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Cell types for our sense of location: where we are and where we are going

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Technological advances in profiling cells along genetic, anatomical and physiological axes have fomented interest in identifying all neuronal cell types. This goal nears completion in specialized circuits such as the retina, while remaining more elusive in higher order cortical regions. We propose that this differential success of cell type identification may not simply reflect technological gaps in co-registering genetic, anatomical and physiological features in the cortex. Rather, we hypothesize it reflects evolutionarily driven differences in the computational principles governing specialized circuits versus more general-purpose learning machines. In this framework, we consider the question of cell types in medial entorhinal cortex (MEC), a region likely to be involved in memory and navigation. While MEC contains subsets of identifiable functionally defined cell types, recent work employing unbiased statistical methods and more diverse tasks reveals unsuspected heterogeneity and adaptivity in MEC firing patterns. This suggests MEC may operate more as a generalist circuit, obeying computational design principles resembling those governing other higher cortical regions.

That of dividing things again by classes, where the natural joints are, and not trying to break any part, after the manner of a bad carver. —Plato, Phaedrus, translated by Harold Fowler

As we try to make sense of our world, our mind attempts to 'carve nature at its joints' to find meaningful categories, or clusters of sensory data, which then form the basis of our thoughts and actions[1]. Similarly, when faced with the complexity of neuroscientific data, our mind attempts to 'carve neural data at its joints' to find meaningful, recurring patterns. One such dominant pattern is the notion of a cell type. Fundamentally, cell types can be thought of as clusters of co-occurring neurobiological features that arise more often than chance. Researchers have defined these features genetically, in terms of recurring gene expression patterns; morphologically, in terms of repeated neural shapes; anatomically, in terms of organized connectivity patterns; or physiologically, in terms of recurring firing rate patterns across stimuli or behavior.

Recently, the goal of identifying all neuronal cell types has taken on prominence in science, as evidenced by the cell atlas project at the Chan Zuckerberg Biohub (https://czbiohub.org/projects/cell-atlas/), the cell type database at the Allen Brain Institute (http://celltypes.brain-map.org/) and the BRAIN Initiative call to identify neural cell types (https://braininitiative.nih.gov/pdf/BRAIN2025_508C.pdf). In part, this push to classify cell types reflects recent technological developments that facilitate the identification and manipulation of genetically defined cell types. In contrast, at the level of systems neuroscience, the quest to understand how the moment-by-moment dynamics of neural circuits gives rise to cognition and behavior has led scientists to focus on physiological firing patterns and search for functionally defined cell types. However, in many brain regions, correspondences between genetically and functionally defined cell types remain unclear. Notable exceptions include specialized circuits at the sensory and motor periphery[2,3]. The retina, for example, possesses clearly defined functional cell types that co-register with genetic and anatomical cell type definitions[4–9]. In contrast, many studies of higher order cortical regions do not report well-defined functional cell types[10–15]. Instead, individual neurons show dissimilar firing patterns that lack a simple relationship to sensory or behavioral correlates, thereby potentially obscuring our understanding of higher-level circuit organization. However, such organization frequently becomes clear when the collective dynamics of a large neural population are considered[10,11].

One explanation for the development of such radically different perspectives might simply involve the limitations of some experimental methods. For example, extracellular recordings alone do not offer access to the genetic or connectivity profile of a cell. Thus, if we could observe multiple cellular features simultaneously, across a range of tasks, then we might discover empirical relationships between a neuron's functional firing patterns and its genetic or anatomical features. However, any such relationships must also be consistent with the lack of clustering in the physiological firing patterns of cortical cells observed in many tasks[12,16]. Such a lack of clustering remains difficult to reconcile with the idea that a cortical neuron's functional firing pattern is completely determined by its genetic or anatomical cell type.

A potentially deeper reason for the diverging views on cell types in the retina versus cortical areas is that these regions lie at the extremes of an axis of teleological evolutionary origin ranging from specialist circuits to generalist circuits. We define specialist circuits as those that solve a set of well-defined tasks that do not fundamentally change over evolutionary timescales. For such tasks, evolutionary processes have had time to bake solutions into relatively hard-wired circuits in which genetic identity, connectivity and physiology are tightly correlated. In contrast, generalist circuits may be designed to be general-purpose learning machines that can solve new tasks evolution could never have

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anticipated. When faced with a fundamentally new situation, generalist circuits must wire up a new circuit solution that never previously existed. In such a new and often recurrent circuit, any individual cell's physiological firing pattern cannot be ascribed to that cell alone, but rather is an emergent property of the entire learned circuit connectivity. In this situation, tight clustering of physiological properties may be more difficult to find, and instead, emergent, dynamical population patterns may provide a more satisfactory conceptual description of learned circuit function[17,18].

