# Entorhinal Cortex

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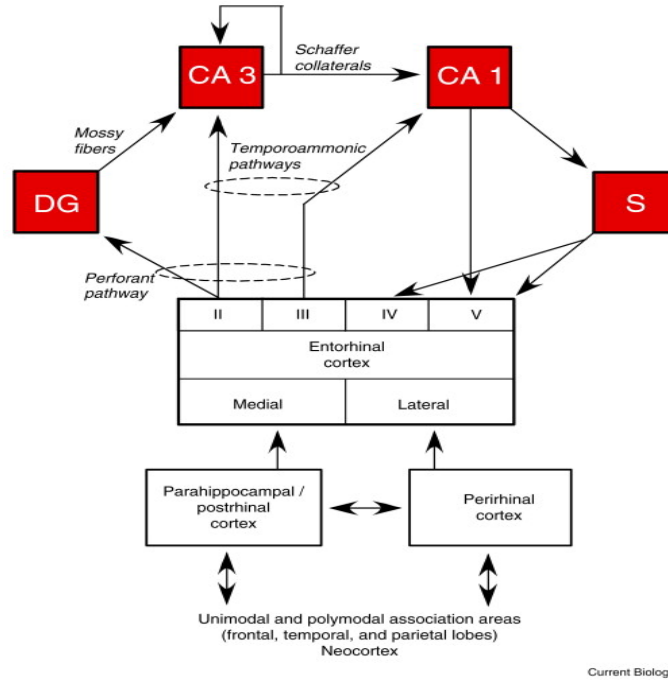
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## 1  Connection



Figure 1: *"A schematic representations of main connections of Entorhinal Cortex.The hippocampus (highlighted in red), defined here as the dentate gyrus (DG), CA3, CA1, and subiculum, is anatomically situated to receive highly processed information from widespread neocortical regions through three temporal cortical areas, the entorhinal, perirhinal, and parahippocampal cortices (in the rat, the term postrhinal cortex replaces the term parahippocampal cortex), as well as through other direct projections to the entorhinal cortex from areas outside the temporal lobe. The figure shows a simplified view of the way in which information enters the hippocampus from the superficial layers (II and III) of the entorhinal cortex and then flows in a largely unidirectional feed-forward direction to the deep layers of entorhinal cortex (IV and V). The medial entorhinal cortex is densely connected with the postrhinal cortex and is specialized for spatial information, while the lateral entorhinal cortex is densely connected with the perirhinal cortex and is specialized for object information. These two processing streams are primarily combined when they reach the hippocampus."[8]*

### 1.1  Input

The entorhinal cortex(EC) is part of the parahippocampal region and it is closely connected with the hippocampal formation and neocortex areas such as parietal cortex, temporal cortex, and prefrontal cortex. It receives both the highly processed sensory information of all kinds from neocortex, and the information regarding ongoing cognitive processes from the hippocampus [57, 5, 28].

- Layer II & Layer III: receive input from perirhinal cortex, parahippocampal cortex, and prefrontal cortex. These inputs are then projected to all subdivisions of the hippocampal formation via the perforant path, which are the major cortical input for hippoccampus.

- Layer V & VI: receive the outputs from CA1 and the subiculum.

## 1.2 Output

- Layer II mainly outputs to DG and CA3;

- Layer III mainly outputs to CA1 and subiculum.

