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The entorhinal map of space ☆

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ABSTRACT

How do we know where we are, and how do we remember the places we visited? Since the discovery of place cells in 1971, our understanding of the brain's maps of external space has exploded. Yet the origin of the place-cell signal remained elusive. The discovery of grid cells in the medial entorhinal cortex (MEC) in 2005 put place cells in a context, since the existence of grid cells pointed to circuit mechanisms that might explain the formation of place cells. In this review, I shall review recent experimental and theoretical advances in the understanding of how space is mapped in the medial entorhinal cortex. I will also review recent studies of interactions between hippocampus and the lateral entorhinal cortex (LEC). Research on spatial mapping in the hippocampal-entorhinal system provides a fundament for future attempts to decipher some of the neural-circuit codes of the cortex.

1. Introduction

The hippocampal region, a brain complex containing the hippocampus, subiculum, and entorhinal cortex (EC), is part of the medial temporal cortex in humans, and stretches through the posterior half of the cortex in the rodent brain (Fig. 1A). Because this region, especially the hippocampus, has a distinct cytoarchitecture, it has attracted anatomists since the first half of the twentieth century (Ramón y Cajal, 1911; Lorente de Nó, 1934). It was not until the second half of the century, however, that studies started to throw light on the function of this region. The first major breakthrough was a report by Scoville and Milner (Scoville and Milner, 1957) on memory loss in patient Henry Molaison (also widely known as H.M.), who had his hippocampal regions surgically removed for the treatment of severe epilepsy. The work indicated that the hippocampus and the entorhinal cortex (EC) play critical roles in the formation of declarative memory, a type of memory that can be consciously recalled such as episodes and facts (Milner et al., 1968; Squire, 1992). Subsequent studies indicated that H.M. as well as other patients with temporal lobectomy also had impairments in spatial navigation and visual maze tasks (Milner et al., 1968; O'Keefe and Nadel, 1978).

Since the early studies of H.M., the hippocampus has had a magnetic impact on those interested in the cellular mechanisms of memory and spatial navigation. The studies of H.M. were followed almost two decades later by the discovery of place cells in the hippocampus (O'Keefe and Dostrovsky, 1971). O'Keefe and Dostrovsky thought it would be informative to study the neuronal correlates of memory by recording neuronal spike activity from the hippocampus during behavior. They implanted miniature electrodes in the hippocampus of rats and recorded activity from individual neurons while the rats moved around in the environment. Many of the cells they recorded fired specifically when the rat was at a

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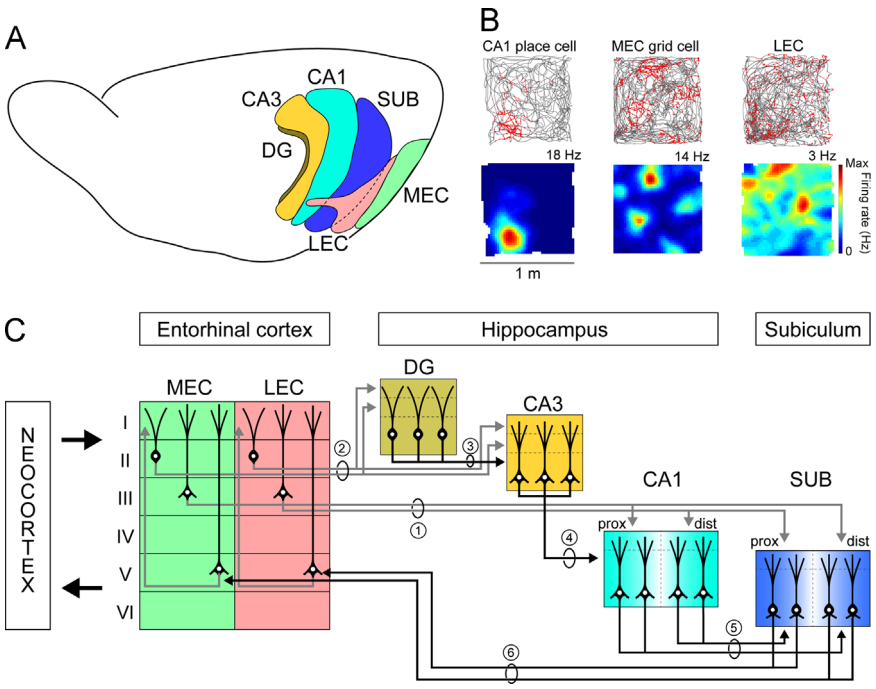


Fig. 1 – Architecture of the rat hippocampal regions. (A) Schematic showing lateral view of key hippocampal regions in the rat brain. The regions include hippocampal subfields CA1, CA3 and dentate gyrus (DG), as well as the subiculum, medial entorhinal cortex (MEC) and the lateral entorhinal cortex (LEC). Modified from (van Strien et al., 2009) with permission. (B) An example place cell in the CA1 (left), an example grid cell in the MEC (middle), and a representative cell with low spatial information in the LEC. Firing rate maps of spikes recorded in 1 m square box are shown. Top, trajectory of animal (gray) with spike positions superimposed (red). Bottom, color-coded rate maps. Color scale to the right. Peak firing rates (Hz) are indicated on top right and shown in red color. (C) Diagram of the major connections of the rat hippocampal formation. The hippocampus receives and sends information from the neocortex via entorhinal cortex. MEC and LEC project to CA1 through direct and indirect pathways. In the direct pathway (1), layer III cells in MEC largely project to proximal CA1 (prox), whereas layer III cells in LEC project to distal CA1 (dist). By contrast, in the indirect pathway, axons of layer II cells in MEC and LEC (2) converge on the same population of cells in the dentate gyrus (DG) and CA3. This mixed information in DG and CA3 is conveyed to CA1 via mossy fibers (3) and Schaffer collaterals (4). Output form CA1 is conveyed to entorhinal cortex mainly via the subiculum (SUB). In this output, information from proximal CA1 is conveyed to MEC via the distal part of subiculum, whereas distal CA1 projects to LEC via the proximal part of the subiculum ((5) and (6)). Modified from (Witter and Amaral, 2004) with permission.

