Path integration and the neural basis of the 'cognitive map'

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Abstract | The hippocampal formation can encode relative spatial location, without reference to external cues, by the integration of linear and angular self-motion (path integration). Theoretical studies, in conjunction with recent empirical discoveries, suggest that the medial entorhinal cortex (MEC) might perform some of the essential underlying computations by means of a unique, periodic synaptic matrix that could be self-organized in early development through a simple, symmetry-breaking operation. The scale at which space is represented increases systematically along the dorsoventral axis in both the hippocampus and the MEC, apparently because of systematic variation in the gain of a movement-speed signal. Convergence of spatially periodic input at multiple scales, from so-called grid cells in the entorhinal cortex, might result in non-periodic spatial firing patterns (place fields) in the hippocampus.

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"…Each place cell receives two different inputs, one conveying information about a large number of environmental stimuli or events, and the other from a navigational system which calculates where an animal is in an environment independently of the stimuli impinging on it at that moment. The input from the navigational system gates the environmental input, allowing only those stimuli occurring when the animal is in a particular place to excite a particular cell.

One possible basis for the navigational system relies on the fact that information about changes in position and direction in space could be calculated from the animal's movements. When the animal had located itself in an environment (using environmental stimuli) the hippocampus could calculate subsequent positions in that environment on the basis of how far, and in what direction the animal had moved in the interim… In addition to information about distance traversed, a navigational system would need to know about changes in direction of movement either relative to some environmental landmark or within the animal's own egocentric space…."[1]

Today, more than thirty years after the discovery of spatially selective place cells in the hippocampus[2] and the proposal that the hippocampus is the neural substrate of a 'cognitive map'[3], it would be difficult to write a more concise and accurate summary of our current understanding of hippocampal spatial encoding dynamics. The prescience of these theoretical suggestions is even more remarkable, given that it was not until 1980 that Mittelstaedt and Mittelstaedt[4] provided the first conclusive demonstration that mammals possess an accurate system for keeping track of relative spatial location by integrating linear and angular motion (path integration; BOX 1), and not until 1990 that Taube, Muller and Ranck[5] published the first full report on the existence of head direction cells, which were found originally in the rodent dorsal presubiculum by Ranck[6]. Nevertheless, the history of the last 30 years of research aimed at characterizing the determinants of hippocampal neuronal activity in freely behaving animals has been rich with controversy, the central debate being whether location *per se* or sensory and cognitive factors provide the best predictor[7–9]. Partial resolution of this debate has been achieved by the discovery that, particularly in area CA3 of the hippocampus, manipulating the external visual cues without altering the location in the environment, can dramatically alter place cell firing rate but not the location of firing[10,11]. The behavioural evidence for path integration in mammals, and its relationship to the firing of hippocampal place cells in the CA1 region, has been reviewed recently[9,12] and will not be discussed further here. Rather, we focus on the questions of the nature of the probable ingredients of the underlying mechanism; where in the brain the circuitry that implements path integration resides; what sets the scale (or resolution) at which space is represented; and how these circuits might be wired up during development.

Box 1 | **Path integration in mammals and some neurophysiological correlates**

Darwin recognized that most animals can use self-motion cues to keep track of their location relative to a 'home base'[128], but it was not until recently that firm experimental evidence for such a path integration process in mammals appeared[4], and it became clear that the brain can not only calculate a homing vector to a fixed location in space, but can also maintain a map-like representation of space using only an initial reference and self-motion information (for reviews, see REFS 9,12). Making use of the strong motivation of female rodents to retrieve pups that have been displaced from the nest to a shallow cup some distance away, it was shown that gerbils can search in complete darkness and return in a direct line to the original location of the nest, even if the nest has been removed (see panel **a**). With the cup at the centre of the dark arena, rotating either the entire arena while the animal was on the cup, or only the cup itself, did not prevent the animal from returning to the same location in the (inertial) laboratory reference frame; however, rotation of the cup through 37 degrees with a slow acceleration profile (0.24 deg s^{-2}), presumably below the animal's vestibular threshold, resulted in a return trajectory error of the same magnitude. In panel **a**, S_{1-3} represent vectors lengths of segments of the outbound journey, and φ_{1-3} are corresponding head directions. Variables x_{1-3} and y_{1-3} are the cartesian components of the segment vectors which, in principle, could be summed to compute the homing vector. 'Starting location' refers to the beginning of the homing trajectory. Insight into the neural basis for angular path integration came from the discovery of head direction cells, the firing rates of which depend on the direction the animal's head is facing (a simulated typical head direction cell tuning curve is illustrated in the polar plot in which firing rate is represented by the radial coordinate and direction is represented by the angular coordinate; see panel **b**). Directional tuning is relative in the sense that, although all head direction cells maintain their directional tunings relative to each other, the network is not bound to any absolute directional reference. For example, the same cell can have different geocentric directional preferences in different enclosures and, in the absence of visual input, head direction cells track head angular velocity and fire over a restricted range of relative directions; however, the network can accumulate directional error with respect to its original setting. Linear path integration is sufficient to update the positional firing of hippocampal pyramidal cells (see panel **c**). On a task in which a rat runs on a linear rail from a moveable box to a fixed goal at the end of the track, pyramidal cells in area CA1 fire in relation to distance from the box as the animal leaves it (over distances of more than several body lengths), before shifting reference frames to fire in relation to visual cues (CA1 light) or, in darkness, the end of the track (CA1 dark). The figure illustrates the configurations of the start box on the track and the journey types, which were presented in random order. Panel **d** shows the correlation matrices of CA1 neuronal ensemble population vectors for each location on the full track versus every location on the full track (Box 1), and for each location on the shortened tracks, in which the box was shifted closer to the fixed goal site (Box 2–Box 5), versus every location on the full track. The black lines represent the reference frame of the box; white lines represent the laboratory/track reference frame. Panel **a** modified, with permission, from REF. 140 © (1980) Springer. Panels **c** and **d** reproduced, with permission, from REF. 33 © (1996) Society for Neuroscience.

a

b

c

d
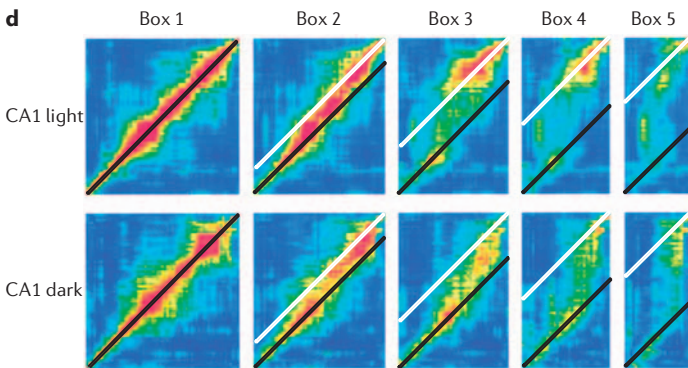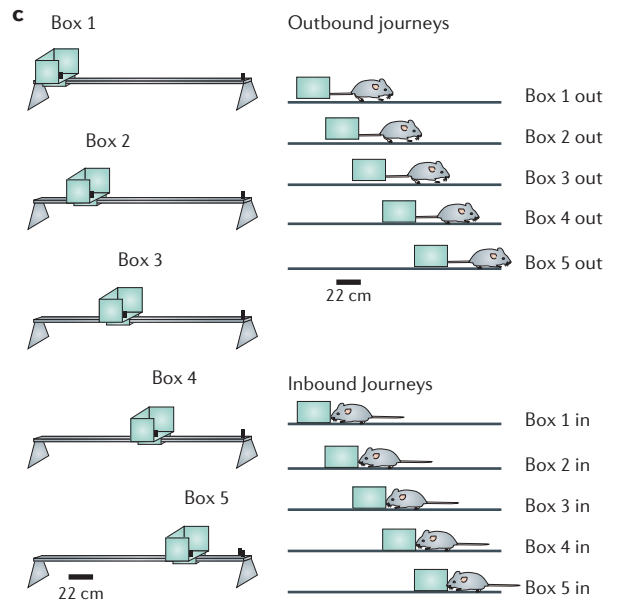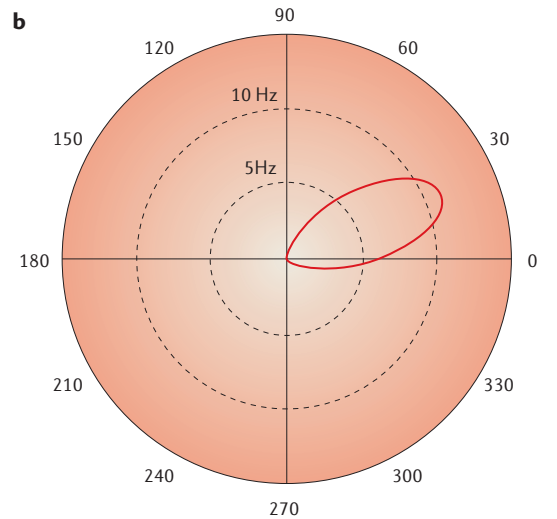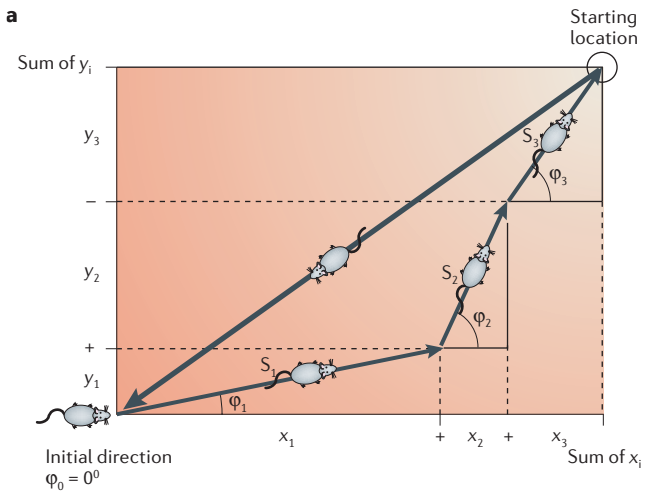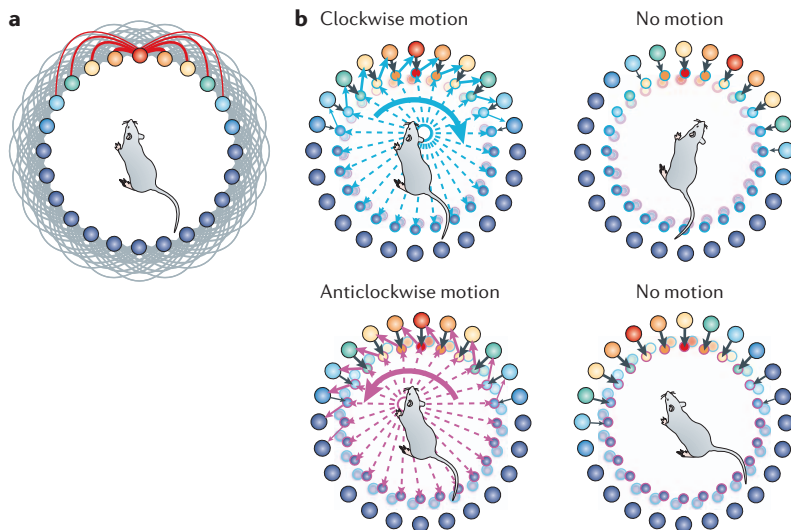
Figure 1 | **One-dimensional attractor map model for head direction encoding based on neural integration of head angular velocity signals. a** | Head direction cells are arranged symbolically in a circle in order of their relative head directional preferences. Each cell (coloured dots) connects with nearby cells with a synaptic strength (or connection probability) that declines as a function of distance (red and grey lines). The network is subject to global feedback inhibition (not illustrated) that limits the total neural activity. Activity in such a network has a most probable configuration in which the activity is focused at one point and declines with distance from that point (warm colours represent high activity, progressively cool colours represent progressively lower activity). Such a network would keep track of head direction if the hill or 'bump' of activity could be made to rotate around the ring in correspondence with changes in head direction. **b** | Rotation of the bump in the clockwise or anticlockwise directions can be achieved by an intermediate group of two types of conjunctive neuron that receive information about head angular velocity from the vestibular system (dashed arrows) and information about current head orientation from the cells immediately above them in the outer ring. The intermediate group of cells must be of two classes: cells receiving information about clockwise motion project to the right of the cells in the outer ring from which they receive input, whereas cells receiving anticlockwise vestibular signals project to the left. These hidden layer cells drive the activity bump in the corresponding direction around the ring. In the absence of motion, activation of all hidden layer cells is assumed to be below threshold. In this figure, only active connections are indicated, with the line thickness representing firing rate.

