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Review

Developmental perspectives on spatial navigation: sensory development, experience, and neuronal heterogeneity

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Spatial cognition in mammals relies on various spatially tuned cell types in the hippocampus and associated brain regions. Recent studies have increasingly explored the developmental timelines of these cells, their characteristics during early life, and the developmental origins of their functional heterogeneity in adulthood. In this review we discuss these findings and propose that the emergence and properties of spatially tuned cells across various developmental stages are shaped by the sequential maturation of multiple sensory and motor systems, as well as by the maturation of local inhibitory circuits. In addition, sensory and navigation experiences crucially influence the development of spatial navigation and episodic memory circuits. Finally, we highlight the diversity of cell types during development, and discuss how this diversity contributes to the functional heterogeneity of spatially tuned cells in adulthood.

The development and heterogeneity of spatially tuned cells

Spatial navigation in mammals depends on neurons that encode location and direction, including place cells, grid cells, head direction cells, and other functional cell types [1]. Extensive and longstanding research in rodents has explored the circuit mechanisms that underlie the spatial selectivity of these cells and the influence of sensory cues on their functional properties. A growing body of research has explored how these cells develop and how episodic memory emerges in early life. These studies have provided a foundation for understanding how spatially tuned cells are formed, and revealed how sensory stimulation, enriched environments, and varied experiences may promote spatial cognition and memory during development and adulthood. Previous reviews have detailed the ontogeny of spatially tuned cells [2–5], the establishment of hippocampal circuits and functions during development in rodents [5,6], and the development of hippocampus-dependent behaviors in rodents and humans [3,7–12].

We summarize here recent advances in understanding the development of the spatial navigation system, primarily in rodents, and examine the links between its maturation and the development of associated systems. First, we discuss how the distinct developmental timelines of different spatially tuned cell types reflect their varying dependence on specific sensory modalities, which themselves mature with different timelines. Drawing on principles from sensory system development, we discuss how the maturation of parvalbumin-positive (PV^+) interneurons regulates the development of the navigation system, and the role of experience in spatial navigation development. Finally, we discuss place cell heterogeneity during development and adulthood, and propose that functionally distinct subtypes of place cells in adults might originate from their divergent trajectories established early in life.

Highlights

The hippocampus and associated brain regions in rodents contain various types of spatially tuned cells, each of which follows a specific developmental timeline, and head direction cells emerge first, followed by border/boundary cells, place cells, and grid cells.

The formation of spatially tuned cells is shaped by both sensory and self-motion cues. Accordingly, the development of spatially tuned cells depends on the sequential maturation of multiple sensory and motor systems, which is regulated in part by maturation of local parvalbumin-positive (PV^+) interneurons within relevant brain regions.

The functional organization of the spatial navigation system is shaped by both genetic programs and experience-dependent plasticity.

The functionally distinct cell types observed in the adult hippocampus may correspond to developmental subpopulations, such as early- and late-emerging place cells, or neurons with different embryonic birthdates.

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The effects of sensory development and experience on the maturation of spatial navigation systems

Sequential development of sensory and motor systems in shaping spatial navigation

The firing of spatially tuned cells is determined by integration of environmental sensory cues, such as visual, auditory, olfactory, and tactile cues [13], as well as self-motion signals arising from vestibular and proprioceptive inputs [14]. These sensory and motor systems follow distinct developmental timelines. In rodents, the vestibular, olfactory, and motor systems are functional from birth. The primary somatosensory cortex, which processes both proprioceptive and tactile information, becomes functional shortly after birth. The auditory and visual systems become functional later, at around postnatal (P) days P12 and P14, respectively. This sequential maturation means that the sensory information available to the developing spatial navigation system changes with age.

In rodents, navigation behavior begins shortly after birth. From the first postnatal week, newborn rodents can move towards their mother's nipples [15]. From the end of the second week they use quadrupedal walking and can explore a wider spatial range [16]. Although in the first postnatal week their navigation ability is very limited, the spatial navigation system is already undergoing crucial developmental processes that are partly based on signals from sensory and motor systems (reviewed in [6]). For instance, spontaneous myoclonic movements, such as startles, twitches, and jerks, generate somatosensory feedback that drives bursts in the entorhinal cortex and, in turn, triggers early sharp waves in the immature hippocampus [17,18]. Thus, before ~P12, hippocampal activity is largely driven by bottom-up sensorimotor inputs which may play a fundamental role in the development of the entorhinal–hippocampus circuits [6]. Later, the hippocampal network gradually acquires the ability to generate internally organized sequences of neural activity, such as sharp wave–ripple-associated replay and theta sequences, which emerge independently of immediate external inputs. Olfactory inputs also play important roles in the coupling between the neonatal olfactory bulb and the lateral entorhinal cortex (LEC), as well as in the development of the LEC–hippocampal network during postnatal weeks 1–2 [19,20]. Thus, the activity of the sensory and motor systems plays an important role in the first two postnatal weeks of spatial navigation system development.

