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Self-localization and the entorhinal–hippocampal system

Kathryn J Jeffery

Self-localization requires that information from several sensory modalities and knowledge domains be integrated in order to identify an environment and determine current location and heading. This integration occurs by the convergence of highly processed sensory information onto neural systems in entorhinal cortex and hippocampus. Entorhinal neurons combine angular and linear self-motion information to generate an oriented metric signal that is then 'attached' to each environment using information about landmarks and context. Neurons in hippocampus use this signal to determine the animal's unique position within a particular environment. Elucidating this process illuminates not only spatial processing but also, more generally, how the brain builds knowledge representations from inputs carrying heterogeneous sensory and semantic content.

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Navigation is a complex cognitive faculty involving many interacting processes and using information from, to a greater or lesser extent, all sensory modalities. It requires an organism to determine its position and orientation (self-localization), its desired position (goal determination), and finally, how to get from one place to the other (route planning).

The problem of self-localization is currently under scrutiny because of recent findings concerning the involvement of the hippocampus and surrounding structures. This article reviews evidence that spatial representation in the hippocampus arises from convergence of highly elaborated but disparate inputs onto common neural matrices, in particular, the entorhinal grid cell system and the hippocampal place cell system, which then perform structure-specific transformations on the information. Understanding this system illuminates not only spatial processing but also the more general problem of how the brain builds 'knowledge structures' from sensory inputs.

Self-localization and the entorhinal–hippocampal system

Behavioral evidence indicates that when an animal localizes itself in a familiar environment it uses several learned cues including the geometry of the environment [1•], landmarks [2], and contextual cues [3•], which it combines with information about its own recent movements (path integration [4]). Neurobiological studies spanning several decades have consistently indicated that a central structure for self-localization is the hippocampus, whose principal neurons, the place cells, are selectively active in specific regions of the environment known as 'place fields' [5] (Figure 1A). Place cells collectively provide a representation of position [6], which could be used for navigation. A long-standing question concerns how place cells determine where to fire, and recent findings in entorhinal cortex, one synapse upstream of the place cells, shed light on this issue.

Place cells receive highly processed multimodal sensory information, and these inputs are functionally segregated [7]. For example, at least in rodents, proximal environmental boundaries primarily specify the location of place fields [8,9•], whereas landmarks have a more prominent role in directional orientation [10,11], particularly if they are more distant [12], and contextual inputs may select which representation activates in a particular environment [13]. Deformation of environments causes a partial but concordant deformation of the place field array [8], suggesting that the boundaries supply place cells with a linear distance metric, telling the cells, in effect, how far the animal is from (some of) them [14]. A complementary angular metric, conveying directional orientation, is processed by the head direction system, a network of limbic structures whose neurons, the head direction cells, show directionally specific firing [15••] (Figure 1C). There is much current interest in determining how these inputs reach the hippocampus, how they are integrated, and how they are updated as the animal moves around.

Origin of angular and linear information

The question of how angular and linear metric information is integrated by place cells has recently been greatly advanced by the discovery that neurons directly afferent to the place cells, in the dorso-medial region of the entorhinal cortex (EC), have both angular and linear metric properties [16••]. These so-called 'grid cells' (Figure 1B) exhibit multiple, evenly spaced place fields

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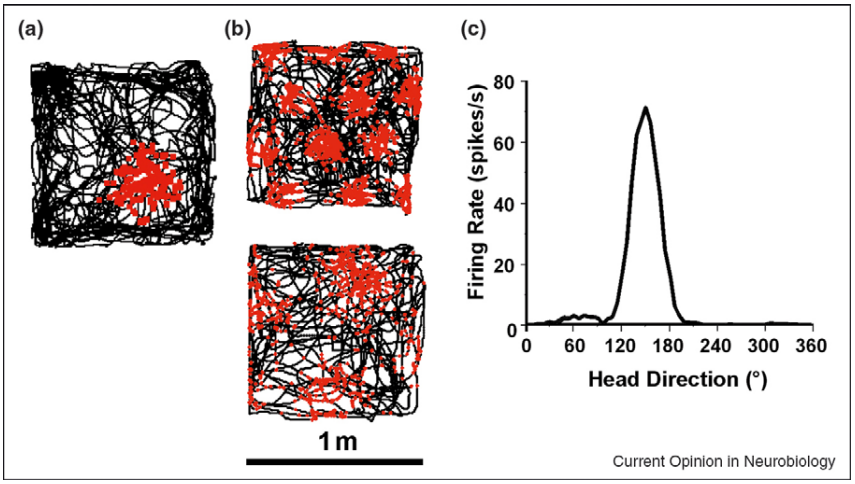
Figure 1



