2010) cells may have come from lateral entorhinal. At this point, the only evidence for grid cells in humans comes from an fMRI study by Doeller et al. (2010) who found evidence for hexagonal spatial correlations in entorhinal BOLD activity.

Broader Roles for the Hippocampus

Our discussion of the possible role for the hippocampus in context-dependent spatial processing begs the question of a possible larger role for the hippocampus in episodic memory. Indeed, the first studies on the classic patient H.M. suggested that his greatest deficits were in learning and remembering new events (Scoville & Milner, 1957). This finding was confirmed by later studies showing that hippocampal patients experience profound deficits in remembering locations and episodes compared to learning new facts about the world (termed “semantic” memory) (Vargha-Khadem et al., 1997). In particular, hippocampal lesions appear to have the most significant effects when patients attempt to retrieve the associated context under which they learned specific items while leaving the ability to recognize a word intact (Yonelinas et al., 2002; Holdstock et al., 2005; Diana et al., 2007). Numerous fMRI studies similarly support a selective role for the hippocampus in episodic memory, particularly in storing and retrieving recently acquired information within specific spatial and/or temporal contexts (Eldridge et al., 2005; Rekkas et al., 2005; Ekstrom & Bookheimer, 2007; Staresina & Davachi, 2009). Invasive single neuron recording studies in patients with electrodes implanted in the hippocampus learning item/scene pairings demonstrate similar results (Viskontas et al., 2006). Together, these data argue for a more general hippocampal role in episodic memory, particularly in associating items with specific experimental contexts. Analogous data exists for the rat, in which hippocampal lesions have implications beyond simple spatial abilities, particularly in the association of stimuli

with contextual representations and the ability to recall rather than simply recognize stimuli (Cohen & Eichenbaum, 1993; Redish, 1999; Eichenbaum et al., 2007).

Egocentric and allocentric representations as forms of episodic memory. One possible way to integrate the above findings on a general role for the human hippocampus in episodic memory with the place cell literature we have discussed so far is that spatial location represents a specialized case of episodic memory representation. As discussed earlier in the chapter, we can conceive of a sequence of place cells as a route or a list of items/objects. This idea would explain the involvement of the hippocampus in both route- based and context dependent memory as a form of multiple maps. According to this conception, when the hippocampus integrates item/route information with contextual representations, slight changes in context will trigger different constellations of place cells based on different maps.

Successful navigation frequently involves computation of new routes and trajectories to a location based on an interaction between the internally- and externally-driven navigation systems. This type of computation frequently involves a form of allocentric memory in which a subject must integrate internal coordinate systems with external landmarks to compute a new trajectory. An example of this type of computation would be something one might experience during driving. Having driven two different roads several times but never explored a third road that connects the two, based on the relative direction of the first two roads and locations of intersection of the third road, one can derive a means of connecting the two roads via the third road. We thus can assume, based on our internal representation of the spatial layout and information provided by the intersection of the third road (visual updating) that it may provide a short-cut to our familiar road, although we have not driven it. This type of computation is, by its very nature, flexible in that information must be utilized and computed in a novel fashion

(Eichenbaum et al., 2007; Johnson et al., 2007). A role for hippocampus in flexible decision-making can describe one possible way in which the hippocampus might be involved in egocentric and allocentric memory as well as episodic memory more generally.