Different types of spatially tuned cells differ in their degree of dependence on distinct sensory modalities. Head direction cells depend primarily on vestibular input, but are also modulated by visual cues, other sensory inputs, and motor-related feedback [21–23]. The vestibular system is functional early in development and supports the early emergence of head direction cells [3], which in rats are detected by P12 [24,25]. However, adult-like, more precise and stable head direction cells appear after eye-opening when visual inputs can anchor the preferred firing direction of head direction cells to external landmarks [24,25]. Path integration depends primarily on self-motion cues generated by vestibular signals and proprioception [14], and accordingly also emerges early, by P17 in rats [26]. Border/boundary cells in the medial entorhinal cortex (MEC) (Box 1) emerge by P16, and their core functional properties already reach the adult level [27]. By contrast, boundary vector cells (BVCs) in the subiculum can be detected from P16, but their spatial specificity and stability do not reach adult-like levels until after P25 [28]. MEC border/boundary cells are mostly tuned to short distances from environmental boundaries [29], whereas some subicular BVCs are tuned to longer-range distances and show reduced wall-aligned directional tuning before weaning [28]. Both MEC border/boundary cells and subicular BVCs can function when animals explore in darkness, which indicates that they are not purely visual [29,30]. The existence of long-range BVCs suggests they are not purely tactile either [30]. Nevertheless, it is reasonable to hypothesize that MEC border cells and short-range BVCs may draw upon tactile cues from whiskers or feet during the first two postnatal weeks, which supports their early emergence by P16. Future experiments such as whisker deprivation starting from

Box 1. Functional cell types that support spatial navigation

Several spatially tuned cell types involved in spatial navigation have been identified in rodent studies [1]. Place cells, that are primarily located in the hippocampus, display higher firing rate when an animal occupies a specific location, and this generates discrete 'place fields' [116]. Grid cells, that are found in the medial entorhinal cortex (MEC) as well as the pre- and parasubiculum, exhibit hexagonal firing fields that cover the entire environment [43,117]. Head direction cells fire maximally when the head points toward the preferred angle, and are distributed throughout the anterodorsal thalamic nucleus, postsubiculum, MEC, retrosplenial cortex, and posterior parietal cortex, among other regions [118]. Border/boundary cells preferentially increase their activity when the animal approaches environmental edges or boundaries, and are located in the MEC and subiculum [29,30,119]. Some of the spatially tuned cells encode space and items in an egocentric frame of reference. Such cells are present in the lateral entorhinal cortex (LEC), retrosplenial cortex, posterior parietal cortex, dorsal striatum, postsubiculum, and postrhinal cortex, among other brain regions, and encode bearing and distance to items in head/body-centered coordinates which facilitates transformations between egocentric and allocentric reference frames [120]. Speed cells in the MEC and hippocampus modulate firing rates in proportion to the running speed of the animal, and this provides a dynamic signal for updating positional estimates and calibrating grid and place cell activity [121].

early ages (e.g., P10) or rearing animals in spherical balls to deprive them of tactile experience with environmental boundaries will be necessary to determine whether the development of MEC border/boundary cells in such conditions is delayed. Furthermore, because border/boundary cells typically respond to one specific boundary [31], the stable directional reference provided by the early-maturing head direction system is likely a prerequisite for their specificity.

Following the emergence of head direction cells and border/boundary cells, place cells can be recorded in rats as early as P16 [3,32,33], and these are referred to as **early place cells** (see Glossary). The properties of early place cells differ markedly from those of adults. For example, early place cells tend to exhibit spatial fields located near to environmental boundaries that are probably contributed by MEC border/boundary cells [27,34]. Grid cells emerge in rats around P21, which coincides with the time when place cells begin to encode central regions of the environment [34]. This developmental transition is also coincident with the maturation of vision: at P17, visual receptive fields are large and poorly defined, but from P19 onward visual acuity gradually improves [35]. Consequently, before P21, animals mainly rely on tactile cues and immature vision to detect nearby walls, whereas after visual maturation they can incorporate distal cues and boundaries that are visible from central locations. Another hallmark of early place cells is their instability across repeated visits to the same environment, and stability gradually increases with age [32,33,36]. This developmental improvement may be attributed to the emergence of grid cells which provide spatial constraints for place field formation [37]. It may also relate to the maturation of sensory processing because studies in adults demonstrate that multimodal sensory integration enhances place field reliability [38]. In summary, early place cells depend on limited, immature sensory inputs (vestibular, olfactory, tactile, and immature auditory and visual inputs) and exhibit weaker spatial information and lower field stability than in adulthood [32,33,36]. As sensory systems mature, **late place cells** emerge which depend upon multimodal sensory inputs (Figure 1).

Importantly, the mechanisms underlying spatially tuned cells may differ between development and adulthood, and the types of sensory information they use could also vary between these stages. For example, in adulthood, when vision is fully developed, vision seems to be able to compensate for the absence of somatosensory feedback, at least in specific behavioral paradigms such as a virtual reality setting and unconstrained body rotation [39]. Although spatial coding in adults is robust to the loss of specific sensory modalities [40–43], this does not necessarily indicate which sensory inputs are crucial during the initial establishment of spatial circuits. Some sensory inputs and neural pathways, although they are not essential for spatial tuning in adulthood and can compensate for one another, nevertheless contribute to refining spatial precision or correcting errors generated by path integration. However, sensory inputs that are dispensable in adulthood could be crucial for the formation of spatial tuning during development, particularly

Glossary

Early place cells: place cells that exhibit spatial coding ability during early development. In rodent studies, they emerge at approximately postnatal (P) days P15–P18 and display identifiable place fields at this developmental time-window.

Engram cells: a group of neurons that are activated during learning and memory formation. Experimentally, engram cells are often identified using activity-based markers such as *c-Fos* and *Arc*. For cells to qualify as engram cells, their later reactivation should be both necessary and sufficient for eliciting the original memory. These cells support memory storage and retrieval by carrying the trace, or 'engram', of an experience.

Infantile amnesia: the inability of adults to recall autobiographical events from early childhood, typically before ~3 years old. In rodent models, infantile amnesia is assessed via the inability of juvenile animals at around P17 to retain long-term memory, which reflects the functional immaturity of the hippocampus and associated memory systems.

Late place cells: in rodent studies, late place cells refer to place cells that do not exhibit place fields initially at P15–P18, but show significant spatial selectivity at later stages of development, such as from P19 onward.