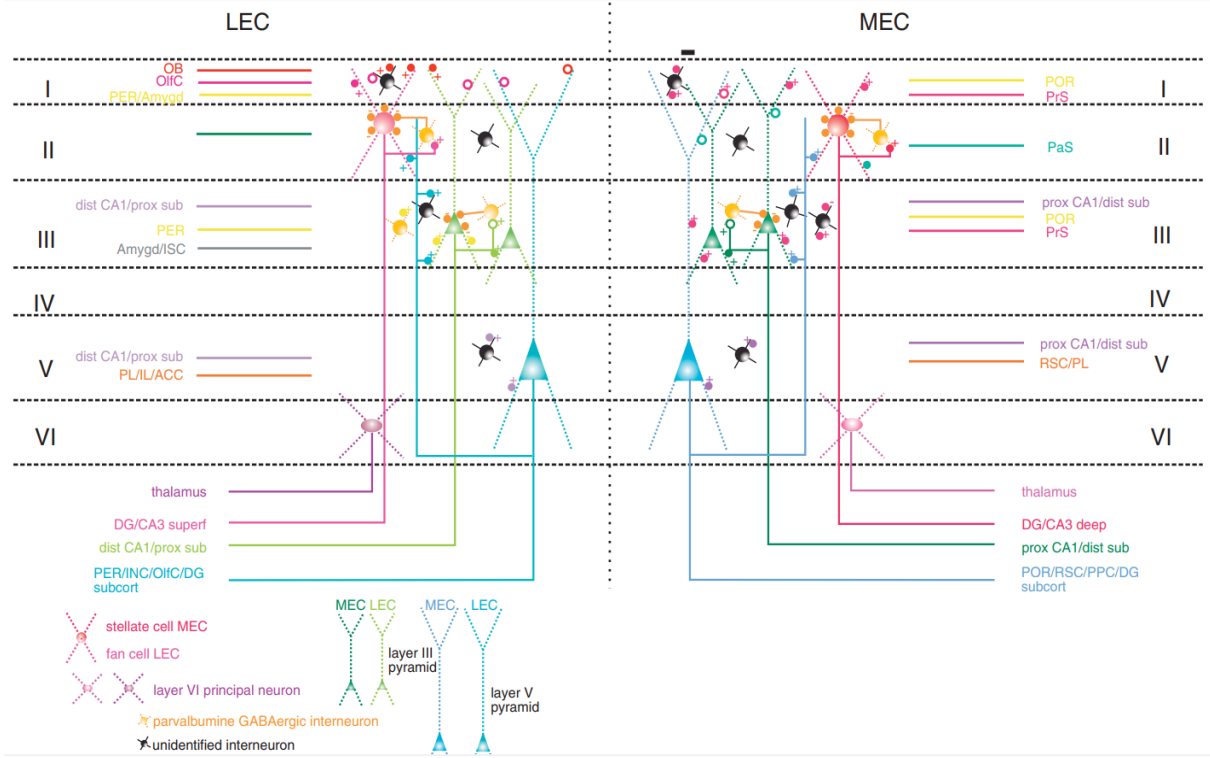- Layer V& VI reciprocate connections as discussed above 1.1.



*Figure 2: "A detailed schematic representations of main neuron types and connections of LEC and MEC. Connections are represented as if concentrated into a single columnar module, disregarding available information on topography and divergence of the various extrinsic and intrinsic connections. Inputs and outputs are color coded and presented with respect to their main layers of termination and origin, respectively. Main interlaminar connections are from deep layer V to layers II and III and are known to show extensive spread along the dorsoventral extent of the EC, likely connecting corresponding portions of MEC and LEC, in register with the longitudinal bands which are reciprocally and topographically connected to different parts along the dorsoventral axis of the hippocampus. Intralaminar connections between principal neurons are most extensive in layers III and V, whereas in layer II the preferential connectivity may be between principal cells and interneurons. Synaptic contacts established anatomically or electrophysiologically are indicated with filled circles and if known the inhibitory or excitatory nature is indicated by a - or a + sign, respectively. Inferred but not yet established synaptic contacts are indicated with open circles. All cell types and their main dendritic and axonal connections are uniquely color coded. Connections with main modulatory systems such as septal complex, monoaminergic systems and thalamus are not represented. Abbreviations: ACC: anterior cingulate cortex; Amygd: amygdaloid complex; CA1-CA3: subfields of hippocampus proper; DG: dentate gyrus; dist: distal; IL: infralimbic cortex; INC: insular cortex; OB: olfactory bulb; OlfC: olfactory cortex; PaS: parasubiculum; PER: perirhinal cortex; PL: prelimbic cortex; POR: postrhinal cortex; PPC: posterior parietal cortex; PrS: presubiculum; prox: proximal; RSC: retrosplenial cortex; sub: subiculum; subcort: subcortical structures such as basal forebrain, amygdala; superf: superficial." [37]*

## 1.3 Main Components

- Medial Entorhinal Cortex (MEC): strongly connected to the postrhinal cortex, presubiculum, occipital and retrosplenial cortices; mainly encodes spatial ("where") information.

