

# Cellular, columnar and modular organization of spatial representations in medial entorhinal cortex

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Spatial discharge patterns in medial entorhinal cortex consist of grid, head direction, border and spatial-band cells. These firing patterns differ from the single-peaked fields of hippocampal place cells, in that they have well-defined geometries and extend throughout the available space. Such discharge properties could contribute to a metric representation of space. Both functional and anatomical evidence point to principal cell diversity, modularity and columnar organization, but linking entorhinal anatomy and physiology remains challenging. Layer 2 microcircuits consist of pyramidal neurons and a stellate cell network, which lacks recurrent excitation and is coupled by disinhibitory inhibition. Intracellular recordings showed that periodic, grid-like firing emerges from depolarization ramps, whereas theta-oscillations determine spike timing. Interference with various inputs to entorhinal cortex abolishes grid activity, often without concomitant loss of hippocampal place activity.

## Addresses

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About ten years ago the seminal discovery of grid cells [1] triggered an outburst of physiological, anatomical and computational studies that transformed the medial entorhinal cortex (MEC) from *terra incognita* into a puzzle of grid cells [1], head direction and conjunctive cells [2], border cells [3], band cells [4\*\*], attractors [5] and interfering oscillators [6]. In this review we focus on recent advances in piecing together this puzzle (for more comprehensive reviews see [7,8]).

## What cell types are there in medial entorhinal cortex?

### Functional classification

Advances have been made in classifying and subdividing cell types in MEC according to their spatial discharge

properties. These include head direction cells, which encode the direction of the animal's head [2], grid cells, which show a periodic hexagonal spatial firing profile [1], border cells, which encode proximity to environmental barriers [3] and more recently described spatially periodic band cells, which lack the signature hexagonal symmetry of grid cells [4\*\*]. While there is broad consensus on the types of spatial discharge patterns in the MEC, quantification of functionally defined cell types turned out to be problematic. Quantitative estimates of grid cells in layer (L) 2, where the highest concentration of grid cells is found, range from 61% [2], 50% [9\*] to 26% [10\*] and possibly even lower [11\*]. It even appears to be unclear, whether grid cells are the most abundant cell type in the MEC, since more band cells than grid cells were recorded in a recent study [4\*\*]. Plausible explanations for such discrepancies across (and within) labs might include (i) a 'grid cell hot-spot hypothesis' according to which there is an anatomical location (somewhere in dorsal medial entorhinal cortex), where grid cells are abundant, (ii) different cell classification criteria and (iii) different sampling biases across recording methods and investigators.

### Morphological classification

Substantial morphological neuronal diversity has been observed in all layers of MEC [12]. In L2, two principal neuronal types have been described, of pyramidal and stellate morphology [13], which have remarkably distinct electrophysiological features. Unlike pyramidal neurons, stellate neurons display prominent sag potentials, which are mediated by the cation-activated hyperpolarizing current ( $I_h$ ), show intrinsic theta-like membrane potential activity, which resembles periodic oscillations (see [14] for review) and intrinsic resonance properties in the theta-frequency range (4–10 Hz) [15]. Even though cell classification might not be strictly binary both physiologically [12,16] and morphologically [12,17], the currently available data suggest that in L2 there is indeed a strong correlation between neuronal morphology and intrinsic properties. Classification of cell types is less advanced in the other layers, where the pyramidal neuron is the predominant principal cell type. While some degree of correlation between morphology and intrinsic properties has been observed in layers L3, L5 and L6 [18–20], a more recent *in vitro* study failed to support this evidence [12].

### Structure–function relationships

Addressing the correspondence between functionally and morphologically identified cells is a key issue in the

cellular neurobiology of MEC. It is essential to address this issue, because computational models of grid cell discharge and more generally of path-integration functions, rely on specific biophysical properties of entorhinal cells [6] and local network structures [21]. Recent methodological advances made it possible to address this issue, either by recording from identified neurons in freely moving [22<sup>••</sup>,23] or virtually navigating rodents [24<sup>••</sup>], or by optogenetic-tagging approaches [10<sup>•</sup>]. A correspondence between morphologically identified neurons in dorsal cytochrome oxidase rich – putatively parasubicular – patches and head direction coding was observed [22<sup>••</sup>], in line with previous observations [25]. Other data indicate a lack of structure–function correlation in L2: grid-like discharge patterns in L2 were observed in a variety of morphologically distinct cell types [24<sup>••</sup>], and optogenetic tagging suggested that the hippocampally projecting L2 cell population, mainly composed of stellate neurons [16,26], consists of a mixture of functionally distinct cell types, including head direction, border, grid and non-spatially-modulated cells [10<sup>•</sup>]. A final assessment of the correspondence between cell function and morphology in MEC will require more detailed phenotyping of larger numbers of cells and refined spatial characterization of identified neurons.