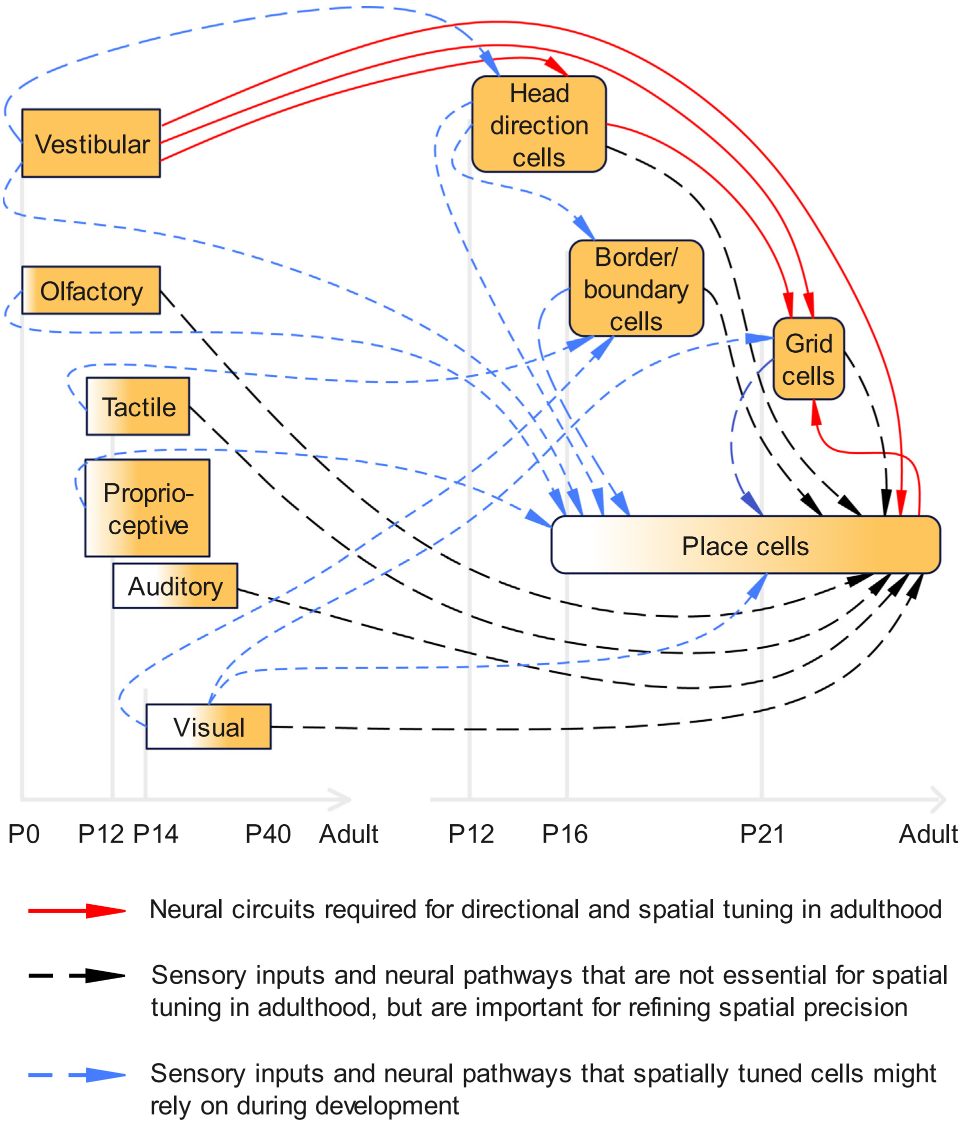

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Figure 1. Coordinated development of spatially tuned cells alongside the sensory systems they rely on. The formation of the place fields of rodent hippocampal neurons is highly robust. For instance, in rats, in the absence of reliable visual, whisker tactile, and olfactory cues, distal auditory information can support place field formation [40]. Similarly, salient olfactory cues can support the formation of stable place fields in the absence of visual and auditory information [41]. When visual, olfactory, and other sensory cues are blocked, the presence of rich tactile cues can guide place field location and enhance their precision [42]. Grid cells in mice are disrupted in darkness [50], whereas in rats they can form without visual input [43]. In rats, impairing vestibular inputs, lesions of head direction cells in the anterodorsal thalamic nucleus, or lesions of the hippocampus result in the loss of grid cells [51], but lesions of grid cells do not eliminate place cells [52]. In rats, head direction cells first appear at postnatal (P) day P12 [24,25], probably driven by the early maturation of the vestibular system; border/boundary cells follow at P16 [27], which might rely on whisker and foot tactile inputs; early place cells emerge from P15–P16 [32,33] and rely on vestibular, olfactory, proprioceptive, and early immature auditory and visual signals, as well as on inputs from head direction cells and border/boundary cells; grid cells mature by P21 [32,33], which coincides with robust vision; and late place cells (>P21) combine multiple sensory modalities and inherit spatial metric information from grid circuits [34].

when other modalities are not yet fully mature or when the intrinsic hippocampal network has not been fully established (Figure 1).