- Lateral Entorhinal Cortex (LEC): strongly connected to the olfactory cortex, perirhinal cortex, and the prelimbic and infralimbic frontal areas [54, 6], mainly encodes non-spatial ("what") information.

Both MEC and LEC output to DG and CA3, and have strong reciprocal innervations with the amygdala, the thalamus, and other subcortical areas. Also, they are interconnected with each other, so in EC the spatial and non-spatial inputs are likely to be already combined. The dorsolateral part of MEC and LEC is innervated with the dorsal hippocampus, the intermediate one with the intermediate hippocampus, and the ventral one with the ventral hippocampus. [50, 7, 44]

## 2  Function

EC encodes "general properties about current contexts that are then used by hippocampus to create unique representations from combinations of these properties" [37].

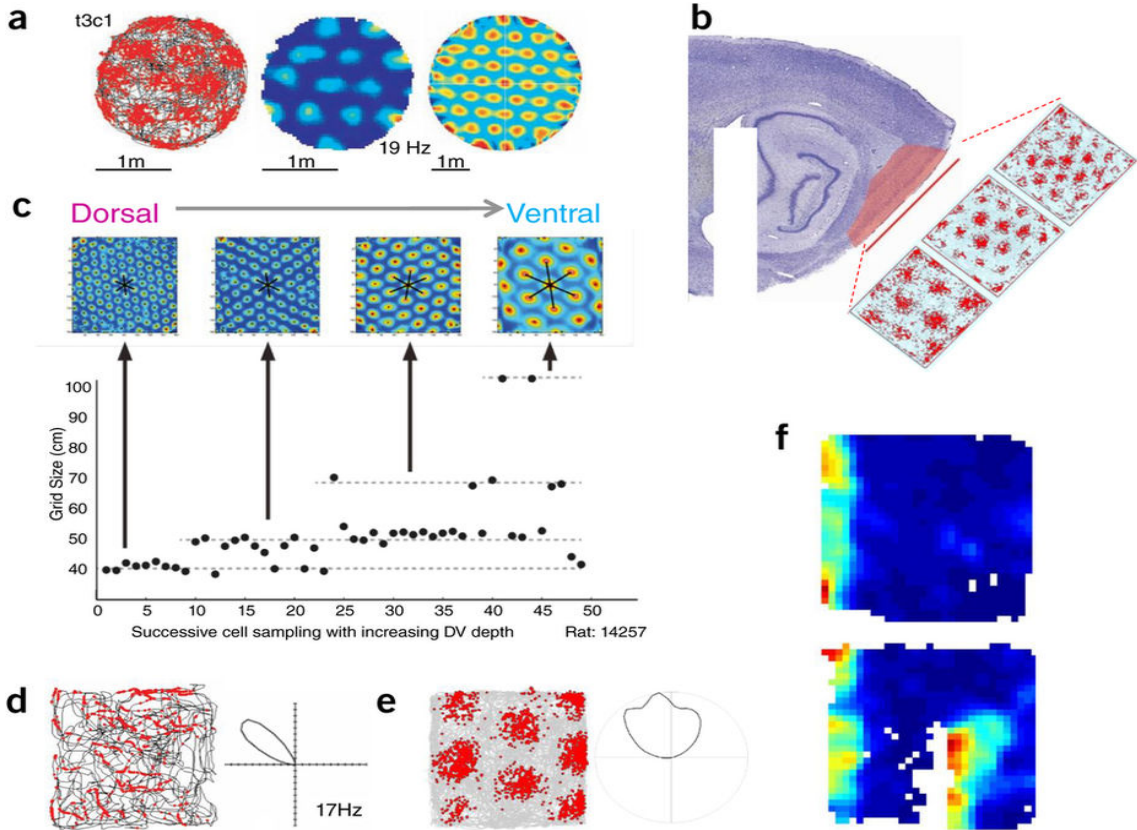### 2.1  Medial Entorhinal Cortex



*Figure 3: "Grid cells, head direction cells and boarder cells in MEC. (a) Firing fields of one of the first grid cells reported in 2005 . Left: trajectory of the rat (black) with superimposed spike locations (red). Middle: color-coded rate map with peak rate indicated (red, peak rate; dark blue, no firing). Right: spatial autocorrelogram, color-coded from blue (r = 1) through green (r = 0) to red (r = 1). (b) Sagittal section of the rat brain showing the hippocampus and the MEC (red) and grid cells of different scales recorded at three locations on the dorsoventral axis (trajectories with spike locations as in (a). Note the expansion of grid scale from dorsal to ventral MEC. (c) Grid cell modules. Top: autocorrelation plots showing grid patterns at successive positions along the dorsoventral axis of MEC. Bottom: grid size, defined as the distance between grid vertices, as a function of position along the dorsoventral MEC axis (positions rank-ordered). Note that the increase in grid size is not linear but discretized, following a geometric order with a factor of approximately $\sqrt{2}$. Mean grid size for each module is indicated by stippled lines. Such modularization is an essential prediction of the attractor map theory if it is to account for variable spatial scaling91. (d) Head direction cell in layer V of MEC. (e) Conjunctive grid & head direction cell in layer III of MEC. (f) Border cell. Color-coded rate maps showing a cell with selective firing along one of the walls of the recording environment. Top: open environment. Bottom: rate map following the insertion of a wall. Note that the border cell responds to the same side of the wall insert as the main wall in the environment."[36]*

- Head direction cells: the firing patterns are according to which allocentric direction that the rat's head is pointing. The preferred firing directions are shown to be distributed evenly in different di-

