

mation in the liver (6). Thus, we investigated the effect of manipulating miR-33 levels in vivo in mice using lentiviruses encoding pre-miR-33, anti-miR-33, or control. Efficient lentiviral delivery was confirmed by measuring green fluorescent protein in the liver (fig. S9D). Consistent with our in vitro results, miR-33 significantly reduced hepatic ABCA1 expression (Fig. 4D; quantification in fig. S9E). It also modestly decreased ABCG1 and NPC1 protein levels, although the effect was not statistically significant. No changes in SR-B1, a cognate receptor for HDL in the liver (7), or other cholesterol-related genes were observed (Fig. 4D). Moreover, an unbiased assessment of hepatic gene expression revealed few significant differences in the expression of other cholesterol metabolism-related genes in mice treated with miR-33 or anti-miR-33 lentiviruses (fig. S10). In vivo overexpression of miR-33 resulted in a progressive decline of plasma HDL, as expected from the requirement of ABCA1 for HDL formation (Fig. 4E), with a 22% decrease achieved after 6 days (Fig. 4F). Conversely, mice expressing anti-miR-33 showed a 50% increase in hepatic ABCA1 protein and a concomitant 25% increase in plasma HDL levels after 6 days (Fig. 4, D to F). Thus, manipulation of miR-33 levels in vivo alters ABCA1 expression and the mobilization of cholesterol to HDL.

To date, only one other miRNA, miR-122, has been shown to have a direct role in cholesterol metabolism (8–10). The expression of miR-122 is highly restricted to the liver, where it is believed to maintain the differentiated state. Silencing of miR-122 down-regulates genes implicated in cholesterol biosynthesis and triglyceride metabolism, increasing hepatic fatty acid oxidation and reducing plasma cholesterol, hepatic fatty acid, and cholesterol synthesis. In contrast, miR-33 is widely expressed in different cell types and tissues, consistent with the hypothesis that it has a more global effect on cel-

lular cholesterol homeostasis. Moreover, we have shown that miR-33 specifically regulates cholesterol transport pathways that mobilize cholesterol from intracellular stores to HDL lipoproteins.

Although the pathways regulating the generation and uptake of LDL cholesterol are well characterized, the molecular mechanisms regulating circulating levels of HDL, the “good cholesterol,” remain poorly defined. The identification of *ABCA1* as the gene mutated in Tangier disease, a condition characterized by a near-deficiency of plasma HDL, revealed its essential role in both HDL generation and reverse cholesterol transport (11–13). Subsequent studies have established that ABCA1 and ABCG1 probably act in a sequential fashion, with ABCA1 lipidating apoA1 to generate nascent HDL particles, which can then promote additional cholesterol efflux via ABCG1 (5). Despite these major advances, it has become clear that the regulation of these pathways is complex and influenced not only by genetic factors but also by posttranscriptional mechanisms (14). Our data provide evidence for a role for miR-33 in the epigenetic regulation of cholesterol homeostasis. We propose that miR-33 functions via a negative feedback loop triggered by the cholesterol content of the cell; under low sterol conditions, the coincident transcription of *SREBF2* and miR-33 coordinate cellular cholesterol homeostasis by simultaneously initiating transcription of cholesterol uptake and synthesis pathways and posttranscriptionally repressing genes involved in cellular cholesterol export.

Our work identifies miR-33 as a potential regulator of two central pathways that control HDL cholesterol: (i) HDL biogenesis in the liver, as reflected by the impact of miR-33 manipulation on circulating HDL levels; and (ii) cellular cholesterol efflux from macrophages, the first step in the reverse cholesterol transport pathway through which HDL and apoA1 ferry excess cholesterol back to the liver for excretion. Because plasma HDL levels show a strong inverse cor-

relation with atherosclerotic vascular disease, there has been intense interest in therapeutically targeting HDL and macrophage cholesterol efflux pathways. Our study suggests that antagonists of endogenous miR-33 may be a useful therapeutic strategy for enhancing ABCA1 expression and raising HDL levels in vivo.

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Materials and Methods

Figs. S1 to S10

Table S1

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Development of the Hippocampal Cognitive Map in Preweanling Rats

Tom J. Wills,^{1*} Francesca Cacucci,^{1,2*} Neil Burgess,^{3,4} John O'Keefe¹

Orienting in large-scale space depends on the interaction of environmental experience and preconfigured, possibly innate, constructs. Place, head-direction, and grid cells in the hippocampal formation provide allocentric representations of space. Here we show how these cognitive representations emerge and develop as rat pups first begin to explore their environment. Directional, locational, and rhythmic organization of firing are present during initial exploration, including adultlike directional firing. The stability and precision of place cell firing continue to develop throughout juvenility. Stable grid cell firing appears later but matures rapidly to adult levels. Our results demonstrate the presence of three neuronal representations of space before extensive experience and show how they develop with age.