Neural network models for path integration

Mechanisms based on self-organizing and self-sustaining neural activity, or attractor dynamics, such as those originally proposed in Hebb's[13] cell assembly theory, have been essential components in several models accounting for path integration and the head direction system in rats[14]. In path integration, the information to be maintained and updated is not a set of discrete items (as are found in Hopfield-type attractor networks for discrete memories); rather, it is a continuous variable representing position or head direction. A continuum of cell assemblies, or a continuous attractor[15–19], is therefore needed to encode position or head direction. Such a continuum can exist in one dimension, as in the case of direction; two dimensions, as in the case of location in the plane; or many dimensions. It is equivalent to a large set of correlated discrete attractors, in which the energy barriers between neighbouring attractors become negligible[20,21].

In the head direction system, consider the head direction cells, which fire selectively with respect to the rat's head orientation (ϕ) as a result, primarily, of neural

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Attractor dynamics
Attractor dynamics refer to the properties of a broad class of neural networks that have one or more stable states. These stable states are determined by the weights of the recurrent connections between the units (neurons) in the network. Depending on the initial conditions, the network will end up in one of the stable states. Attractor dynamics have been used in associative memory models, pattern recognition and as a mechanism for working memory maintenance.
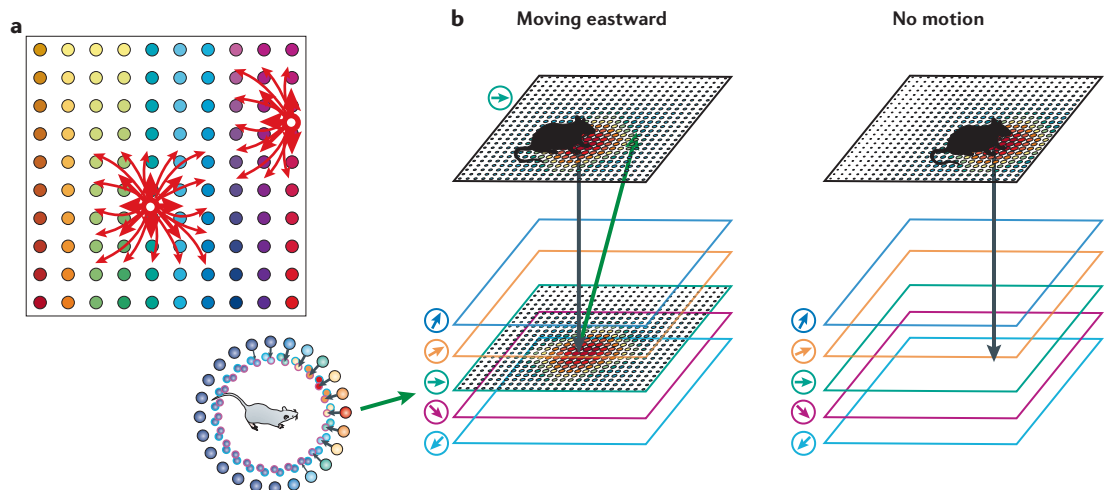
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integration of head angular velocity signals derived from the vestibular system. A model in which the cells are arranged conceptually in a circle, according to preferred direction, and in which the strength of the excitatory connections between two cells decreases with the distance between their respective preferred directions[22–24], would result in a focused activity profile (or activity bump) centred at a direction ϕ (FIG. 1). An activity bump would arise spontaneously because, for a given total activity level, controlled by global feedback inhibition, each neuron within the bump receives the maximum possible excitation from its neighbours; therefore, the bump state is the most stable configuration of such a system. Note that, because the cells are arranged in a circle, there are no edges, so the network is said to have periodic boundaries. In the absence of input other than random noise, the bump location is either stable or subject to a random drift in position; however, large instantaneous changes in bump location are unlikely.

To perform angular path integration, the bump would have to move around the circle in accordance with changes in the head orientation of the rat. This could be achieved by vestibular, rotational visual flow, and other angular velocity inputs that drive the bump in either a clockwise or anticlockwise direction. Suppose an additional circle of neurons (a so-called hidden layer) is interposed between the angular velocity signals and the head direction cells in the outer circle (FIG. 1), and that neurons in this circle encode the conjunction of current head direction, derived from top-down connections from head direction cells immediately adjacent to them in the circle, and angular velocity signals afferent to the network. If conjunctive cells receiving clockwise angular velocity inputs project asymmetrically to the right of the head direction cells from which they receive input, and those receiving anticlockwise inputs project to the left, the bump can be made to move around the circle in a manner consistent with the changing head direction — the system performs angular path integration. Note that the head direction cells in this model encode relative, not absolute, orientation. In the absence of additional sensory inputs, slow changes in head direction (below the vestibular threshold) or synaptic noise will result in disorientation, as shown by Mittelstaedt and Mittelstaedt[4] (BOX 1). However, all cells would maintain their angular firing preferences relative to one another, as is observed in recordings of head direction cells[5].

Continuous attractor-based models for path integration of position in two dimensions can be constructed by a simple extension of the one-dimensional head direction model just described[9,23,25–27]. A two-dimensional continuous attractor network could consist of cells arranged conceptually on a two-dimensional sheet according to their relative firing locations in two-dimensional space. A recurrent synaptic matrix can then be constructed in which the strength of the excitatory connections between two cells decreases in proportion to the physical distance between the cells' respective place fields. Global feedback inhibition would, again, keep the activity from spreading (FIG. 2). As in the one-dimensional model, a bump of focused activity would form spontaneously. Movement

Figure 2 | **Extension of the one-dimensional attractor map concept to two dimensions: a model for path integration.** Neurons arranged in a plane (**a**) have interconnections that decline in strength (or probability) monotonically with distance (red arrows). Notice that a boundary problem exists for connections near the edge of the layer of neurons. A solution for this problem is illustrated in FIG. 3. Global feedback inhibition (not shown) keeps the net activity within a narrow range, leading to a focused spot or 'bump' of activity somewhere in the plane (**b**). The bump can be made to move in correspondence with a rat's motion using an intermediate layer of cells that are conjunctive for position on the plane and head orientation, if the activity of these cells is positively modulated by running speed and the cells encoding a given head direction project asymmetrically to the corresponding side of the cells in the attractor layer from which they receive input. The thresholds are arranged so that these hidden layer cells are silent when there is no motion.

of the activity bump according to speed and directional information alone, thereby tracking the rat's position, could be effected through a two-dimensional hidden layer analogous to the one-dimensional hidden layer in the head direction model[28]. This layer could accomplish the summation of the position (encoded in the continuous attractor layer) and the displacement vector (comprised of head direction and linear speed signals). Cells in this direction-specific layer would encode, conjointly, the rat's position and velocity vectors[9,23,26]; therefore, they would combine head direction and running speed inputs with location information from the attractor layer. Projections from the continuous attractor layer to the hidden layer would connect cells with the same position preference (FIG. 2). The return connections from the hidden layer to the continuous attractor layer, however, would be offset according to the directional preference of the cell of origin: for cells in the hidden layer that are selective for position x, head direction ϕ would project to cells in the attractor layer with an integrated position shifted in the direction ϕ. As a consequence, when the rat moves, velocity modulated cells in the hidden layer, selective for direction ϕ, will be activated and provide an input that shifts the activity bump in the direction ϕ. The rate of increase in the firing rate of hidden layer cells with running speed v would determine the scale of the spatial representation, as seems to be the case in the hippocampus (see below). Briefly, a stronger input from the direction-specific layer would cause the activity bump to move faster, thereby generating a rapidly changing, short-scale representation (small place fields). Reducing the speed dependence of hidden layer cells would cause the activity bump to move more slowly, and would yield a coarser spatial representation (larger place fields).

