

# Spatial representation and the architecture of the entorhinal cortex

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**It has recently been recognized that the entorhinal cortex has a crucial role in spatial representation and navigation. How the position of an animal is computed within the entorhinal circuitry remains to be determined, but the architectural organization of this brain area might provide some clues. Here, we review three organizational principles – recurrent connectivity, interlaminar connectivity and modular organization – and propose how each of them might contribute to the emergence and maintenance of positional representations in entorhinal neural networks.**

## Introduction

Mammals have several strategies for keeping track of where they are in the environment [1–3]. For example, it is possible to determine position by comparing bearings from distal landmarks. This ‘geometric’ strategy, if used alone, depends heavily on the particular external objects and features of the environment, and the relationship between the landmarks must be learned in a map-like manner for each individual environment. An alternative strategy that can be applied more universally is based on ‘path integration’, or the use of self-generated motion cues to form a continuously updated vector-based representation of distance and direction from a fixed reference point [4]. This mechanism confers increased metric accuracy to the representation and it can operate in the absence of specific landmarks. Its weakness, if applied alone (e.g. in complete darkness or in thick fog), is the accumulation of random error as the subject moves away from the reference point. Most animals use a combination of the two mechanisms, where position is continuously computed from self-motion cues but with frequent calibration against external landmarks [5,6].

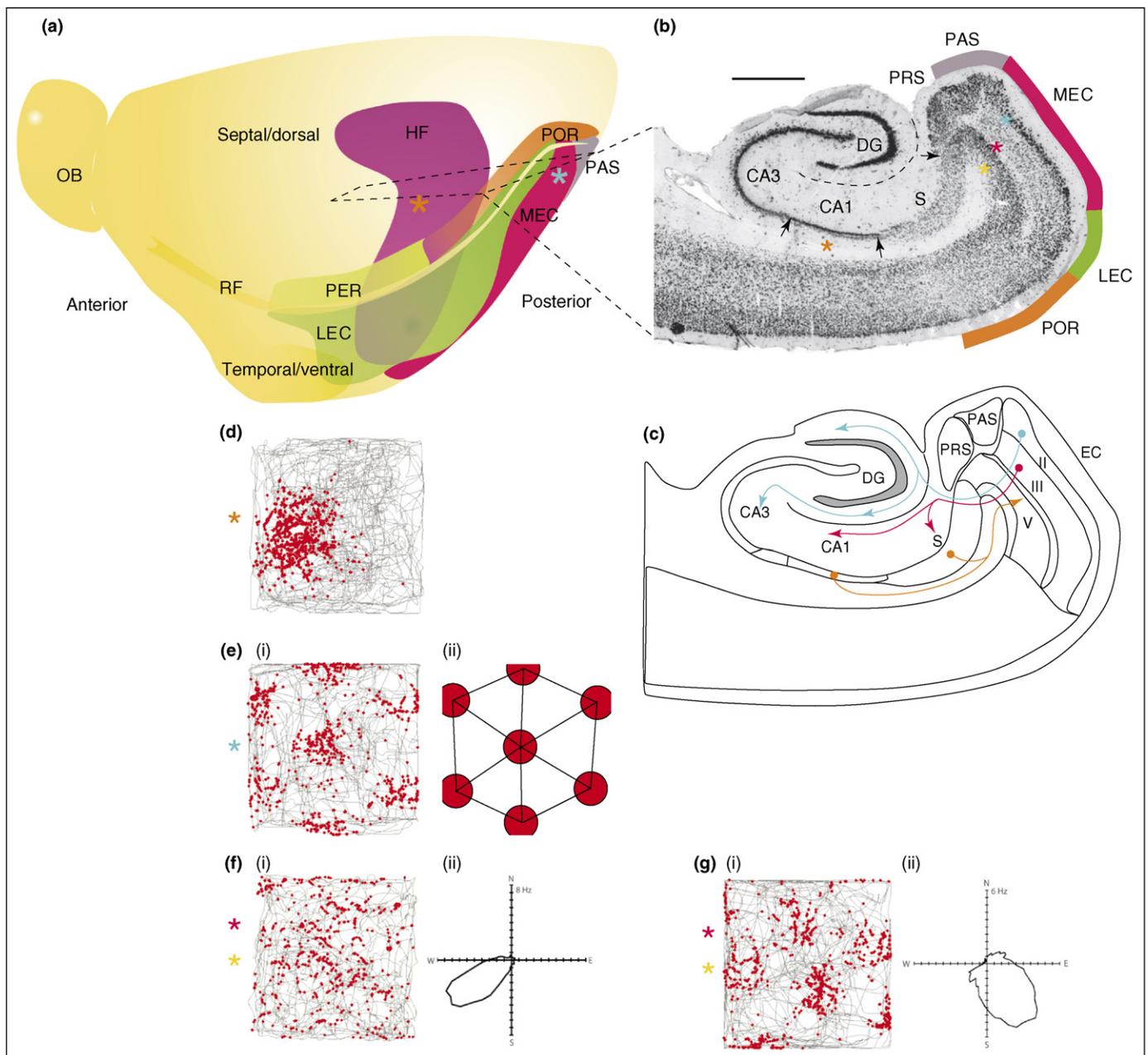
The neural mechanisms responsible for path-integration-based navigation have received much attention in recent years. In mammals, a widespread brain network is likely to be involved. This network includes the hippocampus, where the majority of the principal cells have spatially confined firing fields (‘place cells’; Figure 1a,b,d) [2], and the presubiculum and several other areas where neuronal activity is primarily tuned to the head direction of the animal (‘head-direction cells’) [7]. That positional and directional signals are expressed in different brain regions suggested that the integration of