Phase Precession, Future Thinking, and Episodic Memory. Armed with this theoretical framework for considering episodic memory, we can now begin to try to integrate ideas about rodent phase precession with human episodic memory. Although phase precession has yet to be demonstrated within the human hippocampus, intracranial field recordings from the human hippocampus demonstrate the presence of theta oscillations that increase with movement, much like what is seen in the rodent (Ekstrom et al., 2005). This finding suggests that at least two important components of phase precession, place cells and theta oscillations, are present in the human hippocampus, suggesting the strong possibility that phase precession is also present in the human hippocampus. A fascinating proposal relating to the function of phase precession generally in the rodent and human is the activation of specific sets of place cells to allow “sweeping” through possible sets of sequences of place cells for route planning (Jensen & Lisman, 1996; Johnson & Redish, 2007; Lisman & Redish, 2009). Thus, faced with an intersection, one could potentially envision several different routes based on previous experience and choose the correct choice based on one’s navigational goal. Although the mechanisms in humans for this type of sequential place cell activation have yet to be explored, and the evidence from rodents for the role of sequential place cell activation is as yet unknown, phase precession is an intriguing analogue that potentially relates to episodic future thinking. For example, just as one can imagine what one had for dinner last night, one can imagine what one might have for dinner tonight.

Intriguingly, constructing events in the future, referred to as *episodic future thinking*, may

involve some of the same brain circuits as remembering past episodic memory (Buckner & Carroll, 2007). A superposition of the involved brain areas is practically indistinguishable. For example, similar areas (inferior parietal lobe, frontal cortex, hippocampus) frequently show activation during both retrieval of episodic events and prospective coding (Schacter & Addis, 2007). Furthermore, patients with hippocampal lesions show deficits in imagining and constructing future events (Hassabis et al., 2007). Thus, both humans and rats possess similar neural systems for past thinking and prospective coding. How networks of cells might participate in this process is an intriguing area of future research.

Well-learned routes and semantic memory. While we have spent a significant amount of time discussing reactivation of sequences in rodents in this chapter, we have not devoted much time to this issue in humans. As yet, no single neurons recordings from humans suggest that spiking patterns during sleep and quiet wakefulness may recapitulate those during wakefulness. The only significant hint so far in this direction comes from a study with patients with implanted depth electrodes who viewed videos of familiar, famous characters and then named the videos they saw during a subsequent retrieval task (Gelbard-Sagiv et al., 2008). The pattern of neural firing rate showed significant correlations between encoding and retrieval that was specific to the video recollected. Several lines of behavioral and neuroimaging results also argue for the presence of mechanisms involved in consolidation of memories during sleep (Stickgold et al., 2000; Takashima et al., 2006; Walker, 2009). While evidence on these points is still developing, slow wave sleep likely provides one mechanism for consolidation of episodic memories and rapid eye movement (REM) sleep likely provides a means for strengthening and consolidation of motor memories (Diekelmann & Born, 2010).

Although the details of reactivation and sleep-related consolidation remains to be fully

worked out in humans, there is little doubt that episodic memories typically undergo a process of consolidation, possibly within hours and lasting years, into semantic memories (Ribot, 1882; McClelland et al., 1995; Nadel & Moscovitch, 1997). Semantic memories refer to well-learned facts about the world that may have had an episodic component at some point but due to repetition, particularly across multiple contexts, have lost their unique episodic character. An interesting analogue exists between semantic memory and spatial navigation in that semantic memory may represent a form of well-learned routes that no longer require the hippocampus (Marr, 1971; Redish & Touretzky, 1998a; Day et al., 1999; Tse et al., 2007). In the rodent, there is extensive evidence that when rats use schemas, they rely on cortical rather than hippocampal based mechanisms (Tse et al., 2007). Humans, similarly, likely utilize multiple spatial forms of representation that do not require the hippocampus and may represent spatial layouts in some cases using a more rigid, schema-like form of navigation.

Human extra-hippocampal representation: survey representation in retrosplenial cortex. In addition to the ability to represent first-person navigational information (a direct representation of visual information during navigation likely shared amongst most mammals including rodents), humans have the additional capacity to create pictorial maps of spatial environments (Thorndyke & Hayes-Roth, 1982). Humans typically create maps by picturing spatial information as if looking down on it (*a bird's-eye view*). Survey perspectives involve different cognitive strategies than first person representations because they involve visualization of the relation between different objects and their relative locations directly rather than having to integrate this information across multiple viewpoints. One interesting proposal is that survey representation may be a special case of object representation. According to this conception, a spatial layout may be rendered as a single object with multiple textures that can be