One problem with the two-dimensional model described would have been familiar to pre-Columbus Europeans, who believed that the earth was flat and finite; what happens when the rat runs outside the area represented by the cells? To overcome this difficulty, Samsonovich and McNaughton[26] proposed that the cell array in which the continuous attractor was represented had periodic boundaries, equivalent to a torus[27]. The torus topology is the two-dimensional analogue of the ring topology suggested for the head direction system. This periodic boundary condition implies that, as the rat runs in a straight line, a given cell should activate periodically. So, in a large, two-dimensional environment, each cell would have multiple place fields arranged in a square grid (FIG. 3). However, although hippocampal place cells can have multiple fields in a large enough environment[29,30], periodic fields have never been reported.

Grid cells in the medial entorhinal cortex
The search for the navigational system postulated by O'Keefe[1] focused initially on the hippocampus; indeed, if the environment and the animal's behaviour remain constant, the activity of ensembles of place cells can be decoded to indicate accurately the animal's location within the environment[31]. However, except under unusual experimental manipulations, knowledge of the firing relationships among an ensemble of hippocampal place cells in one environment is of no value in predicting even relative location in a separate environment[32,33]. The spatial codes in the hippocampus for different environments are orthogonal (statistically independent). Although the activity of a place cell can be influenced by, and can become coupled through experience to, conjunctions of environmental features, their firing
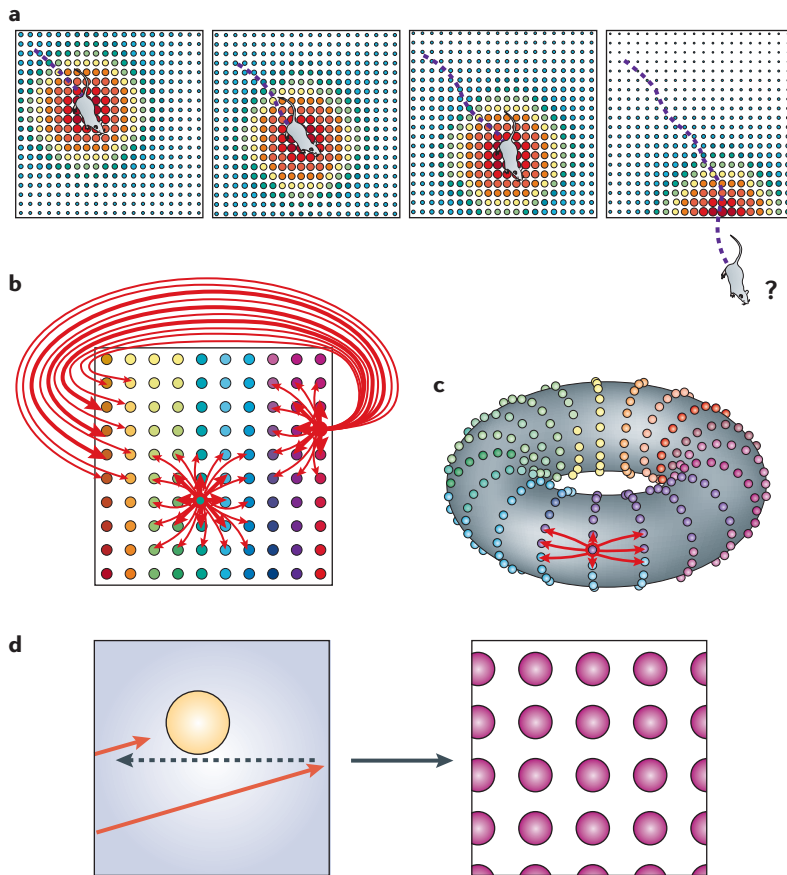
Figure 3 | **Solving the boundary problem for the path integration network. a** | The problem with a planar path integration system is that the size of the mapping space is limited by the number of cells. The rectangles represent a hypothetical 'attractor map' (or 'chart'[26]) without periodicity in the synaptic matrix. **b** | As described in FIG. 2, each node represents a cell, and warm colours represent high firing rates. Samsonovich and McNaughton[26] deal with the problem of edge effects in their path integrator model by postulating that the connections of cells at the edges wrapped around, creating a periodic boundary in two dimensions analogous to the periodic boundary condition of the head direction model. This gives rise to a synaptic matrix with a toroidal topology (**c**). This solution solves the edge effect problem in terms of dynamics, but does not really solve the positional ambiguity problem because it predicts that, if the animal explores a large enough space, each place unit will be activated periodically, giving rise to (**d**) a rectangular distribution of place fields. **d** | The red and black arrows represent the movement of the activity bump across the layer, and its reappearance at the opposite side with sufficient travel in one direction, due to the periodic connection matrix. The right panel illustrates the fact that, if the animal thoroughly explored a sufficiently large environment, a periodic matrix of this type would result in spatial firing fields that repeat at regular spatial intervals, giving rise to a square grid of activity maxima.

Orthogonal
Mathematically, two lists of numbers (vectors) with a correlation of exactly zero are said to be orthogonal. Hippocampal spatial codes are said to be orthogonal with respect to two arbitrary spatial environments if the locations and rates at which cells fire relative to each other are statistically independent.

also reflects how far and in what direction an animal has moved from a reference point, irrespective of the external sensory stimuli that impinge on it at a given moment[28,32–35] (BOX 1). Accumulating evidence suggests that place cells express the output of a path integration mechanism[9,14], but there have been conflicting evidence and views as to whether an intact hippocampus proper either performs, or is even required for, path integration[12]. In agreement with earlier suggestions that the path integration system might involve loops that include the entorhinal cortex[26,36,37], recent studies have pointed to the medial entorhinal cortex (MEC) as a potential location for the path integrator.

Some principal cells in the MEC have sharply delineated firing fields that collectively signal an animal's current position in a small environment as accurately as place cells in the hippocampus[38]. However, in a sufficiently large experimental environment, many MEC cells exhibit a striking feature of their activity that is not seen anywhere in the hippocampus proper: a grid-like structure of place fields repeating at regular intervals over the entire environment, as implicitly predicted by the toroidal chart model[26], except that the unit cell of the grid is not a square but a rhombus with internal angles of 60 and 120 degrees[39] (FIG. 4). Such a rhombus can also be constructed from two oppositely orientated equilateral triangles, giving rise to the descriptive term 'triangular grids'[39]. The two formulations are descriptively, but not necessarily computationally, equivalent.

The geometrical structure and spacing of grid fields in layer II MEC neurons is independent of the size or shape of the environment[39,40]. The grid spacing and grid orientation of neighbouring grid cells is almost identical, but their grids are offset relative to each other in an apparently random manner, and all grid phases (offsets) are equally represented within a small region of cortex[39]. Unlike the hippocampus proper, in which the spatial firing relationship of any arbitrary pair of cells is essentially unpredictable across environments, the relative offset (spatial phase) of grid fields for any two cells appears to be universal (constant across all environments)[40]. This property is analogous to the behaviour of head direction cells, which similarly retain their relative preferred firing directions across environments[5,35,41], and corresponds to the behaviour of the universal chart proposed in theoretical models of path integration[25,26,37]. In addition, some subicular place cells also appear to have such universal properties[42]. Grid orientation and scale at a given dorsoventral position is consistent across all layers of the MEC[43], which would be necessary for a local region of the cortex to act as a path integrator module. Currently there are insufficient experimental data to determine whether grid orientation is consistent along the entire dorsoventral axis.