certain location (O'Keefe and Dostrovsky, 1971) (Fig. 1A and B). O'Keefe and Dostrovsky called these cells place cells. Different place cells fired at different locations such that, as a population, place cells provided an accurate spatial map – a'cognitive map'-of where the animal is at any given time. Following this finding, O'Keefe and Nadel (1978) investigated the rich literature on behavioral impairments following hippocampal lesions and concluded that most findings could be summarized as showing a role for the hippocampus in spatial functions (O'Keefe and Nadel, 1978). Their cognitive map theory was controversial for more than two decades, given the apparent non-spatial impairments of human patients with hippocampal lesions, but the diverging views have finally been reconciled by the recognition that space and declarative memory are tightly coupled. Suppose for example that you have lost your purse: you may recall back the moment last time you saw the purse, and you would try to remember one by one the places you visited and what you did there. Your memory typically involves spatial navigation, and this spatial component may serve as a framework of your memory. The hippocampus may use space as a scaffold for most types of memories (O'Keefe and Nadel, 1978; Leutgeb et al., 2005; Buzsaki and Moser, 2013).

2. Grid cells in the medial entorhinal cortex

The discovery of place cells in 1971 raised a fundamental question: how is the activity of place cells generated? Is it generated intrinsically in the hippocampus, or does it reflect external inputs to the hippocampus? The hippocampus contains a strong excitatory feedforward circuit consisting of dentate gyrus, CA3 and CA1 (Fig. 1C) (Ramón y Cajal, 1911; Witter and Amaral, 2004). Most of its external cortical input to the hippocampus comes from the EC, and the hippocampus also sends much of its cortical output back to the EC. The EC interfaces the hippocampus with a number of cortical regions. In general, superficial layers of EC project to the hippocampus, whereas output from the hippocampus is sent back to the deep layers of the EC, which in turn project to the superficial layers of the EC, thus forming a loop circuit (Kloosterman et al., 2003; van Haeften et al., 2003). The

hippocampus receives entorhinal input via two major routes, often referred to as the direct and indirect pathways (Witter and Amaral, 2004) (Fig. 1C). In the direct pathway, layer III neurons in EC have direct synapses onto pyramidal cells and interneurons in the CA1 subfield of hippocampus. In the indirect pathway, layer II cells in the EC reach CA1 cells via synapses in the dentate gyrus and the CA3 subfield of hippocampus. For both of these pathways, there is a topography of connections in which dorsal, intermediate, and ventral parts of the EC connect to dorsal, intermediate, and ventral parts of the hippocampus, respectively (Witter and Amaral, 2004). The EC is anatomically divided into two distinct parts, medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC; Fig. 1A and C) (Witter and Amaral, 2004). These two regions are located next to each other and share the properties of an allocortical–neocortical transition cortex with four principal cell layers.

Before the turn of the century, it was extensively debated whether the place cell activity was generated locally inside the hippocampus or by way of interactions between the hippocampus and EC (O'Keefe, 1976; Touretzky and Redish, 1996; Sharp, 1999; Redish et al., 2001). Earlier recording studies in the EC reported that cellular activity in EC was only weakly modulated by the animal's location (Quirk et al., 1992; Frank et al., 2000), leading to the notion that computation of position rather occurs within the hippocampus itself. The fact that place-cell activity is maintained after lesions of the dentate gyrus made researchers assume that place representations are generated in CA3, via the recurrent projections of this subfield (McNaughton et al., 1989). If so, what happens if input from CA3 to CA1 is ablated? Edvard Moser, May-Britt Moser and their colleagues addressed this question by surgically disrupting the indirect excitatory loop through the hippocampus. CA3 cells were removed, or projections from CA3 to CA1 were disrupted, and spike activity was subsequently recorded in CA1 (Brun et al., 2002). Surprisingly, CA1 cells maintained their location-specific activity, implying that either place-cell activity is generated inside the CA1 or it is derived from direct input from EC to CA1. Since CA1 does not have recurrent excitatory projections and often is characterized more as a feed-forward circuit, the former possibility was less likely, and Mosers decided to revisit spatial representation in the EC.

The earlier EC recording studies were performed largely in the intermediate portion of the dorsal-ventral axis of the EC (Quirk et al., 1992; Frank et al., 2000). Since place cells had generally been recorded in the dorsal part of the hippocampus, and the dorsal hippocampus mainly connects to the dorsal part of the EC, Mosers suspected that the lack of spatial modulation in the earlier studies was due to the position of the EC electrodes. They thus started recording from the dorsal part of the MEC instead of the more ventral locations examined in earlier studies (Quirk et al., 1992; Frank et al., 2000). As predicted, cells in the dorsal MEC exhibited clear spatially-modulated activity (Fyhn et al., 2004). Later work by Knierim and colleagues showed that only the MEC had spatially-modulated cells and that the LEC had not (Hargreaves et al., 2005). In both studies, MEC cells had multiple firing fields, and it was clear from the first observations that the fields of a single cell were not randomly distributed (Fyhn et al., 2004), but the distribution algorithm remained elusive. To better visualize the pattern of the firing fields, Mosers decided, in 2004, to increase the size of the recording arena. Using a 2 m wide circular environment, they found that the multiple firing fields of MEC cells formed periodic hexagonal patterns (Hafting et al., 2005). Because of the grid-like structure of these patterns, they called the cells 'grid cells'. Grid cells were found to vary along at least three parameters: scale (distance