Except for place cells, grid cells, head direction cells, and border/boundary cells, the developmental trajectories of other spatially tuned cell types, such as cells with egocentric spatial tuning (Box 1), remain to be characterized. Whereas sensory signals are generally encoded in egocentric coordinates (body-, head-, or eye-centered), the four well-characterized spatial cell types utilize an allocentric frame. A key open question concerns which of the two types of representations – egocentric versus allocentric – emerges first. Addressing this question could shed light on how sensory inputs support the formation of spatial cognition. The retrosplenial cortex and the posterior parietal cortex, which play important roles in spatial reference frame transformation [44], contain head direction cells, egocentric boundary cells [45–47], and egocentric landmark cells [47]. Behavioral studies in both humans and animal models have investigated the developmental timeline of egocentric versus allocentric strategies. For example, human infants initially employ egocentric strategies for spatial orientation and navigation before developing allocentric approaches [11,48]. Similarly, rat pups demonstrate egocentric navigation using proximal cues by P17, whereas allocentric strategies that utilize distal cues emerge at ~P20 (reviewed in [11]). Notably, many of these studies that use the Morris water maze to assess these strategies did not consider developmental changes in vision, a factor that can crucially influence the interpretation of proximal versus distal cue-based navigation timelines [49]. Thus, a crucial next step is to compare the developmental trajectories of the neural substrates that underlie egocentric and allocentric representations in spatial navigation systems.

The contribution of local interneuron maturation to spatial navigation system development

The maturation of intrinsic circuits within brain areas of spatial navigation involves several developmental processes. PV^+ interneuron-mediated inhibitory circuits may play a crucial role in the emergence and refinement of spatially tuned cells. PV^+ interneurons play a pivotal role in the development of sensory systems [53]. A well-studied example is ocular dominance plasticity in the primary visual cortex (V1), where PV^+ interneurons gradually mature during development, and once their activity level surpasses a threshold, the critical period of ocular dominance plasticity is initiated [54]. Similarly, in MEC, the inhibitory network [55], particularly PV^+ interneurons [56,57] and their associated perineuronal nets [58], gradually matures during postnatal development. The dorsal MEC develops earlier than the ventral MEC [56,59], and dorsal PV^+ interneurons mature earlier than their ventral counterparts [56,57]. The maturation of PV circuitry in MEC is crucial for the emergence and stabilization of grid cell activity [57].

In the hippocampus, PV^+ interneurons also undergo gradual postnatal maturation [18,56–58]. From P5 to P8, CA1 pyramidal cells in mice are activated by movement, but after P9 they are inhibited during the movement due to somatic inhibition from putative PV^+ interneurons, which marks the emergence of internally generated signals [18]. In mice and rats, the firing rate of the PV^+ interneurons in the MEC and hippocampus has been shown to increase with running speed [60,61], which could be used for path integration [62]. Moreover, PV^+ interneurons play important roles in network oscillations and spike timing of the place cell ensemble [62], as well as in sharp wave–ripples [63]. Developmental increases in theta oscillations and replay [64,65], greater population activity sparseness [36], and enhanced spatial information carried by place cells [32,33,36] are all likely to be dependent on the maturation of PV^+ interneurons. Behavioral studies in mice showed that hippocampus-dependent spatial memory precision – the ability to discriminate between similar contexts – emerges at ~P20–P24 but is absent at P16 [66], accompanied by the increase of densities of PV^+ interneurons and perineuronal nets in CA1 [67,68]. Mature PV^+ interneurons promote the formation of sparse **engram cell** ensembles, thereby supporting precise memory, whereas immature PV$^+$ interneurons in young mice lead to larger and less selective ensembles and imprecise memory [68]. Interestingly, in rodent models of **infantile amnesia** [69], the phenomenon is observed at P17 but not at P24 [69–71], and is regulated by GABAergic circuitry [69,72]. Together, these findings suggest that GABAergic neurons, particularly PV$^+$ interneurons, crucially regulate multiple stages of spatial navigation system development and shape both spatial coding and memory precision across early life (Figure 2).

Nature and nurture in the construction of the spatial navigation system

The origins of spatial cognition have long been debated, and some theories emphasize shaping by the postnatal environment whereas others propose innate mechanisms. To reconcile these views, a biological preparedness–environment interaction model has been proposed [73]. In the context of humans, the model posits that children are born equipped with a geometry-sensitive 'core' which is progressively enriched and restructured by their particular environments. More specifically, children are presumed to be born with an innate sensitivity to the geometry of