Activity patterns of grid cells in layer II can be updated by input from afferent structures[44–46], but recent studies indicate that the integration of directional and positional information takes place within the grid network itself[43], using neurons with conjunctive place and directional properties much like those predicted by Samsonovich and McNaughton[26] (FIGS 2,3). Layers III, V and VI of the MEC contain not only grid cells, but also head direction cells and cells with conjunctive grid and head direction properties. All three cell types are positively modulated by running speed. Conjunctive cells are located predominantly in layers III and V, and the principal neurons there have extensive axonal projections up to the grid cell population in layer II (REFS 47–49), where they could drive the shift in the active grid cell population in a manner consistent with an animal's motion. By way of their superficial dendrites (BOX 2), these conjunctive cells are also likely to receive input from grid cells in layer II, as predicted by the continuous attractor model (FIG. 2). Given the presence of
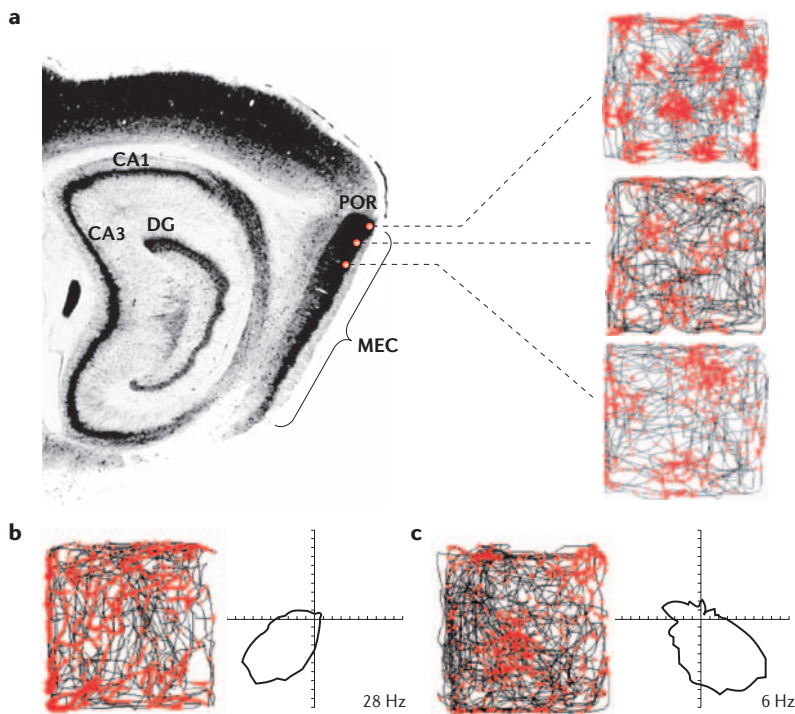
Figure 4 | **Grid cells in the medial entorhinal cortex. a** | Implausible as the idea might have seemed, cells with regular, periodic place fields are found in the medial entorhinal cortex (MEC); however, the arrangement of fields is not rectangular as would have been predicted from the Samsonovich and McNaughton[26] model implemented on a standard torus. Instead, they are distributed with a geometry that can be described as a tiling of rhomboids (or of equilateral triangles alternately rotated 180 degrees). The recording region is illustrated on a sagittal section of brain through the MEC. Each panel is the grid field of one MEC neuron in layer II. The locations of emitted spikes are illustrated with red dots; the paths of the rat as grey lines. The grid scale increases with distance from the border of the MEC with the postrhinal cortex (POR). **b** | In addition to 'pure' grid cells, which encode position only, the deeper layers of the MEC also contain head direction cells that are not modulated by location, and (**c**) conjunctive cells that depend on location and head orientation (polar plots represent directional firing rate). All cell classes are positively modulated by running speed. These are precisely the cell classes predicted in the path integrator model of FIG. 2. DG, dentate gyrus.

Allocentric space
In contrast to egocentric spatial representations, in which locations are encoded relative to a body axis (for example, 'three feet to one's left'), allocentric representations are independent of the observer's orientation (for example, 'three feet to the north of one's current location') or possibly even position (for example, '32°N, 111°W'). A road map is an example of an allocentric representation of space.

Population vectors
A population vector is a list of the instantaneous firing rates of a population of neurons. For *N* neurons, it represents a point in an abstract, *N*-dimensional space. It provides a convenient representation of the state of a neural ensemble.

horizontal connections in MEC layers III and V[50], attractor dynamics could potentially be accomplished in the deeper layers alone[27,51]; in this situation, layer II might act as an output layer, integrating activity from deep cells with different directional preferences to achieve a non-directional spatial representation.

Therefore, as an animal moves through its environment, the location-specific activity in the grid cell network is probably updated principally by a path integration-based mechanism. The spatial code is therefore a relative one, in the sense that the firing of one set of cells is determined by the preceding activity state of the network and the distance and direction moved by the animal in the intervening time, and is not determined directly by the pattern of environmental stimuli received by an animal at a given location. This possibility is consistent with the environmental invariance of the grid field relationships to one another, the imperviousness of the grid structure and spacing to removal or displacement of external landmarks, and the fact that the grids are expressed immediately in a novel environment[39,40].

These observations suggest that grid cells are part of a universal spatial metric similar to the navigation system postulated by O'Keefe[1], and are consistent with the inability of animals with entorhinal lesions to calculate a return path to their home cage on the basis of self-motion cues[52].

Similar to both head direction cells[5,14] and hippocampal place cells[33–35,53], although self-motion is vital for updating the relative position code in the grid network, the spatial coordinate system defined by the grid network can become anchored to the specific landmarks of individual environments. Grids assume similar phases and orientations with respect to external landmarks on repeated exposures to the same environment, irrespective of where the animal starts its run[39]. The association of path integrator coordinates with specific landmarks might take place in the hippocampus, which generates unique representations for individual environments as well as distinguishable events or internal states associated with a given episode in these environments[11,54–57]. Alternatively, this association might occur within the MEC itself, by combining grid activity with specific sensory inputs received from the postrhinal cortex. The MEC grid cells express location specific variation in the amplitude of the grid bumps[39]. This variation might reflect intrinsic inhomogeneities, external information afferent to the entorhinal cortex from other cortical areas, or return projections from the hippocampus to the deep and superficial layers of the entorhinal cortex[47,48,58]. Given that path integrator errors in hippocampal place cells and head direction cells are tightly coupled[35], it appears likely that the alignment of the path integrator system reflects a global network interaction.

What sets the scale of the cognitive map?

A map of allocentric space must be endowed with a scale at which relative distance is represented. One attempt to address the question of scale in the hippocampus made use of a graph theory framework, in which CA3 place cells constituted nodes, with distance being represented by the connection strength between cells[59]. This model provided a possible basis for encoding relative distances and for route planning, but its main drawback was the lack of a plausible mechanism for reading out the synaptic weight parameters. A related proposal is that the distance between two locations is inversely related to the correlation of the population vectors of hippocampal neuronal ensembles active at the two places[60–63]. Although plausible neural mechanisms can be proposed for reading out the similarity of two population vectors, place cell population vector correlations beyond a certain distance are effectively zero. Based on the typical size of a dorsal hippocampal place field reported in the literature, this distance would be only 30–40 cm. However, this difficulty is mitigated considerably by the observation that place field size varies systematically from the dorsal (septal) pole of the hippocampus to the ventral (temporal) pole[62–64]. The scale of the spatial code can be defined in a manner that is independent of any particular definition of a place field by plotting the mean correlation of population vectors as a function of spatial separation (FIG. 5f). In area CA1, the

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Box 2 | Entorhinal cortex anatomy

The entorhinal cortex constitutes the major interface between the hippocampus and the parahippocampal cortex[45,129,130]. The entorhinal cortex curves around the caudal and ventral portion of the hippocampal formation, projects extensively to each of its subfields, and receives strong return projections from area CA1 and the subiculum. It also has complex and only partly understood intrinsic circuitry[46].

Panel **a** shows a ventroposterior view of a rat brain, showing the entorhinal cortex to be located mostly ventral and medial to the rhinal fissure (green line), below the postrhinal (POR) and perirhinal (PER) cortices.

Based on cytoarchitectonics and connectivity, the entorhinal cortex can be divided into medial and lateral subdivisions (MEC and LEC). Both directly and through the POR, the MEC receives 3–4 times more input from occipital, retrosplenial and parietal cortices; the LEC has stronger connections with the PER and, directly or indirectly, the frontal, piriform, insular, olfactory and temporal cortices[45,46]. Axons from layer II of the MEC and the LEC innervate different dendritic segments of the same cells in the dentate gyrus and area CA3. Axons from layer III project to area CA1 and the subiculum, but MEC and LEC terminals segregate along the proximodistal axis of the two subfields[46]. Orthogonally to the medial–lateral subdivision, the entorhinal cortex exhibits a gradient of differences in extrinsic and intrinsic connectivity[45,129,131,132]. The dorsolateral region (dark red), running along the border with POR and PER, receives most of the visuospatial input to the entorhinal cortex and is reciprocally connected to the dorsal part of the hippocampus. Further from the rhinal sulcus (where red turns into blue), the entorhinal cortex receives progressively less input from the sensory association cortices, including PER and POR, and more from various subcortical areas including the hypothalamus and amygdala. These parts of the entorhinal cortex have strong reciprocal connections with the intermediate and ventral regions of the hippocampus.

Panel **b** shows some principal cell types in the entorhinal cortex and their primary dendritic and axonal arborization. Stellate cells in layer II have axonal collaterals in layers I–III; axons from pyramidal cells in layer III collateralize broadly in layers I and III (REF. 49,133,134). Nearby principal cells are connected through extensive recurrent connections in layers III and V but this is less apparent in layer II (REF. 50). The deep layers are strongly connected to the superficial layers. Axons from layer V cells ascend to the pial surface and branch widely when entering the upper three layers[47,58]. Although local collaterals from superficial cells generally remain in layers I–III, layer II and III cells might influence cells in layers III and V because the apical dendrites of layer V extend all the way up to the surface, allowing possible synaptic contact between the layers[47,49,58,135]. The extent of synaptic connectivity between cell classes in the various layers of the entorhinal cortex is not well understood, but the pattern of dendritic and axonal branching, and the common behavioural correlates of deep and superficial neurons[43], suggest that the layers operate as an integrated network with significant computational power even in the absence of the loop through the hippocampus[38]. The diversity of entorhinal interneurons[136] is not indicated in the figure. Blue, axons and axon collaterals; black, soma and dendrites. Panel **a** is modified, with permission, from REF. 43 © (2006) American Association for the Advancement of Science.

half-amplitude width of this function varies from roughly 25 cm at a distance of 1.5 mm from the septal pole to 42 cm at a distance of about 4.5 mm[63]. Linear extrapolation would put the half-amplitude width of the decorrelation function at the most ventral tip at a metre or more.