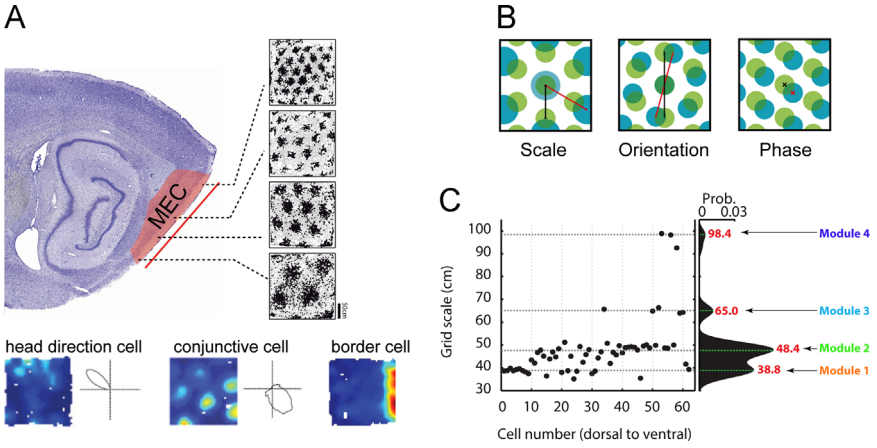


Fig. 2 – (A) (Top) Recording position for grid cells illustrated on a sagittal section of brain through the MEC. Each panel on the right shows the grid fields of one layer II cell. Note the increase of grid cell scale from dorsal to ventral portions of the MEC. (Bottom) Color-coded rate maps showing examples of a head-direction cell, a conjunctive grid x head direction cell, and a border cell. Color scale as in Fig. 1. Head-direction tuning properties are shown in polar plots. Adapted from (Sargolini et al., 2006) and (Solstad et al., 2008) with permission. (B) Grid cells have three dimensions of variation: scale, orientation and phase. (C) Discrete organization of grid scale. Grid scale at successive dorsoventral levels in a single rat. Dots correspond to individual cells. Cells are plotted sequentially in the order that they were recorded during electrode turning from dorsal to ventral parts of the MEC. (Right) Probability distribution showing density of grid cells as a function of increasing grid scale. Size (cm) for the estimated peaks of the grid scale (grid spacing) and module numbers are indicated. Adapted from (Stensola et al., 2012) with permission.

between firing fields), orientation (angle between grid axes and environment) and phase (relative position of firing peaks) (Fig. 2A and B). Grid cells were largely non-directional, meaning that they fired when animals traversed their firing fields, irrespective of which direction the animal was facing. Grid cells were found mainly in all layers of MEC but were most abundant in layer II (Sargolini et al., 2006).

Subsequent work showed that grid cells in MEC intermingle with other functional cell types. The deeper layers (layers III and V) contain cells that fire only when animals face a specific direction ('head-direction cells') (Sargolini et al., 2006). Some cells fire in a grid-like pattern at the same time as they are directionally modulated ('conjunctive grid x head-direction cells'). Other cells fire specifically along the geometric borders of the environment ('border cells') (Solstad et al., 2008) and yet others fire specifically in response to the speed of the animal (Kropff et al., 2015). Grid cells, as well as some of the other cell types, were subsequently found in MEC of bats (Yartsev et al., 2011), monkeys (Killian et al., 2012) and humans (Doeller et al., 2010; Jacobs et al., 2013), suggesting that mammals use a common mechanism for spatial representation.

How do grid cells differ from place cells in their organization at the neuronal population level? One of the most fundamental properties of place cells is that they develop multiple independent representations for different environments, a phenomenon referred to as 'remapping' (Muller and Kubie, 1987; Markus et al., 1995; Colgin et al., 2008). Two distinct types of remapping are found in place cells; 'rate remapping' in which place cells change their firing rates without changing the firing position, and 'global remapping' where place cells reorganize both firing rate and firing position. Simultaneous recordings from place cells and grid cells have shown that global remapping is accompanied by a change in the anchoring of grid cells (new grid phase and new grid orientation), whereas rate remapping causes no change in the location of firing among grid cells (Fyhn et al., 2007). These observations suggest that input from MEC grid cells may give rise to global remapping in the hippocampus, whereas rate remapping may be triggered by signals from other regions than the MEC, such as the direct input from LEC (Lu et al., 2013) or inputs from the medial prefrontal cortex (Navawongse and Eichenbaum, 2013; Ito et al., 2015), relayed via the nucleus reuniens, a midline nucleus of the thalamus (Ito et al., 2015). In contrast to place cells, which each fire in only a small subset of available environments (Wilson and McNaughton, 1993; Alme et al., 2014), grid cells are always active (Fyhn et al., 2007), so long as the animal is awake and moving. It is only the alignment of the grid cells that changes when place cells undergo global remapping (Fyhn et al., 2007).