these signals might take place in a third brain area. Recent observations have implicated the medial entorhinal cortex, a key relay structure for connections between the hippocampus and the presubiculum, as a possible hub in the neural circuitry for spatial representation [8–10]. The aim of this article is to discuss the structural fundament for spatial representation in this region. We will show that key architectural features of the entorhinal cortex, such as recurrent connections, interlaminar connectivity and a modular organization, point to attractor dynamics as a possible mechanism for representation of location in entorhinal neural networks.

## Entorhinal grid cells and representation of location

Early studies of spatial modulation in the entorhinal cortex found that firing fields were weak and dispersed [11], suggesting that place-specific signals might be computed within the hippocampal place-cell network itself. The entorhinal cells recorded in these studies were sampled exclusively from the intermediate-to-ventral parts of the medial entorhinal cortex. More recent work has provided evidence for strong spatial modulation of principal neuron activity in the dorsomedial part of the entorhinal cortex [8] (Figure 1a,e). A key component of this brain system is the ‘grid’ cell [9]. When rats run around in two-dimensional environments, grid cells fire selectively at regularly spaced positions such that for each cell, the multiple firing fields define a repeating triangular pattern that tiles the entire environment that is covered by the animal, similar to the cross points of graph paper, but with an equilateral triangle as the unit of the grid instead of a square (Figure 1e). Grids of neighbouring cells are offset relative to each other, such that all potential positions of the environment are covered by any local ensemble of grid cells. Colocalized cells have identical grid spacing and grid orientations but the spacing increases topographically from the dorsal to the ventral end of the medial entorhinal cortex [8–10]. Collectively, the firing of grid cells with different spacing and orientation mediates precise and unique information to their target cells about where the animal is in the environment [8,9]. The relative offset of the nodes of different colocalized grid cells is invariant across environments [12], suggesting that the map serves as a universal coordinate system for vector-based navigation. The maintenance of grid fields and their relative locations after removal of external landmarks [9] is consistent with this possibility.