The hippocampal cognitive map has been proposed as a Kantian synthetic a priori system, partly or wholly formed geneti-

cally, to serve as a scaffold for representing experiential information about the external environment (1). This suggests that the basic

constituents of the cognitive map develop independently of spatial experience, or might even precede it, and is supported by the early development of spatial cognition in weanling rats (2–4). We tested this idea by looking for place cells (5) in hippocampal region CA1, and for grid (6) and directional cells (7) in medial entorhinal cortex (MEC) as preweanling rats first began to leave the nest and to actively explore their environment (8) [typically on post-

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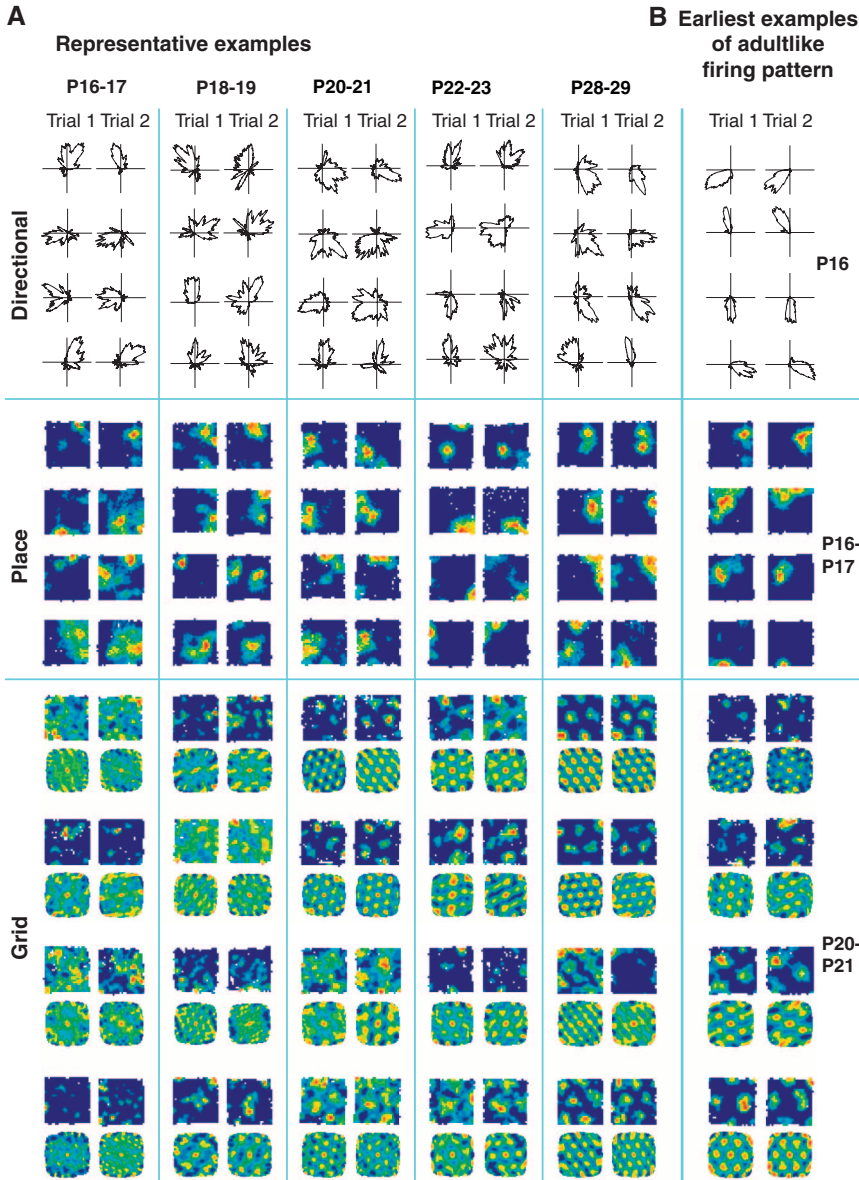
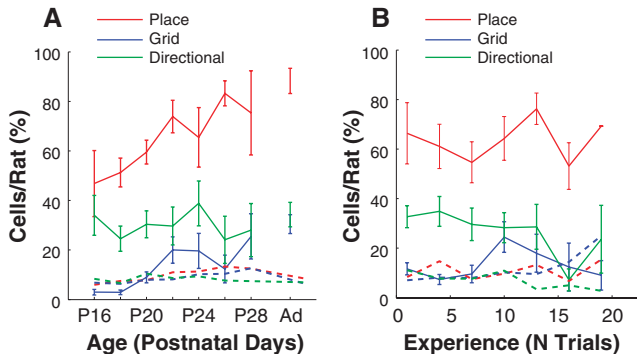


