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# How Do You Build a Cognitive Map? The Development of Circuits and Computations for the Representation of Space in the Brain

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## Keywords

development, cognitive map, entorhinal cortex, hippocampus, navigation, memory

## Abstract

In mammals, the activity of neurons in the entorhinal-hippocampal network is modulated by the animal's position and its movement through space. At multiple stages of this distributed circuit, distinct populations of neurons can represent a rich repertoire of navigation-related variables like the animal's location, the speed and direction of its movements, or the presence of borders and objects. Working together, spatially tuned neurons give rise to an internal representation of space, a cognitive map that supports an animal's ability to navigate the world and to encode and consolidate memories from experience. The mechanisms by which, during development, the brain acquires the ability to create an internal representation of space are just beginning to be elucidated. In this review, we examine recent work that has begun to investigate the ontogeny of circuitry, firing patterns, and computations underpinning the representation of space in the mammalian brain.

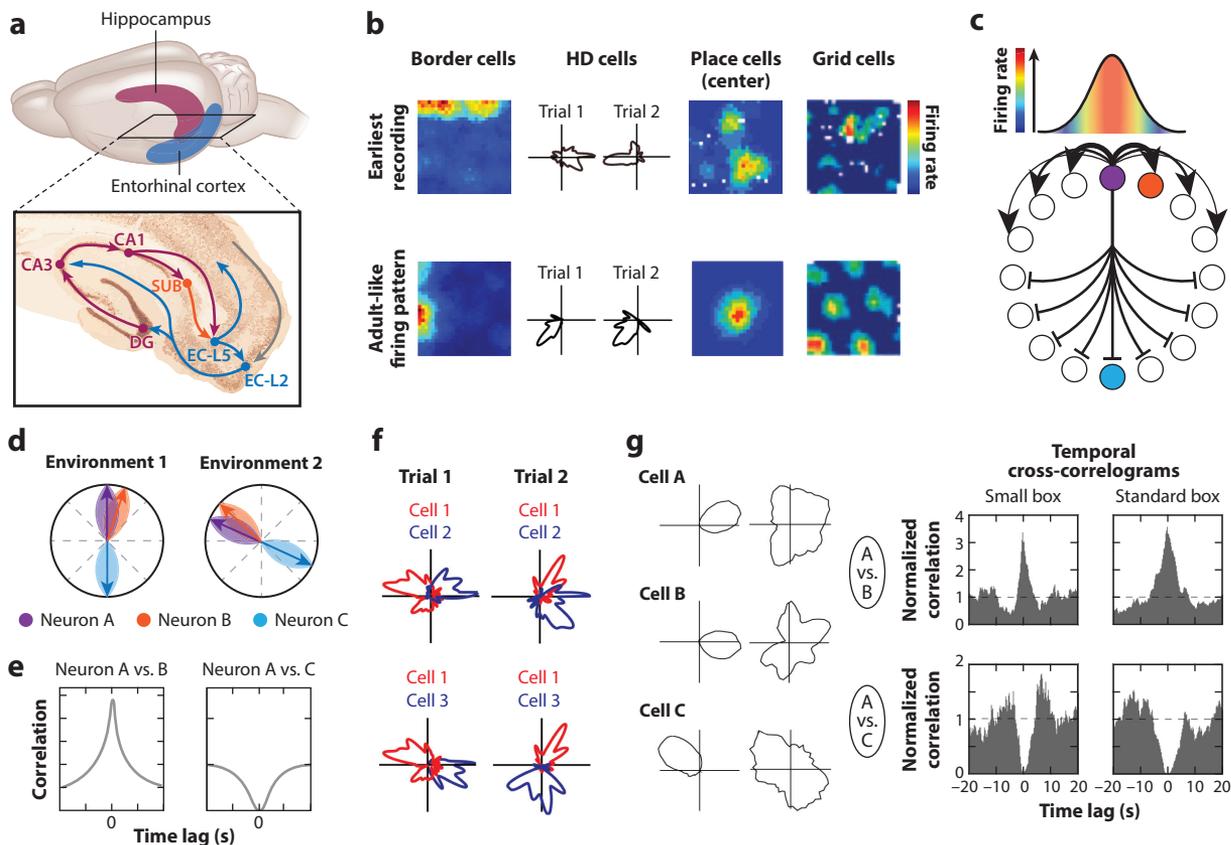
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## INTRODUCTION

Whether it is to satisfy the need to find food, escape a predator, or reproduce, navigation is a fundamental behavior that mobile organisms exploit for their survival. It is therefore not surprising that multiple navigation strategies have emerged across evolution, each differentially relying on combinations of information about the environment, internal cues, previous experience, and instincts. For example, unicellular organisms navigate their environments through a biased random walk in response to gradients of chemical stimuli (Cremer et al. 2019), whereas organisms equipped with a nervous system can integrate present and past multimodal information (e.g., visual landmarks, odors) with internal states to initiate volitional movement (Dudchenko & Wallace 2018).