Here, we discuss the implications of this proposal in the context of cell types in the MEC, a region with coding principles that may fall between the extremes of specialized circuits such as the retina and generalized circuits such as the prefrontal cortex. Many MEC neurons recorded as rodents forage in open arenas show firing patterns with clear correlates of the animal's location[19–22] (**Fig. 1a**). A subset of MEC neurons, classified as grid cells, fire in periodic locations that tile the environment[19,20] (**Fig. 1a**). The crystalline structure of the grid pattern lent support to using tuning-curve features to classify MEC neurons into functionally defined cell types, and thus implicitly suggested that MEC may act as a more specialist circuit. In addition to grid cells, the cell types include border cells, which fire maximally near environmental boundaries[21–23]; head direction cells, which fire when the animal faces a particular direction[24,25]; and speed cells, which change their firing rate with running speed[26,27] (**Fig. 1a**). However, recent evidence suggests MEC may play a more generalist role. Such evidence includes deficiencies in the current classification of functional cell types in MEC and striking flexibility in entorhinal firing patterns in navigational and non-navigational tasks[16,28,29]. Here we begin by discussing the difficulties of quantitatively defining cell types and then present extreme examples of specialist versus generalist circuits. With this theoretical framing in mind, we revisit the issue of cell types in MEC and provide a new proposal for the general function of MEC.

The search for cell types as a statistical problem

Any data-driven approach that asserts the existence of well-defined cell types must solve an essential statistical problem: it must demonstrate the existence of distinct subpopulations, such that neurons within a subpopulation are significantly more similar than neurons across subpopulations. Thus, critical to the notion of cell type is the quantitative definition of similarity. A simple approach to defining similarity is to select a set of neurobiological features and consider each cell as a point in this feature space (**Fig. 1b**). For example, in genetically defined cell types, each axis in this feature space would represent the expression level of a single gene. The similarity between cells is then inversely related to the distance between cells for an appropriately chosen distance metric in this space. A collection of cell types would then constitute tight clusters of cells that occupy a specific location in feature space, with relatively large empty spaces separating the tight clusters.

This view, while appealing, has limitations. The gold-standard outcome of this approach would reveal that every cell type forms a tight cluster along genetic, anatomical and physiological axes (**Fig. 1b**). While this gold standard may be feasible in specialized circuits, generalist circuits may show more diverse profiles. For example, cells may cluster along one subset of axes and spread out along other axes (green dots in **Fig. 1c**). More generally, cells may spread out uniformly along a continuum. Intermediate cases between a continuum and tight clustering can also occur, resulting in a non-uniform density of cells in feature space (blue and red dots in **Fig. 1c**). This could result in a focus on the extreme ends of higher density, potentially yielding an incomplete view of circuit function. Finally, perhaps the most serious pitfalls are that we do not choose the right axes or we cannot measure traits that lie along them. This causes large populations of cells to lie at the origin of the feature space, essentially invisible to any cell type analysis (orange dots in **Fig. 1c**). Below we review how cells cluster in feature space for hypothesized specialized and generalist circuits, and then review the situation for functionally defined MEC cell types.

Examples of specialist versus generalist circuits

The retina serves as an ideal example of a specialist circuit (**Fig. 1d**). The retina must transform complex spatiotemporal light patterns from a large number of photoreceptors into firing patterns in a limited number of retinal ganglion cell nerve fibers. Given the bottleneck presented by the optic nerve, the retina must perform this transformation efficiently, taking into account the statistical properties of natural images[30]. These statistical properties have likely remained invariant across hundreds of millions of years, allowing cell types with consistent genetic, anatomical and physiological definitions to evolve[31,32], with each cell type dedicated to specific aspects of this transformation[4] (**Fig. 1d**). For example, unbiased clustering of genetic, immunohistochemical, electrical and physiological response features led to a general consensus that the mouse retina contains ~50 distinct cell types[9]. The retina is thus moving toward becoming a gold-standard example of a specialist circuit in which physiological function can be ascribed to individual cells in a manner that is correlated with each cell's genetic identity, connectivity pattern and morphology.

In contrast to the efficient coding of natural scenes, a problem defined by image statistics that have remained invariant over evolutionary timescales, many higher order cortical regions must support cognitive processes in which input statistics can change rapidly. For example, autobiographical memory requires rapid associations between vast numbers of highly processed neural representations, such as different individuals, emotions or spatial locations[33]. Evolution could not have anticipated the full breadth of these combinations, and instead, brain regions that support flexible coding, like the hippocampus, may have evolved to operate as general-purpose learning circuits.

A recent example of this principle in prefrontal cortex involves a decision-making task in which different fractions of colored dots move left or right[13] (**Fig. 1e**). Depending on a visual context signal, the monkey must use an eye movement to report either the majority color or the majority direction of motion of the dots (**Fig. 1e**). Over the course of evolution, no monkey has encountered this specific task, yet the monkey can learn this task, and recordings from prefrontal cortex reveal striking neural correlates of the solution. However, these neural correlates do not exhibit any discernible functional cell types, as each neuron encodes different degrees of sensory, motor and cognitive aspects of the task. In contrast, emergent neural population dynamics, obtained through dimensionality-reduction methods, reveal highly organized neural state space dynamics[18] (**Fig. 1e**). These dimensionality-reduction methods yield linear combinations of cells, or population firing patterns, that provide essential clues to the mechanism of context-dependent gating of sensory evidence[13]. Thus, at least for this study, carving neural circuits at the joint of single cells was not as conceptually informative as carving them at the higher-level joint of population dynamics.