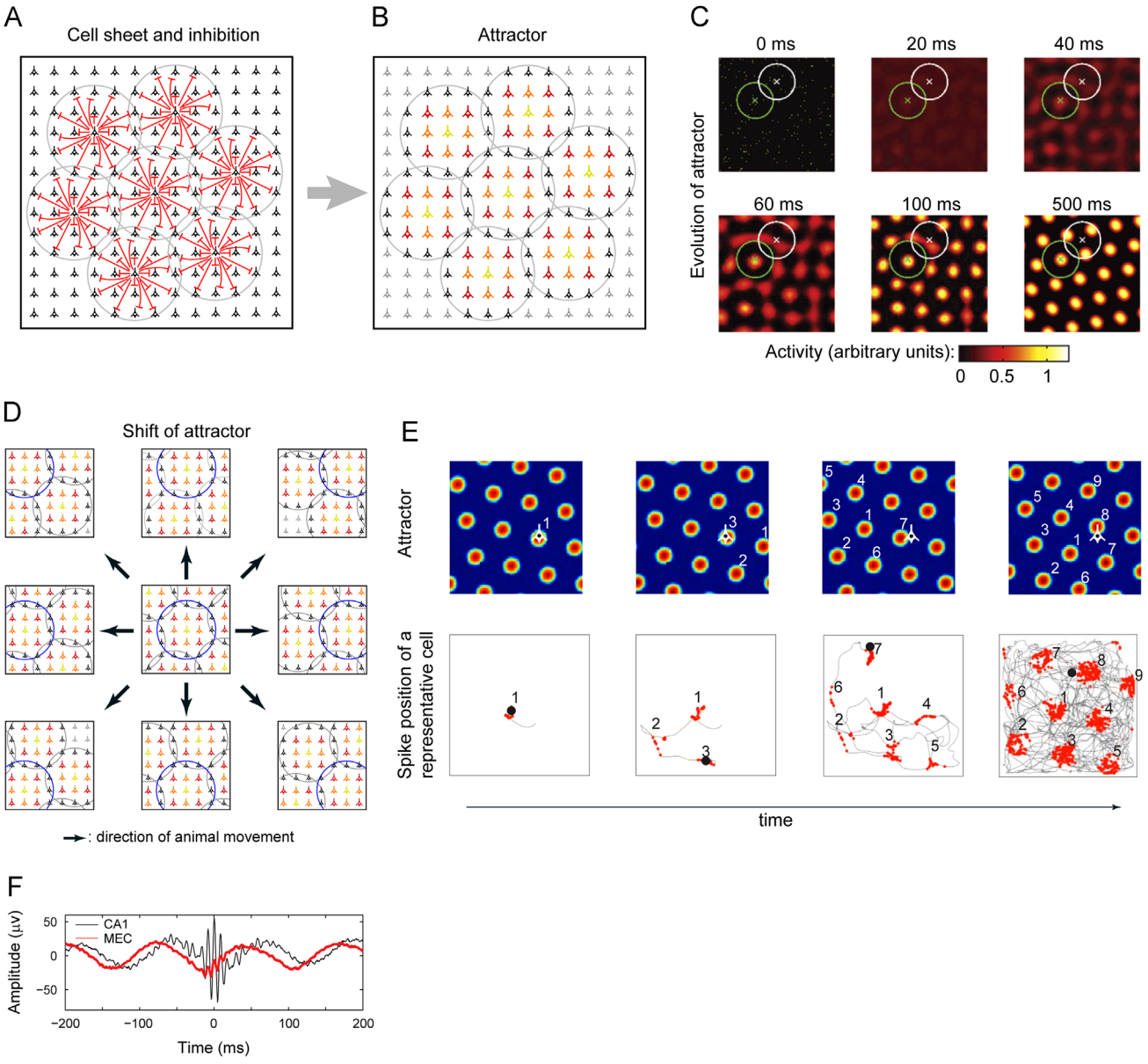
3. Grid cell modules and entorhinal circuit architecture

One of the shared architectures of many cortical regions is a columnar organization, where neurons with similar representation properties form layer-spanning functionally defined clusters. Columnar patterns give rise to topographical 'maps' of cells with different functional correlates in several brain regions, such as the odor maps in the olfactory bulb, the somatotopic map in the somatosensory cortex, and the orientation map in the primary visual cortex of some species (Hubel and Wiesel, 1974; Mountcastle, 1997; Mori et al., 2006). Does the MEC map have similar functional gradients? In the earliest studies of grid cells, the scale of the grid was found to increase from dorsal to ventral MEC (Fig. 2A) (Brun et al., 2008). The increase in grid scale was apparent after averaging data from many animals but it was not clear if the shift from