In mammals, navigation relies on a distributed neuronal network centered around the entorhinal cortex and hippocampus (**Figure 1a**), where the activity of specific populations of neurons is tuned to variables associated with space (Poulter et al. 2018) (**Figure 1b**). In the hippocampus, most neurons increase their activity when an animal moves through specific locations. These are the place cells, each of which is active in restricted portions of the environment (the place field) so that at the population level, the activity of many of them fits together closely to cover the whole environment an animal moves in (O'Keefe & Dostrovsky 1971). In the medial entorhinal cortex (MEC) we find head-direction (HD) cells, which increase their activity when an animal faces a specific direction in allocentric coordinates (Sargolini et al. 2006, Taube et al. 1990a); grid cells, which are active at multiple locations (grid fields) and give rise to a regular triangular lattice tiling the environment (Hafting et al. 2005); and border cells, which are active close to environmental



**Figure 1**

(*a, top*) The drawing indicates the position of the entorhinal cortex and hippocampus within a hemisphere of the rat brain. (*Bottom*) Schematic representations of the major interarea connections of the entorhinal-hippocampal circuitry mapped onto a horizontal section of the hippocampal formation. (*b*) Firing fields of four spatially tuned cell types of the cognitive map recorded in young (*top row*) and adult (*bottom row*) rats running in a square enclosure. Rate map is color coded, with warmer colors indicating higher firing rates. (*Top row*) Spatial tuning of cells recorded in rat pups at the earliest time when each cell type has been recorded. (*Bottom row*) Spatial tuning of cells recorded in adult rats. Panel *b* adapted with permission from (*left to right*) Bjercknes et al. (2014, 2015), Muessig et al. (2015), and Wills et al. (2010). (*c*) Schematic representation shows local connectivity within a sector of the CAN model for HD cells. Arrows represent functional excitatory coupling among adjacent neurons on the ring, while barred connections represent functional inhibition. Coupling strength scales with the thickness of the connection. Firing rate within the local activity bump of the represented sector is color coded as in panel *b*. (*d,e*) Predicted spatial (*d*) and temporal (*e*) firing relationships of neurons on the ring according to the CAN model. Adjacent (neurons A and B) or far-away (neurons A and C) pairs of cells on the ring exhibit spatially conserved angular relationships in their preferred firing directions across different environments (in panel *d*, note the constant angular difference between vectors in the polar plots describing firing of neurons A, B, and C in environments 1 and 2). In a similar manner, close-by neurons (neurons A and B) fire in a temporally correlated fashion across environments and brain states (i.e., with near-zero time lag), while further-away neurons (neurons A vs. C) exhibit anticorrelated firing (*e*). (*f*) Polar plots of three simultaneously recorded rat HD cells before eye opening. Note that the angular relationship between pairs is preserved, as predicted by the CAN model, despite drift in the preferred firing direction of individual neurons between two consecutive trials in the same box. Panel *f* adapted with permission from Bjercknes et al. (2015). (*g*) Example polar plots (*left*) and temporal cross-correlograms (*right*) for three rat HD cells recorded before eye opening. Note that temporal relationships in the firing of pairs of cells are preserved, as predicted by the CAN model, despite changes in the degree of individual spatial tuning when the same cells are recorded in two boxes of different sizes. Panel *g* adapted with permission from Bassett et al. (2018). Abbreviations: CA3/CA1, cornu ammonis areas 3 and 1; CAN, continuous attractor network; DG, dentate gyrus; EC-L2, superficial layers of the entorhinal cortex; EC-L5, deep layers of the entorhinal cortex; HD, head-direction; SUB, subiculum.

boundaries (Lever et al. 2009, Solstad et al. 2008). Additional populations are tuned to speed (Kropff et al. 2015), the location of objects (Hoydal et al. 2019), or a combination of two or more of such variables (Hardcastle et al. 2017).

Collectively, the activity of spatially tuned neurons creates an internal representation of the environment in which an animal moves and a moment-to-moment representation of its position in it (O'Keefe & Nadel 1978). This representation emerges on the first exposure to a new environment and refines upon successive exposures (Barry et al. 2007, Wilson & McNaughton 1993) so that a precise map of the spatial layout and distance relationships between landmarks can be stored beyond immediate contingencies and allows animals to react flexibly to changes by devising new trajectories when the familiar routes are unavailable (Tolman 1948). We refer to this internal representation of space as a cognitive map, by which we mean a rich internal model of the world that is built on the spatial component of an environment and used to organize knowledge gathered through experience (Behrens et al. 2018).

The cognitive map might endow mammals with the ability to perform computations supporting complex forms of navigation such as path integration, in which animals use cues generated by their movements to create and advance the internal representation of their own position (McNaughton et al. 2006, Mittelstaedt & Mittelstaedt 1980). Additionally, the ability to create distinct maps for distinct experiences [pattern separation (Leutgeb et al. 2007)] and to reactivate patterns of activity associated with specific explored trajectories in moments when the animal is not engaged in active navigation [replay (Foster & Wilson 2006, Wilson & McNaughton 1994)] might support the encoding, consolidation, and long-term storage of memories of everyday experiences (episodic memories) and the planning of future trajectories to goals (Olafsdottir et al. 2018). Through these means, animals can store information about similar paths taken over multiple visits to the same environment or extract similarities between analogous experiences in different environments and use this information to guide navigation (Buzsaki & Moser 2013).

The fact that infant mammals, especially those of altricial species, rely on their caregivers to explore the environment (Newcombe 2019) and acquire navigational independence during the first weeks, months, or years of their lives has fueled a long-standing debate about what types of internal representations of space are available to the infant brain and when the cognitive map appears in its adult-like form (Newcombe 2019, Wills et al. 2014).

In this review, we discuss studies that have begun to unravel the developmental underpinnings of the cognitive representation of space. We focus on rodents and detail evidence based on three levels of investigation. First, we describe processes leading to the assembly of the circuitry that supports the cognitive map of space in the entorhinal-hippocampal network. Second, we delineate the time course of maturation of spatially tuned activity patterns of the cognitive map and contemplate what this tells us about the origin of spatial tuning in the brain. Third, we look into the development of computations by which spatially tuned neurons support navigation, and the encoding and consolidation of memories. We end by highlighting unresolved questions, which we believe have the potential, when addressed, of producing meaningful advances in our understanding of how cognitive maps are built during development and how they function in the adult brain.