simultaneously viewed and manipulated through visual imagery (Shelton & Gabrieli, 2002; Thompson et al., 2009). This idea also suggests that survey representation should share mechanisms in common with semantic memory because the operations occur based on familiar layouts of objects and their axes (Shelton & Gabrieli, 2002). Survey representation likely derives largely from parietal and retrosplenial interactions, particularly those concerned with representation of objects within space (Galati et al., 2010), rather than depending directly on the medial temporal lobes. It is a very interesting, but as yet unknown, question whether such survey-like representations also occur in rodents.

Summary

In this chapter, we have explored spatial and non-spatial representations in rodent and human hippocampus. Recordings from both rodents and humans show clear evidence of spatial representations in place cells, but both also include non-spatial representations as well. In the rodent, non-spatial information modulates the spatial, in particular, in the representation of maps and coordinate reference frames. It has been firmly established that the human hippocampus plays roles beyond navigation, particularly in remembering past episodes and planning future events. Experiments in the rodent suggest similar critical roles in episodic memory, and intriguingly, recent experiment analyzing representational sequences in rodent hippocampus suggest possibly roles in planning future events as well.

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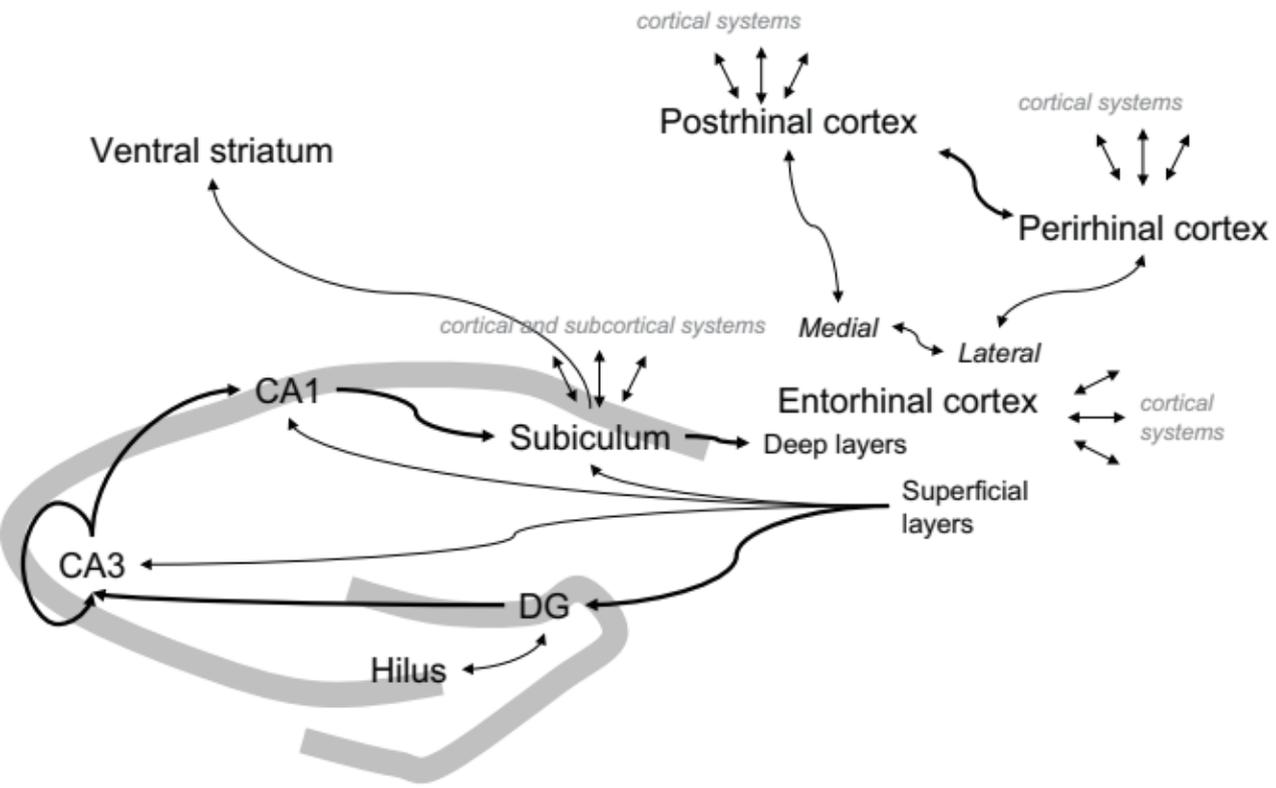
Footnotes