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**Figure 1.** Spatially modulated discharge patterns in the hippocampus and medial entorhinal cortex. **(a)** Posterolateral view of the left hemisphere of a rat brain, with the hippocampal formation (HF, purple) located deep to the cortical surface. The lateral and posterior cortical surface contains a small indentation, the rhinal fissure (RF), which coincides roughly with the border between entorhinal cortex and perirhinal (PER) and postrhinal (POR) cortices. The entorhinal cortex is subdivided into a lateral (LEC, green) and medial (MEC, red) area. The parasubiculum (PAS, grey–purple) is also indicated. The dashed square indicates the position and perspective of the section shown in **(b)**. **(b)** Horizontal section illustrating the cytoarchitecturally defined subfields of the hippocampal formation [the dentate gyrus (DG), hippocampal fields CA3 and CA1 and the subiculum (S)] and of the parahippocampal region [the presubiculum (PRS), parasubiculum (PAS), medial and lateral entorhinal cortex (MEC and LEC) and the postrhinal cortex (POR)] [36]. Coloured asterisks indicate approximate recording sites for spatially tuned cells in CA1 (orange) and MEC layers II (blue), III (red) and V (yellow), illustrated in **(d)** and **(e–g)**, respectively. Scale bar, 100  $\mu\text{m}$ . Arrows indicate borders between subfields of the hippocampal formation. **(c)** Main overall wiring of the entorhinal–hippocampal system, illustrated using the same horizontal section as in **(b)**. Cells in layer II of the entorhinal cortex project to DG and CA3 (blue arrows). Cells in layer III of the entorhinal cortex distribute their axons to CA1 and the subiculum (red arrows). In turn, neurons in CA1 and the subiculum give rise to the major output projections of the hippocampal formation, targeting layer V (orange arrows) and layer III (not indicated) of the entorhinal cortex [36]. **(d)** Place fields of a representative pyramidal neuron recorded in the dorsal part of CA1 (orange asterisks in **(a)** and **(b)** indicate approximate recording location). The rat was running in a box of 1 m<sup>2</sup> floor area during recording. Trajectories are in black, and positions of the rat at which spikes were recorded are in red (superimposed on the track). **(e)** Firing fields of a grid cell recorded in layer II of MEC (blue asterisks in **(a)** and **(b)** indicate approximate recording location). (i) Trajectory of the rat (black) with spike locations superimposed (red). (ii) Schematic representation of the firing peaks, showing their periodic triangular structure (black lines). **(f)** Firing positions (i) and head-direction tuning curve (ii) of a representative head-direction cell as recorded in layer V of MEC (red and yellow asterisks in **(b)** indicate approximate recording locations). This cell shows preferential firing when the head is directed towards the south-west. **(g)** Firing positions (i) and head-direction tuning curve (ii) of a representative cell with conjunctive grid and head-direction properties as observed in layers III and V. This cell fires preferentially when the head is directed to the south-east. Panels **(d–f)** modified, with permission, from Refs [9,10].

How grid cells contribute to the perception of self-location has not been determined. The dynamic representation of place is likely to depend on integration of information about location, direction and distance. In all locations of the medial

entorhinal cortex that have been probed, grid cells intermingle with head-direction cells and with cells that have conjunctive grid and head-direction properties [10] (Figure 1, e–g). Head-direction cells and conjunctive cells

are located primarily in layers III and V of the medial entorhinal cortex. These layers are major target areas of projections from the presubiculum [13,14], which probably convey signals from the head-direction cells in this area [7]. All three cell types – grid cells, head-direction cells and conjunctive cells – are responsive to speed of movement of the animal [10]. Thus, the medial entorhinal cortex receives and expresses the translational and directional input needed to compute a continuously updated metric representation of location.

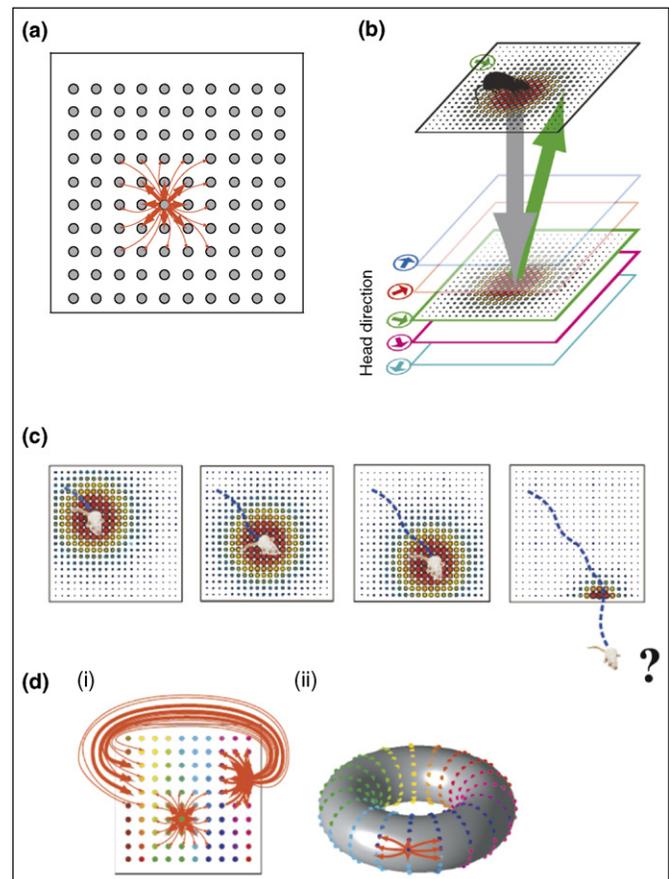
Theoretical studies have proposed that the representation of location in ensembles of entorhinal grid cells is maintained by continuous attractor dynamics. In a continuous attractor network, the changing location of an animal is thought to be represented in a self-sustaining manner by activity in a continuum of neural ensembles that each consist of interconnected cells that have similar firing locations [15–18]. With a certain level of global inhibition, a ‘bump’ of activity will form spontaneously, centred on a set of cells with a common firing location (Figure 2a). If the grid cells in layer II of the entorhinal cortex are part of a continuous attractor network, the activity bump can be envisaged to move between cell ensembles that have different grid nodes as the animal runs around in the environment. The translation of the activity bump might be based on a path-integration-dependent mechanism, where changes in direction and distance are continuously added to the neural representation [19,20] (Figure 2b).

