nature neuroscience

Memory, navigation and theta rhythm in the hippocampal-entorhinal system

György Buzsáki[1] & Edvard I Moser[2]

Theories on the functions of the hippocampal system are based largely on two fundamental discoveries: the amnestic consequences of removing the hippocampus and associated structures in the famous patient H.M. and the observation that spiking activity of hippocampal neurons is associated with the spatial position of the rat. In the footsteps of these discoveries, many attempts were made to reconcile these seemingly disparate functions. Here we propose that mechanisms of memory and planning have evolved from mechanisms of navigation in the physical world and hypothesize that the neuronal algorithms underlying navigation in real and mental space are fundamentally the same. We review experimental data in support of this hypothesis and discuss how specific firing patterns and oscillatory dynamics in the entorhinal cortex and hippocampus can support both navigation and memory.

Navigation is based on two interlinked mechanisms for representation of the spatial environment[1,2], one that provides static position information in a reference frame and another that calculates coordinates based on integration of motion and knowledge of previous positions. The first is often referred to as map-based or allocentric navigation (**Fig. 1**), in which the spatial relationships among landmarks assist in defining the animal's location in the environment[3]. The spatial metric needed for the estimation of distances between landmarks is believed to arise from a second mechanism, often referred to as path integration or egocentric navigation. Path integration requires active movement of the body and computes the distances and turns of the animal as it explores the environment; this mechanism allows the animal to return to its home base using the shortest route[1,2,4,5] (**Fig. 1**). The essential components of the self-referenced navigation system are locomotion speed, elapsed time, head direction and the initial reference position[5]. Map-based and path integration-based representation always work together, but the availability of external landmarks may determine whether allocentric or egocentric strategies dominate. In cue-rich environments, representations may be updated frequently by changes in the configuration of sensory inputs. In environments with few stationary landmarks or complete darkness, path integration may be the default mode[6–8].

The brain systems involved in guiding navigation, the hippocampus and entorhinal cortex, are the same that support declarative memories[9,10]. How are the navigation mechanisms, then, related to the mental 'travel' of memory[11] and planning? As in the dichotomy of the spatial representation, two forms of declarative memory can be distinguished[10]. Semantic memory explicitly defines living things, objects, facts and events of the surrounding world independently of temporal context[10,12], much as an allocentric map defines a location largely independently of how the animal got there. Episodic memory, in contrast, endows the individual with the capacity to learn and recall first-person experiences in the context of both space and subjective time[12] and to use such information for planning actions[13,14], in the same way as location sequences are linked together by a neural path integrator. It has been suggested that explicit, semantic knowledge is acquired progressively as similar episodes are encoded repeatedly by the self-referenced episodic memory system, so that knowledge eventually becomes context independent[10,15,16]. This gradual process is reminiscent of the formation of allocentric maps based on repeated exploration of the environment[17]. The clear parallels between allocentric navigation and semantic memory, on one hand, and path integration and episodic memory, on the other, raise the possibility that the same networks and algorithms support both physical and mental forms of travel. However, this hypothesized evolutionary link does not imply that spatial memory 'incorporates' all memories or that all memories should have spatial components.

To support memory effectively, a neural system evolved for navigation must meet two more requirements. It must have the capacity to store large quantities of seemingly unrelated, or orthogonal, representations, and it must be able to self-generate temporally evolving cell assembly sequences. We suggest that the hippocampus–entorhinal cortex system has the anatomical and physiological properties that make it especially suitable for meeting these requirements and present data that support the hypothesis of phylogenetic continuity of navigation and memory. Most experiments that we discuss were carried out on rodents, but we believe that the conclusions and interpretations based on these 'simpler' animals bear validity for the mechanisms in the human brain as well.

Allocentric maps and semantic memory

There is a general agreement that explicit memories depend on the entorhinal cortex–hippocampal system[10,18], although debate persists whether consolidated semantic information becomes hippocampus independent or continues to depend on the hippocampus forever[19–21]. In the following section, we shall discuss the neuronal processes that

[1]NYU Neuroscience Institute and Center for Neural Sciences, New York University, New York, New York, USA. [2]Kavli Institute for Systems Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway. Correspondence should be addressed to G.B. (gyorgy.buzsaki@nyumc.org).

Received 19 October 2012; accepted 9 December 2012; published online 28 January 2013; doi:10.1038/nn.3304

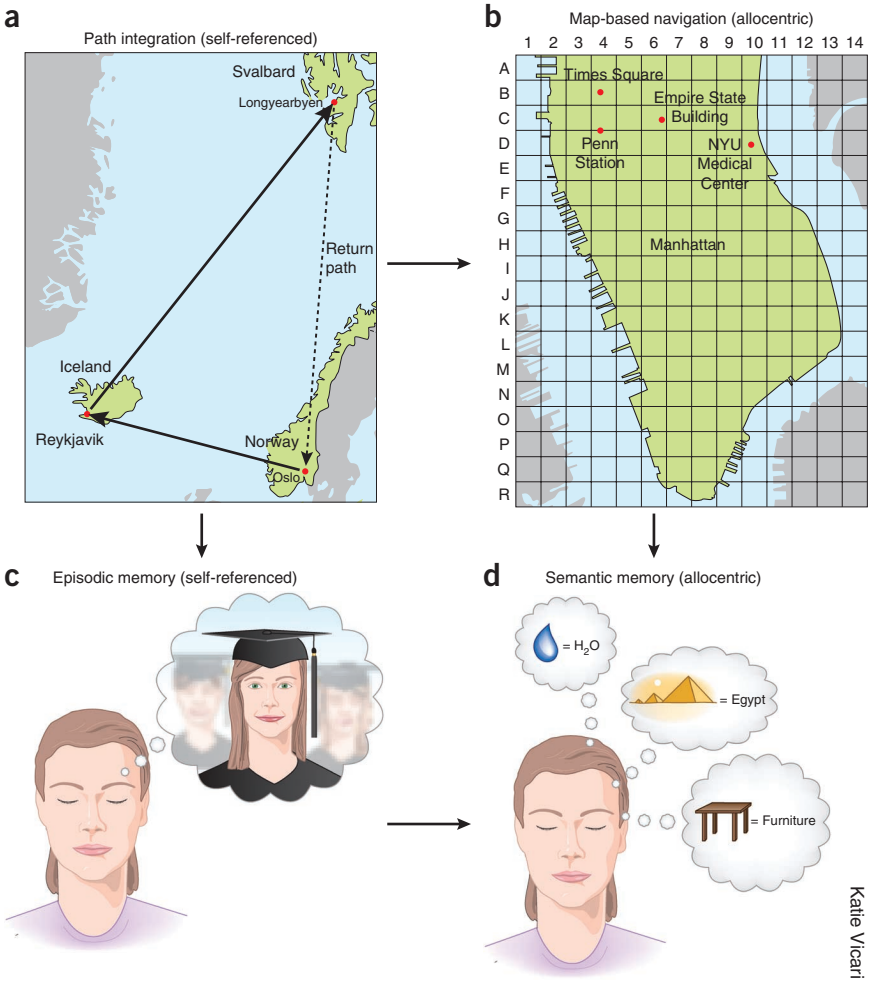

Figure 1 Relationship between navigation and memory. (**a**) Path integration (also known as dead reckoning) is based on self-referenced information by keeping track of travel distances (time elapsed multiplied by speed) and direction of turns. Calculating translocation relative to the start location allows the animal to return to the start along the shortest (homing) path. (**b**) Map-based navigation is supported by the relationships among visible or otherwise detectable landmarks. A map is constructed by exploration (path integration). (**c**) Episodic memory is 'mental travel' in time and space referenced to self. (**d**) Semantic memory is explicit representation of living things, objects, places and events without temporal or contextual references. Semantic knowledge can be acquired through multiple episodes with common elements. We hypothesize that the evolutionary roots of episodic and semantic memory systems are the dead reckoning and landmark-based forms of navigation, respectively.

support allocentric, map-based navigation[22] and illustrate how these algorithms might at the same time support semantic memory. Our central claim is that the neuronal mechanisms that evolved to define the spatial relationship among landmarks can also serve to embody associations among objects, events and other types of factual information.