## **BUILDING CIRCUITS FOR THE COGNITIVE MAP: THE DEVELOPMENT OF THE ENTORHINAL-HIPPOCAMPAL NETWORK**

Tuning to space in the cognitive map critically relies on the transfer of information across subdivisions of the entorhinal-hippocampal network (Bonnievie et al. 2013, Winter et al. 2015). This process might be coordinated by network oscillations, which synchronize firing among spatially tuned neurons (Colgin 2016). Moreover, sensory information from visual, olfactory, and vestibular organs is essential to anchor, calibrate, and stabilize the cognitive map during navigation (Chen

et al. 2016, Hardcastle et al. 2015, Waaga et al. 2022). Thus, we begin by focusing on the assembly and emergence of coordinated activity in the entorhinal-hippocampal network, concentrating on excitatory circuitry (for a detailed account of inhibition, see Cossart & Khazipov 2022, Danglot et al. 2006).

## Neurogenesis and Synaptogenesis

The entorhinal-hippocampal network resides in a C-shaped bulge of tissue within the medial temporal lobe known as the hippocampal formation. Its connectivity is organized in loops (Andersen 2007, van Strien et al. 2009): Information from multiple sensory modalities as well as higher-order areas of the brain is conveyed through the superficial layers of the medial (MEC) and lateral (LEC) entorhinal cortex to the hippocampus proper (Witter & Moser 2006). Here, a trisynaptic loop, where the dentate gyrus (DG) projects to area CA3, which in turn connects to area CA1, creates a pathway that relays information back to the MEC and LEC—this time to their deeper layers—from where it is likely broadcasted back to many cortical and subcortical areas (Sürmeli et al. 2015, van Strien et al. 2009) (**Figure 1a**).

Multiple types of excitatory neurons take part in this loop. While the DG is mostly populated by granule cells and CA3/CA1 by pyramidal cells, stellate and fan cells in the MEC and LEC, respectively, project to the DG and CA3, whereas entorhinal pyramidal cells project to CA1 and the contralateral brain (Witter & Moser 2006). These neurons are born during the second and third week of gestation in rodents, roughly between embryonic day 10 (E10) and E18 in the rat (Bayer 1980), and individual stations of the network exhibit staggered peaks of neurogenesis. While neurogenesis of CA3 and CA1 pyramidal cells peak on E14 and E15, respectively, in the mouse (Deguchi et al. 2011, Soriano et al. 1986), in the MEC a greater temporal difference in maturation and birthdate differentiates stellate cells and pyramidal cells, with the former being born earlier than the latter (Donato et al. 2017). Granule cells represent an exceptional case, since their peak extends to postnatal day 10 (P10) in rodents (Altman & Bayer 1990), and neurogenesis might continue, even though at a diminished rate, throughout life (van Praag et al. 2002).

Neurogenesis has a long-lasting impact on the anatomical and physiological organization of the hippocampal formation. Strikingly, several areas of the entorhinal-hippocampal network exhibit neurogenesis-based topography. In the hippocampus, excitatory neurons of CA1 and DG stratify in a deep-to-superficial fashion according to their birthdate (Bayer 1980, Mathews et al. 2010). In the MEC, while the earliest-born stellate cells are prevalent at the dorsal pole and their later-born counterparts cluster in the ventral tissue, pyramidal cells with different birthdates are homogeneously dispersed along the dorso/ventral axis (Donato et al. 2017). Importantly, birthdate-based topography recapitulates gradients of connectivity, intrinsic properties, and functional tuning to space that are observed in the adult entorhinal-hippocampal network (Cossart & Khazipov 2022). Populations of neurons with similar birthdates (i.e., isochronic neurons) connect preferentially across DG and CA3/CA1, thereby creating neurogenesis-based microcircuits within the hippocampus (Deguchi et al. 2011, Druckmann et al. 2014). Intrinsic properties and functional tuning to space are similar among isochronic neurons but different between neurons with different birthdates (Cavalieri et al. 2021, Huszár et al. 2022), with the earliest-born CA1 neurons exhibiting lower levels of spatial information than later-born neurons (Huszár et al. 2022). Finally, isochronic CA1 neurons exhibit highly correlated place field activity during navigation and fire in synchronized cell assemblies during network oscillations and might therefore function as preconfigured functional units (Huszár et al. 2022).

Once generated, neurons migrate from the hippocampal neuroepithelium toward the hippocampal formation (Andersen 2007, Danglot et al. 2006). The establishment of local versus

long-range connectivity follows an outside-in time course, with long-range connectivity being established largely before the animal's birth, and local connectivity being established afterward (Gomez-Di Cesare et al. 1997, Super & Soriano 1994). Again, neurogenesis defines distinct schedules of synaptogenesis for early- and later-born neurons of DG, CA3, and CA1, which leads to the establishment of selective connectivity across hippocampal subdivisions among neurons with temporally matched neurogenesis and synaptogenesis windows (Deguchi et al. 2011, Druckmann et al. 2014).

### **Sensory Responses and Coordinated Activity During Development**

Mice and rats exhibit specific temporal profiles for the maturation of distinct sensory modalities. While olfactory and vestibular information is already available to the developing brain during the first days of life, vision is one of the last sensory modalities to come online after somatosensation and hearing (Curthoys 1982, Gregory & Pfaff 1971, Landers & Zeigler 2006, Wills et al. 2014). Indeed, activity in the entorhinal cortex is strongly influenced by the activation of olfactory sensory neurons early on. Functional coupling between the olfactory bulb and LEC results in mitral cell activity bursts driving LEC firing as early as P9 (Gretenkord et al. 2019, Kostka et al. 2020). In contrast, responsiveness to somatosensory, auditory, and visual stimuli appears later and reaches adult-like properties by the end of the first month of life (Tan et al. 2017).