The proposal that the entorhinal representation of self-location is based on continuous attractor dynamics makes several explicit assumptions about the underlying cellular and synaptic architecture. We shall discuss, based on available knowledge of the microcircuitry of the entorhinal cortex, whether these assumptions might be valid and, if they are, where and how the various elements of the models could be implemented in the microcircuit.

### Recurrent connectivity

One of the defining conditions for an attractor-based spatial representation is strong recurrent connectivity between cells that fire in similar locations (Figure 2a). During movement in a two-dimensional environment, recurrent connections are thought to be necessary not only for confining the activity to a subset of grid cells that have similar firing nodes, but also for reactivating the same subset each time the animal returns to this position or moves to a different node in the local grid-cell population. But are grid cells interconnected in this way?

In all layers of the medial entorhinal cortex, at least some of the projection neurons have axons that give rise to local collaterals [21]. In general, such collaterals distribute in the layer of origin and in more superficially positioned layers [21]. Axonal collaterals of principal cells in layer V strongly innervate layers V and VI, in addition to the superficially positioned layer III [22,23]. Layer III principal cells provide collateral innervation in layers III, II and I [24,25]. Principal cells in layer II have many collaterals within this layer and in the adjacent portions of layers I and III, and minor innervation of the deeper layers V and VI [26–28]. These examples of elaborate local axonal



**Figure 2.** Model for path integration in a network that has continuous attractor properties [20]. (a) A sheet of neurons arranged conceptually according to their relative positions of firing in a two-dimensional environment. Neighbouring neurons have strong excitatory interconnections (thick arrows pointing out from a representative cell) but the strength of the connections decreases monotonically with distance (thinner arrows). In the presence of global inhibition (not shown), a ‘bump’ of activity will form spontaneously, consisting of mutually connected cells that have overlapping firing fields. (b) The bump can be made to move in accordance with motion of the rat (top sheet) by introducing a separate layer in which cells respond conjunctively to position of the animal in the plane and to its displacement as signalled by head direction (bottom sheet) and running speed (not shown). Connections between the conjunctive cells and the attractor layer are asymmetrical in that the conjunctive cells in the model project to neurons that are slightly offset in firing position (green arrow) compared with the cells from which they receive input (grey arrow). Which cells are activated by the conjunctive cells depends on head direction (indicated in green, in this case) and its running speed (the amount of displacement). (c) Planar models of path integration are constrained by the fact that the mapping space is limited by the finite number of cells in the map. The models need to explain how the animal can keep track of its position when it reaches the boundaries of the represented area. (d) Possible solution to the boundary problem. Samsonovich and McNaughton [18] suggested that the edge problem could be avoided if the cell array had ‘periodic boundaries’ – that is, if cells at one edge of the attractor map were connected with cells at the other edge (i), resulting in a synaptic matrix that has a toroidal topology (ii). In this type of map, cells would be activated periodically when the animal runs in a straight line, similar to what has now been observed in entorhinal grid cells [9]. Modified, with permission, from Ref. [20].

networks in the layer of origin might be taken to indicate that recurrent connectivity is a general phenomenon in the medial entorhinal cortex.