The essential nature of this example has been replicated in recordings from other cortical regions. For example, in motor cortex during reaching movements, the identification of a neural preparatory state—a population-level activity pattern that occurs immediately

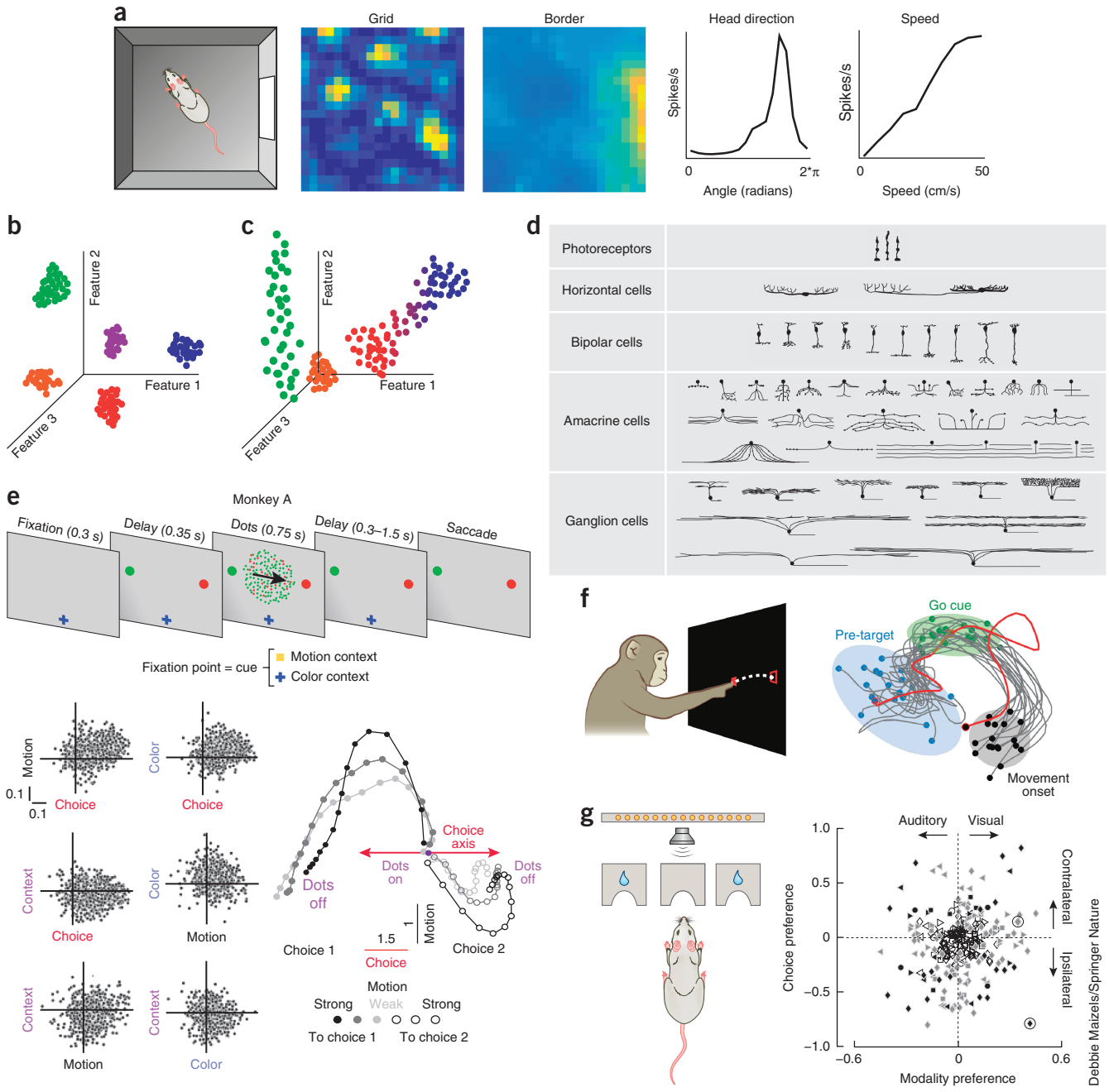

Figure 1 The range at which clear cell type clustering emerges varies across neural circuits. (**a**) Far left: the open field foraging task often used to identify MEC neurons in rodents. Right panels: example tuning curves of grid, border, head direction and speed cells. Spatial tuning curves are color-coded for minimum (blue) to maximum (yellow) values (adapted with permission from ref. 16, Elsevier). (**b**) Schematic of cell type clusters in an arbitrary feature space. Each point represents a cell and is colored by the cluster to which it belongs. In this example, all cell types cluster along each feature independently. (**c**) Schematic of challenges to clustering cell types in an arbitrary feature space. The green cells only cluster along one axis, the red and blue cells exist along a continuum, and the orange cells do not exhibit appreciable values for these features. (**d**) Schematic of retinal cell types (reproduced with permission from ref. 77, Springer Nature). (**e**) Schematic of task employed by Mante *et al.*[13] and cell responses along task parameters. Top: a monkey must choose the target that corresponds with the dominant motion or color of the presented dots. Bottom left: cell responses along motion, choice, color and context axes. Responses are the de-noised regression coefficients from a multivariate linear regression model. Bottom right: the dimensionality-reduced population-level response during the motion context, projected onto the axes of choice and motion (adapted with permission from ref. 13, Springer Nature). (**f**) Left: a reaching task to assess preparatory activity in motor cortex. Right: example motor neural activity during reaching, projected into a two-dimensional latent space. Blue indicates the 100 ms before target onset, green indicates time of the go cue (when the reach could commence) and black indicates the time of movement onset (reproduced with permission from ref. 34, Annual Reviews). (**g**) Left: task used by Raposo *et al.*[12]. The rat chose the left or right port on the basis of the visual, auditory or combined visual-auditory stimulus. Right: modality (visual or auditory) versus choice (left or right) preference for cells recorded in posterior parietal cortex during this task. Preference for the task variables was computed from the area under the receiver operating characteristic curve; for example, a value of +1 for choice preference indicates the neuron always firing more during trials with a contralateral choice. The absence of clustering in this space indicates a lack of functional cell types (adapted with permission from ref. 12, Springer Nature).