As early as P2–4, movements such as startle responses and twitches evoke coordinated activity in large populations of entorhinal and hippocampal neurons, the early sharp waves (eSPWs) (Karlsson et al. 2006, Leinekugel et al. 2002, Valeeva et al. 2019). Beyond eSPWs, coordinated firing produces population bursts and transient oscillations in the beta/gamma band (20–30 Hz) (Leinekugel et al. 2002), which increase their frequency toward the gamma range and become modulated by theta rhythms by the second postnatal week (Cossart & Khazipov 2022). Theta oscillations appear as intermittent bursts by the end of the first week, first during running and voluntary movement and then in sleep (Mohns & Blumberg 2008), and increase in amplitude and frequency until the end of the first month (Langston et al. 2010, Wills et al. 2010).

Taken together, the evidence reviewed so far suggests that responsiveness to sensory stimulation and coordinated activity across large populations of neurons in the entorhinal-hippocampal network emerge progressively during the first weeks of life of a rodent and reach adult-like levels by the end of the first month.

### **The Role of Spontaneous and Sensory-Evoked Activity in Driving Hippocampal Microcircuits Maturation**

In circuits devoted to processing sensory information, patterned excitatory activity from neurons in sensory epithelia acts as a driver for the maturation and refinement of synaptic connectivity across entire networks (Martini et al. 2021). This is the case in the visual system, where spontaneous activity waves originating in the retina drive highly synchronous cortical and subcortical activity patterns to produce retinotopy and support the development of motion detection and sparsification of network activity at eye opening (Ackman et al. 2012, Ge et al. 2021, Meister et al. 1991, Rochefort et al. 2009).

Whether similar phenomena contribute to the functional maturation of the entorhinal-hippocampal network is unknown. Remarkably, maturation of each station of this network depends on excitatory activity from its upstream regions, with the superficial MEC providing the initial signal for the stepwise maturation of neurons and circuitry within the entorhinal cortex and hippocampus (Donato et al. 2017). Similarly, superficial MEC activity precedes hippocampal activation during individual eSPWs (Valeeva et al. 2019). Hence, during development, excitatory

activity from the MEC might have an instructive role for the maturation of neurons and the establishment and refinement of synaptic connections within and across network subdivisions.

Given that the entorhinal-hippocampal network is located at a great synaptic distance from primary sensory organs, whether and how a putative driver might influence coordinated activity during development is unknown. Based on chronic silencing experiments, it was proposed that in higher-order cortical areas like the MEC, specific populations of neurons might act cell-autonomously as developmental drivers in a neurogenesis-dependent fashion (Donato 2017). For the entorhinal-hippocampal network, such a driver role would be played by stellate cells. In the context of network maturation, these cells stand out since, at the population level, they are the first to reach adult-level of maturity. Additionally, their maturation is activity independent and correlates to neurogenesis, and they have been shown to be the primary source of the activity-dependent instructive signals driving downstream network maturation (Donato et al. 2017). This hypothesis remains to be verified, as it has not yet been determined whether specific temporal patterns of coordinated activity, like eSPWs or waves, are necessary for circuit maturation and the functional tuning of the cognitive map.

## THE EMERGENCE OF SPATIAL TUNING IN THE DEVELOPING RAT BRAIN

In the past decade, a handful of studies have recorded single-cell firing properties at multiple processing stations of the entorhinal-hippocampal network in developing rats and delineated the time course of the emergence of spatial tuning in the hippocampal formation. We review this evidence below and ponder how the ontogeny of spatially tuned activity patterns informs us about the assembly and function of the cognitive map.

### The Ontogeny of HD, Border, Place, and Grid Cells

Border and HD cells are some of the first elements of the cognitive map to exhibit adult-like properties in the developing brain (**Figure 1b**). In fact, border cells' abundance, firing rate, and response to the insertion of a new border (emergence of a novel firing field) are similar to those of adults by P17 (Bjerknes et al. 2014). Similarly, the fraction of neurons with significant HD tuning, their stability across repeated exposures to the same environment, and their information content are adult-like by P15–16 in the rat (Langston et al. 2010, Wills et al. 2010).

Such an early maturity of HD cells is striking, given that at that age, rat pups have usually had limited navigational experience, and information from visual landmarks—which polarizes HD responses in the adult (Taube et al. 1990b, Zugaro et al. 2003)—has just become accessible after the eyelids unfuse on P15 (Wills et al. 2014). Even more strikingly, cells with significant HD tuning can be recorded in the dorsal presubiculum, MEC, and the anterodorsal thalamic nucleus as early as P11–12, an age when pups do not leave the nest autonomously and their eyelids are closed (Bjerknes et al. 2015, Tan et al. 2015). At this early time, however, HD signals are qualitatively and quantitatively different from their adult counterparts. In fact, cells with significant directional tuning in pups are less abundant, stable, precise, and informative than those in adults. Hence, HD cells are immature around the end of the second week, and their maturation unfolds rapidly after eye opening.

Place cells in the rat hippocampus can be recorded on P16 (**Figure 1b**), though at this time the number of place cells, their spatial information, and their stability across multiple exposures to the same environment are lower than in adults. Unlike the sudden maturation of HD cells, place cell maturation unfolds over weeks: At the population level, they reach adult-like numbers, stability, spatial information, and coherence only by the second month of life (Langston et al. 2010,

Scott et al. 2011, Wills et al. 2010). Strikingly, in young rats, place cell representation is more accurate along the walls of the recording box, where place fields show higher concentration and exhibit higher firing rates, within-session stability, spatial information, and across-session coherence (Muessig et al. 2015). Such a difference is not dependent on behavioral predisposition, that is, biased exploration of borders, and it rapidly disappears around the time of weaning.