(adapted from reference [56]) Three kinds of spatial-signal-carrying neurons in the rodent limbic system. **(A)** A classical place cell. The black lines show the path of a rat as it foraged in a 60 cm square box, and the red squares show action potentials from a single hippocampal neuron, superimposed on the position of the rat. A typical place cell will, as shown here, concentrate most of its activity in one part of a small environment (the 'place field'). **(B)** Grid cells from dorsal (upper panel) and ventral (lower panel) dorso-medial EC, in the same data format as (A). Data shown as reported in reference [16••]. The figure shows the hexagonal array of firing fields typical of grid cells. Note the change in inter-peak spacing between dorsal and ventral regions. **(C)** Data from a typical head direction cell, showing that firing rate (*y* axis) increases dramatically when the rat's head is within a restricted directional orientation (*x* axis). Figure kindly supplied by Jeffrey Taube.

that spread across the environment in an apparently limitless array, producing a striking hexagonal (or triangular) pattern strongly reminiscent of graph paper. Grid scales increase from dorsal to ventral areas or dorso-medial EC, and the grids from a given animal are randomly 'offset' but seem to have similar orientation ([17••]; Supplementary Figure 4). The even spacing of the grid nodes could plausibly enable metric computations in other neurons, such as place cells [16••]. How such computations are implemented is still a matter of speculation, but the most obvious method is by summation of grids of different scales (as, for example, from different dorso-ventral layers of EC), which would in theory produce widely scattered hot spots of activity with a sparsity comparable to that of place fields [18•,19,20••,21•].

The remarkable metric properties of grid cell grids shift back one synapse the question of where this information comes from. How does a grid cell combine angular and linear information to determine where to lay down its peaks? That the peaks occur at the same spacing for a given neuron even across different environments [16••] suggests an intrinsic (i.e., environment-independent) metric, which must come from processing of angular and linear self-motion information.

The route into EC for angular self-motion inputs, via the head direction (HD) system, has now been worked out in some detail [15••] and involves a circuit from the vestibular nuclei through the dorsal tegmental nucleus, where neurons sensitive to angular velocity are found [22,23], and thence via the lateral mammillary nucleus, anterodorsal thalamus, and post-subiculum to the EC [15••]. Information concerning landmarks, and perhaps optic flow, may come from higher cortical regions such as retrosplenial cortex. Integration of static environmental inputs with self-motion information is thought to take place amongst the HD cells themselves, perhaps mediated by 'attractor' processes [24,25] in which the cells collectively form a stable representation of direction that is updated in accordance with incoming information on angular velocity and abruptly moved (or 'reset') by landmark information. Observations that HD cells always seem to fire coherently, even when sensory cues are dissociated [26•], support the attractor view.

The route for linear self-motion integration into the entorhinal–hippocampal system is far less well established than for angular. A weak correlation has been found between locomotor speed and firing rate for place cells [27] as well as head direction and grid cells [28••]. A single recording session of a probable axon from a highly speed-correlated cell has been reported [29], suggesting the existence of cells that encode speed directly. The speed correlate of place cells depends on the integrity of perirhinal cortex [30], so this may be one route for such information into the hippocampal system. As with angular motion, it is likely that the vestibular component of linear motion is routed via brainstem structures.

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Integration of angular and linear metric inputs

The discovery of grid cells offers an opportunity to determine how the brain combines angular and linear self-motion inputs in order to extract current position, a process known as path integration [4]. Path integration has long been known to influence both animal navigation and place cell activity [31] but the precise nature and location of the integration had remained elusive. Redish and Touretzky presciently suggested that it might take place in EC [32], and the discovery of grid cells supports this view [16••,18•,20••,21•]. Grid cells themselves have both angular and linear metric properties, inasmuch as each grid has a reproducible orientation and regular inter-peak spacing. In addition to grid cells, Sargolini *et al.* have found that the dMEC also contains pure head direction cells and also cells with mixed directional and grid properties [28••], again indicating a convergence of these two disparate information sources.