before motion—could only be achieved when the notion of cell types was set aside and the collective activity of many neurons was considered[14,15,34] (**Fig. 1f**). Also, in a sequence memory task, prefrontal cortex neurons exhibit a high degree of 'mixed selectivity' for various task parameters, which can be an advantageous coding scheme for learning arbitrary rules[10,11,35]. Finally, recent studies posit that neurons in mouse posterior parietal cortex are 'category free', reflecting random combinations of task parameters, and hence inherently defy the notion of functionally defined cell types[12] (**Fig. 1g**). Thus, an emerging body of work is raising the possibility that well-defined physiological cell types, especially in higher cortical regions, may not constitute a fundamental organizing principle for understanding network function.

Defining cell types in medial entorhinal cortex

With the precise cell type identification in the retina and the category-free approach in prefrontal cortex serving as bookends, where does the idea of cell types in MEC fit? A high-order cortical region that supports memory and navigation[36–38], MEC contains neurons that have been classified morphologically[39–41], biophysically[42,43] and genetically[44–46]. However, as mentioned previously, one of the prominent cell type classifications in MEC has been along functional axes (**Fig. 1a**). These MEC cell types are often identified from neural activity recorded as rodents explore open arenas; they include grid, border, head direction and speed cells[19,21,22,24,26] (**Fig. 2a**). To classify these neurons, researchers often calculate a 'score' (for example, grid score), which quantifies specific features of a neuron's tuning curve (for example, 60° symmetry). This score is then compared to that expected by chance, which is determined from a null distribution of scores generated by randomly time-shifting spike trains of a single cell and recomputing the score. This null distribution can be generated from shuffled data pooled across the entire population[47,48] or within the same cell[28] (**Fig. 2a**).

This approach has pushed forward our understanding of how MEC encodes behaviorally relevant information and, in the process, built a framework for hypotheses about the mechanisms generating MEC cell types and their function in navigational behavior[49]. For example, the classification of grid, head direction and speed cells as functionally dedicated cell types led to the hypothesis that MEC is responsible, at least in part, for path-integration-based navigation[19,50]. In addition, studies leveraged the common tuning curve structure of grid cells along the dorsal–ventral MEC axis to demonstrate that grid spatial scale increases discretely along the same axis[19,51], which provided guidance for the type of network architecture computational models could use generate grid cell responses[52–55].

Another benefit of a functionally defined classification approach in MEC is that it captures common computational principles in a neural population wherein the links between functional and genetic or anatomical features remains unclear. In other words, MEC neurons are like the green dots in **Figure 1c**: cells can be classified by their functional properties (features 1 and 3) but remain difficult to classify by other features (feature 2). For example, grid cell firing patterns occur in approximately equal numbers of calbindin D-28K-positive pyramidal cells and reelin-positive cells, two classes of cells that differ in their biophysics, morphology, projections and microcircuit organization[43,44,54–58]. Furthermore, while the biophysical, molecular, and morphological features of MEC neurons vary along the dorsal–ventral MEC axis[46,59,60], grid cells have been identified across this entire axis, although this dorsal–ventral organization is likely to contributes to the dorsal–ventral expansion of grid spatial scale[55,59,61,62]. Finally, classification of speed cells by genetic or morphological features remains challenging, as speed coding is observed in both interneurons and excitatory principal neurons[26,27,56]. Thus, functional definitions remain the primary modus for MEC cell type classification, as the functional axis remains the only known coordinate frame in which subsets of MEC neurons show clear correlates to behavior.

However, despite the insights gained from using tuning curves to classify MEC cell types, this approach carries limitations. One disadvantage is that classified neurons must exhibit a tuning curve that follows an experimenter-defined shape. The number of classified MEC cells then relies on the heterogeneity of experimenter-defined shapes, rather than the true heterogeneity of tuning. This can result in an incomplete picture of the coding principles neurons might follow for a given behavior (**Fig. 2b**). In MEC, for example, many papers utilize tuning curve scores that result in narrowly defined MEC cell types (**Fig. 2b**), leaving the features encoded by most MEC cells unclassified[26] like the orange dots in **Figure 1c**. A second issue arises from classifying cell types by requiring scores to surpass a threshold (**Fig. 2a**). This could result in the discretization of a population of neurons that possess an underlying continuous representation of navigational variables. Indeed, recent data indicated the strength with which conjunctive MEC cells encode multiple navigational variables falls along a continuum[16], generating a distribution similar to the red and blue dots in **Figure 1c**. Finally, tuning curves assume a static relationship between an external sensory stimulus and the neural response. Thus, this framework will miss behavior- or state-dependent coding properties.