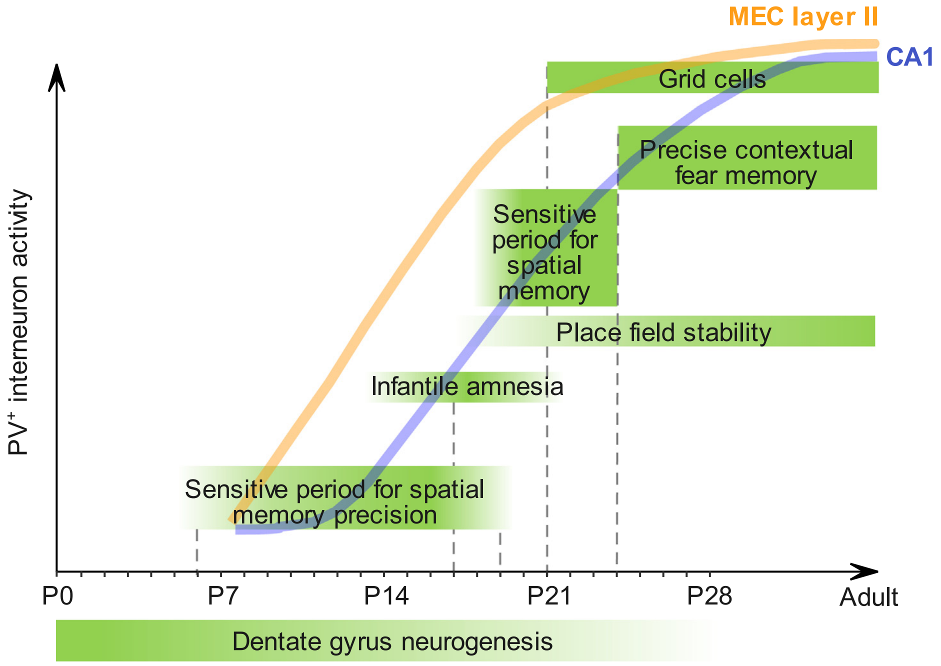

Figure 2. The development of parvalbumin-positive (PV$^+$) interneurons and key developmental milestones of the rodent spatial navigation system and learning/memory systems. PV$^+$ interneurons in medial entorhinal cortex (MEC) layer II (blue curve) and CA1 (red curve) mature gradually during development, as shown in rats [57,58]. A particular threshold level of PV$^+$ interneuron activity might be necessary for grid cell formation [57]. An early experience-sensitive period for refining spatial memory precision exists roughly from postnatal (P) days P6 to P19; during this period, early-life adversity can delay and early-life enrichment can accelerate the development of contextual fear memory precision, which normally manifests by P24 [67]. These early-life interventions are accompanied by slowed or accelerated formation of the perineuronal nets that enwrap PV$^+$ interneurons [67]. Infantile amnesia-like behavior is observed at P17 but not at P24 in rats [69–71]. This phenomenon may be attributed to abundant newborn granule cells during this developmental stage [83], and is also regulated by GABAergic circuitry [69,72]. The place field stability in CA1 gradually increases during development. The low stability at P17 might result from robust dentate gyrus neurogenesis, and could potentially contribute to infantile amnesia [36,84]. In addition, early spatial experience during the sensitive period between P18 and P24 could significantly enhance adult spatial memory, a process that requires medial prefrontal cortex engagement [81]. In sum, a specific level of PV$^+$ interneuron activity (or the amount of their surrounding perineuronal nets) and the presence of postnatal neurogenesis in the dentate gyrus might be key players in grid cell emergence, CA1 place field stability, long-term memory formation, and hippocampus-dependent episodic-like memory precision.

space, such as distance to objects, angles, and layout shape, which predisposes them to encode the geometric layout of their environment and to reorient themselves using shape-based cues; this 'geometric core' is then progressively enriched by the specifics of the environment, such as landmarks and locomotor experience, as well as spatial language and symbols. Thus, over development, innate preparedness and learned input continually interact to yield increasingly flexible and abstract spatial representations [73].

Experiments in animal model have shown, for example in rats, that place cells are present by P15, when rat pups first explore outside the nest [32,33]. Head direction cells are detected as early as P11, even before eye-opening [24]. By P15, hippocampal neuronal ensembles can reliably encode discrete spatial locations along a linear track [65]. These observations support, to some extent, an innate foundation for spatial coding. However, rat pups, before their first laboratory exploration at P15, already engage in spatially directed behaviors in the nest environment, such as orienting toward the dam's nipple or navigating within the nest [3]. These early behaviors suggest that there may not be a clear dichotomy between 'preconfigured' versus 'experience-dependent' map formation. Instead, the functional organization of the spatial navigation system is likely to arise from the interplay between genetic blueprints and experience-dependent plasticity [6]. Moreover, the hippocampus develops over a prolonged trajectory [12,66], which allows an extended period during which sensory and navigational experiences can shape learning.

Structurally, the afferent circuitry and neurotransmitter systems that support spatially tuned cells – including glutamatergic excitatory and GABAergic inhibitory inputs, cholinergic septohippocampal projections, serotonergic raphe–hippocampal pathways, and noradrenergic innervation from the locus coeruleus – are already established early in development [6,74]. In rodents, many crucial neural connections in the spatial navigation system form prenatally. For example, the connectivity of CA1 pyramidal neurons with local interneurons and with MEC pyramidal neurons strongly correlates with their embryonic birth dates [5,6]. The projection patterns from entorhinal to the hippocampus and from the medial septum to the hippocampus emerge before birth [6]. The clustered distribution pattern of calbindin$^+$ cells in layer II of the MEC can be observed at embryonic day 18 [59]. Projections from the retrosplenial cortex to the parahippocampal region begin at P1 and exhibit adult-like topography [75].

Experiences play crucial roles in the development of grid and place cells. Rearing rats in spherical enclosures for 2–3 months reduces the proportion of grid cells and weakens their periodic firing patterns [76]. These deficits recovered to normal after short-term training (7 days) in a standard environment [76]. Similarly, when rats were raised in spherical environments until P17–P24, place cells exhibited weaker spatial tuning and impaired pattern separation compared to age-matched normally reared rats [77]. Hippocampal sequence replay during sleep was also reduced, but significantly recovered after 4 days of training in a linear track. Moreover, mice that lost vision at 1 month of age exhibited more stable head direction tuning than sighted mice, and outperformed congenitally blind mice on some metrics [78], indicating that brief postnatal visual experience refines adult head direction cell tuning for better adaptation to the environment. These findings suggest that the formation of spatially tuned cells relies on preconfigured networks that are refined by early experience.

Behavioral studies further support the roles of early-life experience in spatial navigation. In humans, upbringing environments strongly affect navigation abilities: individuals raised in non-urban environments demonstrated superior navigation skills, and their performance was closely linked to the topological features of their surroundings; this difference exists in both males and females and persists throughout the entire lifespan [79]. In rodents, rat pups that acquired more frequent movement between maternal nipples during nursing showed enhanced spatial memory during adolescence [80]. In rats, enhancing spatial exploration during infancy (P18–P24) increased adult medial prefrontal cortex *c-Fos* expression and improved performance on an object-location memory recognition task [81].