According to the path integrator model (FIG. 2), the size of the place field, and therefore the scale at which space is represented in the brain, is controlled not by external input but by the relationship between the speed of the rat and the speed at which the activity bump moves across the attractor layer. The notion that hippocampal neuronal activity is tightly coupled to voluntary motion, in particular locomotion, was first substantiated by Vanderwolf and colleagues[65,66], who showed that the largest amplitude of rhythmic slow activity, or theta rhythm, in the CA1 field of the hippocampus was associated with walking, and that the amplitude increased with speed. During unrestricted natural locomotion, the amplitude of hippocampal theta waves increases essentially linearly with running speed, or distance displaced during ballistic movements such as jumping[60,67,68]. Running speed also monotonically affects the firing rate of hippocampal pyramidal cells and many interneurons, at least over most of the normal range of locomotion speeds (up to ~30–40 cm sec^{-1}) (REFS 61,63,69,70). Interestingly, when animals trained to tolerate tight restraint are moved passively through the environment, the activity of place cells at a given location in the unrestrained condition is practically abolished[71], suggesting an important role of motor set (the preparedness for movement) in driving hippocampal neurons.

A deeper insight into the role of self-motion in determining the scale factor of the hippocampal spatial code came from a study in which potential sources of self-motion information available to a moving rat were systematically altered[60]. When self-motion signals are attenuated, the hippocampus behaves as if the rat were moving more slowly, over a smaller distance, making place fields appear substantially (roughly threefold) larger (FIG. 5). These effects were associated with large reductions in the gains of the functions relating amplitude of the hippocampal theta rhythm and cellular firing rate to movement speed. Therefore, the scale of hippocampal place fields might be determined by a movement-speed signal that is generated outside the hippocampus through a summation of components related to ambulation, vestibular activation and optic flow. A corollary of this conclusion is that the change in spatial scale along the septotemporal axis of the hippocampus might be explained by a systematic variation in the gain of the motion signal. This hypothesis was confirmed[63] by showing that the functions relating theta amplitude and relative firing rates of CA1 principal cells and interneurons to running speed become systematically less steep as the recording location moves temporally along the septotemporal axis.

Grid fields also scale up along the dorsoventral axis of the MEC[38,39]. At the most dorsal end of the MEC, from which projections arise to the more septal portion of the hippocampus, grids are dense, with a spacing of 35–40 cm[39,43]. The spacing increases approximately 1.5 times over the next 1 mm, which corresponds to approximately one-quarter of the dorsoventral axis of the MEC. More ventral locations have not been systematically explored, but existing data from the authors' laboratories indicate that grid and/or place field scale
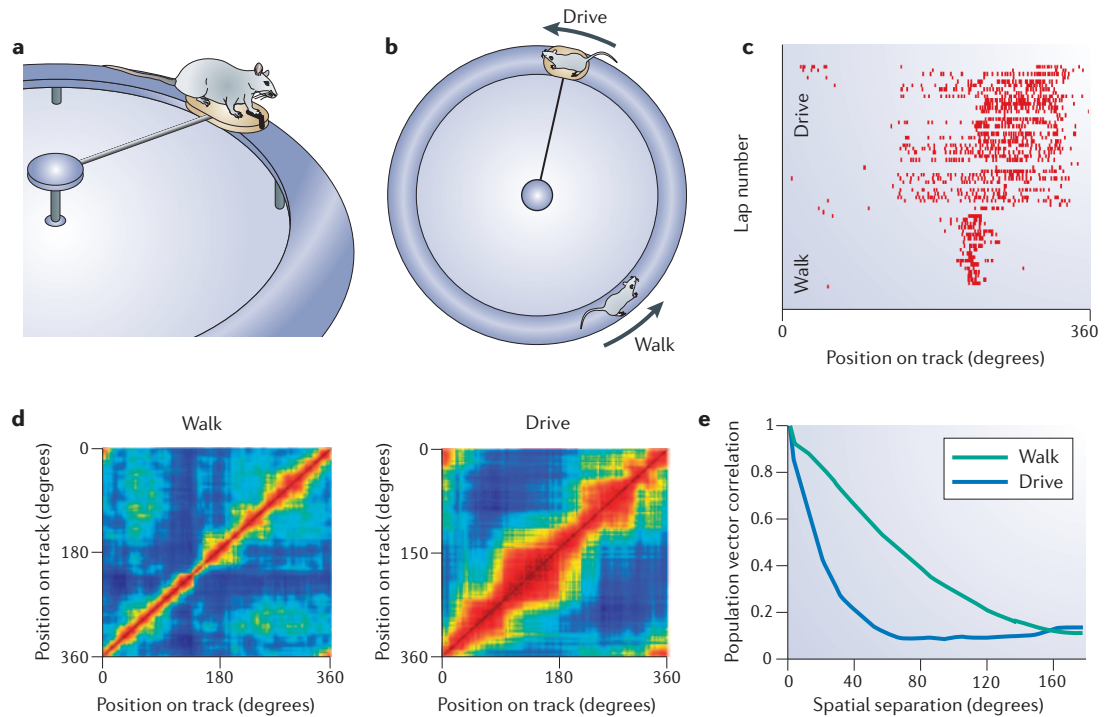
Figure 5 | **Changing the gain of the self-motion signal changes the scale of the spatial representation. a** | Rats were trained to press a lever to activate a mobile platform which moved around a circular track, and to stop at particular locations for a reward[60]. **b** | Laps of driving were interspersed with laps of walking. During driving, individual place fields were roughly threefold larger, peak firing rates were lower, and fewer cells expressed place fields on the track. There was also a reduction in the slopes of the functions relating electroencephalogram theta rhythm amplitude and cell firing rate to movement speed. **c** | A spike raster from one representative neuron during walking and driving. Each row reflects a single lap around the circular track (represented linearly) and the tick marks represent spikes emitted as a function of location during each lap. In this example, the field remained approximately in the same location, but often the fields changed locations unpredictably or disappeared (that is, they were remapped). **d** | Population vector correlation matricies showing that during driving, the population vectors became decorrelated much more slowly as a function of location than during walking. **e** | Average population vector correlations versus spatial separation for walking and driving. In the absence of the motor and proprioception components of the self-motion signal, the network behaves as if the rat is moving more slowly, and around a smaller track.

Theta rhythm
Spontaneous oscillatory activity (4–12 Hz) detected in the local field potential of the rat hippocampus. The theta rhythm is produced by large ensembles of hippocampal neurons oscillating in synchrony, and is coherent in phase throughout the hippocampus. Its amplitude, however, varies systematically along the septotemporal axis of the hippocampus.

'Beat' effect
When two pure tones (or periodic signals of any kind) of different frequencies are added together, a tone of lower frequency (the difference between the two fundamentals) emerges due to the gradual shift of relative phase of the two signals, which causes cancellation and summation alternately. In music terminology, this lower frequency is called a 'beat'.

is perhaps of the order of one to several metres at the most ventral locations. It is not yet known whether the scale increases linearly.

From periodic grids to non-periodic place fields

The combination of grids at variable scales might provide an economical, high-resolution spatial coordinate system for navigation over a large space, and could explain why hippocampal neurons downstream from the MEC do not express grid-like fields, but nevertheless express increasing place field size along the septotemporal axis. If grid cells had a single, common scale, the hippocampal code might be expected to repeat itself at intervals corresponding to a single period of the grid. However, if hippocampal activity reflects the summation of the outputs of many grids with different spacings, the cycle for repetition might be very large (FIG. 6), enabling each position to be expressed by a unique pattern of collective activity. The repetition cycle could be considerably larger than the scale of the largest grid, because of 'beat' effects, such those seen when two cosine functions with slightly different frequencies summate, giving rise to frequency components much slower than either of

the generating functions, depending on the difference between the frequencies. When multiple grid fields at different scales are summated, a single dominant peak arises, the scale of which is set by the smallest scale of the input set. Because each point on the septotemporal axis of the hippocampus receives input from a limited range of MEC cells (BOX 2), this idea can explain why place fields in the hippocampus also scale up along the septotemporal axis.

An important point to note is that, according to the simple path integrator model (FIG. 2), only one scale is possible because the bump of activity must move coherently. Therefore, different scales must be achieved by having multiple weakly interacting or non-interacting path integrator modules. Simply varying the gain of the speed signal across modules would then give each module a characteristic spatial scale.