An animal's spatial coordinates are encoded by a range of interacting cell types with defined activity profiles. The two most striking firing patterns are perhaps those of the 'place cells', discovered in the hippocampus[1], and the 'grid cells', discovered in the medial entorhinal cortex (**Fig. 2**)[23]. Grid cells have multiple firing fields that span the entire available space in a periodic hexagonal pattern, which provides a metric to the neural representation of space[23]. Grid cells are present throughout the medial entorhinal cortex and in the pre- and parasubiculum but are most abundant in layer 2 of medial entorhinal cortex[24,25]. Deeper layers often contain cells with stronger representation of some grid axes than others[26], and grid cells are intermingled with head direction cells[25]. In addition, the medial entorhinal cortex contains a smaller number of 'border cells', which line up in specific orientations along specific geometric boundaries of the environment[27]. These cell types were all discovered in rats, but place cells, grid cells and head direction cells have since been found in other species[28–30].

The functions of each cell type are yet to be determined, but the periodic fields of the grid cells provide a metric to the neural representation of space, in the same way that head direction cells provide a directional reference frame. Border cells may assist in the assessment of the allocentric distances by triangulation and perhaps in scaling the grid size to accommodate to the size of the discoverable environment. The availability of direction, position, distance and boundary information in the entorhinal cortex makes this brain

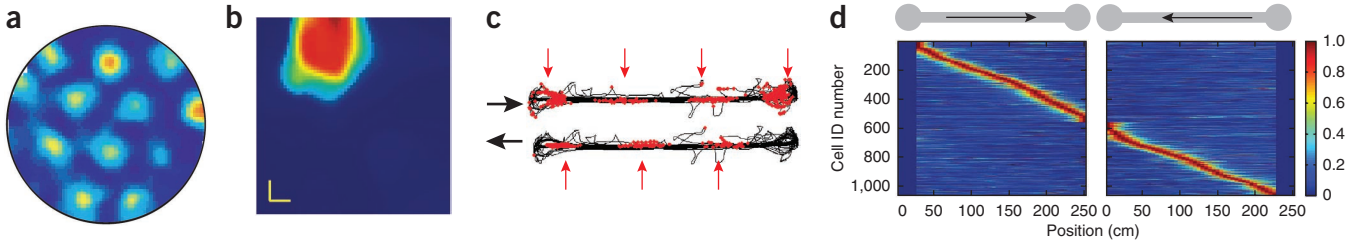

Figure 2 Grid cells and place cells. (**a**–**d**) Firing patterns of entorhinal (**a**,**c**) and hippocampal (**b**,**d**) principal cells in a two-dimensional open field (**a**,**b**) and one-dimensional track (**c**,**d**). (**a**) Grid cell from layer 2 of the entorhinal cortex recorded from a rat exploring a 2-m cylinder. Note increased firing rates (warmer colors) throughout the environment at the apexes of tiling triangles. (**b**) Singular place field of a CA1 pyramidal neuron recorded from a rodent exploring a square 1 × 1 m. Firing rate of the neuron is color-coded. (**c**) On a 2-m-long linear track, entorhinal neurons fire at regular intervals (red arrows) but at different positions during left and right journeys. (**d**) Firing rates of pyramidal cells on a track. CA1 pyramidal cells have typically a single field, present mainly in one direction of travel. Each row represents a neuron. Firing rates are peak-normalized, color-coded and ordered by their peak rates during right or left direction (arrow) of travel. Panels **a**,**c** reproduced with permission from ref. 23, **b** from ref. 74 and **d** from ref. 35.

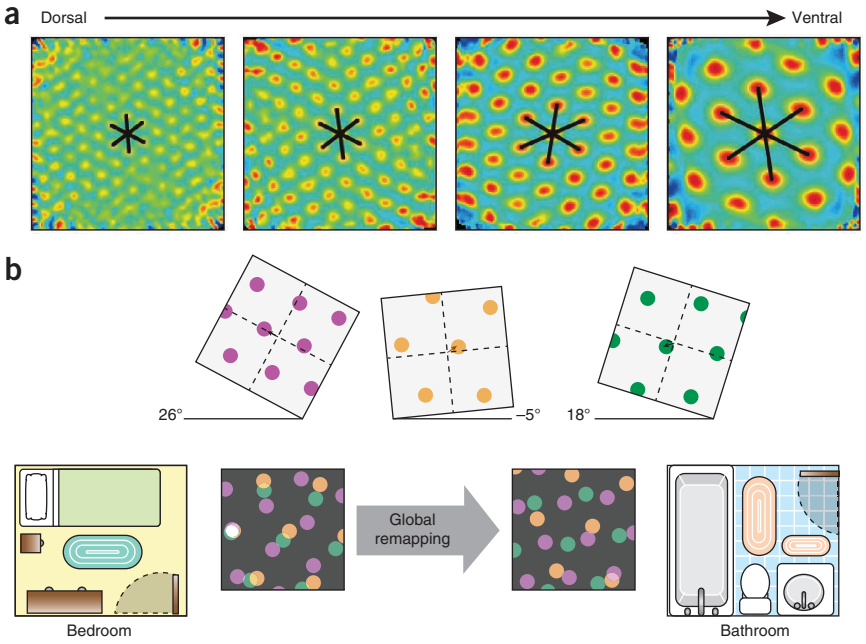

Figure 3 Modular organization of the grid-cell network. (**a**) Stepwise increase of grid spacing at successive dorsoventral levels of medial entorhinal cortex. Spatial autocorrelograms for four example cells (one per dorsoventral module). (**b**) Remapping of hippocampal place cells in two environments. Top panels show responses of three grid cells to a change in the environment. Independent responses are illustrated by different degrees of rotation and translation. Bottom panels show inputs from the grid cells, each from a different module (purple, green and orange), at different locations in the environments. The three grid cells provide input to a particular CA3 cell (white spot at left) sufficient to cause it to fire when, and only when, the nodes of the three grids overlap. This occurs only at one location in this example. In the second environment, the altered coactivity of the grid cells activates a different subset of place cells at each location, and global remapping is observed in hippocampal place ensembles. Panel **a** reproduced with permission after ref. 32, **b** after ref. 33.

structure an ideal candidate for computing the spatial metric of the surrounding environment[22,25]. Unlike hippocampal place cells, which fire differentially in different environments[31], grid cells, border cells and head direction cells are active in all environments and often behave in a coherent manner[27]. The preservation of spatial and directional firing relationships in local ensembles of such cells implies that the entorhinal cortex generates a metric that can be applied universally across environments[5,22,23].

How could the spatial maps of the medial entorhinal cortex subserve memory formation? The organization of the grid-cell network provides some clues. Grid cells are arranged as semi-independent modules or clusters along the dorsal-to-ventral axis of the medial entorhinal cortex, with small grid scales dominating in dorsal parts and large grid scales being more abundant in ventral parts. Steps in grid scale go hand in hand with quantal shifts of orientation and asymmetry in the grid pattern[32]. Different modules may respond independently to changes in the geometry of the environment. The functional autonomy of the grid modules has important consequences for representation of space in downstream hippocampal cell populations (**Fig. 3a**). Their ability to respond differentially to reconfiguration of the environment supplies a rich combination of efferent patterns to the hippocampus[33], which may be sufficient to generate large numbers of discrete maps individualized to the vast number of environments the animal visits in its lifetime.