Fig. 3 – (A–B)Schematic illustration of grid cell formation in an attractor network model. (A). Virtual sheet of MEC neurons arranged conceptually according to relative proximity of anatomical connections. Each cell sends recurrent inhibitory input to neighboring cells located within a given distance of itself (red lines). Note that inhibition is illustrated only for seven cells in this figure, although every cell has inhibitory connections to the surround. (B) Competition between inhibitory influences will cause activity to evolve towards a stable attractor state where the cluster of active cells is arranged in a close-packed hexagonal pattern. Highly active cells (yellow) inhibit neighboring cells. Cells that receive inhibition from multiple yellow cells (black, along the circumference of each circle) become inactive. This pattern of activity leads to a hexagonal arrangement of firing rates across the layer. (C) Spontaneous emergence of hexagonally patterned activity in the cell sheet in (A) and (B) as predicted by computational modeling. In this figure, 'hotter' colors represent high activity rates of individual cells. Inhibitory connection radii of two example neurons are shown as white and green circles. A hexagonal pattern emerges after inhibitory competition starts. Adapted from (Couey et al., 2013) with permission. (D) Shift of hexagonal attractor by animal movement. Arrows indicate direction of animal movement, and the cellular sheets show the resulting state of cellular activity. Neighboring cells in the attractor sheet are activated in accordance with the animal's direction and speed of movement in the environment. The speed and direction-induced shift results in change of spike firing rate for individual cells. Since the stable state can shift gradually, it is called as a continuous attractor. (E) Formation of grid cell firing pattern. Shift of activity in the attractor sheet (top) and resulting spatial representation in an example grid cell (bottom). The location of the example cell in the attractor cellular sheet is indicated in white. When the animal moves around in the environment, the activity in the network shifts according to the direction of the animal movement, based on input from cells that encode instantaneous speed (Kropff et al.,2015). This shift of network activity results in a wax and wane of the activity in the example cell. Since the attractor has a hexagonal pattern, the resulting spike position in the real environment also becomes a hexagonal pattern. Numbers in white and black indicate activity peaks and grid fields, respectively. Note that the activity in the attractor sheet that is heat-mapped in (C) is now color-mapped in this figure. This activity map should not be confused with rate maps of individual grid cells (e.g. Fig. 1B). Adapted from (Bonnevie et al., 2013) with permission. (F) Fast gamma oscillatory coupling recorded simultaneously from the MEC and CA1 of the hippocampus. When fast gamma oscillations were observed in CA1 (black), similar oscillations were present in the MEC (red). Adapted from (Colgin et al., 2009) with permission.

dorsal to ventral was graded in individual animals, or if the expansion was step-like. In 2012, Stensola, Stensola and colleagues were able to record activity from almost 200 grid cells of the same animal. This made it possible to demonstrate, within animals, that grid cells cluster into a small number of modules with discrete grid scales (Fig. 2B) (Stensola et al., 2012). Grid cells recorded over 2 mm of the dorsoventral axis of the MEC could usually be divided into 4 or 5 discrete clusters or modules (Fig. 2B). Cells from the same module responded in a coherent manner to changes of the environment, whereas distinct modules responded independently. This suggested that each module corresponds to a distinct cellular network that generates grid cell activity more or less on its own.

How are these modules organized within the MEC circuit? The module with the shortest grid spacing consisted primarily of cells near the dorsal border of MEC, although such cells were scattered at lower density along the entire axis. At more ventral levels, modules with successively larger grid spacing were recruited, in addition to the modules with smaller spacing values. At the most ventral locations, cells from four or five modules were present. This nested form of organization is different from the gradual transition in functional properties in sensory cortices with topographical organization. The correspondence between functional modules and anatomical clusters is yet to be determined. In recent studies, two independent groups reported that the MEC has bulb-like assemblies of pyramidal cells in layer II (Kitamura et al., 2014; Ray et al., 2014). The space between these bulbs is filled with stellate cells. Bulbar pyramidal cells and non-bulbar stellate cells can be distinguished by differential expression of calbindin and reelin, respectively, but it remains to be determined whether grid cells are predominantly pyramidal cells or stellate cells and whether clusters of these cell types correspond to discrete modules of grid cells. Future work employing large-scale imaging techniques at single-cell



resolution, together with anatomical identification of cell types, will probably settle this issue in the near future.

4. Mechanisms of grid cell formation

The discovery of grid cells immediately raised questions about how the grid pattern is generated. Hexagonal firing patterns do not correspond to any sensory input, suggesting that the pattern is generated intrinsically in the brain, presumably in the MEC itself. A range of computational models have been proposed to explain the origin of the grid pattern. In an early class of models, referred to as 'oscillatory interference models', grid fields were proposed to arise intrinsically in individual grid cells as a consequence of interference between theta oscillations in the external field and slightly faster theta oscillations within the individual cell (Burgess et al., 2007; Hasselmo et al., 2007; Blair et al., 2008; Burgess, 2008). The intrinsic oscillation was thought to depend on the animal's velocity in a given direction, enabling the interference wave to be translated to a spatial wave (a band pattern) in that particular direction. Different velocity-controlled oscillators were thought to have preferred directions that differed by approximately 60 degrees, such that their combined input, in conjunction with the stable global theta oscillation, created a hexagonal firing pattern in cells that received these particular inputs. The interference model has provided a theoretical framework for studies of grid cell mechanisms but the model has recently suffered major challenges, reflecting the observation that interference waves are apparently not present in intracellular recordings from grid cells (Domnisoru et al., 2013; Schmidt-Hieber and Hausser, 2013) as well as the finding that grid patterns can be recorded in the absence of theta oscillations in bats (Yartsev et al., 2011).

Another class of models, termed 'attractor network models', suggests that grid fields are generated from networks of MEC cells with specific anatomical connections (Samsonovich and McNaughton, 1997; Fuhs and Touretzky, 2006; McNaughton et al., 2006; Burak and Fiete, 2009; Navratilova et al., 2012; Couey et al., 2013). An attractor is a semi-stable state of activity towards which activity in a network will progress, unless external input puts the activity on a different track, towards another attractor. The inputs that drive activity between attractor states may in some instances be continuous (Amari, 1977), such as in the representation of space or direction (McNaughton et al., 1991; Tsodyks and Sejnowski, 1995; Zhang, 1996; Samsonovich and McNaughton, 1997). Attractors are thought to be maintained by strong excitatory connections between neurons with similar properties. In the case of spatial representation, these connections would be between place cells (Tsodyks and Sejnowski, 1995; McNaughton et al., 1996; Samsonovich and McNaughton, 1997) or grid cells (Fuhs and Touretzky, 2006; McNaughton et al., 2006) with similar firing locations. Connections between cells with similar but not identical firing locations would enable the activity pattern to be translated across the neuronal sheet based on inputs signaling the animal's current speed and direction.