Remapping in the hippocampus

A crucial step in encoding a new episodic memory is the minimization of similarities between the new representation and representations that already exist in the network. The hippocampus is thought to contribute to
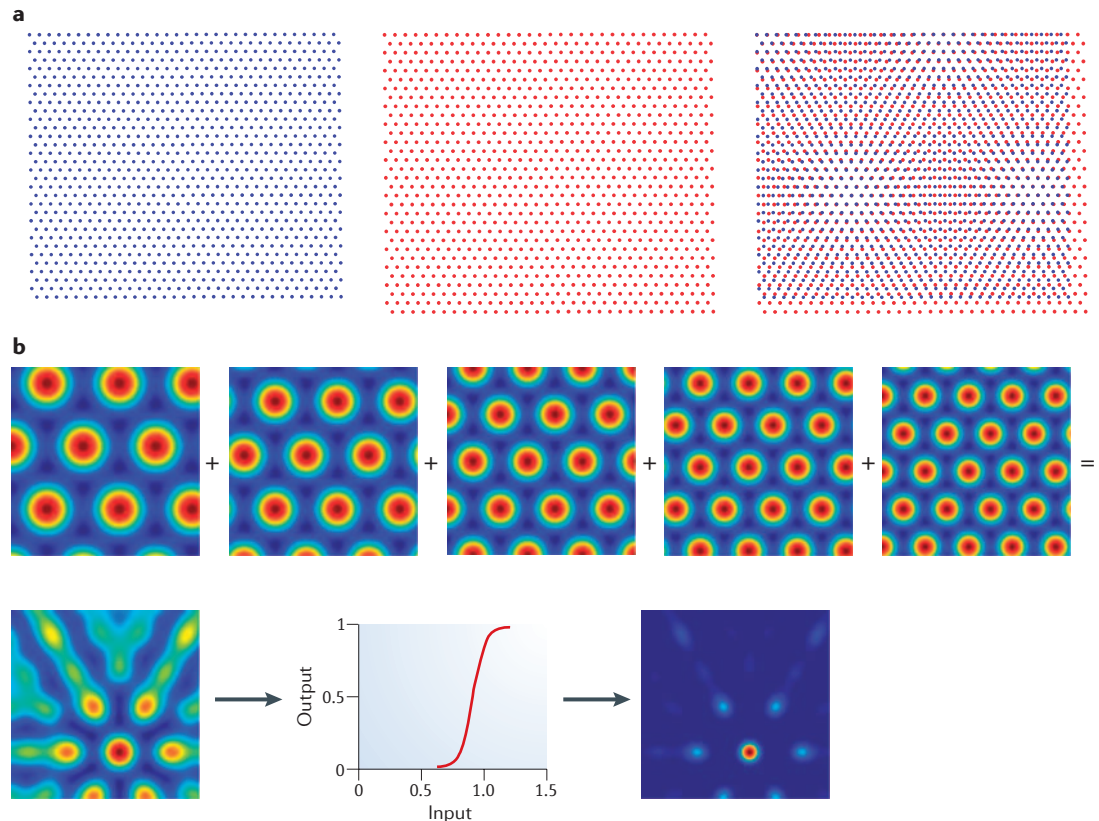
Figure 6 | **Combining multiple periodic grids at different spatial scales can result in non-periodic place fields.**
a | The effects of slight variation in grid scale (6% in this case) on the periodicity of a mapping space defined by the superimposition of the output of two grid modules. In general, the summation of two periodic signals that differ in frequency gives rise to a signal with amplitude maxima that occur with a much lower frequency (the difference between the fundamental frequencies). **b** | Multiple grid fields with different scales, as expressed by cells at different dorsoventral levels of the medial entorhinal cortex can be combined, for example, by linear summation, resulting in an activity field that has only one large maximum. The spatial frequency of the patterns increases systematically from left to right. A simple thresholding operation applied to the summed grid fields (here implemented by a sigmoidal function shown in red) yields a field that is restricted to a region of space. This is a potential mechanism for the generation of non-periodic place fields such as those observed in the hippocampus.

this through a pattern separation process, whereby small differences in cortical input patterns are amplified as they propagate through the hippocampal network, creating differences in the locations and/or firing rates for place fields[72,73]. This process, often referred to as remapping[74], has been observed after changes in a subset of the sensory cues (such as the geometrical shape or colour of the test chamber) in an otherwise constant environment[75–77]. It can also be induced by changes in task demands, such as a shift from a free foraging task to an instrumental running task[78], or by changes in the relationship between the current setting of the head direction system and the salient external cues[35]. In old animals, complete remapping can occur spontaneously in a highly familiar environment from one visit to the next[79].

The first indications of remapping were observed in area CA1, yet most theoretical models would suggest that, based on the connectional divergence and the recurrent connectivity of the earliest stages of the hippocampal input, remapping in the CA1 reflects pattern separation mechanisms upstream in the dentate gyrus and CA3 subfields. Based on analogies with the cerebellum, where

decorrelation has been postulated to be accomplished by the dispersal of incoming sensory information onto a vastly expanded layer of granule cells before the information reaches the associative synapses of the Purkinje cells[80,81], it has been suggested that input from the entorhinal cortex is decorrelated as it is spread out onto a larger number of granule cells in the dentate gyrus[72]. In addition, the firing of the granule cells is sparse, and each granule cell makes synapses with only a limited number of CA3 pyramidal cells, suggesting that a combination of mechanisms might potentially contribute to decorrelation of cortical information. Whether these hypothetical mechanisms represent the origin of the orthogonalization required for remapping in the hippocampus remains to be determined; however, when rats are tested in two similarly shaped enclosures with different background contexts, the subsets of cells active in area CA3 in the two rooms are completely orthogonalized, showing no more overlap in activity than expected by chance[82,83]. The strong orthogonalization of spatial representations in the CA3 points to pattern separation as a major function of the early stages of hippocampal formation.

In 1952, Alan Turing[91] proposed a mechanism for how structures could emerge spontaneously in chemical systems, and suggested that such a mechanism could underlie pattern formation in nature (that is, morphogenesis). In the proposed mechanism, diffusion-driven instabilities could occur in a homogeneous mixture of chemically reacting species, producing spatially periodic patterns. The chemical reactions considered involve an auto-catalytic activator species. The increase in the activator provokes the increase in a counter-balancing inhibitory species. A crucial requirement for the Turing instability is that the diffusion rate of the inhibitor is larger than that of the activator; this allows for local growth of the activator being limited in its spread by the faster diffusing inhibitor. This scheme will repeat itself in the spatial domain, eventually producing structures with a characteristic wavelength. Although the Turing instability has been studied intensively in theory, it was in 1990 that Castets *et al.*[137] managed to experimentally produce the Turing pattern in a chemical system. They used the chlorite-iodide-malonic acid (CIMA) reaction, in which iodide and chlorite are the activator and the inhibitor, respectively. Castets *et al.* performed the reaction in a gel loaded with polyvinylalcohol, which is a macromolecule that has a slow diffusion rate. Importantly, the macromolecule partly binds the iodide, effectively slowing down the diffusion of the activator. Under these conditions, Turing structures emerged spontaneously in the gel. Depending on the reaction parameters, the emergent patterns consist of either regular grids, reminiscent of medial entorhinal cortex grid fields (panel **a**), or stripes (panel **b**), reminiscent of ocular dominance bands in the visual cortex. Neural networks consisting of mutually excitatory principal cells and feedback inhibitory cells can produce such Turing instability as well, by making the range of inhibitory connections longer than the excitatory ones. Figure reproduced, with permission, from REF. 138 © (2002) World Scientific.
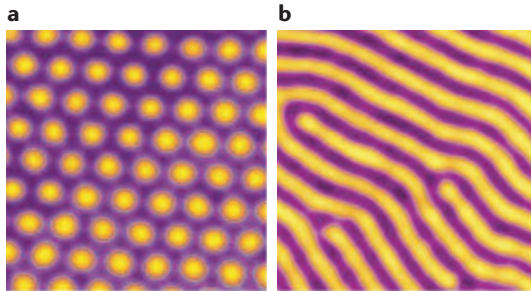
Recent observations have indicated that remapping in the hippocampus has two different modes, referred to as global remapping and rate remapping[11]. Global remapping is a complete reorganization of the hippocampal place code, expressed by independent rate and place distributions in the different test conditions. Global remapping is normally induced when the animal moves between different environments (for an exception, see REF. 84), but it can also occur after substantial changes in cue configuration at a single location[85], as observed in the first studies of remapping[76,77]. Rate remapping refers to a selective change in the distribution of firing rate with no change in the place code[11]. Rate remapping can occur when the animal is tested with different cue configurations in the same location. Both forms of remapping take place in both CA3 and CA1 regions, but the distinction between them is most striking in the CA3 (REF. 11).

Preliminary data suggest that global remapping and rate remapping are associated with different population dynamics in entorhinal grid cells[40,86]. When global remapping is induced in area CA3 by changing a number of box features (including the geometry and the floor texture) without moving the enclosure, the induction of hippocampal remapping is invariably accompanied by a coherent offset of the grid fields of simultaneously recorded colocalized MEC neurons. When global remapping is induced by moving the rat to a different room, the population grid is not only displaced, but is typically also rotated. Rate remapping in CA3, induced by changing only the colour of the recording enclosure, was not accompanied by any realignment of the grid fields, suggesting that the non-spatial information triggering this form of remapping might be conveyed to the hippocampus either by a minor redistribution of firing rates within the spatially constant population grid in the MEC or by inputs from other brain regions.

Among the other brain regions that could provide non-spatial sensory input to the hippocampus, the strongest candidate is the lateral entorhinal cortex (LEC), the cells of which do not appear to exhibit spatial activity[87]. The LEC has strong bidirectional connections with the piriform, insular, olfactory and temporal cortices[45,46], which could provide it with multimodal sensory input sufficient to trigger rate remapping in the hippocampus.

Alternative cortical pathways to the hippocampal region include direct projections from the presubiculum and parasubiculum[88], and the perirhinal and postrhinal cortices[89,90]; however, except perhaps for the projection from the parasubiculum to the dentate gyrus[88], these connections are sparse compared with the entorhinal input, and their terminals reach only limited parts of the transverse axis of the hippocampus.

Theory for grid network self-organization

The regularity of MEC grid fields, the independence of their spatial relationships from external influences, their colocalization with conjunctive cells and the motion sensitivity of all cell classes appear, in principle, sufficient to implement path integration. These factors also suggest that MEC circuits underlying grid fields could become organized early in development, possibly in a manner that is relatively independent of experience. An experience-independent developmental process is also suggested by the fact that large-scale MEC grids (and hippocampal place fields) are observed in ventral regions of the hippocampal formation in laboratory rodents, which have had little, if any, exploratory experience in environments larger than a typical rodent housing cage. How might the hypothetical periodic synaptic matrix of the grid layer be self-organized?