An alternative way to advance the field is to apply more unbiased methods—analysis techniques that can better confront cell type diversity and do not rely on assumptions regarding tuning curve shapes. One example of such an approach is the use of statistical models that learn the relationship between a set of variables and a single-neuron spike train[63–68] (**Fig. 2c**). These models can be built to have the flexibility to learn any tuning curve shape for a given variable (for example, position) while maintaining the power to determine whether that variable significantly explains neural spiking. This latter aspect of the framework is critical, as it offers an explicit report as to whether knowing a variable significantly explains spiking variability, resulting in an approach more robust to heterogeneity in behavior compared to the score-based approach. While the model-based method still requires the researcher to identify the variables to which a neuron might respond, this framework allows considerable freedom in the mapping from external variables to neural spike trains. Although information about tuning curve shape is inherently absent, tuning curve features can be quantified from the learned mappings and cells such as grid cells still identified. However, as we discuss in the following section, the flexibility of this framework provides a more inclusive, and richer, view of MEC coding properties than previously suspected.

The axes for defining entorhinal coding

Indeed, recent works employing statistical models have revealed high degrees of heterogeneity and multiplexing in MEC neurons. First, by fitting models of speed-dependent firing, researchers demonstrated that speed tuning is heterogeneous, as the sign of this relationship can be positive or negative and the shape can take linear, saturating or non-monotonic forms[16,26,27]. Expanding on this result, the application of a statistical model in which position, head direction and running speed were used as variables to explain neural spiking empirically demonstrated that a high degree of heterogeneity exists for the encoding of all navigational variables in MEC (**Figs. 2c** and **3a**)[16]. In this approach, the position, head direction and/or running speed of a mouse over time were fed as inputs to a linear-nonlinear Poisson (LN) model. This information was then used to try to produce a spike