rections.They were first found in presubiculum and parasubiculum [52, 51], then they were found in layers IIIVI of the rat MEC. It is quite likely that the presubiculum one gives input to the EC head direction cells[56]. Many head direction cells are co-localized with grid cells, and conjunctive with grid or head direction neurons (Figure 3e) in MEC layer IIIVI, and pre/parasubiculum. This points to "a computational mechanism for imposing the angular component of path integration on grid cells" [36]. Head velocity signals in the lateral mammillary nuclei project to head direction cells in EC ,[47], which "might enable head direction cells to infer direction at the timescale of behavior" [36].

- Grid cells: firing pattern is hexagonal and repeat periodically. The grid cells are mainly in MEC layer II, and some are in layers III and V. The relationships between phase and orientation among grid cells do not change when relocating to a new environment [12, 60], especially among the grid cells with similar scales [48]. The orientation are mainly influenced by distal cues and the geometry of the environment [15, 26, 49], and the environmental boundaries limit the variabilities of grid cells (when the animal is close to walls), suggesting an error correction mechanism as in the path integration model [17]. The phase of the firing is random among cells, similar as the random spatial relationships among place cells [40, 39, 21]. Moreover, the grid cells in MEC has larger scales from dorsal to ventral parts, similar as the place cell firing fields increase from dorsal to ventral hippocampal formation [23, 24]. The scales and the orientation of grid fields are discretized, and cells with the same scale have similar orientations and similar theta cycles.[48] In terms of temporal encoding, theta phase precession is apparent in layer II but not much in layer III, and the theta phase precession persists when connections with the hippocampal formation is damaged. [14]

- Border/Boundary cells: fired "exclusively along geometric borders of the local environment", the borders can be walls or edges [46]. Some of them are conjunctive cells with head-direction, but not grid information. They appears in MEC layers II, III and V[41] and the subiculum [29]. Comparing to the boundary vector cells (BVC) in the subiculum, the border cells in MEC does not have distance tunings. But "given the unidirectional wiring of the hippocampal circuit, the cells in MEC, rather than those in the subiculum, are more likely to provide major input to hippocampal place cells" [36], and this is supported by the studies with developing rats - place cells fire close to borders mature earlier, similarly to MEC border cells[1], whereas place cells fire in the center of the room appear later, similarly to as grid cells [38].
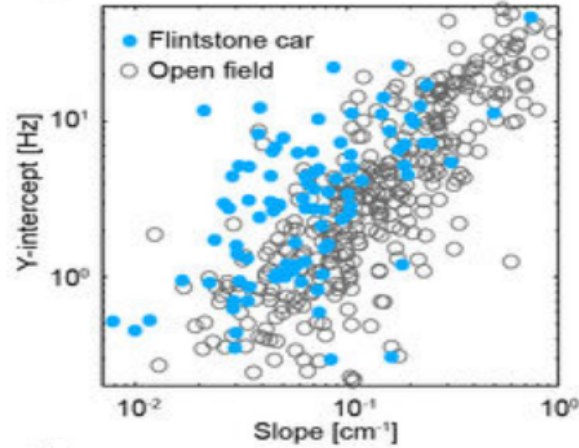