How do the highly periodic entorhinal grids arise from these inputs? One possibility is influence from a periodic input, and recent attention has focused on the possibility that grids are modulated by the limbic theta rhythm, the 7–12 Hz sinusoidal EEG oscillation originating in brainstem structures and transmitted throughout the entorhinal–hippocampal system. The observation that place cells are sensitive to theta [5] including, intriguingly, to theta phase [33] has long suggested that theta could carry a movement signal that place and grid cells could use to calculate distances. In this light, Burgess *et al.* [34••] have suggested that grids arise as the result of an interference between this incoming theta rhythm and intrinsic membrane oscillation [34••,35], a proposition supported by the recent finding that intrinsic membrane potential oscillations in layer II stellate cells show a decrease in frequency from dorsal to ventral regions of dorso-medial EC [36••], which parallels the observed increase in grid scale along this axis [16••]. An alternative model, proposed by Blair *et al.* [37••], is that grids arise from Moiré interference between pairs of smaller 'theta grids' with slightly different spatial scale or orientation. In contrast to oscillatory models, the attractor models by Fuhs and Touretzky [18•] and McNaughton *et al.* [20••] propose instead that the hexagonal pattern of grids arises as a result of a dynamic tension between local excitatory and inhibitory processes, resulting in speed-modulated movement of an 'activity bump' over an imaginary surface. These hypotheses await testing with experiments in which either theta or local interactions are parametrically manipulated.

The influence of environmental information

The entorhinal grid cell area may plausibly function as a path integrator, but effective self-localization requires processing of environmental cues such as landmarks in order to 'initialize' the integrator. In addition, once self-localization has occurred there needs to be an ongoing, mutually corrective interaction between path integration and environment-based positional signals because perception of landmarks can be erratic, while path integration is inherently prone to accumulating errors [38].

It was recognized some time ago that one possible site of such integration is the place cells [39] because environmental cues such as landmarks [40] or terrain slope [41] appear to have the capacity to 'reset' place fields. The influence of environmental cues on place cells is experience-dependent [42–44] and indeed, one function of the EC–hippocampal system may be to discover, and then remember, which aspects of a given environment are constant and which can vary.

Although place cells can acquire responses to environmental cues, such cues also appear to play a part in resetting grid cell grids [16••], so the effect on place cells might be via these. The reproducible offsets and orientations of grids in a given environment, together with the observation that grids often have environment-specific minor irregularities (such as slightly misaligned peaks) that persist from trial to trial, suggest that grids are anchored to a given environment by environmental cues. In support of this, deformation of a familiar environment, but not a novel one, causes grids to partially deform [17••] (Figure 2) just as place fields do [8]. As with the place fields, the amount of grid deformation is less than that of the environment itself, suggesting a conflict with the self-motion cues that act to stabilize the grid. It is not clear how this anchoring occurs, but one possibility is that it is via learned feedback connections from the place cells themselves [21•]. An alternative possibility is that the information comes through another cortical route such as lateral EC, whose neurons carry largely non-spatial information [45]. With repeated exposure to the conflict the environmental cues gradually lose influence, a plasticity that has also been seen following conflict between directional landmarks and self-motion cues in place cells [43], and with a time course similar to the 'slow remapping' of place cells in re-scaled environments [44].

The role of context in self-localization

Landmarks and path integration are clearly important in self-localization, but equally important to an animal is knowing which environment it is in. Non-spatial, 'contextual' cues can enable disambiguation of otherwise similar geometries [13] and thus be used to uniquely identify an environment. The system can use these cues to decide whether similar but non-identical constellations of cues reflect minor transformations of the same environment ('pattern completion') or two similar but separate environments ('pattern separation'). It has been suggested that the function of the sparsely connected dentate gyrus is pattern separation [46], with pattern completion taking place in the highly interconnected CA3 recurrent network [47]. There is experimental sup-