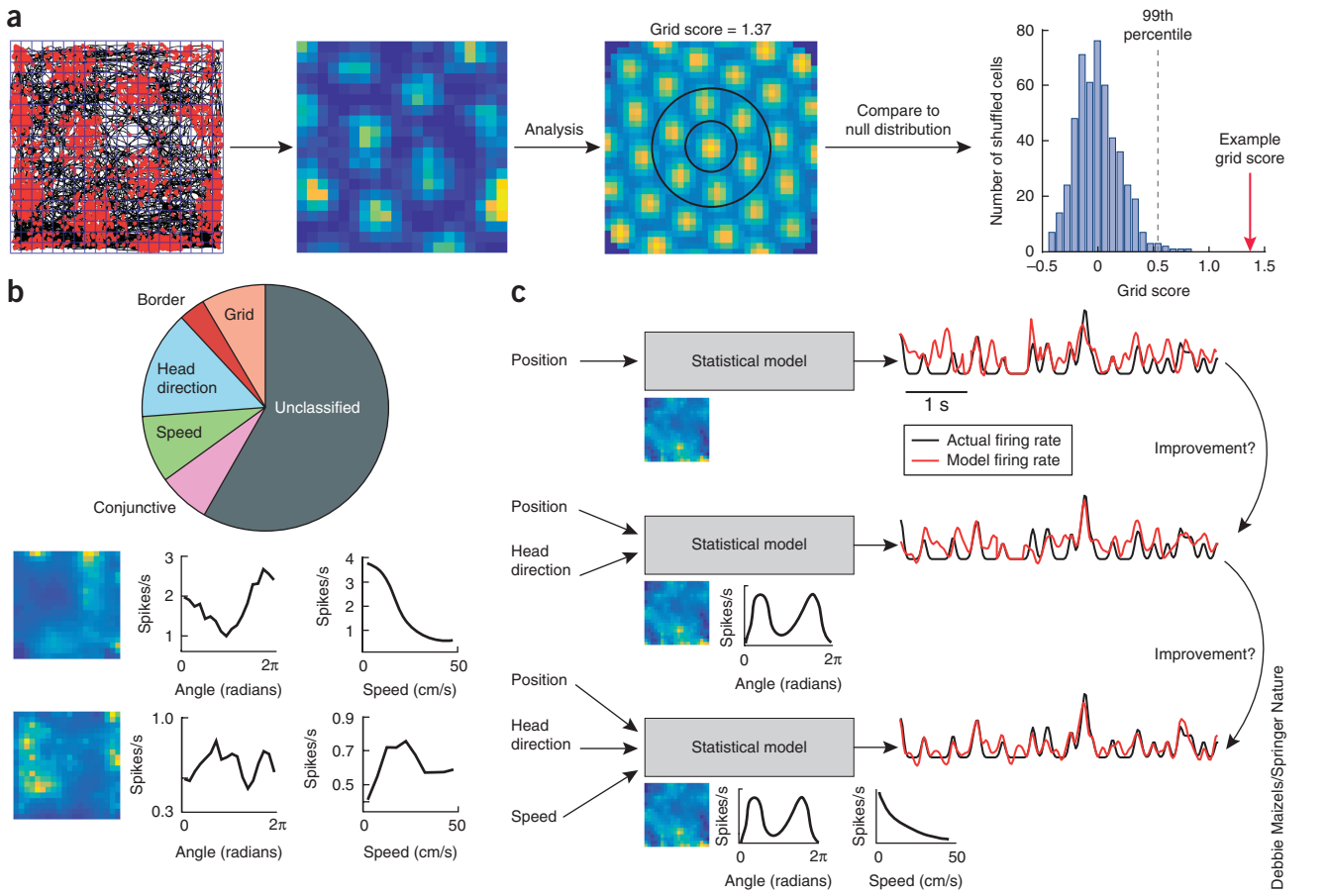

Figure 2 Capturing coding in MEC using a tuning-curve score versus model-based method. (**a**) Schematic of the tuning curve and score method conventionally used to characterize grid cells and other functionally defined MEC neurons[47,78]. Far left: spatial tuning of a grid cell in a 1 m × 1 m open arena. Red dots denote neural spikes and black lines indicates the animal's trajectory. Blue grid denotes the spatial bins used to generate firing rate tuning curves. Middle left: firing rate tuning curve. Each pixel corresponds to the average spikes per second of the grid cell at that binned spatial position and is color-coded for minimum (blue) and maximum (yellow) values. Middle right: spatial autocorrelation of the tuning curve. To generate a grid score, the inner ring of fields (delimited by the inner and outer circles) is first rotated 30, 60, 90, 120 and 150 degrees and correlated to the original ring. The grid score is the minimum correlation at 60 or 120 degrees minus the maximum correlation at 30, 90 or 150 degrees. Right: distribution of 500 grid scores generated by adding a random amount to the spike train of the given cell (modulo the length of the session) and recomputing the grid score. The blue line denotes the 99th percentile of the shuffled distribution, while the red arrow indicates the actual grid score for this example cell (adapted from ref. 16, Elsevier). (**b**) Top: chart of MEC cell classifications based on the score method. Based on data set used by Hardcastle *et al.*[16]. Bottom: examples of position (left), head direction (middle) and speed (right) tuning curves that are not characterized by the score method. (**c**) Schematic of a model-based approach using the forward-search method to identify the set of navigational variables encoded by the cell. In this approach, position, head direction and speed information are used to predict neural spikes. Black lines indicate the actual firing rate of a neuron and red lines indicate the model-predicted firing rate. The model uses this information by learning a set of parameters (images under "Statistical model") that transform the animal's position, head direction or speed to firing rate. Single-variable contribution to neural spiking can be assessed by analyzing the performance of the simplest model (top of diagram) and continually adding variables to this model to see whether performance improves.

train matching, as closely as possible, that observed from an MEC neuron. This approach detected navigational encoding in 71% of MEC neurons, a higher number than the 41% detected from the score approach used by most published papers[16] (**Figs. 2b** and **3a**). Further, this model identified a higher degree of multiplexing than the tuning curve score approach (37% versus 7%). In a similar vein, recent work using spatial information captured spatial coding in the vast majority of MEC neurons, with grid and border cells composing only a small minority of these position-encoding cells[28]. As spatial information quantifies the degree of positional information carried by a single spike and does not make strict assumptions about tuning curve shape, this approach is similar in spirit to model-based approaches. However, unlike model-based approaches, the use of spatial information does not provide a model capable of predicting spiking in novel navigational settings[16]. Taken together, these studies support the idea that MEC coding is highly heterogeneous and contains many cells with unconventional yet meaningful coding features[16,28].

Multiplexing in MEC also extends to coding nonspatial stimuli. In rats required to associate odors with reward, a subset of grid cells encodes information about the context of the reward rather than just the spatial location of the animal[69]. Moreover, tasks with more complex behavioral demands than open field foraging have revealed substantial heterogeneity in the repertoire of variables MEC cells encode. For example, in a task using a treadmill to force rats to run in place for a specific time, a model-based analysis revealed that subsets of MEC cells encode time elapsed, distance traveled or a combination of both variables[70] (**Fig. 3b**). This hints at the idea that while MEC circuit computations may have evolved to support the traversal of trajectories through physical space,