Grid cells are the latest of the four main spatial cell types to emerge, since the earliest grids were recorded at P20 in the developing MEC (Langston et al. 2010, Wills et al. 2010) (**Figure 1b**). At this time, their numbers, precision, and stability are lower, and their periodicity is more irregular, than in adults. Hence, grid cells acquire their adult-like properties during postnatal development. There is disagreement, however, about the speed of this process, with reports of a sudden and overnight increase in precision, stability, and periodicity around weaning (Wills et al. 2010), while others demonstrate a slow and protracted increase in spatial tuning that unfolds over weeks (Bjerknes et al. 2014, Langston et al. 2010).

As this evidence suggests, even though a rudimentary representation of space can be recorded at a time when rodents have had limited experience of navigation outside their nest and information about visual landmarks is scarce, spatial tuning in the developing brain is far from mature (**Figure 1b**). The entorhinal-hippocampal network must therefore go through developmental processes that produce an increase in precision, stability, and number of spatially modulated cells to a degree and with a time course that are cell type specific. Thus, fundamental questions remain unanswered: What is the origin of the rudimentary cognitive map observed before spatial exploration? What mechanisms drive the maturation of the brain representation of space? To what extent is the increase in precision of HD, place, and grid cells interdependent? And what role, if any, is played by early sensory experience in these processes?

### **The Interplay Between Sensory Experience and Network Dynamics in the Emergence of the Cognitive Map**

One of the most striking examples of spatial tuning emerging before large-scale navigation comes from HD cells, which can be recorded before eye opening in the rat (Tan et al. 2015). This finding was a breakthrough, since in adults, vision has a fundamental role in entraining HD signals (Taube et al. 1990b, Zugaro et al. 2003), and theoretical models proposed that distal visual landmarks might entrain the immature HD network to produce sharp tuning during development (Hahnloser 2003). How HD signals can emerge before patterned visual information becomes available and whether other sensory modalities beyond vision might shape the firing of developing HD cells are still open questions. In adults, even though normal-sighted animals exhibit significant impairment in HD cells when navigating in darkness, HD signals from congenitally blind animals are stable, thereby suggesting that the HD code can be established in the complete absence of visual experience (Asumbisa et al. 2022). Moreover, HD cells from congenitally blind mice are locked to olfactory stimuli, which also have the potential to modulate HD tuning in sighted animals when visual inputs are scarce, thus suggesting that sensory modalities other than vision can be used when visual information is unavailable, as is the case before eye opening.

A different question is to what degree the developing brain exhibits the types of population dynamics that support the spatial tuning of HD cells in the adult (Knierim & Zhang 2012, Peyrache et al. 2015). Traditionally, the HD network has been modelled as a continuous attractor network (CAN) in which neurons connect with each other according to specific connectivity rules so that close-by neurons are strongly connected with each other, and excitatory connectivity strength decreases while inhibitory connectivity increases as a function of distance (McNaughton et al. 2006, Skaggs et al. 1995) (**Figure 1c**). In such conditions, a transient imbalance between excitation and inhibition results in the emergence of a local bump of activity, whose position can move along

the network through a continuous range of stable network states. In a network where neurons are arranged in relation to each other as if lying on a ring, and the activity bump is translated along the ring based on the combination of a velocity signal with visual information, individual neurons exhibit sharp tuning to stimuli mapped on a sector of the ring, as is the case for HD cells.

According to the CAN model and because of its rigid connectivity, pairs of neurons are predicted to fire with similar angular relationships across conditions when individual preferred firing directions are not preserved, for example, when an animal explores distinct environments (Taube et al. 1990b) (**Figure 1d**). Moreover, pairwise correlations between neurons are predicted to be conserved across brain states, for example, between active exploration and when the animal is disengaged from sensory stimulation during sleep (Chaudhuri et al. 2019, Peyrache et al. 2015) (**Figure 1e**). Thus, a conserved correlation structure in the activity of pairs of neurons across experiences and brain states has been taken as a proxy for the presence of attractor dynamics in the HD network (Peyrache et al. 2015). Strikingly, network-wide coherence and constant angular difference can be observed in HD cells even before eye opening (Bassett et al. 2018, Bjerknes et al. 2015) (**Figure 1f,g**), suggesting that the rigid connectivity architecture underpinning the attractor is already established before vision becomes predominant. Visual cues might then have a dominant role in anchoring attractor dynamics soon after eye opening, concomitant with the rapid increase in HD cell stability and precision.

Similar considerations are relevant for the development of grid cells, whose regular activity pattern is thought to emerge from a CAN where instead of a ring, neurons are arranged in relation to each other as if lying on a donut-shaped surface [i.e., a torus (Burak & Fiete 2009, Fuhs & Touretzky 2006, Gardner et al. 2022, McNaughton et al. 2006)]. In the adult, grid cells with similar phases (i.e., correlated activity when the animal navigates in a specific environment) maintain the same correlation in a different environment or during sleep (Fyhn et al. 2007, Gardner et al. 2019, Trettel et al. 2019, Yoon et al. 2013), indicating that the rigid connectivity of the attractor is preserved regardless of changes in sensory stimuli. Strikingly, the earliest corecorded grid cells maintain a similar functional coherence despite changes in the sensory landscape since they rotate in tandem following the rotation of visual cues (Wills et al. 2012). As in the case of HD cells, this coherence might suggest that the rigid connectivity architecture of the CAN, posited to underlie grid cell firing, is present as soon as these cells can be recorded. However, it remains to be determined whether the torus attractor is in place before exploration and before any prospective grid cells can be recorded, and what types of changes to the structure of the attractor or its dynamics characterize the developmental maturation and refinement of grid cells.