*Figure 4: Scatter plot showing slope and y intercept of regression lines for each entorhinal speed cell recorded in the bottomless car (blue circles) and in the open field (grey circles). Note wide range of slopes and y intercepts. [25]*

- Speed cells: the firing rate of speed cells is linear to the moving speed of the animal, no matter it is volunteer movement or passive movement. The linear relationship is mostly positive [25, 20] . The intercept and slope of the linear relationships varies as shown in Figure 4. This speed encodings are context-invariant (do not have much spatial oe directional information, independent of visual input, and persists in darkness). Speed cells are positively modulated by acceleration. It is believed to update grid-cell firing patterns because its firing dynamics is 5080 ms ahead of grid cells. Speed cells is also be found in the hippocampus and in or around presubiculum, but the ones in the hippocampus overlap

strongly with other cell types, and "no direct link could be found between speed cells and place cells in the hippocampus" [25] Some of the speed cells' firing rate saturate rather than linear to running speed.[20]

- Speed signals are also represented by theta oscillatory frequency in MEC, but there is no consistent relationship between the firing rate and oscillatory frequencies. When the locomotor input is removed, this theta frequency speed signal is weakened while the speed cell firing rate relation as mentioned before is strengthened. Therefore, the two types of speed signals are believed to be independent of each other [20]. (The theta rhythm speed tuning also happens in the hippocampus, and it is shown that "speed tuning of hippocampal theta rhythm amplitude is sufficient to enable accurate reconstruction of distance traveled" [53].)

Note: MEC grid cells, border cells, head direction cells, and speed cells also persist during sleep. This "points to a fundamental difference between hippocampal and entorhinal spatial maps: hippocampal circuits are high-dimensional and capable of storing a very large number of patterns, while MEC maps are low-dimensional and rigid, expressing the same intrinsic structure in all behavioral contexts, as would be expected for a path-integration-based map that keeps metric properties constant across contexts and environments".[36]
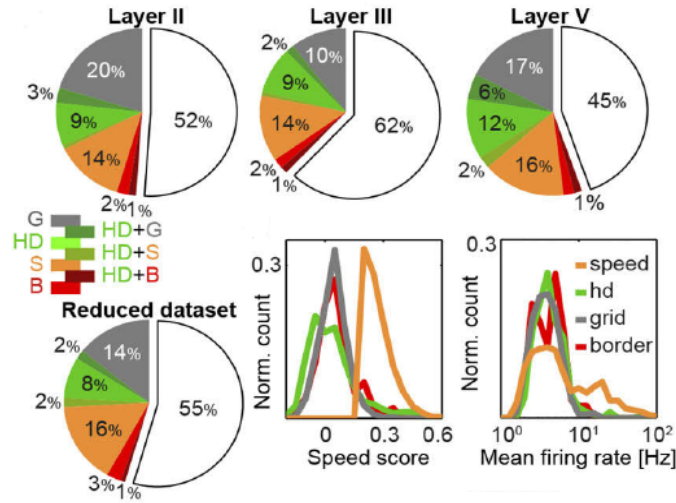


Figure 5: "Top row, pie charts showing distribution of functional cell types and their overlaps across entorhinal layers (only proportions higher than 1%). Bottom left, recording across multiple days can generate an unwanted bias in the estimation of population sizes, since a single cell could be counted many times. To avoid this bias, the original data set were reduced by discarding a cell if another cell had been recorded at a distance of less than 200 mm on the same tetrode on an earlier day. In this reduced population of 608 cells, 18% were speed cells, confirming that the population size estimation is free of this kind of bias. Bottom middle, distribution for different cell categories of speed score. Bottom right, firing rate averaged over non-silent periods (firing rate>1 Hz; right). (G, grid; HD, head direction; S, speed; B, border.") [25]

## 2.2 Lateral Entorhinal Cortex

- Object cells: activate whenever the rat meets an object at a specific location, no matter what exact object is. Some continue firing minutes, days, or even weeks after the removal of the object. The information about objects may derive from the perirhinal cortex, which is involved in object-recognition and familiarity [9]

- Trace cells: fire at places where objects have been located. The difference between object cells and trace cells are that the latter one do not rester the current object presence. [55].