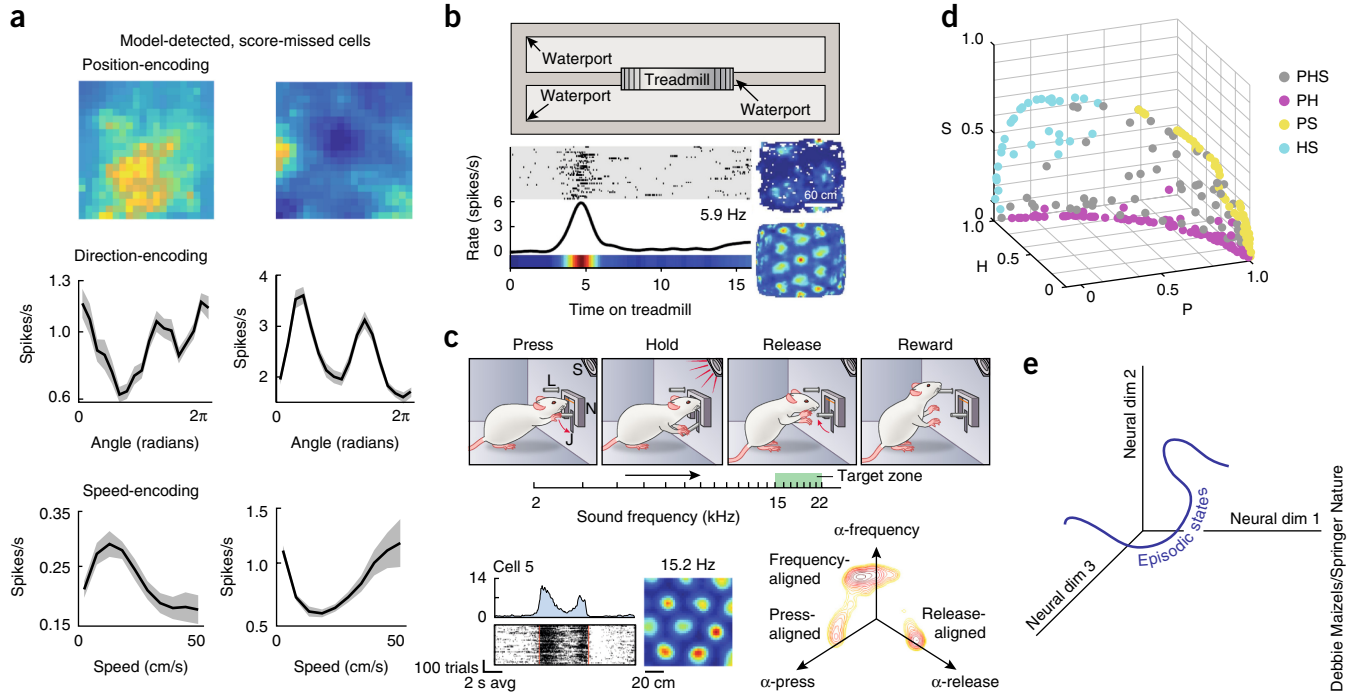

Figure 3 Entorhinal neurons represent multiple task variables in heterogeneous ways. (**a**) Cells with low grid, border, head direction and speed score that were detected as encoding position (top), head direction (middle) or speed (bottom) by a model-based method. Gray shading represents s.d. across 30 bootstrapped iterations of the model-fitting procedure (adapted with permission from ref. 16, Elsevier). (**b**) Task used by Kraus *et al.*[70] and example results. Top: as part of a spatial alternation task on a figure-8 maze, animals ran in place on a treadmill that varied in speed and running duration. Bottom: a subset of grid cells encodes time on the treadmill, in addition to location in two-dimensional space. Shown are the temporal firing pattern on the treadmill (left), the spatial firing rate map (top right) and spatial autocorrelation (bottom right) of an example grid cell (adapted with permission from ref. 70, Elsevier). (**c**) An auditory frequency task in which rats pressed a bar to play sequentially higher auditory frequencies, releasing the bar when a learned frequency was played. A subset of grid cells, as assessed in a two-dimensional environment, responded to the initial press, the release or a given frequency (example at bottom left). When plotted in a space defined by linear model coefficients that capture tuning to frequency, lever pressing or lever releasing, MEC neurons cluster along these three axes (bottom right); α corresponds to the value of the model coefficient for the indicated variable (adapted with permission from ref. 72, Springer Nature). (**d**) MEC neurons detected as encoding combinations of position (P), head direction (H) and speed (S) plotted in a variable-contribution space. This space represents the normalized contribution of each variable to spike prediction, which is computed from differences in the performance of models of varying complexity. In this space, MEC neurons lack significant clustering (reproduced with permission from ref. 16, Elsevier). (**e**) Schematic of the episodic state hypothesis. The axes denote a dimensionality-reduced space of three dimensions (dim) onto which neural data are projected, while the blue line illustrates the potential trajectory of population-level neural data in this space during a behavioral task.

they can also generalize to encode variables necessary to support spatiotemporal trajectories through mental space, such as an episodic memory[71]. Extending this idea, recent work examined MEC coding as rats navigated through a one-dimensional auditory space[72] (**Fig. 3c**). In this task, rats pressed a bar to increase the frequency of an auditory tone, which took a variable amount of time, and then released the bar once the tone reached a learned frequency. Subsets of classically defined grid, border and head direction cells encoded different task variables, with their activity aligning to the initial bar press, a specific auditory frequency or the bar release[72] (**Fig. 3c**). Interestingly, MEC neurons did not respond during passive playback of the auditory stimulus, consistent with the idea that MEC neural responses reflect navigation through a behaviorally relevant stimulus space regardless of the coordinate frame of that space. Future work using such complex tasks combined with neural recording will further answer to what extent MEC is a generalist circuit that can encode any set of variables relating to real or imagined navigation. Combined, these studies also raise the idea that at least in certain tasks, functionally defined cell types can be found in MEC. Whether these task-specific functional cell types map to genetic or anatomical features, or how they behave across many tasks, remain intriguing questions.

In contrast, recent analyses using the LN model demonstrate that MEC neurons are likely to encode navigational variables along a continuum and that subsets of MEC neurons change their coding across behavioral states, which is more consistent with a generalist circuit[16]. For example, the strength with which MEC neurons encode multiple navigational variables (for example, position and head direction) exhibits a continuous distribution[16] (**Fig. 3d**) and therefore defies classification into highly discrete functionally defined cell types. In addition, this approach revealed state-dependent changes in the encoding of navigational variables by MEC neurons. In particular, many MEC neurons dynamically alter the variables they encoded during fast versus slow running speeds. For example, some MEC neurons that encode head direction at slow running speeds encode both position and head direction at high speeds[16]. Such dynamic codes could extend to variables beyond speed, such as time or attentional state, ideas future work could aim to address. Combined, the above studies raise the possibility that MEC is a highly adaptive and flexible brain circuit whose distribution of responses recorded in any experiment will depend strongly on the task used to probe MEC function. Moreover, unbiased statistical methods may be required to reveal the richness of this function.

A generalist role for medial entorhinal cortex

Recent results, as reviewed above, demonstrate more heterogeneity and state dependence in MEC firing patterns than previously suspected[27].