Early insights into some universal principles that might underlie grid network development came from a theoretical proposal by Alan Turing in 1952 (REF. 91). He proposed that a simple reaction-diffusion chemical mechanism could produce spatially organized structures spontaneously, through competition between reagents termed activators and inhibitors. If inhibitors diffuse faster than activators, spatial patches can emerge in which the activator concentration is high, surrounded by areas of high inhibitor concentration. Therefore, this spontaneous symmetry breaking, which has been observed in chemical reaction systems, can create structures with periodic spatial properties such as stripes of alternating regions of high activator or high inhibitor concentration, or grids of many, roughly circular, regions of high activator concentration surrounded by regions of high inhibitor concentration (BOX 3). These regions typically appear in their closest packing density configuration, and therefore resemble MEC grid fields. Turing proposed that

such a mechanism could be responsible for some types of morphogenesis or pattern formation in biology.

This simple reaction-diffusion mechanism also has a neuronal implementation[92]. Consider a network of excitatory and inhibitory neurons arranged randomly but with uniform density on a cortical sheet, and with a connection strength that decreases with distance. If the connections of inhibitory cells extend over a wider range than the connections of excitatory cells[93] (difference of Gaussians or Mexican hat connectivity profile; FIG. 7), the symmetry can be broken, allowing for patterns to emerge spontaneously. This connectivity profile is related to that of the continuous attractor networks described in FIGS 1–3, in which a global, uniform inhibition leads to a stable state with a single activity bump. In the case of the Mexican hat connectivity, the finite range of the inhibition allows for continuous attractors with multiple activity bumps. In a two-dimensional domain, several types of structure can emerge. The simplest type is a striped firing pattern that resembles the ocular dominance columns in the visual cortex. A second type of firing pattern is a grid-like arrangement of activity bumps. The spatial wavelength of the activity pattern is determined primarily by the width of the Mexican hat connectivity profile. The striking and unexpected regularity of both the Turing symmetry breaking and the grid cell phenomenon is so compelling that a possible connection between the two is unlikely to have escaped the attention of many who are familiar with both[94]; indeed, at least two theoretical proposals for grid cell mechanisms based on these principles have already appeared[51,95].

However, the idea that the Turing grid emerges as a topographical pattern on the MEC implies that grid cells that are near one another in cortical space would have grid fields with similar phases. By contrast, grid cells recorded from the same tetrode have widely scattered grid phases[39]. To overcome this problem, it has been suggested[51] that modules of the hypothetical MEC topographic grid might be small, and therefore could contain so few neurons that a single recording electrode might record a wide range of grid phases. This seems unlikely, because the regularity of the Turing structure is highly dependent on the cooperative activity of many cells, and the system presumably must operate in the face of considerable noise. Theoretical studies[19] have shown that the stability of continuous attractors is sensitive to the sorts of inhomogeneities that would be expected in networks containing few neurons. This argues against a topographical arrangement of grid cells in the adult MEC and provides a challenge to topographic models that require Mexican hat-like connections among topographically arranged grid cells.

The compromise that we propose is that larger-scale, topographically organized grids of activity might be a feature of the immature cortex during early postnatal development (approximately weeks 1–2). We assume that the necessary Mexican hat connectivity can be implemented by having a mixed layer of interconnected excitatory and inhibitory neurons, with longer-range connections in the latter, so that no self-organizing process is required at this stage. We hypothesize that
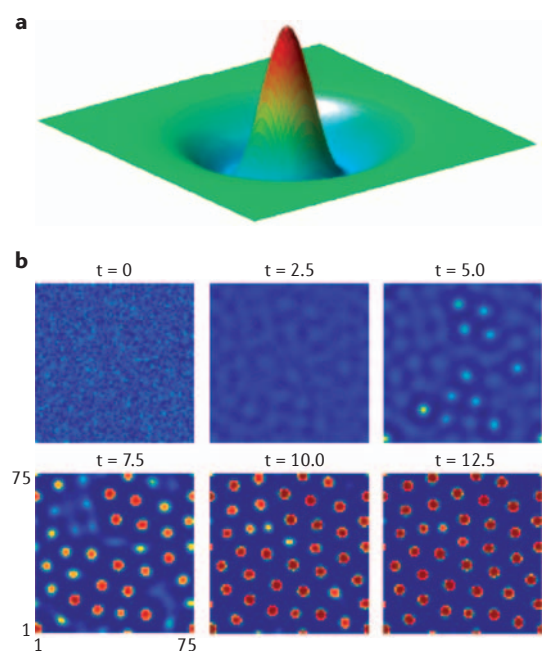
Figure 7 | **Symmetry breaking and the emergence of a grid-like firing pattern.** The Turing symmetry-breaking mechanism[91] described in BOX 3 has a simple analogy in the behaviour of neural nets with feedback excitation and surround inhibition. **a** | The 'Mexican hat' connectivity profile required for pattern formation. Colours represent net excitation (red) and inhibition (blue) as a function of distance from an arbitrary point on the layer of cells. The connections of inhibitory cells extend further than the connections of excitatory cells. **b** | A network simulation demonstrating the emergence of an ordered activity pattern from random initial conditions. The cells are arranged in a 75-by-75 array representing a cortical sheet. Initially the activity of the cells has no spatial structure, but with time the initial symmetry is broken and patches of increased firing emerge arranged in a triangular (rhomboidal) structure. Eventually this pattern stabilizes. Colours represent firing rates of the neurons in the array: warm colours represent high activity, progressively cool colours represent progressively lower activity.

such an early developmental phenomenon could guide the development of multiple modules in the MEC, generating a toroidal synaptic matrix in each, but without topography in the physical layout of the neurons. Such modules would form the basis for grid cell behaviour in the adult and, in particular, could account for the steep gradient of spatial scales observed along the dorsoventral axis. The hypothesis has four components (FIG. 8): a developmentally transient 'teaching' layer, endowed with Mexican hat connectivity that results in Turing symmetry breaking (the 'Turing layer'); a set of modules analogous to a cortical column, in which intrinsic connectivity is relatively high but interactions with other modules are relatively weak; and two well-known types of activity-dependent synaptic modification rule, for which there is abundant biological evidence. The requisite synaptic modification rules are a competitive learning rule (such as soft competitive learning[96], or a variant of the well-known BCM (Bienenstock–Cooper–Munro) rule[97]) that

Difference of Gaussians or Mexican hat
If two Gaussian curves with different variances are subtracted from one another, the outcome is a curve that has a central peak with surrounding troughs (or vice versa). Depending on the difference in variance of the initial curves, the outcome can resemble a sombrero or 'Mexican hat'. This description has been applied, for example, to simple cells of the visual system with excitatory centres and inhibitory surrounds.

Tetrode
Extracellular potentials generated by a spiking neuron decline with distance from the current source. A tetrode is a four channel recording probe that can be used to isolate spike trains simultaneously from multiple neurons within a small region of brain, based on the relative amplitudes of spikes appearing simultaneously on the different channels.

incorporates an activity-dependent shift from LTD to LTP[98,99], and Hebbian associative LTP.

The proposal is simple. First, imposing realistic neural dynamics such as accommodation and/or synaptic noise can be shown, in principle, to cause the grid structure in the Turing layer to drift randomly while preserving grid orientation. So, over a period of time, the Turing layer grid would visit all possible grid phases. Second, random connections from the Turing layer to all of the modules, if subject to a suitable competitive plasticity mechanism, would generate cells that are selective for specific phases of the Turing grid. However, there would not be any topographic organization in the modules — neighbouring cells would not have correlated phases,

which is consistent with what is observed in the MEC where neighbouring cells do not, in general, have correlated grid phases, but all cells in a column have the same grid orientation. The same principle is widely used in models for the activity-dependent development of feature selectivity in sensory systems[100,101]. Finally, Hebbian associative plasticity within a module will generate a synaptic matrix in which neurons tuned to similar Turing layer grid phases will be strongly coupled, whereas cells with opposite phase tuning will be weakly coupled. As illustrated in FIG. 8, such a mechanism would generate, within each module, the toroidal synaptic matrix that could underlie grid cell behaviour in the adult. We assume that, once the task of self-organizing the synaptic
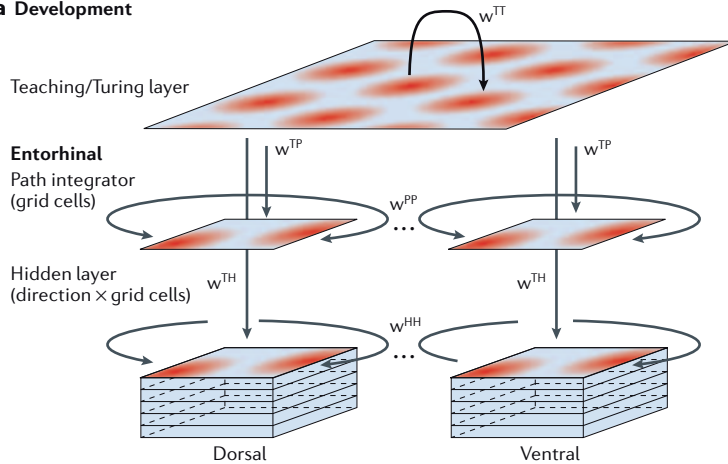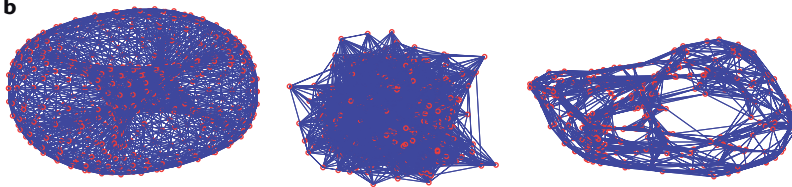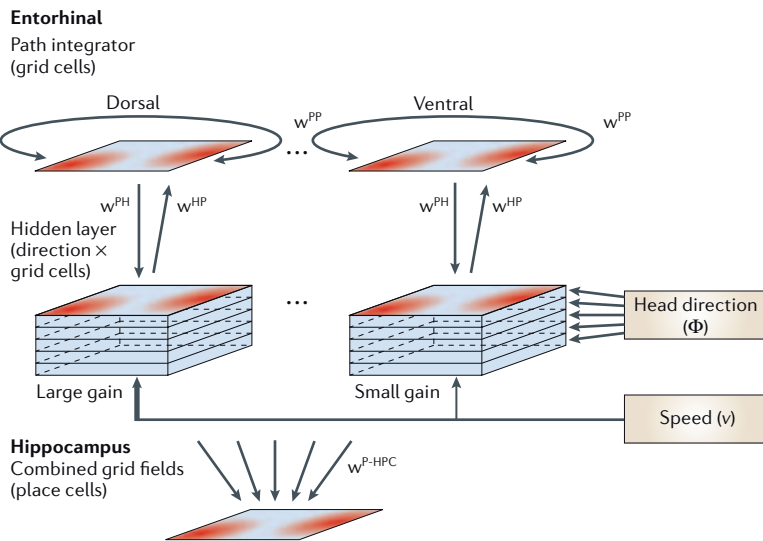