However, not all local connections are excitatory. Whereas there are marked excitatory interactions among local cell groups in layers III and V, excitatory interactions have been reported to be virtually absent in layer II [29], where the largest proportion of grid cells is thought to reside [10]. These observations imply either that there is only limited lateral influence between grid cells in layer II

or that such influences are indirect, with axons from layer II cells targeting inhibitory interneurons such as basket and chandelier cells, which in turn might have a selective influence on firing of the principal cells [30]. But how can the activity be transferred between grid cells when the connections are largely inhibitory? Under some conditions, perisomatic GABA-mediated inhibition can in fact facilitate spike generation in the target neurons. After an inhibitory postsynaptic potential, neurons can show 'rebound' activation due to a decrease in the firing threshold of the cell, reflecting the time constants of voltage-sensitive channels [31,32]. Because interneurons that have perisomatic terminals frequently target large numbers of neurons, rebound activation represents an efficient mechanism for phase-locked activation of large populations of principal neurons [33,34]. It is conceivable that such a rebound mechanism, mediated by local basket cells, is sufficient for synchronization and reliable activation of ensembles of grid cells that have similar grid fields.

The spontaneous formation of an activity bump in a continuous attractor network demands more widespread inhibition than excitation. As we have already described, this requirement is most likely to be met in layer II, but for layer III the intrinsic connectivity pattern is less clear. Layer III principal neurons are strongly innervated by local inhibitory neurons [35], but some of the inhibition that constrains the activity bump in layer III might also be imposed by extrinsic inputs through feedforward inhibition. This in turn raises the possibility that the proposed attractor dynamics of the entorhinal cortex are under outside control. Although cortico-hippocampal connections are generally thought of as excitatory [36], local connections from layer V to layers II and III in medial entorhinal cortex terminate almost equally on principal neurons and interneurons [23], as do the inputs from the presubiculum to medial entorhinal cortex [14]. It remains to be investigated whether the overall excitation exerted by these inputs is less widespread than the inhibitory effect, although the finding that presubicular inputs cause mainly inhibition in layer III [37] speaks in favour of a more widespread inhibition. Because the input from the presubiculum also produces mainly excitation in layer II [37], possible laminar differences in spatial distribution of excitation and inhibition need to be assessed.

To summarize, there is clear evidence for recurrent connectivity between principal cells of the medial entorhinal cortex. What remains to be determined is, in particular, which cell types in the different layers are connected, whether there are differences between layers, and how extrinsic afferents interact with defined entorhinal cell types.

### Interlaminar connections

To translate the active representation between grid cells that have different firing locations, it is necessary to assume there is some asymmetry between inputs and outputs of the conjunctive cells in layers III and V that combine information about position, head-direction and running speed [10,18,20] (Figure 2b). The conjunctive cells are thought to receive position input from active grid cells in the continuous attractor network in layer II

or elsewhere. This signal is then combined with head-direction and speed information from other sources (e.g. the presubiculum [7]), and the output is projected back to the attractor layer to translate the active representation in a direction and at a distance consistent with the head-direction and speed inputs [20]. To move the representation, the output must be sent to cells that have firing positions slightly offset from those of the cells that provide the input (Figure 2b). The input and output cells in the grid layer could be far apart, but they are more likely to be anatomically close because grid cells that have different firing nodes can be recorded using a single tetrode [9]. The proposed translation mechanism enforces clear constraints on the connections between the deeper and superficial layers of the entorhinal cortex.