Fig. 1. Development of directional, place, and grid cell firing with age. **(A)** Four representative examples of each type of firing are shown across a range of ages for two consecutive trials (left and right columns): polar plots for directional firing, firing rate maps for place cells, firing rate maps (above) and spatial autocorrelograms (below) for grid cells. Example cells were chosen to have mean values of both the spatial firing criterion variable and intertrial stability within one standard deviation of the appropriate group mean. **(B)** The earliest examples of directional, place, and grid firing corresponding to the classical examples found in adults.

Fig. 2. The proportions of cells per rat fulfilling the criteria for directional (green), place (red), and grid (blue) cells as a function of age **(A)** or experience of the testing environment **(B)**. Solid lines represent the mean percentage of cells per rat that fulfilled the spatial firing criteria; error bars represent \pm SEM over all rats. Dotted lines represent the $P = 0.05$ significance level for the mean percentage of cells for each cell type, based on spike-shuffled data (see 9).



natal day 16 (P16) in our experiment] (9) (see fig. S1 for typical recording locations).

We recorded 567 hippocampal pyramidal cells and 1514 medial entorhinal cells from 42 male rats between the ages of P16 and P30 as they foraged for food in an enclosure, using miniaturized microdrives and recording locations matched across ages (9) (fig. S2, C to E). Cells were categorized as directional, place, or grid cells if their spatial firing characteristics exceeded the 0.05 significance level of the relevant measures [spatial information (10) for place cells, gridness (6, 11) for grid cells, Rayleigh vector for directional cells] in spatially shuffled data for the corresponding age and region (9).

When do the three types of spatial firing first appear, and how do they develop with age? Representative examples of cells recorded across ages P16 to P29 are shown in Fig. 1A and, in

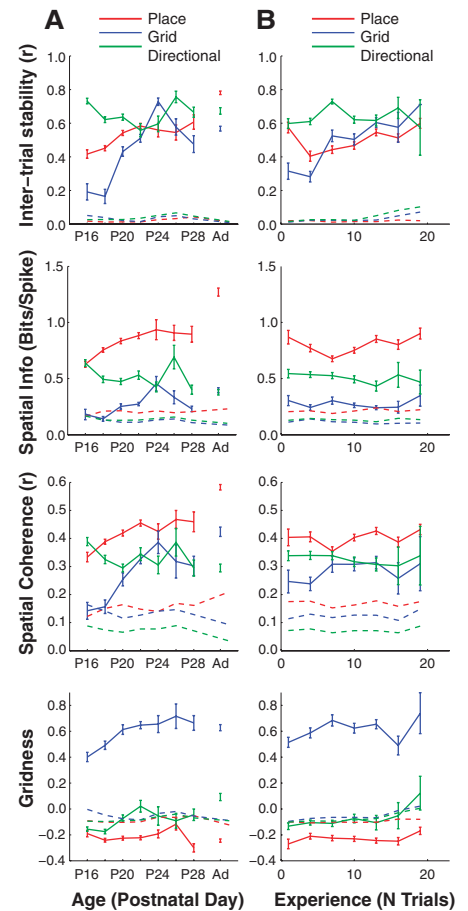


Fig. 3. Spatial firing properties of the directional (green), place (red), and grid cells (blue) as a function of age **(A)** and experience of the testing environment **(B)**. Shown (from top to bottom) are the stability (spatial correlation trial-to-trial), quality (locational or directional spatial information per spike), spatial coherence, and gridness of firing of the three cell types. For summary statistics, see fig. S8A. Dotted lines represent the $P = 0.05$ significance level of expected mean value of spatiality for each cell type based on spike-shuffled data; solid lines represent the mean over cells (\pm SEM).

Fig. 1B the earliest examples of stable adultlike firing found in directional (P16), place (P16 to 17), and grid cells (P20 to 21). See figs. S3 to S6 for the complete data set and fig. S7 for the distributions of the relevant measures across all cells recorded in MEC and CA1.