A challenge for the continuous attractor models of grid cells has been that there are essentially no excitatory connections between stellate cells – the major cell type of MEC layer II, where the most prototypical grid cells are located. Stellate cells are almost exclusively connected via inhibitory interneurons (Dhillon and Jones, 2000; Couey et al., 2013). In more recent versions of the attractor models, grid cells have been proposed to form sheets of cells in which each cell sends inhibitory projections to cells with similar grid phases (red lines in Fig. 3A) (Couey et al., 2013; Pastoll et al., 2013). If each cell inhibits cells within a certain radius in a network of grid cells arranged according to grid phase, the inhibitory projections will compete with each other, leading the network to stabilize in a hexagonal equilibrium state (Fig. 3B and C). In this cellular sheet, the least inhibited cells would be the cells that fire at the animal's current position. A slight shift of the position of the animal results in a shift of the attractor in the direction that the animal is moving in external space (Fig. 3D). Head-direction input and speed information would be sources for inducing this shift. The shift of the attractor results in change of firing rate for individual grid cells. Since the firing peaks are distributed periodically in the sheet, periodic grid-like patterns of firing fields will be generated for each cell as the animal moves forward in the environment.

Direct proof for or against attractor models is still missing but several indirect observations are consistent with the existence of attractors, such as the organization of grid cells in modules (Barry et al., 2007; Stensola et al., 2012). Attractor models of grid cells operate on the assumption that grid cells have similar orientation and spacing, suggesting a correspondence between attractors and individual grid modules. One critical weakness of the attractor models is their sensitivity to noise, and the assumption of strong connectivity between grid cells with similar but not different grid phase, remains to be tested (Moser et al., 2014a). The detailed network mechanisms involved in grid cell formation is still elusive but the recent advances in our understanding of grid cells point anyway to the importance of computational modeling as a key tool for addressing mechanisms of grid formation and other forms of patterning in cortical networks.

5. Function of grid cells in navigation and memory

The biological functions of grid cells, conjunctive cells and border cells are yet to be determined. However, regardless of their exact function, the constant distance between the grid fields and the orientation of the grid axes jointly provide the brain with a metric for the animal's local space (McNaughton et al., 2006; Moser and Moser, 2008; Giocomo et al., 2011; Moser et al., 2014b). Speed cells provide distance signals that grid cells may use to update firing in accordance with the position of the animal, and border cells may anchor the grid to geometric reference frames in the environment. Together, these cell types equip the MEC with information about position, direction and distance in relation to local boundaries, making the MEC an ideal structure for computing the instantaneous position of moving animals.

A key element of the computation of position is 'path integration', the ability to determine position from self-motion cues such as proprioceptive feedback or visual flow

(Mittelstaedt and Mittelstaedt, 1980; Muller and Wehner, 1988; Etienne and Jeffery, 2004; McNaughton et al., 2006). Several lines of experimental evidence support the use of path-integration information in the activation of grid-cell patterns in the MEC. First, grid cells retain their hexagonal firing pattern even when they are recorded in the complete darkness, with all visual inputs removed (Hafting et al., 2005; Fyhn et al., 2007). Second, grid cells fire at constant locations despite continuous changes in speed and direction by the animal, suggesting that the local circuit has a mechanism for calculating distance and direction moved based on instantaneous velocity information. Third, when grid cells were recorded in a hairpin-shaped linear environment where the animal walks through multiple consecutive alleys (Derdikman et al., 2009), grid cells reset at the beginning of each alley, displaying a similar pattern in each part of the maze. Truncation of the track shifted the firing fields such that the distance from the beginning of the arm was retained, a result expected if firing is determined by the distance walked by the animal but not by external visual or other sensory landmarks. Fourth, the MEC contains cells whose firing rates increase linearly with the speed of the animal, independently of which environment the animal is in (Kropff et al., 2015), exactly as required for a path-integrator mechanism by which the subset of active grid cells at any time is updated in accordance with the animal's movement in the environment, regardless of the content of that environment. Finally, behavioral studies have shown that the lesions of the MEC impair the ability to return to the home cage on the basis of self-motion cues, suggesting that the MEC is necessary for path integration in mammals (Parron and Save, 2004; Kim et al., 2013).

The modular organization of grid cells is supposed to provide a mechanism for representation of large numbers of memories in the hippocampus (Buzsaki and Moser, 2013; Rowland and Moser, 2014). Because grid cells in different modules show independent realignment in response to changes in the geometry of the environment (Stensola et al., 2012), and possibly to other experiences, the combination of active grid cells is likely to be different for every single environment experienced by the animal. The combination of grid phases resulting from the remapping would be very large for even a small number of grid modules since the number of possible grid phases is, in principle, unlimited. If place fields in the hippocampus are generated by summation of input signals from grid cells belonging to different modules (O'Keefe and Burgess, 2005; McNaughton et al., 2006; Solstad et al., 2006) (Fig. 3E), each with a different change in phase or orientation, the combinatorial expression of modules in MEC may generate a sufficient number of discrete activity patterns in the hippocampus for almost unlimited numbers of memories to be stored in place cells.