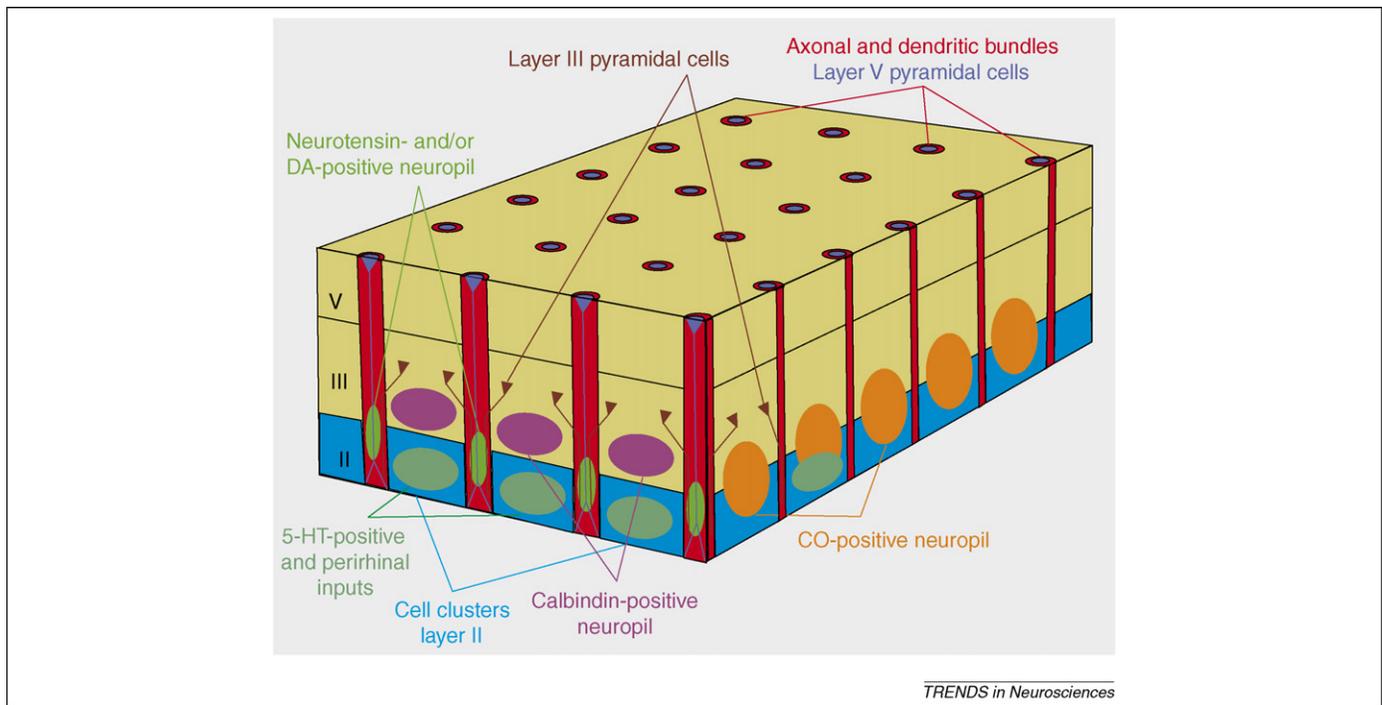
The sparse collateral projection from layer II to the deeper layers [26–28] indicates that connections from superficial grid cells to deeper conjunctive cells must be mediated primarily by way of local synapses from layer II cells onto the apical dendrites of cells in layer III and V. Vice versa, axons from layer V cells ascend through layers III and II, where they form synapses with principal cells in these layers [23,38]. Projections from layer III cells to layer II cells have not been studied in detail [36]. It remains to be established whether a single layer III or V cell that receives input from one or several layer II cells has other layer II cells as its output targets. Because the cells in layers III and V might have conjunctive grid and head-direction properties, it is also important to determine whether the same cells receive input from head-direction cells in the dorsal presubiculum.

### Modular organization

It can be difficult to implement a range of grid scales and grid orientations in a single continuous attractor network [20]. The dynamic representation of the position of an animal might instead require a modular organization of the grid-cell network where grid cells that have different spacing and orientation are organized into discrete weakly interacting or non-interacting spatial units, each corresponding to a semi-separate attractor network. Such a modular organization would enable the location of the animal in the environment to be represented in parallel at multiple spatial scales. But is there any anatomical evidence for such modularity?

The entorhinal cortex, and in particular the medial subdivision, has several architectonic and connective features suggestive of modular organization, such that a column-like organization, comparable to that in the isocortex, becomes apparent [39] (Figure 3). Columns are groups of vertically linked cortical cells across two or more layers that have common properties. They appear anatomically as periodicities in neurons, intrinsic circuitry, dendritic and axonal clusters, or molecular markers [39,40].