1. It is important to distinguish “path integration” in the sense of maintaining a representation of a distance to a home-base from “path integration” meaning integration over a path variable (sometimes referred to as a “path integral”). In order to reduce confusion, we will consistently use the term “dead reckoning” for maintenance of a position representation, updated from motion cues (Gallistel, 1990).

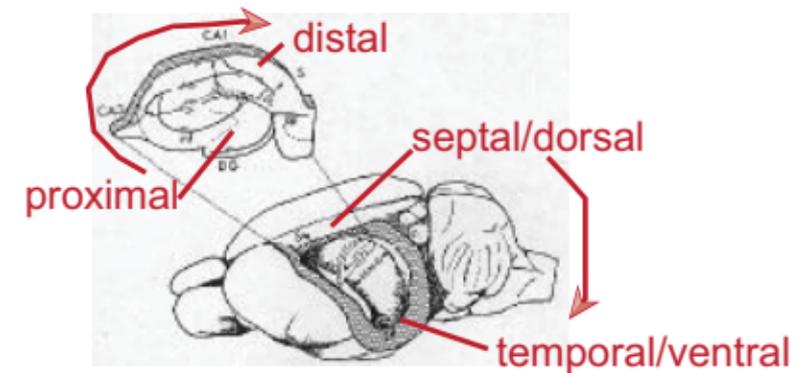
2. Head direction cells are the other primary spatial tuning curve seen in rat navigation tasks. They show generally unimodal tuning curves to the orientation of the rat in space (the direction in space that the head is facing). They are found in a network of structures, including postsubiculum, entorhinal cortex, the dorsal nucleus of the anterior thalamus, and the lateral mammillary bodies. Generally, they have properties similar to place and grid cells: (1) they show landmark sensitivity, but those landmarks are associated with internal representations, not the other way around, and (2) they do not remap between environments. See Taube (2007) and Redish (1999) for reviews.

3. Since parahippocampal cortex is one of the major inputs into the hippocampus (via entorhinal cortex), these lesions may affect functionality in the hippocampus. It is also important to consider that lesions in humans are opportunistic — human lesions are produced for a reason

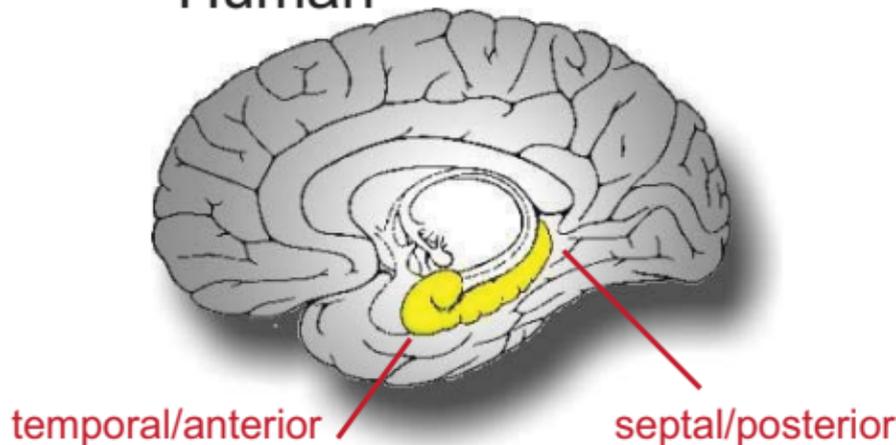
other than the actual experiment being performed (usually due to stroke or surgical intervention, such as to treat seizures). Neither of these types of lesions can be expected to strictly obey anatomical boundaries. In most studies, though, including the ones cited above, authors typically demonstrate focal deficits based on structural MRIs. These caveats about patient lesions studies are important to keep in mind, and argue for the importance of validating these findings using other testing modalities. In the case of parahippocampal cortex involvement in navigation, fMRI studies also argue for a role for this structure in spatial cognition.