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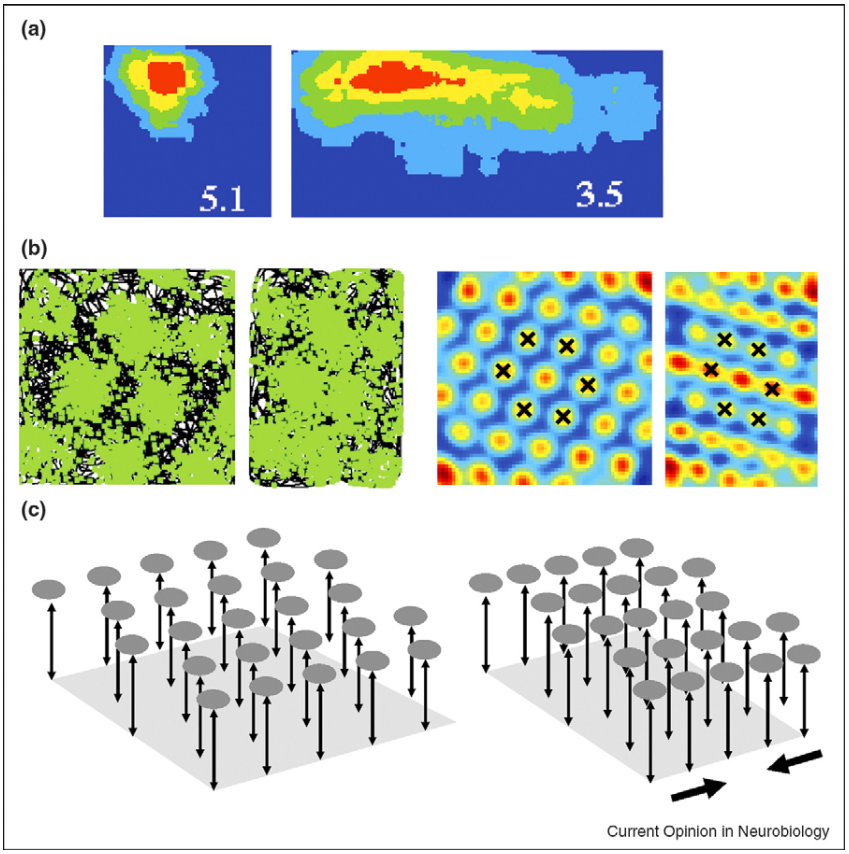
Figure 2



Environmental influences on place and grid cells. **(A and B)** show that in a familiar environment, deformation of the environment causes a partially congruent deformation of hippocampal place fields and grid cell grids. (A) The place fields are shown as contour plots reflecting smoothed firing rate. Note that when the square environment was extended, the field extended in the same dimension. Data adapted from reference [8] (B) Left plots, raw spikes from a grid cell showing that compression of a large square environment caused compression of grids along the same axis, but to a lesser extent. Right plots, the same data expressed as a spatial autocorrelation, in order to illustrate more clearly the periodicity of the activity. The crosses show the centres of the six peaks surrounding the central point. Note that after compression of the environment (right plot) the peaks shift closer together in the 'horizontal' but not the 'vertical' dimension. Adapted from reference [17••]. **(C)** Schematic illustration of how grids may be 'attached' to the environment on first exposure (left) so that subsequent compression of the environment compresses the grids in the same dimension. That this process is incomplete (B) suggests a counteracting influence from internal self-motion cues.

port for these proposals: for example, interference with NMDA-receptor-based plasticity in CA3 has been shown to impair retrieval of an established place field pattern [48], while such disruption in the dentate gyrus impairs the ability of cells to distinguish environments [49••].

Contextual changes modulate place cells either by altering the firing rates of the cells but not their field locations, a process known as 'rate remapping' [50,51], or by altering both rate and field location ('global remapping'). The amount of context change needed to evoke remapping may reflect how the system is balanced between pattern completion and pattern separation, and this balance may be regulated by attractor dynamics in the CA3 network [39,52]. Experimental observations not only support the pattern separation/completion dichotomy but also add a third possibility, because incomplete context changes frequently cause only a subset of cells to change their activity. This 'partial remapping' [53] seems to reflect a mixture of both pattern separation *and* pattern completion and may function to allow conflicting associations to be encoded on a common neural substrate [3•].