### **What Can We Learn from the Sequential Maturation of Spatially Tuned Cell Types? The Development of Place Cells**

Following the discovery of grid cells, it was hypothesized that the linear summation of their activity was responsible for the emergence of place tuning in the hippocampus (Monaco & Abbott 2011, Solstad et al. 2006). Although distorted grids can convey sufficient information to support a positional code (Stemmler et al. 2015), the discovery that, during development, place cells could exist before grid cells appeared, together with the observation that place cells could survive the loss of grid cell periodicity (Koenig et al. 2011) as well as direct silencing of MEC inputs (Miao et al. 2015), provided important challenges to the linear summation model. An alternative model then gained traction, whereby an accurate and stable place code resulted from the thresholded sum of boundary-encoding cell activity (Hartley et al. 2000). This model was corroborated by the fact that border cells exhibited mature properties before place cells (Bjerknes et al. 2014), and that place cell representation was more accurate close to borders of the recording box before weaning (Muessig et al. 2015). In this scenario, grid cells might contribute to the stability and precision of

place fields located near the center of the box given that these center fields mature with a time course that reflects the appearance of the MEC grid (Muessig et al. 2015).

To what extent grid cell activity shapes place cell tuning during development and in the adult remains an open question. It is important to note, however, that in the adult CA1, self-generated and possibly preconfigured sequences of place cell activity can emerge spontaneously when an animal is running on a sensory-poor treadmill in darkness (Villette et al. 2015), during the delay phase of a spatial task (Pastalkova et al. 2008), or during a time-keeping task (MacDonald et al. 2011), suggesting that a navigation-independent place cell scaffold might be present in the hippocampal network. Strikingly, stereotyped sequences of neuronal activation have also been reported in the superficial layers of the adult MEC as the neuronal instantiation of an ultraslow network oscillation (Gonzalo Cogno et al. 2022), during the delay phase of a decision-making task (Heys & Dombeck 2018), or in relation to the estimation of episodic time (Tsao et al. 2018). How these sequences emerge during development, and to what extent they influence the emergence of spatial tuning in the entorhinal-hippocampal network, is still an unresolved question.

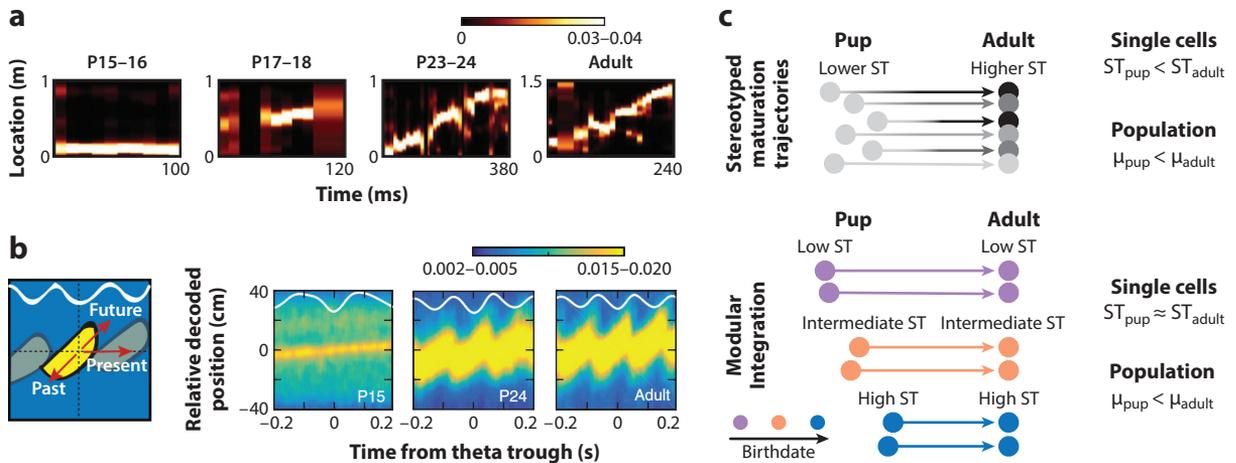
## **THE DEVELOPMENT OF CORE COMPUTATIONS FOR NAVIGATION AND SPATIAL LEARNING**

So far, we have described the development of spatially modulated activity patterns of individual neurons within the cognitive map. However, coordinated activity across neuronal populations underpins the use of cognitive maps for navigation, spatial learning, and memory. In this section, we explore the development of population-based computations with a specific focus on developing hippocampal place cells.

### **Cell Assemblies and Their Temporal Dynamics: the Development of Replay and Theta Sequences**

During navigation, an animal's trajectory through space is reflected in the sequential activation of its place cells, with a bidirectional encoding/decoding relationship between spatial behavior and place cell sequences (Drieu & Zugaro 2019). Because place cells tend to fire at progressively earlier phases of the theta cycle as the animal transverses the place field [phase precession (O'Keefe & Recce 1993)], similar sequences are played out at a compressed rate during a theta cycle [theta sequences (Skaggs et al. 1996)] so that the spike sequence of neurons firing within each cycle binds a sequence of past, present, and future locations. Additionally, during sleep or rest and in association with hippocampal sharp wave ripples (SWRs), place cell sequences are reactivated to replay past explored trajectories (Foster & Wilson 2006, Wilson & McNaughton 1994), which might support the consolidation of memories of previous experiences (Gillespie et al. 2021) or the planning of paths to remembered goals (Pfeiffer & Foster 2013). Consistent with these proposed roles, inhibiting ripples impairs hippocampal-dependent learning and navigation (Girardeau et al. 2009). Hence, place cell sequences might have a fundamental role in memory, decision-making, and planning of future trajectories.