The formation of numerous independent maps in the hippocampus has obvious advantages for memory formation, as it allows the network to store new representations in a manner that minimizes interference with previously stored memories. The orthogonal nature of hippocampal representations is expressed in its ability to 'remap' between experiences and environments[31] (**Fig. 3**). Even minor changes in the configuration of landmarks or the motivational context can completely alter the firing pattern of the hippocampal place cell population. As a result, each environment can be represented by a unique combination of active place cells and place fields. The apparent orthogonalization is strongest in the CA3 subfield[34,35], where firing locations of any two cells across environments are no more correlated than expected by chance[34]. By virtue of the vast and densely connected random graph of recurrent collaterals between neurons in this area[36], the CA3 region has the ability to read and register the rich combinatorial output of the entorhinal cortex grid modules. The multiplicity of representations may be generated by independent changes of grid maps in the medial entorhinal cortex, but the orthogonalization may also benefit from intrinsic architectural properties of the hippocampus. The latter may be accomplished in two steps. First, the entorhinal cortex–mediated pattern is separated into subpatterns by the distinctive and low-divergence connectivity of granule cells to CA3 targets[37,38]. Second, the CA3 region can compute the distance relations among the discretized subpatterns and represent those relationships by the synaptic weights between the CA3 place cells and CA3-CA1 projections[39]. Taken together, the combined entorhinal cortex and hippocampal mechanisms may enable the storage of very large numbers of arbitrary associations without interfering with one another.

If the hippocampal–entorhinal cortex system were developed only for navigation, the large combinatorial space and the large numbers of potential cell assembly combinations would be surprising. First, insects can navigate effectively with much simpler circuits and many fewer neurons[40]. Second, in navigating rats, the local environment can be mapped at centimeter precision by just a dozen or so grid cells[33] or place cells[41]. We suggest that the rich variety of orthogonal representations generated by the modular representation of space during mammalian evolution laid the ground for storing independent representations for the wide variety of environments and experiences encountered by the animal every day. This enlarged representational capacity of environmental details could be what distinguishes the mammalian brain from the brains of species in which navigation is based on much smaller circuits.

The growth of networks that enable the storage of millions of situations in the mammalian brain and the evaluation of the relationships among them may also form the basis for representing and categorizing explicit knowledge. The same mechanisms that define unique positions and their relationships in a map can be used to define or symbolize events, objects and living things[10,19]. Many experiments demonstrate that recognition and recall of objects or events are associated with unique constellations of firing patterns in the entorhinal cortex–hippocampal system in a variety of species[21,41–46]. Examples of semantic 'encoding' are also available from human epilepsy patients,

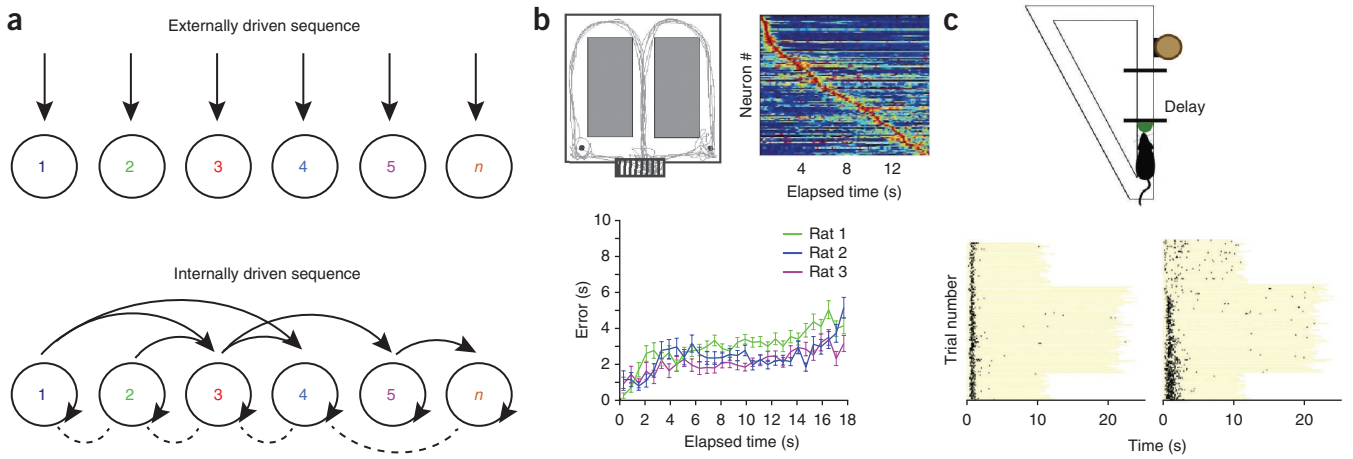

Figure 4 Cell assembly sequences, space and time tracking. (**a**) During physical travel, successive assemblies of neurons (1 to *n*) respond sequentially owing to the changing constellation of environmental landmarks and/or proprioceptive information from the body (top). During mental travel, sequential activation is supported by self-organized patterning[59]. Not only first order (neighbor) but also higher order (non-neighbor) connections can be represented in strongly connected recurrent networks. (**b**) Inferring elapsed time from self-organized cell assembly sequences during wheel running in a spontaneous alternation task. Top left, the rat's travel path superimposed on the maze. The start area is the wheel (bottom). Top right, normalized firing rate sequence of neurons during wheel running, ordered by the latency of their peak firing rates (each line represents a cell). Bottom, accumulating errors of time prediction (in seconds) calculated from a probabilistic model for inferring elapsed time from the phases of spikes with respect to theta oscillation. Note high precision of time prediction during the entire episode of wheel running. (**c**) Time tracking by neuron sequences during the delay part of a task of a working memory go/no-go task in a linear maze (top). The delay varied between 10 and 20 s in consecutive blocks, as indicated by the length of the yellow lines (bottom). Some neurons maintain their spike timing (left), whereas others 're-time' (right) when the length is abruptly changed. Panel **b** reprinted with permission from ref. 65, **c** from ref. 93.

in which selective firing of hippocampal and entorhinal cortex neurons has been evoked by specific words, objects or individuals, largely independently of their physical characteristics[47,48]. The classification of items, events and situations on the basis of semantic proximity shares many features with the distance relationship among landmarks[49]. Similarly to the embodiment of the spatial relations among objects in the cognitive map[1], models of semantic relatedness use a metric based on topological similarity and a neuronal network equivalent of vector distance for defining relationships among words[49,50], which can be ably assisted by the pattern completion and separation mechanisms of the entorhinal cortex–hippocampus system[38,51] in partnership with the neocortex[19–21].

Self-referenced navigation and episodic memory

Beyond phenomenological similarities between episodic memory and egocentric travel, recent work in humans indicates an extensive overlap in the brain networks supporting navigation, remembering the past and thinking about the future[52,53]. The key properties of episodic memory involve binding disparate and often arbitrary details together into a coherent event and the recollection of self-centered past experiences in the context of time and space in which the events occurred[1,14]. Characteristically, snippets of cues can trigger a long process of recollection, which is often grouped or chunked into shorter sub-episodes. Although re-experiencing the past appears as a continuous process, we are consciously aware of only short segments of the episodes at any one time, pointing to an important cooperation between structures and mechanisms responsible for long-term storage of declarative knowledge and working memory. Many excellent reviews have summarized the overlapping nature of brain systems involved in navigation, episodic memory, imagination and planning of actions[1,10,18,52,53]. Below we will discuss the physiological mechanisms that may support these seemingly disparate functions, focusing on self-organized cell assembly sequences, multiple-timescale representation and theta oscillations.