What makes place cells remap when the context changes? One possibility is that they are driven by grid cells that have also responded to the change [16••,54••]. Indeed, Fyhn *et al.* showed that although grids maintain constant orientation, offset, and rate when changes are made to a familiar environment after which place cells only show rate remapping, they alter both their offsets and orientations (but not rates) in a completely new environment in which place cells express complete remapping [54••]. These authors proposed that complete remapping of place cells is driven by this grid realignment, whereas

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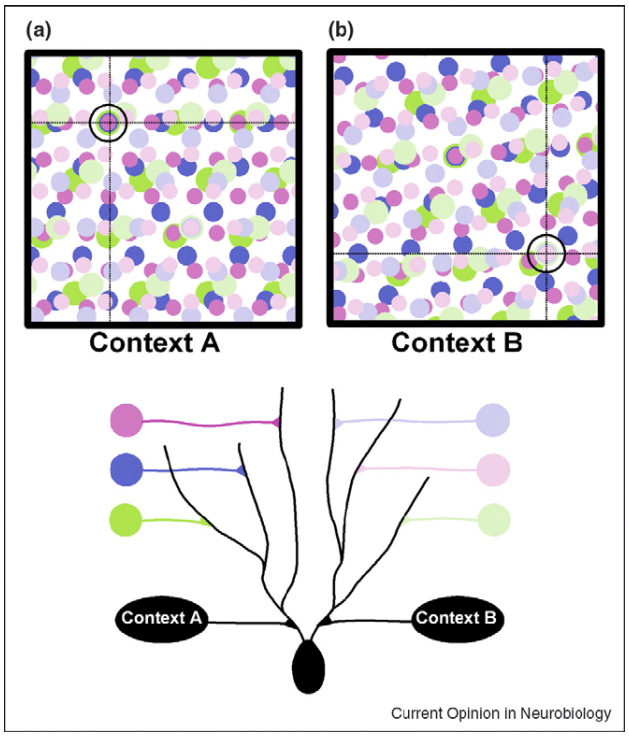
rate remapping occurs in the absence of grid shift and has some other cause. However, to explain why place fields do not merely offset by the same amount as the grids, it is necessary to assume either that the grids offset by different amounts or that not all grids have the same orientation in a given animal, both propositions for which there is, as yet, scant evidence. Partial place cell remapping is not explained by such a scheme either, unless it is assumed that not all grids undergo realignment.

An alternative possibility, which accommodates both rate remapping and partial remapping, is that context changes not only shift grid offsets but also alter which grids drive a given place cell, causing an apparent jump in field location [13]. Such switching could, hypothetically, be mediated by interactions occurring in the dendrites of hippocampal neurons, in which grid cell inputs could be selected by context-carrying inputs arriving on the same dendrites (Figure 3). The modulation of spatial inputs by contextual ones is important not only for understanding self-localization, but also because it touches on the issue of whether other kinds of non-spatial information, such as events, could also be represented by hippocampal neurons [55].

Figure 3



(A) How context-specific place fields could be formed from grids of differing spatial scale but similar orientation. Shown here are six grids (differentiated by color hue and/or saturation for clarity), using a similar illustration scheme as employed in reference [54••] (their Supplementary Figure 12) to demonstrate how grids might superimpose to form place fields. It is assumed that in Context A, a place cell is functionally connected to three of the grids (the dark-colored ones). At the point where the grids superimpose (intersection of dotted lines) the drive onto the cell is sufficient to cross firing threshold and the cell activates, generating a place field at that place. **(B)** In Context B, the grids realign and reorient. In addition, the place cell functionally disconnects from the first three grids and connects to three new ones (light-colored), thus producing a field in a different place and appearing to have 'remapped'. **(C)** An illustration of how such functional connection and disconnection might occur via dendritic interactions downstream of the grids. A hippocampal neuron (e.g. a dentate granule cell) is contacted by entorhinal grid inputs terminating on the distal dendrites and context-carrying inputs on the proximal dendrites. Depending on which context inputs are active, only some of the grid inputs will be able to drive the cell. Thus, the context inputs act to switch, or gate, the grid inputs.

Conclusion

Self-localization is an important cognitive faculty that requires integration of static environmental information (boundaries, landmarks and contextual cues) with dynamic self-motion cues (path integration). The recent discovery of grid cells provides important insights as to how this multi-sensory integration (schematized in Figure 4) may be performed.