- Odour recognition and association with space: LEC exhibit "great odour-evoked power change in local field potential activity, and the firing patterns are odour-specific" [58]. The LEC is described to be highly involved especially when the memory load is heavy and the task involved odors [27]. When rats learned to navigate based on odour cues, "the entorhinal-hippocampal coupling was observed specifically in the 2040-hertz frequency band and specifically between the distal part of hippocampal area CA1 and the lateral entorhinal cortex" [22].

- LEC also has weakly spatial modulated cells [18].

Note: The difference in the functions of MEC and LEC "can be modulated by the behavior (navigation vs. exploration) and/or cognitive demand. Different behaviors such as goal-directed navigation and exploration may result in different involvement of the MEC and LEC for the processing of distal landmarks and proximal landmarks. When the cognitive demand is high (for example when the animals have to process a large amount of information or when they need to form complex associations between stimuli), the what (LEC) and where (MEC) specialization in two areas are more obvious than when the demand is low. This suggests that the MEC and the LEC tightly cooperate and work in a flexible manner to integrate the what and where information in episodic memory upstream the hippocampus." [44]

## 2.3   Scales

Mentioned in the description above.

## 2.4   Evidence of Building Blocks / Modularization

EC is the place that gives but also receives information to/from the hippocampus, as well as other cortical/subcortical areas. The specialized but also interconnected representations of spatial and non-spatial information can be viewed as different modules. The different scales in the representations can be viewed as building blocks.

## 2.5   Evidence of Lateralization

It was reported that the volume of the left EC is different in the patients who are progressing to ALzheimer or just in a stable mild cognitive impairment state, and the volume is "inversely correlates with the level of alpha band phase synchronization between the right anterior cingulate and temporo-occipital regions".[31].

## 2.6   Empirical Lesion studies

- Leisions of either MEC or LEC partly influence hippocampal place cell performance. Lesions on MEC do not remove place cell firings in hippocampus, but the stability of their firing patterns are affected [16]. Lesions on LEC lesions remove the rate remapping of the place cells if geometry or the color of the maze changes.[30].

- Lesions on MEC strongly impact the temporal coding in CA1, which messes up the memory encoding with various temporal delays.[42]

- Lesions on EC do not impair object recognition but impair the association among objects and places [10].

For more review on lesion studies, check here: [44]

# 3   Computational Model

- Oscillatory interference models of grid cells described that the grid patterns are formed by theta rhythm interference[4, 2, 19]. However, this model requires a linear relationship across different grid scales, and it was observed that grid patterns present without theta rhythmicity [59].