Episodic recall by internally generated cell assembly sequences. How does the brain generate and store sequences? We hypothesize that the mechanisms for representing a path through an environment are similar to those used to represent sequences in memory (**Fig. 4a**). Like the position-dependent sequential firing of neurons along a linear path, sequences of arbitrary items in episodic memory tasks are essentially unidimensional. Therefore, the same encoding mechanisms can be used for temporal integration of positions and episodic items[54]. The dominantly unidirectional linking of items in episodic memory, analogous to linking of place cells[55], can explain two important principles of free recall: asymmetry, or the fact that forward associations are stronger than backward associations[56], and temporal contiguity, or the fact that recollection of an item is facilitated by the presentation or spontaneous recall of another item that occurred close in time to the item just recalled[56]. There are also key differences between mechanisms of navigation in the physical world and mental recall. A fundamental difference is that while the navigation system can rely on environmental or body-derived cues, as it does in invertebrates, 'simulated' or 'internalized' travel[12,14,57] requires internally generated cell assembly sequences (**Fig. 4**).

In addition to reporting the instantaneous position of the animal or the explicit identity of objects and events, neurons in the hippocampus can also predict where the animal is coming from or where it is going[45,58]. When environmental or body-derived signals are kept constant—for example, during running in a wheel in a memory task—perpetually changing neuronal assembly sequences are present in the hippocampus[59] (**Fig. 4b**). The unique patterns of the cell assembly sequences can reliably predict an animal's correct or even erroneous choice in a maze many seconds before the actual motor turn. It has been hypothesized that such self-organized cell assembly sequences or neural 'trajectories' underlie the numerous episodes recorded in one's lifetime[59]. Because many more sequences can be generated than the numbers of the member neurons, the syntactical rules underlying self-evolving neuronal trajectories can enormously expand the memory

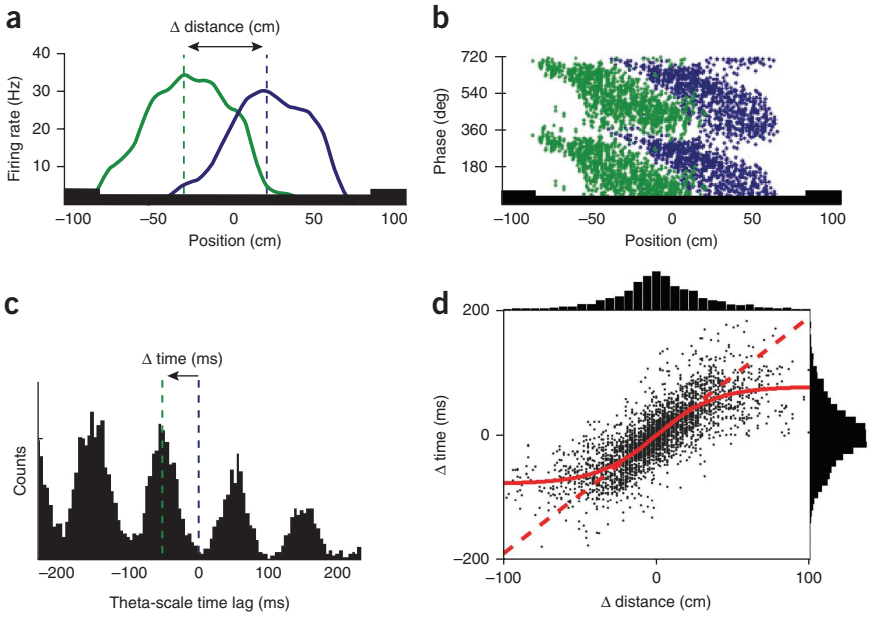

Figure 5 Theta oscillations link assembly sequences. (**a**) Overlapping place fields of two hippocampal neurons (green and blue) on a track. (**b**) Theta phase of each spike as a function of position in the place fields of the two neurons. Note precession of spikes from late to early phases as the rat crosses the place fields[83]. Two theta cycles are shown for clarity. (**c**) Cross-correlation between the reference (blue) and overlapping (green) place cells. Δ time is the time lag between the spikes of two neurons within the theta cycle ('theta time'). (**d**) Correlation between the distances of place field peaks and theta-scale time lags for >3,000 pairs of CA1 place cells. Note that the duration of the theta cycle limits distance resolution (red sigmoid curve). Panels **a**–**c** reproduced with permission after ref. 86, **d** after ref. 84.

capacity of the hippocampal system[60]. In short, assembly sequences in the hippocampus can be generated by two different but possibly interacting mechanisms, driven, respectively, by external inputs (environmental or body-derived cues) and internal self-organization (**Fig. 4a**). Self-organized cell assembly sequences disengaged from the environmental or body-derived inputs, in turn, may support mental travel.

Chunking of paths and memories. How long is a sequence? Neuronal representation of travel paths does not consist of long uninterrupted neuronal chains but are often broken up into repeating chunks by prominent landmarks, state changes or reinforcers. Furthermore, the firing characteristics of grid cells and place cells are context dependent. In corridors or on elevated tracks, the firing fields of entorhinal cortex grid cells in one direction are generally independent of the positions in the other direction[61]. Similarly, the omnidirectional place fields of hippocampal neurons[62] become unidirectional in linear environments, such that different sets of neurons are active at each location in the two directions of travel[63]. The independent representations of travel paths in opposite directions (**Fig. 2**) may reflect mechanisms similar to those underlying remapping between different environments, such as independent resetting among modules of the entorhinal cortex grid map. Chunking is even more prominent in complex environments. When different segments of a maze are geometrically similar, such as for the corridors of a hairpin labyrinth, hippocampal and entorhinal cortex neurons fire the same sequences in each corridor, although distinct sets of neurons fire on opposite journeys[7,35,64]. The chunking of the neuronal representation at each entry point can be assisted by resetting of the path integrator[7] or of the self-organized cell assembly trajectories by a new initial condition[65]. Chunking is an efficient way to limit the accumulation of error inherent in long sequences and is a frequent strategy for encoding episodic information[66]. We suggest that chunking is a common property of path integration–based navigation and episodic memory systems.

Temporal organization of exploration and episodic memory

The hallmark of episodic recall is that fragments of information in short time windows predict the spatio-temporal evolution of episodes at longer timescales[12,14]. A narrative can be initiated by a single cue and can move forward more effectively than it can move in the reverse direction[56]. We suggest that both of these features can be achieved by a multiple-timescale organization of neuronal assemblies that hippocampal theta oscillations enable.

The multiple-timescale organization of neuronal assemblies. A postulated mechanism of internally generated neuronal sequences is the perpetual interaction among the multitude of brain rhythms maintained by cross-frequency coupling[67]. A prominent example of cross-frequency coupling in the hippocampus and entorhinal cortex is the theta phase-modulation of gamma power[68,69], which has been shown to correlate with memory performance in both rats[70] and humans[71–73]. This multiple-timescale organization is also evident in the spiking activity of hippocampal neurons (**Fig. 5**). Place cells representing the same spatial position or item form assemblies in the time window of gamma cycles[54,74,75]. Which neurons are considered members of an assembly is determined by their downstream 'reader' neurons. If the collective spiking of an upstream population occurs within the membrane time constant[76] (10–30 ms) of the reader neurons, it will be classified as a single event by the readers. Spikes of other upstream neurons outside this integration window are relegated to other assemblies, thus representing separate events and resulting in the discharge of other reader neurons[60]. The 'assembly window' coincides with the time window of spike timing–dependent plasticity and the time constant of $GABA_A$ and AMPA receptors, whose interactions give rise to the gamma rhythm[77,78]. Given the 10- to 30-ms lifetime of hippocampal cell assemblies[74], five to nine assemblies, each residing in a gamma cycle, can be active in a theta cycle[68].