In addition, by moving to tasks with relevant nonspatial variables, MEC neurons have been shown to play roles in representing navigation along more diverse trajectories than through physical space alone. Taken together, these results suggest that MEC behaves more like a generalist than specialist circuit. If so, what is the general computational principle governing MEC codes?

One possibility is that the MEC, potentially in conjunction with the hippocampus, computes what we call the episodic state of the animal (**Fig. 3e**). The episodic state is the minimal function of the past stream of sensory and motor experience that is required to predict either future sensory experience or future actions that lead to reward. For example, during spatial navigation, knowledge of the position and velocity of the animal is sufficient to predict its future sensory experience over short timescales. It is important to note that position and velocity are abstract variables, meaning they are not directly accessible to the animal via a set of dedicated primary sensory receptors. Instead, they must be computed from lower-level sensory and motor variables that are directly accessible in the sensorimotor periphery. The presence of high-level position and velocity coding in MEC during spatial navigation suggests that MEC acts in the computation of episodic state by extracting these abstract variables from the peripheral sensorimotor stream. If this is the case, then MEC circuitry could contribute to the computation of episodic state in diverse scenarios beyond just spatial navigation.

Data at least support the idea that MEC can improve the computation of episodic state in the context of spatial navigation. For example, application of the LN model to different speed bins revealed that MEC neurons encode more information about spatial location at high than at low running speeds, an example of improved computation of episodic state for navigation[16]. However, the power of MEC to compute general episodic states, and the limits thereof, could be more broadly tested by examining MEC neural responses as animals perform tasks in environments that set up novel contingencies between past motor actions, past sensory experience and future sensory experience and reward. This could be achieved, in rodents for example, with virtual reality technology[73,74]. Moreover, if episodic state computation really is the generalist function of MEC, then at what joints might we best carve function out of data from entorhinal cortex? Taking cues from previous successful analyses in other generalist brain regions[10–15], we may wish to analyze MEC data at the level of population patterns rather than single cells. In essence, the minimal goal of any circuitry that computes episodic state is to assign different neural population patterns to different states, thereby tracing out a neural manifold of firing patterns as a function of the episodic state. There may be higher order emergent structure in this neural manifold that is not apparent at the level of highly heterogeneous single cells, and this higher order structure may provide clues into the mechanisms of episodic state computation in MEC. Indeed, theoretical work has shown that across many neural networks trained to solve the same complex task, correspondences in neural representations at the level of single neurons can be rare while correspondences at the level of population patterns can be common[75]. This theory, in addition to empirical work[10–15], motivates the search for relationships between neural activity and behavior at the level of population patterns rather than single cells, not only in MEC but also in other generalist circuits solving complex tasks.

Discussion

In this Perspective, we present a new way of thinking about MEC functional cell types, born of unbiased statistical approaches for defining how MEC cells encode information. Moreover, we posit a potentially useful specialist–generalist conceptual axis for thinking about the relationship between cell types and network function across diverse brain regions. We propose that, given the high degree of heterogeneity and adaptivity of MEC firing patterns, the circuit may behave more like generalist circuits such as the prefrontal cortex, rather than specialist circuits such as the retina. As a result, it may be more useful to conceptualize MEC function in terms of higher-level population patterns, rather than in terms of single-neuron functional cell types.

Overall, our discussion of generalist circuits raises a central issue: if functionally defined cell type clusters are not prevalent in recordings from higher order cortical regions[12–16], then what role do genetically and anatomically defined cell types play in generalist network function? In specialist circuits, genetically and anatomically defined cell types have been extremely useful to identify because of the tight correlation between such defined cell types and single-cell physiology. We propose that, in contrast, in generalist circuits, the diversity of genetically and anatomically defined cell types exist not to determine single-cell physiological firing patterns but rather to implement a general-purpose learning circuit in which plasticity enables the circuit to learn new population patterns relevant for a task. Then the critical question to ask is: how do different cell type features, such as layer specificity, subcellular localization of connectivity, and plasticity rules conspire to subserve general purpose learning? While it may not be the case that the conjunction of these cell type features determine the final learned single-cell physiological firing patterns, they certainly must define the path whereby the generalist circuit translates new problems into new network solutions.

Another interesting possibility is that brain regions we consider to be generalist circuits still implement canonical computations that are largely invariant across regions[76]. In this case, differences in physiological responses across such circuits could simply reflect differences in their upstream inputs, even though the underlying transformation from input to output is similar across circuits. Understanding such circuits then necessitates a shift in perspective from understanding neural representations to understanding neural transformations, which would require simultaneous measurements of circuit inputs and outputs. With such measurements in hand, one may be able to discover specific functions for genetically identified cell types in implementing different aspects of the transformations, if not the representations, underlying canonical circuit computations. Whether a single or a small set of canonical computations repeated across the brain would be powerful enough to solve a great diversity of generalist tasks that evolution could not anticipate is an intriguing open question.

In summary, while there is a strong drive to identify cell types, it remains unclear whether a conceptual understanding of how our cognitive capabilities arise from the dynamics of circuits in our brain will be found at the level of single cells and cell types. After all, it is highly likely that a virtuoso musician has the same complement of genetically identifiable cell types as any other human, but not all humans can generate beautiful music. Thus, to understand the neural dynamics underlying our greatest achievements, we may have to conceptually carve neural function at some higher level of organization beyond individual cells and their types.

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