Two studies have focused on the time course of the maturation of place cell sequences in the rat hippocampus, revealing that the development of hippocampal replay and theta sequences might progress along multiple stages (Farooq & Dragoi 2019, Muessig et al. 2019). In the first phase, up to P16, offline reactivation events during SWRs represented discrete locations and failed to bind multiple places into a coherent trajectory. The second phase was characterized by the emergence of replay of longer and longer sequences, in an age-dependent but experience-independent manner, which lasted up to weaning (P22), after which entire trajectories started to be replayed



**Figure 2**

(a) Developmental time course of the appearance of replay. Examples are given of location-depicting, partial, and global trajectory replay events recorded during on-track rest epochs across development. The y axis shows the decoded position of the rat calculated based on the firing of place cell sequences during replay events (the decoded probability is color coded). The x axis shows time from the start of a replay event. (b) Developmental time course of the appearance of theta sequences. The y axis shows the decoded position of the rat calculated based on the firing of place cell sequences during individual theta cycles (the decoded probability is color coded). The x axis shows time from the trough of the theta oscillation. White curves show the session-averaged theta oscillation. The leftmost panel shows a schematic representation of the binding on past, present, and future locations within individual theta sequences. (c) Alternative models to explain the population-wide increase in the degree of spatial tuning (ST) of the cell types of the cognitive map. (Top) In stereotyped maturation trajectories, all neurons might begin their maturation trajectory with homogeneously low degrees of ST and go through stereotyped developmental processes to increase their tuning with time. Longitudinally, individual neurons would exhibit greater levels of precision, stability, and information content in adults than in pups ( $ST_{\text{pup}} < ST_{\text{adult}}$ ). This would result in a similar trajectory for the mean population value of ST ( $\mu$ ), which would be higher in the adult than in the developing network ( $\mu_{\text{pup}} < \mu_{\text{adult}}$ ). ST is color coded, with darker colors indicating cells that exhibit higher levels of ST. (Bottom) In modular integration, neurons with similar birthdates, which are characterized by distinct degrees of ST in the adult network, might already exhibit functional diversity at the start of their developmental trajectory. Longitudinally, an individual neuron's developmental changes in ST might be limited and the end point largely set by the neuron's birthdate (i.e., their ST in pups would be close to their value in adults:  $ST_{\text{pup}} \approx ST_{\text{adult}}$ ). At the population level, the progressive integration into the network of distinct cohorts of isochronic neurons, each characterized by different degrees of ST, might drive the population-wide increase of ST with time, so that here, too, the mean population value of ST would be higher in the adult than in the developing network ( $\mu_{\text{pup}} < \mu_{\text{adult}}$ ). Birthdate and ST are color coded, with different colors indicating cohorts of isochronic neurons with different birthdates and darker shades indicating cells that exhibit higher levels of ST. Panels a and b adapted with permission from Farooq & Dragoi (2019).

(Figure 2a). Interestingly, the two studies diverge such that one suggests a coordinated emergence of replay and theta sequences (Muessig et al. 2019), while the other observes a sequential and possibly independent emergence of the two temporal dynamics (Farooq & Dragoi 2019) (Figure 2b). Further studies are needed to solve this issue and to correlate the emergence of place cell sequences with cognitive processes such as consolidation and route planning, which impinge on such population-wide phenomena.

## The Emergence of Remapping During Development

The ability to encode, store, and recall distinct memories for distinct experiences (a process known as pattern separation) critically relies on structures of the hippocampal formation (Colgin et al. 2008, Treves & Rolls 1994). The place cell code can support this computation upon exposure to distinct environments, when extensive remapping [i.e., a change in a neuron's firing rate or place

field location (Leutgeb et al. 2005, Muller & Kubie 1987)] indicates that rats have created distinct maps for distinct enclosures.

In infant rats, CA1 place cells remap at a similar rate to and extent as those of adults already at an age when grid cells are unstable and do not exhibit regular firing [at P16 (Muessig et al. 2016)]. The fact that the place cell code exhibits associative memory properties even at a time when grid cells are irregular and memories of early-life experiences are unspecific and tend to become progressively inaccessible with age (infantile amnesia) is striking, and it supports the idea that the hippocampus, albeit immature, is involved in memory processes of the infant brain (Donato et al. 2021, Travaglia et al. 2016).

### **Relying on Self-Motion Cues to Guide Navigation: Path Integration in the Developing Entorhinal-Hippocampal Network**

Path integration refers to an animal's ability to integrate self-motion information about linear and angular acceleration to calculate and update an internal representation of its own position in space (McNaughton et al. 2006, Mittelstaedt & Mittelstaedt 1980). In this framework, retaining a sense of the total angle and distance traveled allows animals to calculate a direct return path to an initial home location (i.e., a shortcut) even when distal visual cues are unavailable or after having traversed a convoluted and semirandom outbound journey (Etienne & Jeffery 2004, Tolman 1948).

Grid cells are thought to be involved in computations for path integration given that their multifield firing patterns fit the prediction of models (Fuhs & Touretzky 2006, McNaughton et al. 2006), that self-motion information has a strong influence on their firing (Campbell et al. 2018), that genetic manipulations selectively disrupting their regularity impair the animal's ability to path integrate (Gil et al. 2018), and that an artificial neural network trained to perform path integration can develop grid-like representations in its hidden layers (Banino et al. 2018). However, in adult animals, place cells are also able to integrate self-motion inputs to keep track of the animal's position in space (Chen et al. 2013), and place cells can rely almost exclusively on self-motion information to establish their firing fields (Gothard et al. 1996). The question of whether self-motion coding in place cells might be inherited by grid cells was addressed in a developmental framework when Bjercknes et al. (2018) revealed that self-motion information was sufficient to induce stable place field formation before the appearance of stable grid fields, that is, as early as P17 in the rat, which was taken as an indication that the developing hippocampus was able to path integrate in the absence of a mature grid cell signal. Notably, however, theoretical work has demonstrated that distorted grids have the potential to convey sufficient information to support a positional code (Stemmler et al. 2015), and other factors might come into play to support path integration in developing animals, such as a disproportionate influence of borders or the presence of self-organized place cell sequences (Villette et al. 2015), which might provide self-motion information regardless of positional information. How such factors contribute to path integration in the developing brain remains to be determined.