Interneurons provide important mechanistic insight into experience-dependent maturation of spatial navigation and hippocampus-dependent learning. As noted above, the maturation of PV$^+$ interneurons regulates the development of sensory, spatial navigation, and memory systems. Importantly, PV$^+$ interneuron maturation depends not only on age but also on experience. In V1, the maturation of PV$^+$ interneurons requires early visual experience [54]. Similarly, in the hippocampus, PV levels are increased 48 h after learning at P17 in rats; suppressing PV$^+$ interneurons disrupts the formation of infantile long-term memories, whereas enhancing their activity promotes the memories [82]. Early-life adversity from P6–P16 in mice delays the development of perineuronal nets and impairs the development of episodic memory precision, and performance falls below that of controls at P24; by contrast, early-life enrichment from P6–P19 increases the perineuronal nets and accelerates episodic memory precision, and performance surpassing that of controls by P20 [67]. It remains an open question whether early sensory and spatial exploration promotes PV$^+$ interneuron maturation in the spatial navigation system, and thereby drives the maturation of spatially tuned cells. Together, these studies highlight common principles that govern the development of sensory, spatial navigation, and memory systems, and suggest the presence of shared rules of neural circuit maturation across different brain systems (Table 1).

Cell-type diversity in the developing and adult spatial navigation system

Heterogeneity of spatially tuned cells during development

There is functional heterogeneity among spatially tuned cells during development. Longitudinal calcium imaging of the rat hippocampus shows that early place cells maintain high spatial coding abilities across different environments throughout development, suggesting that they represent a distinct subpopulation within CA1 neurons [36]. CA1 pyramidal neurons are generated in an

Table 1. Similarities and differences between the development of the hippocampus and the binocular region of primary visual cortex (V1b) in rodents

	Hippocampus	V1b
Developmental window	Both regions undergo protracted postnatal development	
Cellular heterogeneity in development	Early place cells exhibit high spatial information content across environments, whereas other cells show low spatial selectivity [36] Early binocular neurons display binocular response, whereas others remain monocular [106]	
The effects of experience on the cellular transcriptome	Whether experience affects cell-type composition in specific hippocampal subregions remains unknown	Visual experience is required for the specification of spatially continuous upper-layer excitatory cell types [106]
Experience dependence of functional cell types	Early geometric experience deprivation (e.g., spherical environment rearing) decreases spatial information, but this can be reversed by brief exposure to a normal environment [76,77]	Early adverse visual experience (monocular deprivation or dark rearing) permanently disrupts the proportion and tuning selectivity of binocular neurons [106]
Experience dependence of brain function	Early-life experience affects the development of hippocampus-dependent episodic-like memory [67] Visual experience influences V1b-dependent visual functions (i.e., stereoscopic vision and depth perception) [35,107]	
Plasticity of the circuit	Plasticity of the circuit in hippocampal CA1 persists throughout life [108]	Binocular circuitry is shaped by visual experience from eye-opening (P14) to ~P36 [107]
Inhibitory neuron development	PV$^+$ interneurons and perineuronal nets mature with age and are experience-dependent in both the hippocampus [56,58,67] and V1b [54]	
Roles of BDNF and TRKB	BDNF promotes the maturation of hippocampus-dependent memory [82]; it is necessary for maintaining infantile memory traces and closing the infantile amnesia period [70], and can rescue the delayed maturation of memory caused by aversive experience during a sensitive period [67] BDNF promotes the maturation of visual cortical circuitry and regulates the visual critical period [109,110]; it can rescue the delayed development of visual acuity caused by visual deprivation (dark rearing) [111]	

inside-out pattern, where early- to late-born neurons are positioned along the deep-to-superficial radial axis of the pyramidal cell layer [85,86]. A tempting hypothesis is that early place cells correspond to the earliest-born CA1 neurons [born at around embryonic (E) day E13]. Recent work, however, demonstrates that early place cells are distributed across both deep and superficial layers rather than being confined to the deep layer [36]. Nevertheless, it remains an open question whether early place cells are related to neurons born at specific intermediate embryonic stages (e.g., E15), which are located in both layers. In addition, it would be important to determine whether early place cells exhibit specific gene-expression profiles that might potentially reflect distinct developmental programs.

Grid cells may also have developmental heterogeneity. Recent research shows that, in rats, a small number of cells can develop into grid cells after geometric border deprivation, although their proportion is lower than in normally reared rats [76]. Notably, after several days of training in a normal environment, the proportion of grid cells rapidly increased [76]. It is unclear whether there is a distinct subtype of grid cells that can emerge without prior spatial experience, and whether these cells have different properties, transcriptomic profiles, or functional roles.

Functional subtypes of spatially tuned cells in adulthood and their possible developmental origins

Adult hippocampal neurons exhibit considerable heterogeneity [87–89]. Single-cell transcriptomics has identified distinct transcriptomic subpopulations among CA1 pyramidal cells that correspond to various functional cell types [90]. Functionally, hippocampal CA1 neurons exhibit different features. For instance, some cells can form place fields in the absence of multimodal sensory cues, although the reliability is poor, whereas others cease firing under impoverished sensory conditions [38]. This suggests that the former population can form place fields with minimal sensory input, may possess inherently higher excitability, and require minimal synaptic drive, whereas the latter requires strong synaptic drive from multiple sensory inputs to generate place fields. In addition, adult hippocampal neurons exhibit diverse intrinsic properties. For example, distinct populations of cells differ in their firing rates and burstiness, and these properties remain stable across environments [91]. Some neurons are more prone to become place cells [92–94], likely due to higher intrinsic excitability [95]. Place cells that are recruited as engram cells exhibit a higher firing rate than other place cells [96,97], suggesting greater excitability. Moreover, studies have identified two distinct CA1 populations – 'rigid cells' that contribute to the neuronal sequences both before and after maze exploration, and 'plastic cells' that are recruited to the neural sequence after learning [98]. Rigid neurons exhibit higher firing rates and contribute to stable pre-existing networks, whereas plastic cells fire at lower rates, adjust their activity during learning, progressively refine spatial specificity, and have fewer place fields [98]. It has been proposed that rigid cells may generalize across contexts, whereas plastic cells may distinguish between contexts [98].