- Path integration / attractor models of grid cells, speed cells, head direction cells, boundary cells, and place cells: see Figure 6 [33, 11, 3].
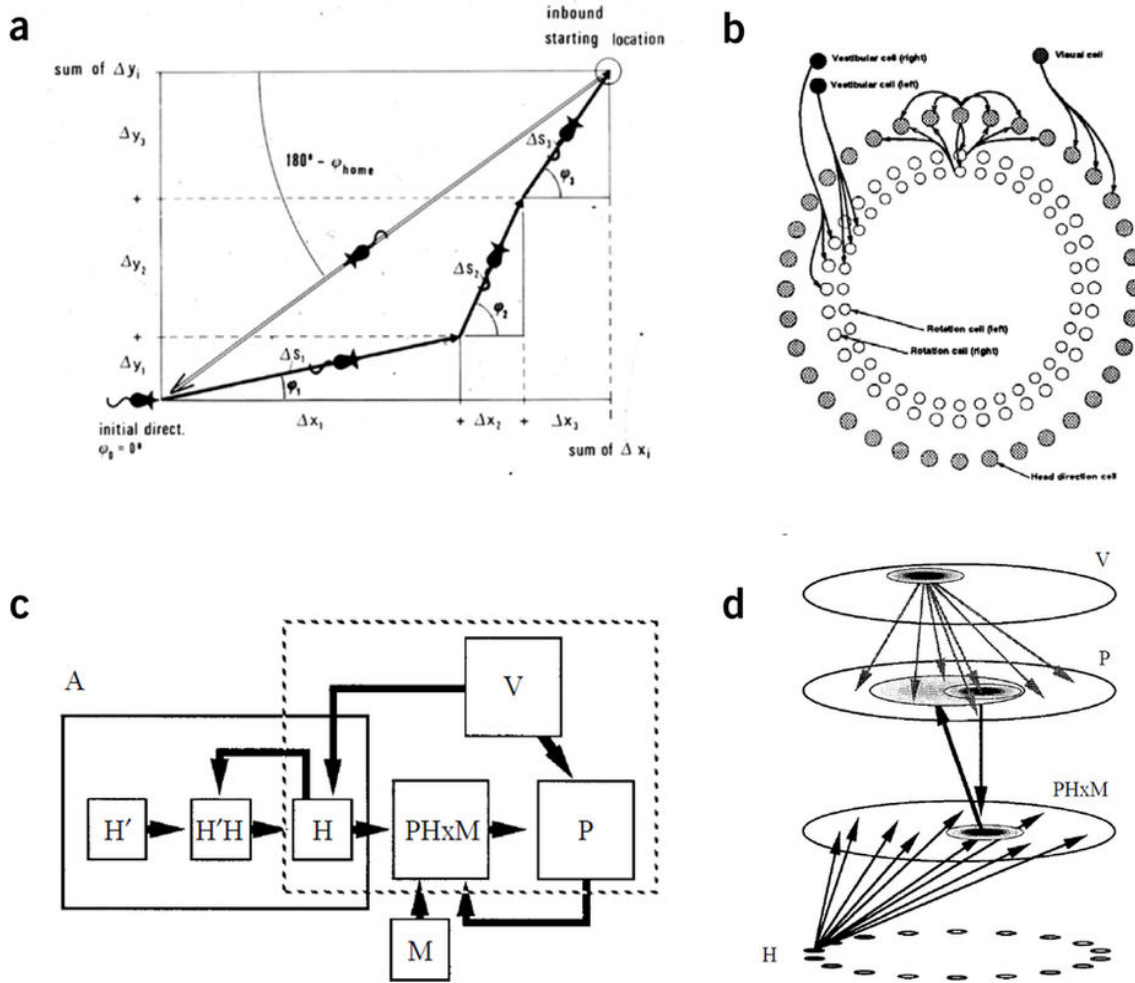
*Figure 6: "(a) Illustration of the Mittlestaedt & Mittlestaedt 1980 experiment [35, 33]. This experiment showed that rodents can perform angular and linear path integration. A female mouse returns directly to her nest after finding a lost pup in total darkness but makes a heading error if she is rotated below vestibular threshold before starting the inbound journey. (b) The Skaggs et al. continuous-attractor model from 1995 proposed to explain how head direction cells arise through integration of head angular velocity signals from the vestibular system [34, 45]. Updates in the head direction (attractor) layer were performed by a hidden layer of cells conjunctive for head angular velocity and starting head direction, whose return projections to the head direction layer are offset according to the sign of rotation. Such conjunctive cells have been found in several regions of the brain. (c,d) The continuous-attractor model for path integration in two dimensions, as proposed by McNaughton et al. in 1996 [32] and simulated by Samsonovich and McNaughton in 1997 [43]. H', head angular velocity; H'H, conjunctive cells; H, head direction; P, place cells; M, speed cells; PHM, cells conjunctive for place and head direction and modulated by speed; V, external sensory inputs that were assumed to associatively bind to both H cells and P cells to enable correction of drift error in the path integrator and to enable resetting of the integrator upon entry to a familiar environment." [36]*

For more computational models, see [13, 36] for reviews.

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