Thus, the dual functions of the theta oscillation mechanism are to bring together and link cell assemblies into the temporal range where they can be modulated by synaptic plasticity, and at the same time segregate them within the available phase space[54,60]. The phase segregation of adjacent place cells may be brought about by perisomatic interneuron-mediated inhibition[79–81] (**Fig. 6**). There are three interrelated consequences of the theta phase segregation of cell assemblies. First, the firing sequences of neurons on the descending phase, trough and ascending phase of the theta waves represent the sequences of the past, current and future positions of the animal's journey[75,82]. Second, the time delays between overlapping place cells at the sub-theta-cycle scale are proportional to the time differences between their peak firing activities in physical space; that is, the time it takes for the animal to travel between the peaks of their place fields (**Fig. 5a–d**). As a result of this relationship, the travel distances between landmarks during navigation are expressed in the

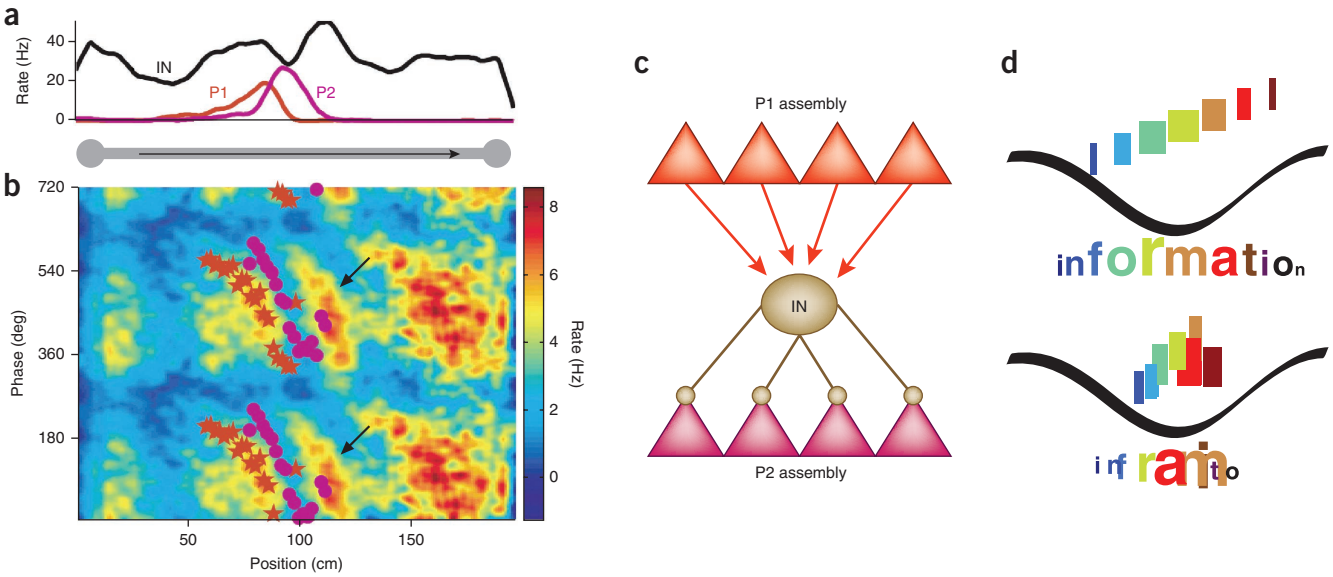

Figure 6 Cell assembly segregation role of theta oscillation. (**a**) Place fields of two pyramidal cells (P1 and P2) and a putative basket cell interneuron (IN) on a linear track. (**b**) Mean phase precession of P1 (red stars) and P2 (magenta dots), superimposed on the interneuron's color-coded and smoothed density of firing in theta phase space. Note the similar phase slopes of P1 and the interneuron and firing minima of the interneuron in the phase space of P2. (**c**) Model of theta phase selection by means of inhibition between competing assemblies. The interneuron is driven by the assembly of which P1 is a member and prevents discharge activity of a competing assembly of which P2 is a member. (**d**) Cartoon of phase segregation of seven cell assemblies in the entire phase space of the theta cycle (top). Perturbation of perisomatic inhibition reduces assembly segregation[81] so that 'information' from the scrambled assembly sequence will become difficult to read out by downstream observer mechanisms (bottom). Panel **a** reproduced with permission after ref. 80.

temporal domain by a time-compressed format in the theta waves[75,82]. Third, the oscillation frequency of the waxing-waning spike activity of place cells is faster than the frequency of the 'background' population, which is also reflected by the local field potential theta rhythm. This brings about a frequency interference pattern, known as phase precession[83] (**Fig. 5b**), which is due, at least partially, to the millisecond time delays between adjacent place cells[82,84]. These temporal mechanisms determine the size of the place field (that is, its 'lifetime') and the slope of phase precession[82,84]. Similar temporal rules may govern the phase precession and the size of the grid in the entorhinal cortex[85].

The theta time compression mechanisms constrain how space and memory are represented, because the delays between the place cells limit the number of cell assemblies in the theta cycle[54,86]. In turn, the duration of the theta cycle limits the distances that can be linearly resolved by the sequential activity of neurons in a given environment, resulting in a sigmoid relationship between theta-scale time lags of spikes and distance representations by place cell pairs[75,79,86] (**Fig. 5d**). As a result, upcoming locations that are more proximal to the animal are given stronger representation within a given theta cycle, with poorer resolution of locations in the distant future[86]. The size of place fields and grids of individual neurons and the distance representations of neuron pairs scale with the size of the environment[3,31,86]. In a way, the theta-nested assembly organization can be conceived as a 'zooming' mechanism, which provides a relatively coarse resolution of a large environment but an increasingly finer spatial resolution in smaller environments, with more neurons devoted to a given area of space, increased co-firing among cells in each theta cycle and increased overall firing in the population[86]. An attractive property of this arrangement is that sub-theta cycle time lags also allow place and grid cells to continue to represent the same positions and distances at different speeds of locomotion[80,83,86] because the oscillation frequency of place and grid cells increases in proportion with the animal's velocity[80,85] and the time lags within the theta cycle remain largely independent of firing rate changes[86].

The mechanisms of theta compression and expansion can effectively serve memory mechanisms. If locations are regarded as analogous to individual items in a memory buffer[15,54,87], the theta-nested assembly organization limits the number of items that can be stored within a single theta cycle[54]. Accordingly, only a limited amount of information can be recalled from memory stores and consciously experienced at any given time. Analogously to zoom representation of distances, an episodic recall can have a fine spatiotemporal resolution for the conditions and context that surround a recalled event, whereas the relationships among items with longer temporal separation are progressively less resolved[56]. Moreover, temporally closer events are recalled with more sensory and contextual details than temporally distant events[49]. As the content of recall moves forward in time, the upcoming events can gain high contextual resolution[75], as predicted by the physiological organization of theta-nested assemblies.

Linking past and present experiences by theta oscillations. In addition to creating chains of events surrounding the seed situation, theta oscillation mechanisms may help link events that are separated at longer timescales. For example, during navigation in the rat, the interleaving assemblies representing the current location are occasionally replaced by an entirely different assembly in a single theta cycle[74], as if the rat 'mentally jumped' transiently to another location. Such jumps from one representation to another are frequent when the identity of the environment is made ambiguous by training rats in two visually distinct environments and 'teleporting' them from the one to another by changing the light patterns. In this case as well, the cell assembly contents, representing either one or the other environment, can switch back and forth in a few or even single theta cycles[88]. Extended, 'look-ahead' sequences representing large distances, from the start to the

goal, can also occur, especially at critical junctures of choice behavior in memory tasks[89,90]. Place cells also often intermingle with internally generated 'retrospective' and 'prospective' neurons[45,58,59].