Although hippocampal neurons can be classified into distinct subpopulations based on their intrinsic excitability, which may be associated with differential gene expression, inhibition also contributes to shaping these functional subpopulations. For example, inhibition is relatively low in juvenile animals, and yields larger engram ensembles and less precise memories [68]. Moreover, neurons with a higher propensity to become place cells can become more sparsely active as inhibition increases; thus, in a novel environment, reduced inhibitory interneuron activity leads to the recruitment of more place cells [99,100]. In addition, coupling between interneurons and excitatory neurons born within the same temporal window contributes to the establishment of the unique properties of those excitatory neurons [85,101].

These functionally distinct subtypes of cells may already show different properties during development, and are possibly related to the early and late place cells (Figure 3). At ~P17–P18 in

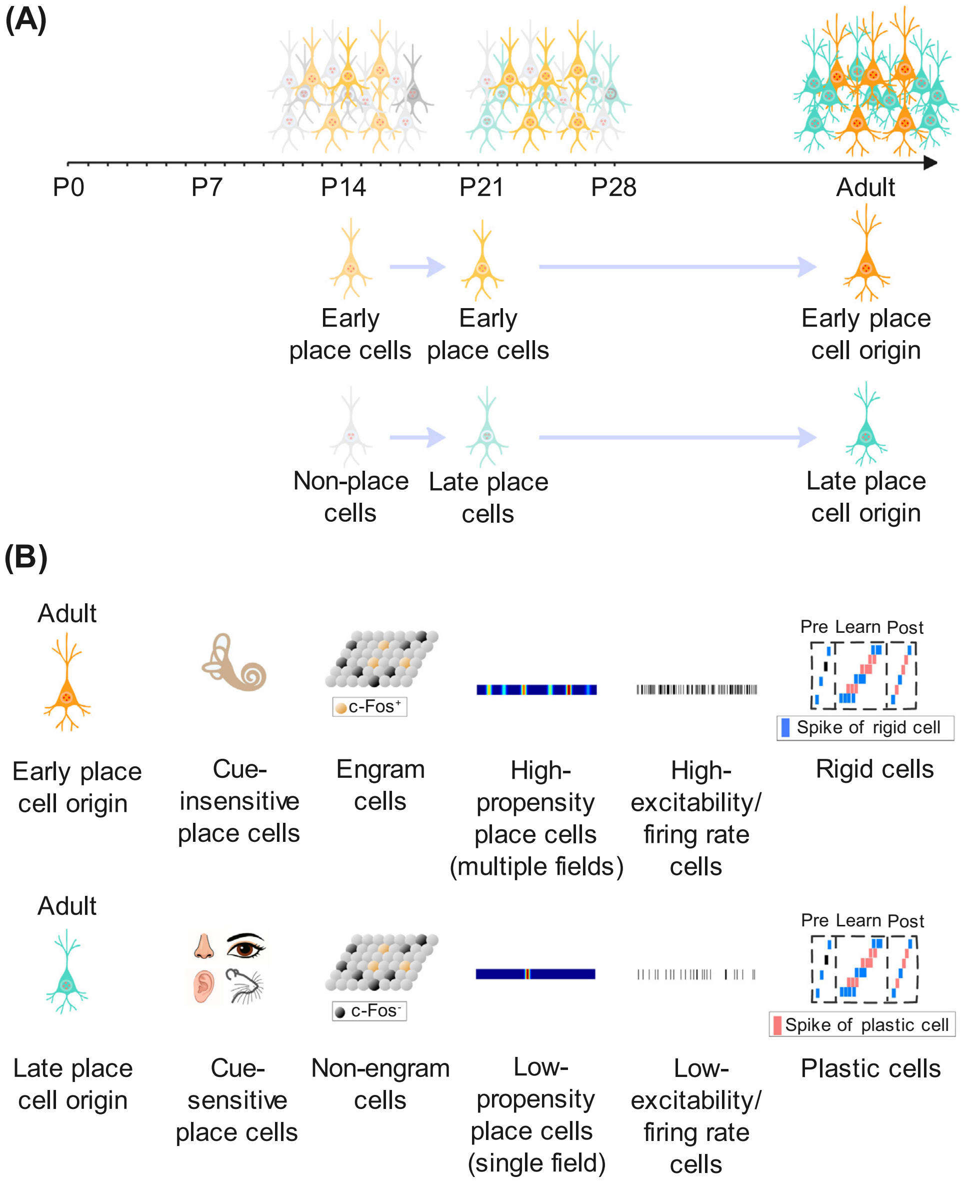

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Figure 3. Functional heterogeneity of place cells during development and adulthood. (A) Developmental time of place cell maturation in rodents. As early as postnatal (P) days P15–P18, a subset of hippocampal neurons – possibly marked by unique gene-expression profiles – are specified as early place cells that emerge before full maturation of multiple sensory modalities, whereas a distinct cohort of late place cells emerge later, possibly with a different molecular signature [32,33,36,65,105]. This functional distinction between early and late place cells may persist into adulthood and potentially give rise to functionally diverse place cell populations. (B) In adults, place cells comprise multiple functional subtypes [87,88,91]. Although parallel mechanisms for place field generation ensure population-level robustness in spatial coding, individual neurons may form place fields in a context- and cue-dependent manner. Some cells may rely primarily on idiothetic inputs (e.g., vestibular, proprioceptive, and motor efference cues) and use path integration to establish place fields, whereas others may additionally require multimodal sensory cues [38]. Some place cells may be preferentially recruited into memory engrams, whereas others are not [96,97]. Some neurons exhibit higher baseline firing rates than others [91]. A subset of neurons are rigid (blue) and participate in sequences both before and after learning, whereas others are plastic (red) and predominantly contribute to the sequence only after learning [98]. This heterogeneous landscape of place cell function might arise from varying developmental origins, such as distinctions between early and late place cell cohorts [36], or from the embryonic and early postnatal wiring of hippocampal circuits [85,86].