6. Dynamics of MEC-hippocampal connectivity

Activity in grid cells is thought to provide a major spatial input to place cells in the CA1 of the hippocampus (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Solstad et al., 2006; Zhang et al., 2013). However, the CA1 area receives input also from CA3, via the indirect intrinsic pathway of the hippocampus. How do these signals from MEC and CA3 interact? Is there a gating mechanism to balance their influences? Colgin and colleagues have shown that a form of gating between MEC and CA3 inputs is achieved by synchronized oscillatory activity between pairs of regions (Colgin et al., 2009). Two prominent types of oscillatory activity have been found in the MEC: theta (6–12 Hz) and fast gamma (60–100 Hz) oscillations (Mitchell and Ranck, 1980; Chrobak and Buzsaki, 1998). These oscillations are nested in the sense that fast gamma oscillations occur at specific phases of the theta oscillations, a phenomenon referred to as cross-frequency coupling (Chrobak and Buzsaki, 1998). Spike timing of most MEC cells, including grid cells, occurs at specific phases of the fast gamma oscillation (Chrobak and Buzsaki, 1998; Colgin et al., 2009; Mizuseki et al., 2009; Quilichini et al., 2010). Theta and fast gamma oscillations in MEC resemble oscillations in CA1 (Chrobak and Buzsaki, 1998; Mizuseki et al., 2009), and these oscillations, in MEC and CA1, are temporally coupled (Colgin et al., 2009) (Fig. 3F). The coupling of spike activity in MEC and CA1 would allow one region to synaptically influence the other much more efficiently than if activity of the two regions was temporally distributed (Fries, 2005). This synchronization occurs in different frequency bands for CA1-CA3 and CA1-MEC coupling. In the connection between CA3 and CA1, coupled oscillatory activity was observed in the slow gamma frequency band (25–50 Hz) (Colgin et al., 2009). In contrast, CA1 and MEC were coupled primarily in the fast gamma band, from approximately 60 Hz and upwards. Thus, CA1 networks may be able to toggle between CA3 and MEC inputs, alternating between these sources of input, and this may take place multiple times per second (Colgin et al., 2009). What we see in a time-averaged rate map of a place cell is the accumulation of incoming signals from both sources.

7. Functions of the lateral entorhinal cortex

In contrast to the strong spatial modulation of MEC cells, principal cells in the LEC exhibit little spatial modulation (Fig. 1B) (Hargreaves et al., 2005). This distinction in the cellular correlates, together with the distinction in cortical input and output between the MEC and LEC, led to the idea that the MEC and LEC form two parallel pathways that send spatial and non-spatial information to the hippocampus, respectively (Burwell, 2000; Witter et al., 2000; Knierim et al., 2006; Igarashi et al., 2014a). What types of 'non-spatial' information do LEC cells represent then?

The LEC receives massive input from olfactory sensory regions including the olfactory bulb and piriform cortex (Haberly and Price, 1978; Igarashi et al., 2012). In the anterior part of the LEC, as much as 45% of the afferents are from the piriform cortex (Witter and Amaral, 2004). Eichenbaum and colleagues have reported that cells in the LEC respond to odor cues when rats are trained to perform an odor-guided delayed nonmatch-to-sample task (Young et al., 1997). I recently observed that LEC layer III cells gradually develop representations of odors during learning of a task where animals associate odor types with the location of a subsequently available food reward (Igarashi et al., 2014b) (Fig. 4A and B). Collectively, these results suggest that representation of