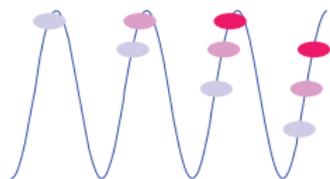
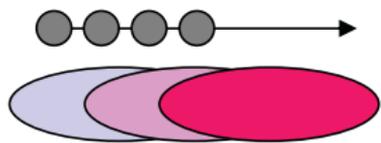
Rat



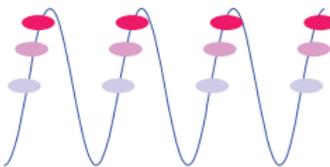
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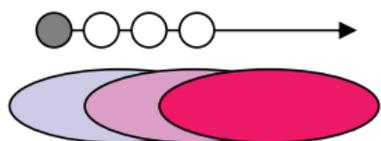
A Linear progression towards a goal.



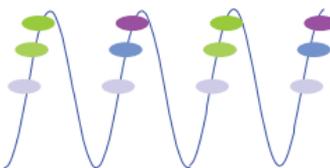
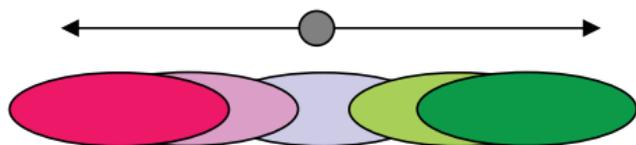
B Stable position. (Hirase et al 1998)



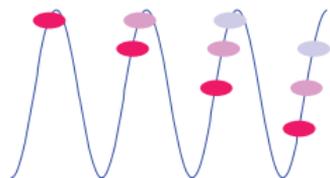
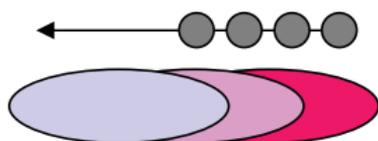
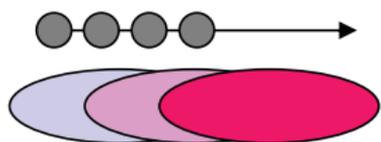
C Mental progression towards a goal. (Pastalkova et al 2008)



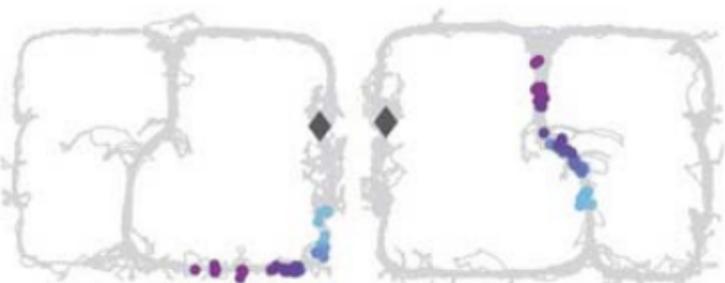
D Deliberation. (Johnson and Redish, 2007)



E Bidirectional phase precession (Battaglia et al 2004, Huxter et al 2008)