Figure 8 | **Developmental model for an anatomically non-topographic MEC path integrator. a** | During development, topographically arranged firing rate patterns form in the Turing (teaching) layer owing to spontaneous symmetry breaking in a network with short-range excitatory and long-range inhibitory connections (w^{TT}; 'Mexican hat' connectivity, see FIG 7). Owing to neuronal adaptive properties and noise, the firing rate patterns will drift, exploring all spatial phases but maintaining a constant orientation. The Turing layer projects to multiple modules in the developing path integrator (w^{TP}) and the hidden layer (w^{TH}), which might correspond to columns in the medial entorhinal cortex (MEC). One dorsal and one ventral module are illustrated here. Note that, although for convenience the cells in the path integrator and hidden layer are illustrated as topographic sheets, these cells are assumed to be randomly arranged in the brain. Excitatory connections are formed by Hebbian plasticity (w^{PP}). Competitive synaptic plasticity in w^{TP} and possibly w^{TH} result in different cells within a module developing selectivity for different Turing layer grid phases. Hebbian synaptic plasticity within each module results in cells with nearby grid phase preferences becoming selectively coupled. Therefore, the resulting synaptic matrix (w^{PP}) will have periodic boundaries (FIG. 4b), even though the cells themselves are arranged at random. **b** | A three-dimensional linear embedding[139] illustrating the toroidal periodic topology of the synaptic matrix (w^{PP}) for ideal, hand-wired connections implementing periodic boundary conditions of the path integrator. Numerical simulations of the model allowed the synaptic matrix w^{PP} to form as a consequence of drifting patterns in the Turing layer: prior to learning no topological structure was present in w^{PP} (middle panel), whereas after learning the synaptic matrix assumes a toroidal structure implementing the periodic boundary conditions (right panel). **c** | Once the self-organization is complete, we assume that the cells of the Turing layer or their connections are eliminated, leaving the adult form. The variation in spatial wavelength during path integration of the grid fields expressed by cells in each module is determined by the gain of the velocity input to the hidden layer, which can be accomplished by varying either the number of velocity tuned inputs or the relative strength of their connections. A large gain will drive the activity bump relatively fast, resulting in grid patterns with a small spatial wavelength (dorsal). A lower gain moves the bump more slowly, resulting in grid patterns with a larger spatial wavelength (ventral). Finally, the activity from multiple modules in that path integrator is combined in the hippocampus. This results in spatially unambiguous firing

matrix within the MEC modules is accomplished, the Turing layer cells would either undergo reallocation to another function by rewiring, or perhaps be removed.

Several features of the adult and developing brain support the proposals made above. The first is the abundance of evidence for modular or columnar organization in the cortex[102]. In particular, the entorhinal cortex has a clearly modular anatomical organization in the adult, although it is perhaps more obvious in the LEC than the MEC. Layer II is separated into alternating patches that are interleaved by bundles of dendrites and axons from cells in the deeper layers, particularly in layers III and V (REFS 103,104). The diameter of the dendritic and axonal bundles in the entorhinal cortex is roughly 400–500 μm. Such anatomical modules could possibly correspond to the postulated functional modules. Second, during early postnatal development, the neocortex undergoes a complex constellation of spontaneous slow oscillations of correlated activity, which are implicated in the development of cortical connectivity patterns[105–107]. In some cases, waves of excitation can propagate at speeds of up to several hundred microns per second[108–111]. In other cases, distinct columns or 'domains' of increased intracellular free Ca^{2+} appear transiently. Waves of excitation are particularly evident in slices of postnatal entorhinal cortex. Third, there is abundant evidence for patterns of connectivity and/or actual neural populations that are expressed early in development and that disappear in the adult. For example, early in development cortical layer I contains an oscillatory network involving Cajal–Retzius cells, which largely disappear in the adult[109].

Conclusions and problems for further study

The discovery of grid cells and conjunctive 'grid × head direction' cells, and their suggested relationship to existing models for path integration, can be regarded as a success for the combination, during the past three decades, of concepts derived from theoretical and computational studies with empirical neurophysiology. However, there remain many unanswered questions. The continuous attractor model discussed here is but one of a class of similar models with different specific implementations and sometimes different predictions. For example, similar dynamics arise if the recurrent symmetrical connections leading to the attractor dynamics and the asymmetrical connections leading to translation of the activity bump are all contained within the same physical layer[23,51]. This might be a technical detail, but it could lead to different ideas about the roles of individual layers and cell classes. Which of these detailed models, if any, will prove correct remains for future neurophysiological and anatomical studies to determine. Unfortunately, neuroanatomical understanding of the details of the wiring diagram of the entorhinal area have lagged considerably behind the hippocampus proper, for the reason that, until now, there has been no behavioural correlate of MEC cells as compelling as the hippocampal place cell phenomenon to drive new hypotheses and studies. We expect that the discovery of grid and conjunctive cells in the MEC will mark a vital turning point in the focus of anatomical

investigation. An example of the potential discoveries to be made from further study of this network is the recent evidence that neighbouring stellate cells in layer II of the MEC could have limited excitatory interconnections[50]. This might place the attractor dynamics in the deeper layers and leave layer II with a computational task to accomplish before sending its output to the CA3 and the dentate gyrus.

Furthermore, in this review we have ignored the rich behaviour of hippocampal and entorhinal cortical neurons in the frequency domain. In behaving rats, cellular firing in this system is subject to complex interactions with local field oscillations at the theta and gamma frequencies, which arise from both intrinsic cellular mechanisms and system-level interactions[112]. The striking phenomenon of 'phase precession'[113–115] in hippocampal neurons is a case in point. Hippocampal place cells exhibit a systematic, 360 degree phase retardation in their firing relative to the local theta field as a rat traverses the place field. They continue to exhibit a single cycle of this phase shift after either manipulation of place field size by changing self-motion cues[60] or experience-dependent place field expansion due to LTP-like synaptic plasticity during repeated route following[68,69,116]. Phase precession in the hippocampus has been suggested as a possible mechanism for compressing sequences of neural activity into a narrow time window comparable to the time constant of the NMDA (N-methyl-D-aspartate) receptor, so that asymmetrical Hebbian synaptic plasticity can record the sequence or route[113]. However, available data suggest that phase precession in area CA1 can be observed from the first time a rat enters the route[117], making it difficult to understand how the hippocampus can compress a sequence that it has not yet experienced. Skaggs et al.[113] suggested that phase precession might originate in the entorhinal cortex, and this speculation has recently been confirmed for layer II MEC grid cells[118]. Because, according to the current model, the interaction of periodic MEC grids at various scales can give rise to a virtually limitless sequence of hippocampal place fields, phase precession in the MEC could indeed be used to generate the phenomenon in the hippocampus, and so possibly provide the basis for sequence encoding there.

Finally, a crucial outstanding question, in terms of understanding the role of the hippocampus in either navigation or memory, concerns the form of the output code of the hippocampal formation and how this output is used by the widespread cortical and subcortical regions that receive it. Outputs from the hippocampus back to the rest of the cortex arise principally from the deep layers of the entorhinal cortex and from the subiculum[46]. These outputs are thought to have a vital role in providing a contextual tag for consolidation of episodic memories stored in distributed neocortical modules[119–125]. It is now known that the superficial neocortical layers that receive the bulk of entorhinal output tend to show much more spatial context-dependent encoding activity than the deeper layers[126]. In addition, evidence indicates that during sleep and quiet

wakefulness, the hippocampus plays back repeated short sequences of activity patterns generated during preceding behaviour[127]. Given that area CA1 could contain convolved information about the location and content of a temporally extended experience[11], one might speculate that the two output structures, the subiculum and deep layers of the entorhinal cortex, might parse the data projected to the neocortex into distinct non-spatial and spatial components respectively. Clearly much remains to be learned about the hippocampal formation and its interaction with the rest of the brain, but our current understanding of it underscores the growing paradigm shift in the neurosciences away from thinking about neural coding as being driven primarily by bottom-up, sensory inputs, but rather as a reflection of rich and complex internal dynamics.

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FURTHER INFORMATION
Battaglia's homepage: http://www.science.uva.nl/~battagli/
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