rats, early place cells exhibit strong spatial coding across multiple environments and days [36]. They may represent a subpopulation with high intrinsic excitability, a high propensity to form place fields, or even serve as engram cells in adulthood. They could also correspond to rigid cells and display place fields across multiple environments. By contrast, the late place cells might represent plastic cells that learn to encode the environments in the later stage of a session, similarly to how they display place fields at later developmental stages, such as after P19–P20. Future studies are warranted to explore the links between molecular and functional cell types during development, as well as in adulthood, to pinpoint specific molecular markers for early place cells and late place cells. Another goal for future work would be the development of reliable long-term tracking methods for individual functional subtypes.

Neuronal functional diversity observed in adults can be linked, in some cases, to the different birthdates of neurons in the circuit. In mice, hippocampal neurons generated on the same day share transcription-factor makeup and time-window of synaptogenesis, which makes them more likely to form reciprocal connections and exhibit similar physiological properties [86,102,103], and thus enables them to have similar functions [85,104]. In the context of spatial maps, mouse hippocampal CA1 neurons with the same birthdate tend to wire together and exhibit similar place fields across environments [85]. These findings suggest that neurons sharing the same birthdate tend to establish connections during development and form a subpopulation with a specific function. Thus, differences among birthdate-defined subpopulations contribute significantly to hippocampal functional heterogeneity, which highlights the importance of diversity formed during the earliest stages of development [86]. In CA1, neurogenesis follows a radial organization, from early- to late-born neurons, such that neurons in the deep and superficial layers, which have different birthdates, exhibit distinct properties [87,88]. However, neurons along the radial axis of CA1 originate from progenitor cells generated in at least three distinct developmental stages [86], and neurons generated at intermediate dates, that are anatomically located in both layers, may therefore form a distinct subpopulation. In CA3, the relationship between birthdate and radial distribution is less pronounced, but functional distinctions are clear: late-born (E15) neurons facilitate memory retrieval soon after encoding and aid in memory consolidation through plasticity, whereas early-born (E12) neurons are pivotal for long-term memory [104]. In the dentate gyrus, neurons generated between E14.5 and P7 exhibit radial stratification, whereas those born at E12.5 are distributed more uniformly across the granule cell layer and display unique physiological properties [103]. Moreover, neurons that share the same birthdate across subregions of the hippocampus may also assemble into functional ensembles. In summary, it is possible that distinct functional neuronal subtypes emerge from specific temporal windows of neurogenesis and thereby contribute to the developmental foundations of hippocampal circuit diversity.

Concluding remarks and future perspectives

Spatially tuned cells in the mammalian spatial navigation system arise through the sequential maturation of sensory and motor systems, the refinement of local inhibitory circuits, and the shaping influence of experience. The spatial navigation system is composed of multiple spatially tuned cell types, each of which can include distinct subtypes. Different types and subtypes of spatially tuned cells may show distinct dependencies on specific sensory inputs and experiential factors during development. Thus, it will be crucial to investigate the developmental dynamics of these cell types and subtypes, as well as to elucidate the innate and experience-dependent mechanisms that govern their maturation (see Outstanding questions). There is heterogeneity within the same type of spatially tuned cells both during development and in adulthood, and another important goal for future work will be to examine whether and how the functionally diverse subtypes observed in adulthood correspond to cells that have followed distinct developmental trajectories.

Outstanding questions

What are the developmental timelines of spatially tuned cells that encode space and items in an egocentric reference frame, compared to those cells that adopt an allocentric reference frame, including place cells, grid cells, head direction cells, and border/boundary cells?

In what ways do early experience manipulations, such as early-life environmental enrichment, sensory deprivation, and geometric border deprivation, influence the developmental trajectories of various spatially tuned cells?

Are the developmental trajectories of different types of spatially tuned cells differentially influenced by sensory and spatial experiences in early life, and are they selectively sensitive to manipulations of specific sensory modalities?

Are there distinct subgroups of place cells or grid cells whose developmental trajectories depend differently on early-life sensory experiences?

How does the maturation of PV^+ interneurons regulate the emergence and refinement of various spatially tuned cells?

What are the mechanisms that underlie the formation of early place cells? Are there genetic markers that distinguish early place cells from late place cells, and do early place cells arise from neurons that are born within a specific embryonic time-window?

How do the functionally distinct subpopulations of place cells observed in adults correspond to the early and late place cell groups identified during development?

With the application of emerging techniques, such as longitudinal imaging and advanced cell subclass-specific labeling approaches [112], one goal for future work will be to map the developmental timelines of distinct functional cell types in the navigation system. It would also be valuable to develop approaches to genetically access specific cellular subtypes and navigation circuits, and elucidate how genetic programs and experience interact to sculpt spatial navigation circuitry.

The development of sensory systems, which has been studied extensively, could provide particularly valuable insights. Developmental neurobiology has revealed conserved principles across sensory systems, such as transcriptional control of cell fate, circuit wiring specificity, the regulation of circuit organization by GABAergic neurons, and activity-dependent circuit refinement [53,113,114]. Some of these principles have also been shown to apply to spatial navigation systems [6,67,69,115]. Future research in this direction could deepen our current understanding of spatial cognition and episodic memory, and uncover general principles of brain development.

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Declaration of interests

The authors declare no competing interests.

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