We can conclude, on the basis of data reviewed here, that EC is the site of convergence of angular and linear metric information that is integrated with static environmental cues to form a higher order representation (position) in hippocampal neurons. Angular and linear signals are, themselves, the products of a cross-modal integration between self-motion-generated and environmental information. The challenge now is to derive an understanding of these processes, to identify the route for environmental and motion information into the entorhinal system, to determine how entorhinal grids form and are calibrated, and how these in turn combine to create place fields in hippocampal neurons and enable accurate self-localization.

Understanding sensory integration by grid and place cells is proving to be important not only for its contribution to spatial cognition but also, more broadly, for the insights it offers regarding how the brain builds knowledge structures. Visual landmark information and vestibular motion signals are vastly different in nature, but we now see that these inputs converge on neural systems whose function is to construct a superordinate, supra-modal representation that the inputs can each operate on in their different ways. To the extent that these representations have some kind of logical relationship to parameters in the real world (such as position or heading), they can be said to have 'meaning', and each representation is in itself a form of 'knowledge'. Thus, the entorhinal–hippocampal system provides a substrate with which the system can derive new knowledge (of position) from other forms of incoming knowledge (heading, velocity, etc.). It seems likely that analogous superordinate representations underlie multi-sensory integration and the building of knowledge structures in other cognitive domains.

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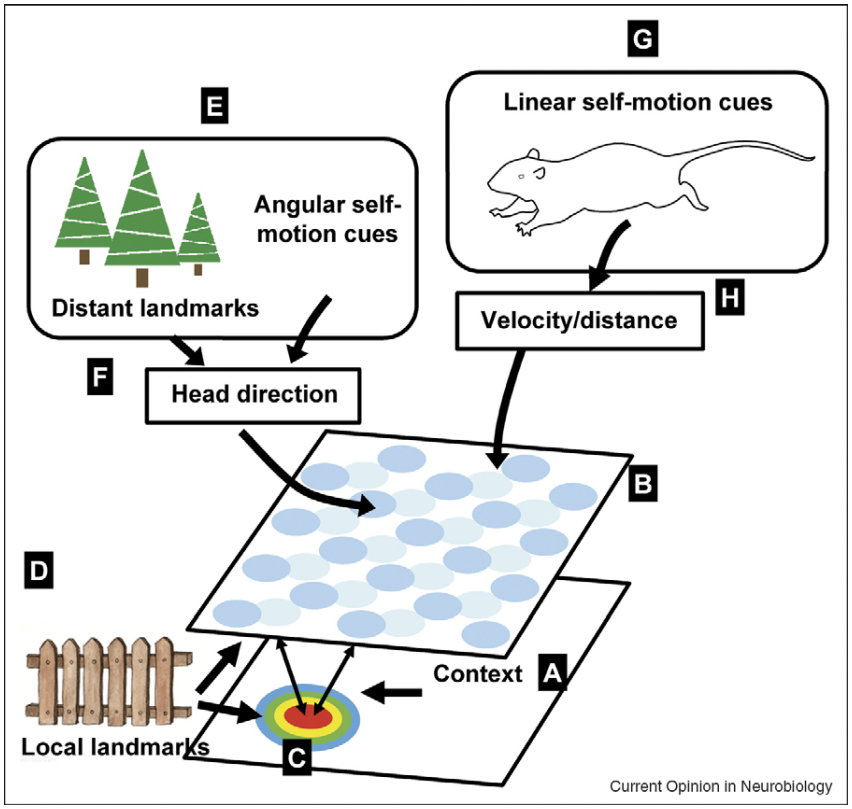
Figure 4



Schematic illustration of the hypothetical functional connectivity of the entorhinal–hippocampal place system. Salient elements of the system are indicated by the letter labels. Contextual cues **(A)** control which grid cells **(B)** are connected to which place cells, thus generating (by summation) place fields **(C)**. Local landmarks **(D)** then anchor the grids, perhaps via feedback from the place cells. Within the angular metric domain, distant landmarks, together with angular self-motion cues **(E)** set and update the head direction system **(F)**, which in turn orients the grid cell grids. Similarly in the linear domain, linear self-motion cues **(G)** are integrated to form a velocity/distance **(H)** signal that enables updating of grid cell activity. This in turn will update place cell activity and enable appropriate ongoing associations to the landmark array.

Acknowledgements

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