### **LOOKING AHEAD: HOW DO YOU BUILD A COGNITIVE MAP?**

The evidence reviewed so far suggests that the developing rodent brain is able to create a cognitive map of the environment before any large-scale navigation and before crucial sensory information becomes available. The fact that HD, border, and place cells could be recorded in rat pups before or around the time when they start exploring the world has been taken as an indication that the brain is endowed with a representation of space a priori, that is, without any experience of exploring a location, and that the cognitive map includes some form of innate constructs that emerge before navigation (Palmer & Lynch 2010).

While the presence of some degree of spatial tuning before experience supports this view, it is evident that at least some spatially-tuned activity patterns in the developing brain are qualitatively and quantitatively different from their adult counterparts in terms of abundance, precision, information content, and stability (**Figure 1b**). Hence, we must conclude that the cognitive map goes through an extensive process of refinement during development, and it is fascinating to hypothesize that two different principles might be at play for the emergence of an adult-like representation of space. One might be intrinsically programmed and unfold independently from sensory or navigational experience to produce the rudimentary spatial tuning observed in rats before eye opening and exploration beyond the nest. On top of this self-generated, innate spatial blueprint would then be a second, experience-dependent set of processes that might adjust innate spatial representations to the statistics of the environment an animal is brought up in and turn the cognitive map into an optimal model of the environment (Berkes et al. 2011), as detected in adult animals.

In this framework, it is interesting to note that our knowledge of the impact of early-life experience on the development and function of the cognitive map is limited. Preliminary results suggest that when rats are deprived of access to distal visual landmarks during early life, grid cells fail to appear at the proper developmental age and instead rapidly acquire their hexagonal symmetry only upon exploration of regular environments (Kruger et al. 2014). Decades of research in sensory systems by means of early-life sensory deprivation experiments have revealed the existence of temporally restricted periods during postnatal development in which specific molecular signals and network-wide phenomena, driven by the maturation of fast-spiking inhibitory neurons, confer enhanced structural and functional plasticity to cortical circuits, the so-called critical periods (Hensch 2005). It is tempting to propose that critical period-like processes might play a role in the development of circuits and computations of high-end cortical areas, specifically in the development of the cognitive map, just as much as they play a role in the development of circuitry devoted to sensory perception. In the entorhinal-hippocampal circuit, a critical period might be identified with the establishment of the rigid connectivity architecture of the attractor networks that, in the adult, support the rapid emergence of HD and grid cells upon novel experiences. Critical period-like mechanisms have been recently implicated in the maturation of the hippocampus's contribution to the encoding and consolidation of memories of early-life experiences during the period of infantile amnesia (Travaglia et al. 2016). In the future, it will be important to exploit more extensive and comprehensive controlled-rearing conditions to identify the mechanisms driving the maturation of the cognitive map.

How the attractors for grid and HD cells are assembled during development remains an open question, given that performing longitudinal recordings of the same neurons over multiple stages of development, which would be crucial to reveal the ontogeny of population dynamics of CANs, is prohibitive. In much the same way, the mechanisms driving longitudinal changes in stability, information content, and coherence within individual neurons remain to be determined. Changes in these parameters with development have been considered at the population level as the increase in the mean population value over multiple cells and animals pooled together. Such an increase could be due either to all cells refining their tuning with time or to the sequential addition of populations of neurons characterized by more and more precise and stable tuning properties (**Figure 2c**). The fact that, in the adult network, parameters like stability, precision, and information content continue to be heterogeneous across the recorded population raises questions about how much of this heterogeneity is inherited from development and to what extent all neurons of a specific cell type go through the same stereotypical developmental trajectories. As previously indicated, it has been suggested recently that many properties, from connectivity to intrinsic properties to the degree of tuning to space, correlate with a neuron's birthdate and are shared among isochronic neurons (Cavalieri et al. 2021, Cossart & Khazipov 2022, Deguchi et al. 2011, Huszár et al. 2022). Since

populations of isochronic neurons mature and integrate into the entorhinal-hippocampal network in a sequential order recapitulating their birthdate (Deguchi et al. 2011, Donato et al. 2017), it is tempting to propose a new framework, where development consists of the integration of functionally distinct modules composed of genetically and functionally homogeneous populations of neurons whose properties and connectivity are determined by the time of their neurogenesis. In such a scenario, the increase in specificity, information content, and stability of spatially tuned activity patterns during development would be due not exclusively to the refinement of single neurons' properties but also to the integration of distinct isochronic populations comprising neurons with higher and more stable tuning to space (**Figure 2c**).

To tackle the questions highlighted in the previous paragraph, it will be necessary to develop novel approaches to study the activity of large populations of developmentally defined neurons at single-cell resolution longitudinally through development. Our hope is that recent technological and computational advancements, which have transformed our understanding of how adult neuronal networks support an animal's behavior, will soon be deployed to study the ontogeny and maturation of cortical representations. The application of such advanced approaches and the tight cooperation between theoreticians and experimentalists, which have characterized the field since its inception, might be fundamental to revealing how the cognitive map is built during development. This knowledge could in turn deepen our understanding of the mechanisms underlying cognitive map functions in adults and guide targeted interventions for the restoration of physiological patterns of activity when pathological conditions impair spatial representations.

## DISCLOSURE STATEMENT

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