The above examples demonstrate that theta cycles do not simply compress first-order sequences of past and upcoming positions of travel[82] but can chunk large parts of the environment, without replaying all actually visited locations. Such nonsequential, higher-order connections are possible because place fields have long 'tails' that provide opportunities for spikes of neuron pairs with distant place fields to fire together, at least occasionally, in the same theta cycle. The large place fields of neurons in more ventral parts of the hippocampus and the large grid size in the more ventral parts of the medial entorhinal cortex may be especially important in creating higher-order links and may provide the flexibility needed for efficient navigation[64,91]. These same neuronal mechanisms can enhance the flexibility of episodic memory as well. In the same way that an infinite number of paths can connect the origin and end point of a journey, a recalled story can be told in many ways, connecting the beginning and end through innumerable variations. The neuronal mechanisms that allow the selection of the optimal path in navigation in the physical world can also support the optimal selection of the sequence parts of the experienced memory. Episodic recall is rarely a true sequence of the original experience, and an episode experienced over hours, days or at longer scales can be summarized in a compressed sequence that includes many shortcuts. Theta timescale compression is also beneficial for the continuity and temporal asymmetry requirements of free recall[56], for solving transitive inference problems[92], for supporting higher-order associations and for solving shortcut and detour problems in both spatial and mental navigation[39]. Overall, the ability of the theta mechanism to flicker between current, past and future situations provides physiological support for the mental travel model and may also be the mechanism for imagining past and future situations[13,53].

Tracking subjective time by cell assembly sequences

Temporal ordering of events is fundamental to both episodic experience and action planning[14]. However, no dedicated mechanisms may be needed for sensing time. The same cell assembly sequences that keep information about past memories and planned goals of the animal can also faithfully track the passage of time and bridge noncontiguous events[59,65,93,94] (**Fig. 4b**). Notably, time estimation error from the theta-bound evolving cell assembly sequences does not increase proportionally to the duration of elapsed time but stays asymptotically low even after tens of seconds of delays[65]. The within-cycle sequences may serve as an error-correcting mechanism of time tracking[65]. As is the case of place cells in a maze, the compressed temporal sequences within theta cycles predict the evolution of the real time sequences of neuronal activity during the delay portion of a memory task[59]. This multiple-timescale mechanism may explain why each snippet of a recalled episode is experienced as if it was occurring in real time, because the temporal dynamic during recall is supported by the same mechanism as during the encoding process.

The hypothesis that a single neuronal algorithm serves both to order events and to provide temporal context is also supported by experiments showing that, when the imposed delay between the cue and response is altered, the sequential structure of cell assemblies changes in accordance with the response patterns of place cells during navigation. Although some cells remain anchored to the beginning of the delay, as place cells are anchored to the start box[8,86], most neurons form a completely new trajectory, in a manner resembling the remapping of place cells in response to context change[93] (**Fig. 4c**). Keeping track of time by evolving cell assembly sequences at the seconds to minutes timescale may be a general rule in the cerebral cortex, including in the prefrontal[95] and retrosplenial[96] areas. To bridge longer intervals, further mechanisms may be required[97,98].

Overall, the available experimental evidence indicates that mechanisms of entorhinal cortex-hippocampus-dependent memories evolved from mechanisms introduced to compute relationships of landmarks and to track the movements of the body in the environment. As active exploration is a prerequisite for the computation of distances and calibration of landmark relationships, we submit that movement is the primary source of the brain's ability to remember past experiences and plan future actions.

Challenges and questions

Recent progress on the relationship among navigation, memory and oscillations raises as many questions as it has answered. We list here a few pertinent issues.

1. Perhaps the most challenging question is the meaning of the various firing patterns, including place cells, grid cells and irregularly spaced neurons, to the target networks of the hippocampus-entorhinal cortex system. Does it matter for the downstream actuator networks whether space and memory items are represented by geometrically spaced or irregular patterns? Do regularly firing neurons carry more weight than neurons with less rigorous firing patterns? Presumably, the code has time frames with clear demarcation of the beginning and end of messages, which should be coherent across neuronal populations. Is theta oscillation a critical part of this mechanism, or do other forms of coordinating mechanisms exist?
2. Hippocampal neurons in primates rarely fire in theta-rhythmic manner, and continuous local field potential theta rhythm is observed only infrequently[30]. Place and grid cells have been described in bats without apparent theta modulation[28,29]. Can the temporal coordination role of internal rhythms be substituted by other means, such as echolocation emission in bats, as occurs with saccadic eye movements in the visual system in primates? Neurons in the hippocampus and entorhinal cortex can be 'driven' by external cues and may persist in showing position-dependent firing even after theta oscillations cease[24,99]. Grid cells with either strong or no theta modulation often coexist, even at the same location. Yet in the presence of theta oscillations, place and grid cells are more pronounced, have higher peak rates and are more stable. Is theta coordination more important for memory than navigation, as memory depends primarily on internally generated neuronal sequences?
3. Are independent changes in grid maps of different modules instrumental in generating new representations in the hippocampus, and if so, by what mechanisms? Are there intrahippocampal mechanisms for further segregation of representations? How many representations can be generated, and what mechanisms determine their independence? Is the hippocampal output important for generating and maintaining grid formation in the entorhinal cortex and subicular complex, and if so, how do hippocampal activity patterns contribute to properties of grid cells and grid maps?
4. The hippocampal-entorhinal cortex system has a bidirectional, topographically arranged communication with the cortical mantle. Do the different septotemporal segments of this system map onto the neocortex similarly in animals with more complex brains and with a growing share of higher-order cortical areas? Does the region corresponding to the ventral quadrant of the rodent hippocampus grow disproportionally relative to the dorsal part in primates, and what are the consequences of any such shifts in cortical-hippocampal communication?

5. An interesting problem is the dominant direction of flow of neuronal activity in the entorhinal cortex–subiculum–hippocampus system. During memory encoding, the entorhinal cortex is believed to drive the hippocampal circuits, as it does in navigation, in a manner that, at least partly, must rely on external cues[32]. During spontaneous recall, the direction of flow is from the hippocampus to the entorhinal cortex[43,100] but it is not known how this reversed flow is used during navigation. Yet on account of the postulated similar algorithms governing navigation and memory, one may speculate that once a path in the maze is learned, the sequential activation of hippocampal neurons can be temporally disengaged from external landmarks, as when driving a car to work on a long-practiced route. This raises the question of whether the direction of neuronal activity in the entorhinal cortex–hippocampus flips back and forth during navigation.
6. We become aware of our recollections only after segments of the neuronal sequences enter the working memory system. Does this conscious operation require only the prefrontal cortex, or are interactions with the rest of the cerebral cortex also needed?

ACKNOWLEDGMENTS

We thank G. Fishell for comments, Heather McKellar for assistance, and the US National Institutes of Health (NS34994; MH54671; NS 074015), International Human Frontiers Science Program Organization (RGP0032/2011), James S. McDonnell Foundation, Global Institute for Scientific Thinking, European Research Council ('CIRCUIT' Advanced Investigator Grant, Grant Agreement 232608), Louis-Jeantet Prize for Medicine, Kavli Foundation and Centre of Excellence scheme of the Research Council of Norway for support.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Published online at http://www.nature.com/doifinder/10.1038/nn.3304.
Reprints and permissions information is available online at http://www.nature.com/reprints/index.html.