One of the most striking indications of column-like organization in the entorhinal cortex, which is shared with most other limbic cortices, is the clear bundling of pyramidal-cell dendrites from the deeper layers (especially layers III and V) [41]. These dendrites, similar to those of pyramidal cells in the isocortex, receive numerous



**Figure 3.** Columnar-like organization of the entorhinal cortex. This summary illustrates the dendritic and axonal columns (red) of layer V pyramidal cells (dark blue) as a regularly distributed component of the module, probably mediating interconnectivity between deep and superficial layers. Dendrites of layer III cells (brown) join these bundles on their way to penetrate layer II, where they form the characteristic cell islands of this layer (bright blue). The inter-island space receives input from other fibre systems, including neurotensin-positive and dopamine (DA)-positive fibres (bright green) and dense innervation from the presubiculum (not shown). Neuropil in layer III that is associated with the cell clusters contains specific fibre components such as a calbindin-positive plexus (purple). Layer II cell clusters and adjacent portions of layer III also stain densely for cytochrome oxidase (CO, orange), whereas perirhinal inputs and inputs expressing 5-hydroxytryptamine (5-HT or serotonin) preferentially distribute to layer II clusters (dark green).

synapses on their way to the superficial layers [13,38, 41–44]. Within the dendritic bundles, there are also axonal collaterals from layer V cells that form synapses in layers III, II and I [23]. The alternating bundles are further apparent as cyclic variations in the densities of GABA-positive and calbindin-positive dendrites [42,45]. The bundles are  $\sim 400\text{--}500\ \mu\text{m}$  in diameter in both monkeys and rats [25,46].

Dendritic and axonal bundling contributes to modularity because, when perforating through layer II, the bundles give this layer a patchy or island-like appearance. The cell islands are clearly distinguishable, although they are more conspicuous in primates than in rodents [47,48]. In humans, cell islands in layer II are  $500\text{--}1000\ \mu\text{m}$  in diameter [42], which is in the range of the diameter of the average isocortical column. Generally, the cell islands in layer II have a higher metabolic activity [42,49] and, in the human brain, they have a separate and uniquely organized blood supply [42]. Finally, inputs from the presubiculum to the medial entorhinal cortex show regular alterations in terminal density, indicative of a periodic and modular arrangement [50,51].

The idea that column-like modules span layers of the entorhinal cortex receives further support from the clustering of cells that have similar grid spacing and grid orientation [9] and the preservation of grid correlates across cell layers [10], despite significant variation in the inputs to these layers [36]. In addition, carbachol-induced gamma oscillations in medial entorhinal cortex synchronize across layers in patches of  $\sim 600\text{--}800\ \mu\text{m}$  diameter, with a decline in coherence as distance increases

further [52,53]. The synchronization depends strongly on reciprocal interactions between inhibitory interneurons and excitatory principal cells of superficial and deep layers [52,54]. This, together with reports that exploration of a novel environment causes expression of glycogen phosphorylase (a marker of activity) to increase in a modular manner in layers I and II but to decrease in layer III [55], suggests that functional modularity in the network depends on activity state and behaviour.

It is apparent from these observations that the anatomical organization of the medial entorhinal cortex is modular, although it remains to be established whether these modules also imply a modular representation of the spatial environment. A modular map could have wide-reaching consequences for how information is stored in the hippocampus [12]. If entorhinal modules operate relatively independently of each other, convergence of output from those modules could enable the formation of highly differentiated representations in the target area, because different subsets of the receiving cell population would be activated for each combination of the inputs. Such differentiation is expressed in the hippocampus as the ability of place cells to undergo complete ‘remapping’ in response to minor changes in the sensory or motivational features of the environment [56–58]. A modular organization of the entorhinal spatial map might facilitate remapping and other forms of pattern separation during memory storage.

### The boundary problem

A fundamental question that confronts all attractor models of spatial representation is whether the underlying

connection matrix has boundaries. With a finite number of available neurons in a two-dimensional connectivity matrix, the activity bump might reach points where it cannot move further (Figure 2c). What happens at these points? Does the animal get lost? Or how are the boundaries avoided? One suggested solution is that activity translates more readily across some parts of the matrix sheet than others, with representations fading out as the bumps approach the boundaries of the attractor surface [19]. Such differential translation might be achieved by differences in inhibition, although specific wiring schemes have not yet been proposed. Another possibility is that the underlying synaptic matrix is periodic, such that, for each direction of movement, in a series of interconnected active neurons, the last cell will connect back to the first cell of the sequence [18,20] (Figure 2d). If the distribution of activity repeats itself, as it does in grid cells at regular intervals as the animal crosses a surface, boundaries will never be reached and special computational solutions might not be required for these situations. However, whether there is such periodicity in the entorhinal synaptic matrix is unknown, and its existence is difficult to investigate using current neuroanatomical methods. One can imagine that with high-resolution imaging of action potentials in local ensembles of grid cells [59], it might one day be feasible to approach this essential question experimentally.