### Is medial entorhinal cortex modular?

#### Functional modularity

Initial work provided functional evidence for discrete grid cell clusters, since locally recorded grid cells were typically found to display similar spacing and orientation [1], and grid spacing was observed to increase in discrete steps along the dorsoventral axis [27,28<sup>•</sup>]. In a recent study [28<sup>•</sup>], Stensola *et al.* explored grid cell modularity in great detail by recording from a large portion of the dorsoventral and mediolateral extent of MEC within a single animal. The authors described a small number (up to 4–5 in the dorsal half of MEC) of anatomically overlapping, functional modules with distinct scale, orientation, asymmetry and theta-frequency modulation of grid cell activity.

#### Anatomical modularity

Large scale modularity is a prominent organization principle of limbic cortices, and in particular of MEC (for review see [7]). Modularity is observed in superficial layers (L2–3) and most prominently in L2. Virtually in all mammalian species analyzed to date, and most prominently in humans and primates [29,30] L2 has a modular anatomical appearance, which is apparent as discrete clusters of neurons (termed ‘islands’). A number of molecular markers stain selectively the cell clusters in the islands, or distribute in between the islands [31–35]. Metabolic markers displaying a marked modular distribution, like cytochrome oxidase (which is most prominently modular in the primate and human [30] but also in the rodent brain [22<sup>••</sup>]) and glycogen phosphorylase

(which stains patches in L1 and L3 [36]) have been described.

Cytochemically distinct subpopulations of neurons have also been described, which display a modular distribution within the superficial layers of MEC. Calbindin positive neurons in the rodent (in L2, [37]) and in the human and primate brain (upper L3; [33,34]), a subset of neurofilament-labeled neurons in L2 [34] and a subset of L3 neurons [38] show clear modular arrangement and dendritic bundling. Terminal fields of neuromodulatory afferents also display preferential clustering in superficial layers of MEC [39,31] and afferents from the presubiculum cluster in patches in L3 and L1 [40]. Anatomical modularity is supported by *in vitro* electrophysiological evidence [41].

#### Structure–function correlations

As for functionally and anatomically defined cell types, we do not know yet, if there is a correspondence between functionally and anatomically defined modules.

### Is medial entorhinal cortex columnar?

#### Functional classification

Neurons in the cerebral cortex tend to be vertically organized in functional units, referred to as ‘columns’, where neurons share similar response properties. The seminal work of Hubel and Wiesel [42] in cat primary visual cortex showed that there is a major response transformation in the cortical input layer (L4 in visual cortex), where unoriented spot-like thalamic inputs are transformed into oriented responses, which are then relayed to other cortical layers. In MEC, functional evidence for a columnar organization is provided by the distribution of grid cell properties, which are locally correlated throughout all layers [28<sup>•</sup>]. It is not known, however, whether a similar input transformation as in visual cortex is happening in MEC.

#### Structural classification

Early work provided evidence for a columnar arrangement of deep-to-superficial interlaminar connections [43,44]. In a recent study [45<sup>•</sup>], these connections have been analyzed in greater detail by recording from morphologically identified neurons in L2 and uncaging glutamate in the deep layers. The authors described a restricted, columnar arrangement of ascending projections, which were two times smaller for stellate than for pyramidal neurons ( $\sim 200$  versus  $\sim 400$   $\mu\text{m}$ ), indicating that the latter cell types can integrate a broader range of ascending synaptic inputs.

### What are the microcircuits of medial entorhinal cortex?

Microcircuit analysis in MEC has greatly advanced in the last few years, in particular with respect to our circuit understanding of MEC L2. Two recent *in vitro* studies provided evidence for the lack of recurrent excitatory

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