1. O'Keefe, J. & Nadel, L. *The Hippocampus as a Cognitive Map* (Oxford Univ. Press, New York, 1978).
2. McNaughton, B.L. *et al.* Deciphering the hippocampal polyglot: the hippocampus as a path integration system. *J. Exp. Biol.* **199**, 173–185 (1996).
3. O'Keefe, J. & Burgess, N. Geometric determinants of the place fields of hippocampal neurons. *Nature* **381**, 425–428 (1996).
4. Thompson, E. & Varela, F.J. Radical embodiment: neural dynamics and consciousness. *Trends Cogn. Sci.* **5**, 418–425 (2001).
5. McNaughton, B.L., Battaglia, F.P., Jensen, O., Moser, E.I. & Moser, M.B. Path integration and the neural basis of the 'cognitive map'. *Nat. Rev. Neurosci.* **7**, 663–678 (2006).
6. Knierim, J.J., Kudrimoti, H.S. & McNaughton, B.L. Interactions between idiothetic cues and external landmarks in the control of place cells and head direction cells. *J. Neurophysiol.* **80**, 425–446 (1998).
7. Derdikman, D. *et al.* Fragmentation of grid cell maps in a multicompartment environment. *Nat. Neurosci.* **12**, 1325–1332 (2009).
8. Gothard, K.M., Skaggs, W.E., Moore, K.M. & McNaughton, B.L. Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. *J. Neurosci.* **16**, 823–835 (1996).
9. Scoville, W.B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* **20**, 11–21 (1957).
10. Squire, L.R. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99**, 195–231 (1992).
11. Suddendorf, T. & Corballis, M.C. The evolution of foresight: what is mental time travel, and is it unique to humans? *Behav. Brain Sci.* **30**, 299–313; discussion 313–251 (2007).
12. Tulving, E., Donaldson, W., Bower, G.H. & United States Office of Naval Research. *Organization of Memory* (Academic, New York, 1972).
13. Buckner, R.L. The role of the hippocampus in prediction and imagination. *Annu. Rev. Psychol.* **61**, 27–48, C21–C28 (2010).
14. Tulving, E. Chronesthesia: conscious awareness of subjective time. in *Principles of Frontal Lobe Function* (eds. Stuss, D.T. & Knight, R.C.) 311–325 (Oxford Univ. Press, New York, 2002).
15. Buzsáki, G. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* **15**, 827–840 (2005).
16. Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M. & Tanila, H. The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron* **23**, 209–226 (1999).
17. Lever, C., Wills, T., Cacucci, F., Burgess, N. & O'Keefe, J. Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature* **416**, 90–94 (2002).
18. Hasselmo, M.E. *How We Remember: Brain Mechanisms of Episodic Memory* (MIT Press, Cambridge, Massachusetts, USA, 2012).
19. McClelland, J.L., McNaughton, B.L. & O'Reilly, R.C. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* **102**, 419–457 (1995).
20. Nadel, L. & Moscovitch, M. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* **7**, 217–227 (1997).
21. Manns, J.R., Hopkins, R.O., Reed, J.M., Kitchener, E.G. & Squire, L.R. Recognition memory and the human hippocampus. *Neuron* **37**, 171–180 (2003).
22. Moser, E.I., Kropff, E. & Moser, M.B. Place cells, grid cells, and the brain's spatial representation system. *Annu. Rev. Neurosci.* **31**, 69–89 (2008).
23. Hafting, T., Fyhn, M., Molden, S., Moser, M.B. & Moser, E.I. Microstructure of a spatial map in the entorhinal cortex. *Nature* **436**, 801–806 (2005).
24. Boccara, C.N. *et al.* Grid cells in pre- and parasubiculum. *Nat. Neurosci.* **13**, 987–994 (2010).
25. Sargolini, F. *et al.* Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* **312**, 758–762 (2006).
26. Krupic, J., Burgess, N. & O'Keefe, J. Neural representations of location composed of spatially periodic bands. *Science* **337**, 853–857 (2012).
27. Solstad, T., Boccara, C.N., Kropff, E., Moser, M.B. & Moser, E.I. Representation of geometric borders in the entorhinal cortex. *Science* **322**, 1865–1868 (2008).
28. Yartsev, M.M., Witter, M.P. & Ulanovsky, N. Grid cells without theta oscillations in the entorhinal cortex of bats. *Nature* **479**, 103–107 (2011).
29. Ulanovsky, N. & Moss, C.F. Hippocampal cellular and network activity in freely moving echolocating bats. *Nat. Neurosci.* **10**, 224–233 (2007).
30. Ekstrom, A.D. *et al.* Human hippocampal theta activity during virtual navigation. *Hippocampus* **15**, 881–889 (2005).
31. Muller, R.U. & Kubie, J.L. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J. Neurosci.* **7**, 1951–1968 (1987).
32. Stensola, H. *et al.* The entorhinal grid map is discretized. *Nature* **492**, 72–78 (2012).
33. Fyhn, M., Hafting, T., Treves, A., Moser, M.B. & Moser, E.I. Hippocampal remapping and grid realignment in entorhinal cortex. *Nature* **446**, 190–194 (2007).
34. Leutgeb, S., Leutgeb, J.K., Treves, A., Moser, M.B. & Moser, E.I. Distinct ensemble codes in hippocampal areas CA3 and CA1. *Science* **305**, 1295–1298 (2004).
35. Mizuseki, K., Royer, S., Diba, K. & Buzsáki, G. Activity dynamics and behavioral correlates of CA3 and CA1 hippocampal pyramidal neurons. *Hippocampus* **22**, 1659–1680 (2012).
36. Li, X.G., Somogyi, P., Ylinen, A. & Buzsáki, G. The hippocampal CA3 network: an *in vivo* intracellular labeling study. *J. Comp. Neurol.* **339**, 181–208 (1994).
37. Treves, A. & Rolls, E.T. Computational analysis of the role of the hippocampus in memory. *Hippocampus* **4**, 374–391 (1994).
38. Leutgeb, J.K., Leutgeb, S., Moser, M.B. & Moser, E.I. Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science* **315**, 961–966 (2007).
39. Muller, R.U., Stead, M. & Pach, J. The hippocampus as a cognitive graph. *J. Gen. Physiol.* **107**, 663–694 (1996).
40. Menzel, R., Geiger, K., Joerges, J., Muller, U. & Chittka, L. Bees travel novel homeward routes by integrating separately acquired vector memories. *Anim. Behav.* **55**, 139–152 (1998).
41. Wilson, M.A. & McNaughton, B.L. Dynamics of the hippocampal ensemble code for space. *Science* **261**, 1055–1058 (1993).
42. Hampson, R.E., Byrd, D.R., Konstantopoulos, J.K., Bunn, T. & Deadwyler, S.A. Hippocampal place fields: relationship between degree of field overlap and cross-correlations within ensembles of hippocampal neurons. *Hippocampus* **6**, 281–293 (1996).
43. Miyashita, Y. Cognitive memory: cellular and network machineries and their top-down control. *Science* **306**, 435–440 (2004).
44. Suzuki, W.A., Miller, E.K. & Desimone, R. Object and place memory in the macaque entorhinal cortex. *J. Neurophysiol.* **78**, 1062–1081 (1997).
45. Wood, E.R., Dudchenko, P.A., Robitsek, R.J. & Eichenbaum, H. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* **27**, 623–633 (2000).
46. Kumaran, D. & McClelland, J.L. Generalization through the recurrent interaction of episodic memories: a model of the hippocampal system. *Psychol. Rev.* **119**, 573–616 (2012).
47. Heit, G., Smith, M.E. & Halgren, E. Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature* **333**, 773–775 (1988).
48. Quiroga, R.Q., Reddy, L., Kreiman, G., Koch, C. & Fried, I. Invariant visual representation by single neurons in the human brain. *Nature* **435**, 1102–1107 (2005).
49. Trope, Y. & Liberman, N. Construal-level theory of psychological distance. *Psychol. Rev.* **117**, 440–463 (2010).