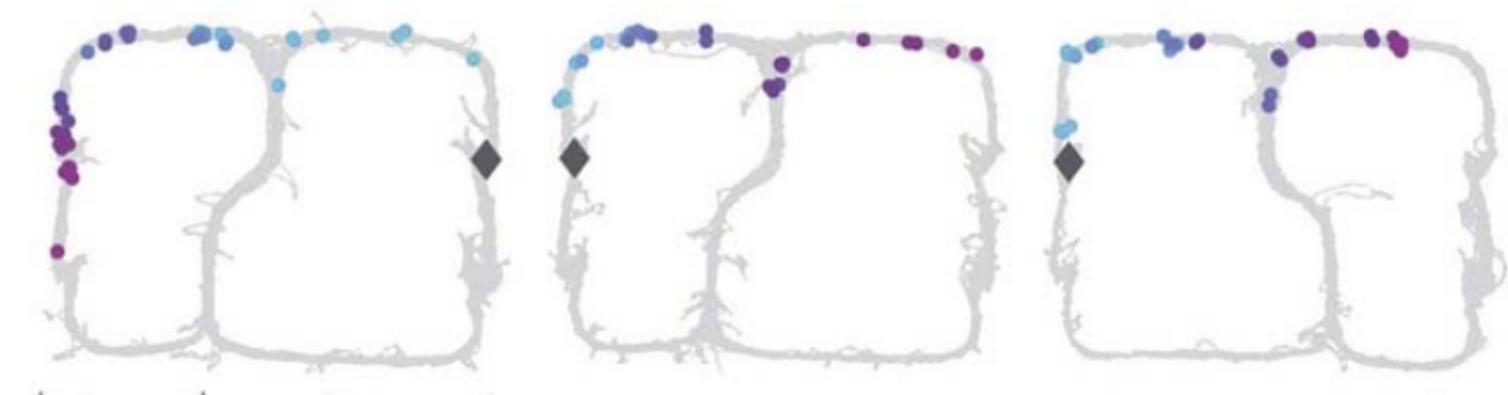
forward sequences



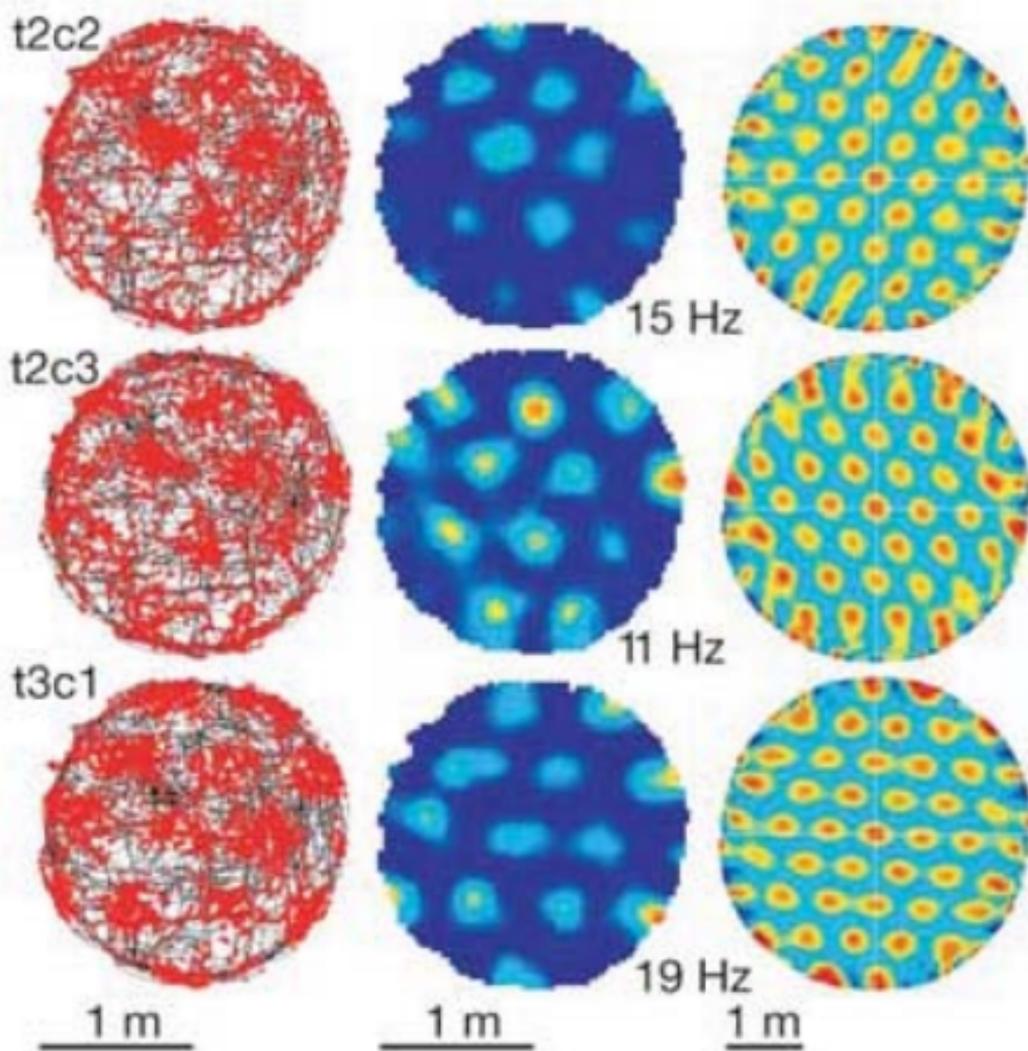
backward sequences

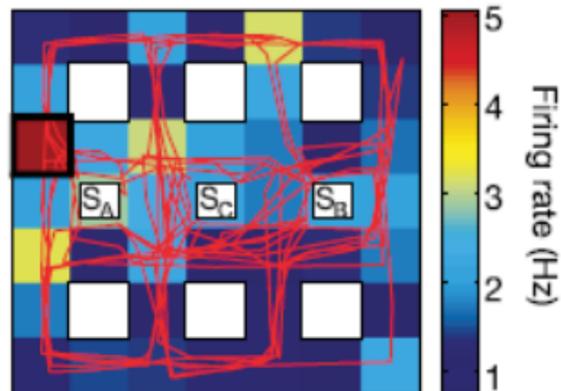