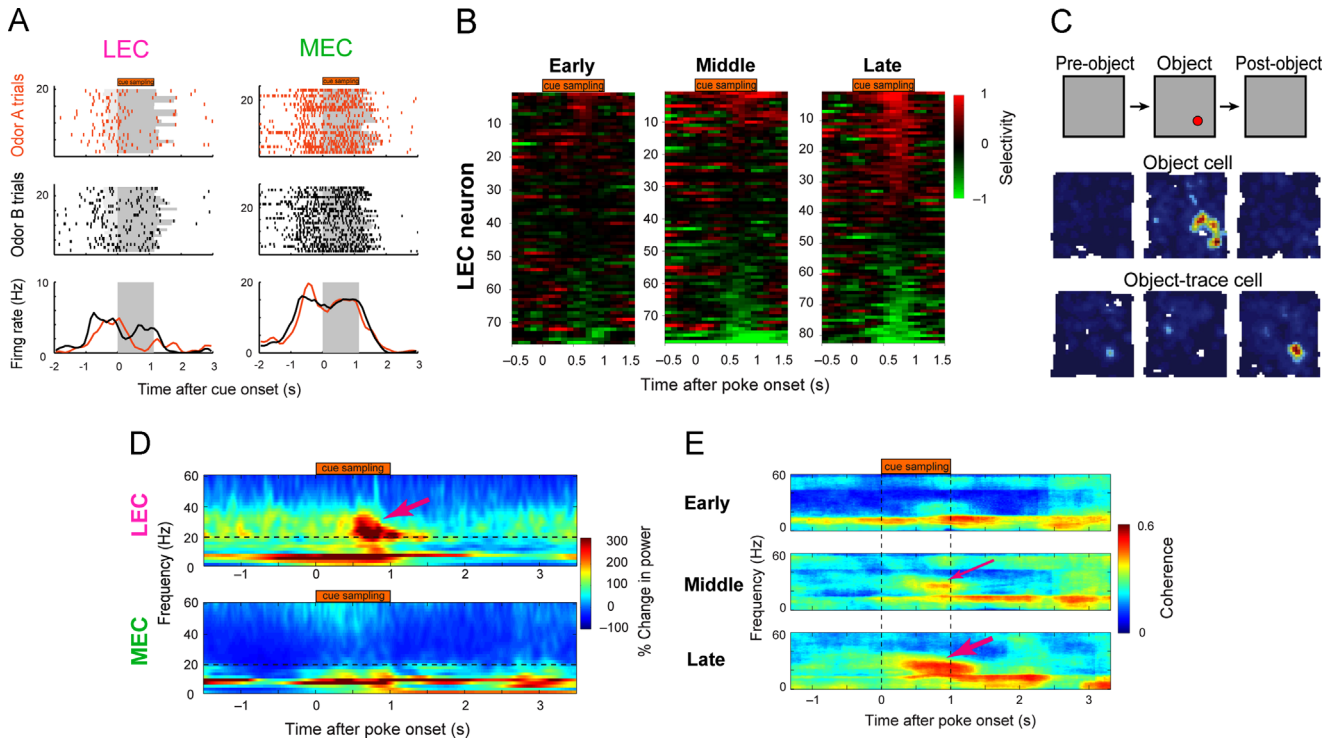


Fig. 4 – (A) Spike raster plots showing example cells that fired differentially to two odors in the odor-place association task. This LEC cell fired more strongly to odor B than odor A. By contrast, the MEC cell fired similarly to the both odor cues. (B) Development of cue selectivity in LEC cells. Each row shows one cell around the time of odor sampling. Selectivity for odor cues is calculated and color-coded (green and red indicate complete selectivity for right and left, respectively). Cells showed development during the course of odor-place association learning. (C) Firing rate maps of an example object cell and an object trace cell in the LEC. The object cell was active when a discrete object was placed in the environment (red dot). The object-trace cells started firing on trials after the object were removed from the environment. Adapted from (Tsao et al., 2013) with permission. (D) Time-resolved power spectrum of averaged local field potentials in the LEC (top) and MEC (bottom) during cue sampling period. The LEC showed 20–40 Hz oscillations whereas the MEC did not. (E) Development of coupling between the LEC and CA1 of the hippocampus. Coherence is color-coded as the index of the degree of oscillatory coupling. Coupling increased at the 20–40 Hz band from early through middle to late phases of the odor-place association learning. (A)–(B) and (D)–(E), adapted from (Igarashi et al., 2014b).

odor-related information is one of the major roles of the LEC. Sampling of odors drives LEC input to the hippocampus so that hippocampal place cells can update representations with information about olfactory stimuli in the spatial environment.

But LEC cells do not only process olfactory information. In recording studies where discrete objects were introduced inside the environment, selected LEC cells were active when the animals were in close proximity to these objects (Fig. 4C) (Deshmukh and Knierim, 2011; Tsao et al., 2013). These objects could have a combination of visual, tactile and olfactory properties. Interestingly, a number of LEC cells fired at the place of the objects only after the objects were removed, suggesting either that these cells represent changes in cue configurations or that they provide a memory trace of the objects(Tsao et al., 2013). The exact function of these cells remains to be determined, however.

8. Dynamics of LEC-hippocampal connectivity

Theta-fast gamma oscillations play a key role in the MEC-hippocampal interaction but does LEC-hippocampus interaction use the same mechanism? In the local field potential of LEC, theta and fast gamma oscillations are weaker than those observed in the MEC when animals run in an open environment (Deshmukh et al., 2010; Igarashi et al., 2014b). However, the LEC shows prominent oscillatory activity in the 20–40 Hz band when the animals sample odor cues and their movements are minimal (Fig. 4D) (Igarashi et al., 2014b). The firing of LEC cells during odor sampling was phase-locked to the 20–40 Hz oscillations. Similar oscillations were also observed in the distal part of the hippocampal CA1 region, which receives direct input from the LEC. When animals learned the association task, 20–40 Hz oscillations in these two regions became tightly coupled, a finding directly showing that the increase of oscillatory coupling relates to behavioral performance (for review, see Igarashi, 2015). When the animals made error trials, the coupling was lost, suggesting that 20–40 Hz oscillations may be part of the mechanism for communication between the LEC and CA1 during memory formation and retrieval (Fig. 4E). Although the generator for the 20–40 Hz oscillations has not been identified, olfactory regions such as the olfactory bulb and piriform cortex may be candidates that actively entrain LEC

oscillations when sensory input is present (Martin and Ravel, 2014). The MEC did not exhibit 20–40 Hz oscillations. In the process of merging spatial input from MEC and updating sensory input from LEC, it would be advantageous for the hippocampus to select either of these inputs using distinct oscillatory frequency bands.

9. Conclusion

Since the discovery of grid cells, a great amount of experimental evidence has been acquired in the MEC. The existence of grid cells, head-direction cells, border cells and speed cells, as well as conjunctive forms of these cell types, suggests that the MEC may contribute to spatial navigation and memory by providing the brain with a spatial metric system. Because grid cells have strong environmental correlates and are easy to record and manipulate, they have also paved the way for computational analyses of cortical function. A number of computational models have explained how interactions of multiple cell types generate the activity patterns of grid cells and place cells. These studies provide clues to a future understanding of how place cell activity is generated in the hippocampus. By contrast, our efforts to understand the functional roles of the lateral counterpart of the EC, the LEC, has just started. It is becoming clear that the MEC and LEC have distinct and presumably complementary functions that support memory and possibly also navigation. Some clues about the mechanisms for interactions between MEC and LEC on one hand, and the hippocampus on the other, have been obtained, but how interactions between these three areas ultimately lead to storage and retrieval of memories, and how they enable animals to navigate from one place to another, remains to be determined.

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