50. Navigli, R. & Lapata, M. An experimental study of graph connectivity for unsupervised word sense disambiguation. *IEEE Trans. Pattern Anal. Mach. Intell.* **32**, 678–692 (2010).
51. Nakashiba, T. *et al.* Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* **149**, 188–201 (2012).
52. Buckner, R.L. & Carroll, D.C. Self-projection and the brain. *Trends Cogn. Sci.* **11**, 49–57 (2007).
53. Burgess, N., Maguire, E.A. & O'Keefe, J. The human hippocampus and spatial and episodic memory. *Neuron* **35**, 625–641 (2002).
54. Jensen, O. & Lisman, J.E. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends Neurosci.* **28**, 67–72 (2005).
55. Lisman, J.E. Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate-CA3 interactions. *Neuron* **22**, 233–242 (1999).
56. Howard, M.W. & Kahana, M.J. Contextual variability and serial position effects in free recall. *J. Exp. Psychol. Learn. Mem. Cogn.* **25**, 923–941 (1999).
57. Shrager, Y., Kirwan, C.B. & Squire, L.R. Neural basis of the cognitive map: path integration does not require hippocampus or entorhinal cortex. *Proc. Natl. Acad. Sci. USA* **105**, 12034–12038 (2008).
58. Frank, L.M., Brown, E.N. & Wilson, M. Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* **27**, 169–178 (2000).
59. Pastalkova, E., Itskov, V., Amarasingham, A. & Buzsáki, G. Internally generated cell assembly sequences in the rat hippocampus. *Science* **321**, 1322–1327 (2008).
60. Buzsáki, G. Neural syntax: cell assemblies, synapsembles, and readers. *Neuron* **68**, 362–385 (2010).
61. Mizuseki, K., Sirota, A., Pastalkova, E. & Buzsáki, G. Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. *Neuron* **64**, 267–280 (2009).
62. Muller, R.U., Bostock, E., Taube, J.S. & Kubie, J.L. On the directional firing properties of hippocampal place cells. *J. Neurosci.* **14**, 7235–7251 (1994).
63. McNaughton, B.L., Barnes, C.A. & O'Keefe, J. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp. Brain Res.* **52**, 41–49 (1983).
64. Royer, S., Sirota, A., Patel, J. & Buzsáki, G. Distinct representations and theta dynamics in dorsal and ventral hippocampus. *J. Neurosci.* **30**, 1777–1787 (2010).
65. Itskov, V., Pastalkova, E., Mizuseki, K., Buzsáki, G. & Harris, K.D. Theta-mediated dynamics of spatial information in hippocampus. *J. Neurosci.* **28**, 5959–5964 (2008).
66. Wickelgren, W.A. Webs, cell assemblies, and chunking in neural nets: introduction. *Can. J. Exp. Psychol.* **53**, 118–131 (1999).
67. Buzsáki, G. & Draguhn, A. Neuronal oscillations in cortical networks. *Science* **304**, 1926–1929 (2004).
68. Bragin, A. *et al.* Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* **15**, 47–60 (1995).
69. Colgin, L.L. *et al.* Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* **462**, 353–357 (2009).
70. Tort, A.B., Komorowski, R.W., Manns, J.R., Kopell, N.J. & Eichenbaum, H. Theta-gamma coupling increases during the learning of item-context associations. *Proc. Natl. Acad. Sci. USA* **106**, 20942–20947 (2009).
71. Axmacher, N. *et al.* Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proc. Natl. Acad. Sci. USA* **107**, 3228–3233 (2010).
72. Canolty, R.T. *et al.* High gamma power is phase-locked to theta oscillations in human neocortex. *Science* **313**, 1626–1628 (2006).
73. Griesmayr, B., Gruber, W.R., Klimesch, W. & Sauseng, P. Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task. *Neurobiol. Learn. Mem.* **93**, 208–215 (2010).
74. Harris, K.D., Csicsvari, J., Hirase, H., Dragoi, G. & Buzsáki, G. Organization of cell assemblies in the hippocampus. *Nature* **424**, 552–556 (2003).
75. Dragoi, G. & Buzsáki, G. Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron* **50**, 145–157 (2006).
76. Koch, C., Rapp, M. & Segev, I. A brief history of time (constants). *Cereb. Cortex* **6**, 93–101 (1996).
77. Whittington, M.A., Traub, R.D., Kopell, N., Ermentrout, B. & Buhl, E.H. Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *Int. J. Psychophysiol.* **38**, 315–336 (2000).
78. Buzsáki, G. & Wang, X.J. Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* **35**, 203–225 (2012).
79. Maurer, A.P., Cowen, S.L., Burke, S.N., Barnes, C.A. & McNaughton, B.L. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J. Neurosci.* **26**, 13485–13492 (2006).
80. Geisler, C., Robbe, D., Zugaro, M., Sirota, A. & Buzsáki, G. Hippocampal place cell assemblies are speed-controlled oscillators. *Proc. Natl. Acad. Sci. USA* **104**, 8149–8154 (2007).
81. Royer, S. *et al.* Control of timing, rate and bursts of hippocampal place cells by dendritic and somatic inhibition. *Nat. Neurosci.* **15**, 769–775 (2012).
82. Skaggs, W.E., McNaughton, B.L., Wilson, M.A. & Barnes, C.A. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* **6**, 149–172 (1996).
83. O'Keefe, J. & Recce, M.L. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* **3**, 317–330 (1993).
84. Geisler, C. *et al.* Temporal delays among place cells determine the frequency of population theta oscillations in the hippocampus. *Proc. Natl. Acad. Sci. USA* **107**, 7957–7962 (2010).
85. Burgess, N. & O'Keefe, J. Models of place and grid cell firing and theta rhythmicity. *Curr. Opin. Neurobiol.* **21**, 734–744 (2011).
86. Diba, K. & Buzsáki, G. Hippocampal network dynamics constrain the time lag between pyramidal cells across modified environments. *J. Neurosci.* **28**, 13448–13456 (2008).
87. Lisman, J.E. & Idiart, M.A. Storage of 7 +/– 2 short-term memories in oscillatory subcycles. *Science* **267**, 1512–1515 (1995).
88. Jezek, K., Henriksen, E.J., Treves, A., Moser, E.I. & Moser, M.B. Theta-paced flickering between place-cell maps in the hippocampus. *Nature* **478**, 246–249 (2011).
89. Johnson, A. & Redish, A.D. Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. *J. Neurosci.* **27**, 12176–12189 (2007).
90. Gupta, A.S., van der Meer, M.A., Touretzky, D.S. & Redish, A.D. Segmentation of spatial experience by hippocampal theta sequences. *Nat. Neurosci.* **15**, 1032–1039 (2012).
91. Kjelstrup, K.B. *et al.* Finite scale of spatial representation in the hippocampus. *Science* **321**, 140–143 (2008).
92. Dusek, J.A. & Eichenbaum, H. The hippocampus and memory for orderly stimulus relations. *Proc. Natl. Acad. Sci. USA* **94**, 7109–7114 (1997).
93. MacDonald, C.J., Lepage, K.Q., Eden, U.T. & Eichenbaum, H. Hippocampal "time cells" bridge the gap in memory for discontiguous events. *Neuron* **71**, 737–749 (2011).
94. Hasselmo, M.E. Arc length coding by interference of theta frequency oscillations may underlie context-dependent hippocampal unit data and episodic memory function. *Learn. Mem.* **14**, 782–794 (2007).
95. Fujisawa, S., Amarasingham, A., Harrison, M.T. & Buzsáki, G. Behavior-dependent short-term assembly dynamics in the medial prefrontal cortex. *Nat. Neurosci.* **11**, 823–833 (2008).
96. Harvey, C.D., Coen, P. & Tank, D.W. Choice-specific sequences in parietal cortex during a virtual-navigation decision task. *Nature* **484**, 62–68 (2012).
97. Mankin, E.A. *et al.* Neuronal code for extended time in the hippocampus. *Proc. Natl. Acad. Sci. USA* **109**, 19462–19467 (2012).
98. Naya, Y. & Suzuki, W.A. Integrating what and when across the primate medial temporal lobe. *Science* **333**, 773–776 (2011).
99. Koenig, J., Linder, A.N., Leutgeb, J.K. & Leutgeb, S. The spatial periodicity of grid cells is not sustained during reduced theta oscillations. *Science* **332**, 592–595 (2011).
100. Fell, J., Klaver, P., Elger, C.E. & Fernandez, G. The interaction of rhinal cortex and hippocampus in human declarative memory formation. *Rev. Neurosci.* **13**, 299–312 (2002).