#### **Do the lateral and medial entorhinal cortex have a common architecture?**

The discovery of grid cells in the medial entorhinal cortex [8,9] clearly triggered a search for explanatory mechanisms and architectures. In the lateral entorhinal cortex, neurons exhibit little spatial modulation [60]. Inputs from the head-direction system in the presubiculum project selectively to the medial entorhinal cortex, stopping suddenly at the border with the lateral subdivision [47,50]. Thus, the lateral entorhinal cortex is probably not involved in path integration, but its specific functions remain elusive.

Only recently have more data become available with regard to intrinsic organization of the lateral entorhinal cortex. Recent studies point to several similarities between the lateral and medial subdivisions of the region. In layers V and III of the entorhinal cortex, the electrophysiological and morphological properties of the principal cells are virtually indistinguishable in the two subdivisions [38,43,61]. In layer II, there might be differences in the tendency to express rhythmic subthreshold oscillatory dynamics, but in both subdivisions the principal cells apparently form part of a recurrent network [26,61]. Terminals of inputs to the lateral entorhinal cortex from the perirhinal cortex, amygdala and dopaminergic cells of the ventral tegmental area of the mesencephalon show a tendency to cluster in relation to the cell islands in layer II (Figure 3) [42,62–64], similar to what has been described for presubicular projections to medial entorhinal cortex [50,51]. Furthermore, similar to presubicular projections, inputs from the perirhinal cortex to the lateral entorhinal cortex provide strong feedforward inhibition, with >30% of excitatory perirhinal fibres terminating onto presumed inhibitory interneurons [65]. Although the data are not

conclusive, it is likely that a comparable intrinsic and extrinsic column-like connective architecture is present in lateral and medial entorhinal cortex [42].

#### **Interaction between entorhinal cortex and hippocampus**

The discovery of a path-integration-based system for metric representation of self-location in the medial entorhinal cortex suggests that the primary function of the hippocampus is not the dynamic computation of location. However, the hippocampus might be important in landmark-based navigation, which, because of the unique landmark configurations of different environments, rely heavily on episodic memory, in which the hippocampus is strongly involved [66–68]. Similar to the medial entorhinal cortex, the hippocampus can store representations of the spatial environment [69], but these representations are probably different in that spatial location is only one component of the representation [70] and a multitude of representations can be stored for the same environment or the same event sequence [18,66,71]. Nonspatial inputs can be mediated, for example, by direct input from the lateral entorhinal cortex [60]. Individual neurons in the dentate gyrus and CA3 of the hippocampus can integrate signals from the two entorhinal subdivisions [36], enabling them to associate self-motion-based and landmark-based information during learning [9,66,71–73].

When an animal is re-exposed to an environment it has been in before, the storage of conjunctive spatial and nonspatial representations in the hippocampus might enable the proposed path integrator in the entorhinal cortex to reset at regular intervals, for example via return projections from the hippocampus through the deep layers of the entorhinal cortex [74]. Understanding the dynamic interactions between representations in the entorhinal cortex and the hippocampus will be a major research goal during the next few years. It is possible that linear causal models, in which the superficial layers of the entorhinal cortex are thought of as hippocampal inputs and the deeper layers as hippocampal outputs, might no longer be appropriate for understanding the dynamics of the medial temporal lobe.

#### **Concluding remarks**

The entorhinal cortex has several architectural characteristics that might constrain how various parts of the network contribute to spatial navigation. We propose that the architecture of the medial entorhinal cortex, as it is currently known, fits with the recently proposed existence of a continuous attractor-based network for path integration in this area. However, we also indicate that many details of the assumed architecture remain elusive. We conclude that the lateral and medial subdivisions of the entorhinal cortex probably have an overall similar architecture, supporting a column-like functional organization. What needs to be established is whether the grid cell in the medial entorhinal cortex has a non-spatial counterpart in the lateral entorhinal cortex. Finding such a counterpart should not only help us to understand the role of the parallel pathways that are mediated through the lateral and medial entorhinal cortex [36], but also greatly improve

our potential to understand the relationship between neural architecture and function.

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