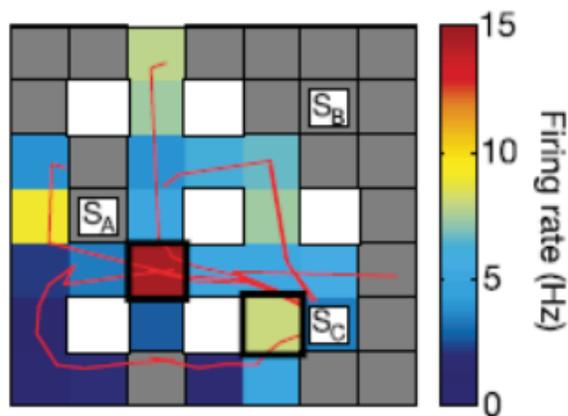
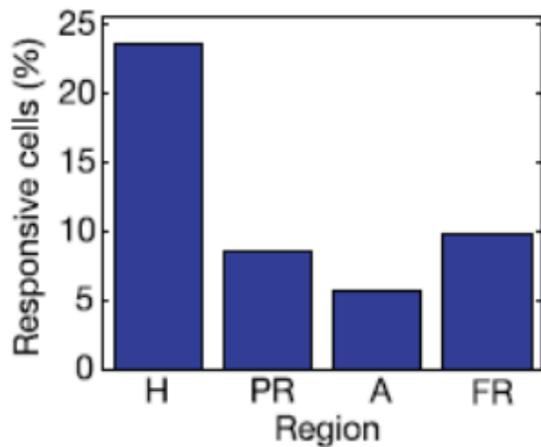


shortcut / untravelled but conjoined paths



start  end



a**d****b****e**