Adultlike proportions of directional cells were present from the earliest age point, and these cells exhibited adultlike stability and quality (Figs. 2A and 3A, and see fig. S8, A and B, for statistical analysis). Somewhat higher proportions of directional cells were found near the border with parasubiculum (fig. S9) than in the heart of MEC, but did not increase with age in either region. It is noteworthy that directional tuning was also tighter in this border region (fig. S9C). This strong directional signal may originate in the presubicular head-direction cells, as preliminary recordings from this region revealed adultlike directional cells at very early ages (P14) there too (fig. S9, D and E).

Significant proportions of place cells are also present initially (Fig. 2) but continue to increase toward adult levels throughout development. Although cells with multi-peaked firing were also found early in MEC, significant proportions of classical adultlike grid cells first appeared only at around P20 and increased rapidly to near-adult levels by P22 (fig. S8B).

A critical attribute of spatial representations is their stability over time, which provides a reliable environmental representation suitable for long-term memory (12). The correlation of firing rate maps from one trial to the next is typically 0.6 or higher for all three cell types in the adult (Fig. 3A). Stability measures during development show the same pattern as proportions of cells:

Directional firing has adultlike stability from the earliest age; stable place cell firing is also present initially but continues to improve throughout development; and stable grid cell firing is initially almost nonexistent but develops rapidly at around P20 (Fig. 3A and fig. S8, A and B).

The quality of spatial encoding can be fairly compared across cell types by using the spatial information per spike [regarding location for place and grid cells and direction for directional cells, significantly high in early place cell firing but increasing throughout development, and reaches adult levels in grid cells at P24 (Fig. 3A and fig. S8, A and B).

We are able to dissociate the effects of age from effects of experience in the testing environment because we began recording from different animals at different ages. Effects of experience on place cell stability at P18 to P19, and grid cell firing stability at P22 to P30 were seen, but these were weaker than the corresponding increases with age. All other effects reflect age alone (Figs. 2B and 3B and fig. S8A). (The independent effects of age and experience separately are shown in fig. S10.)

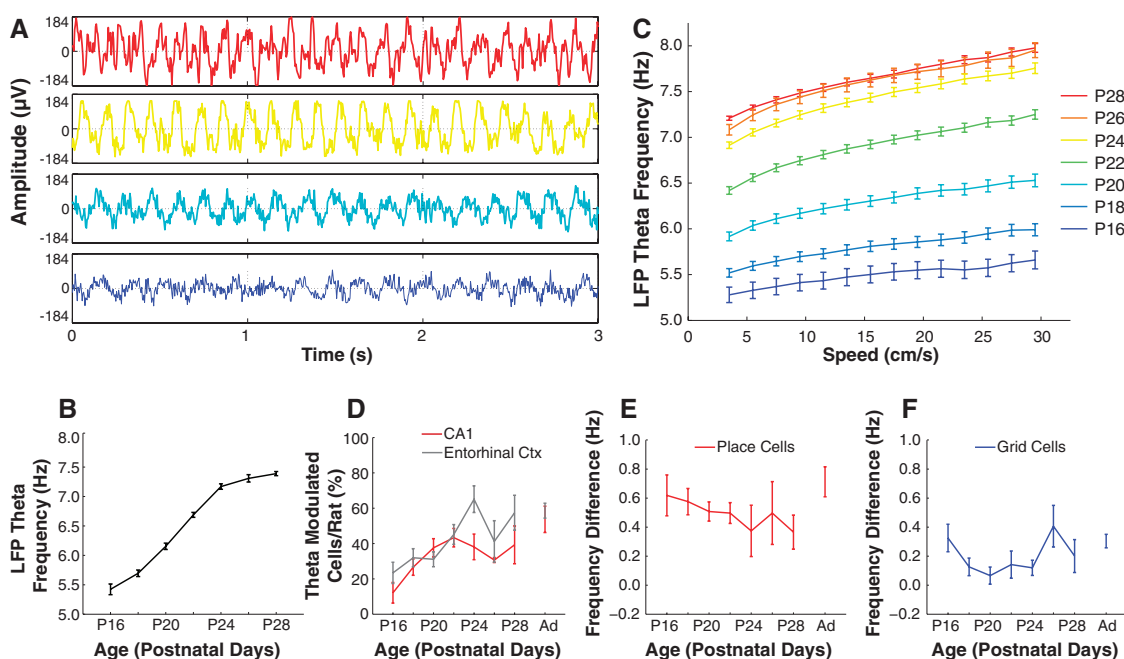
In adult rats, the firing of place and grid cells is carefully timed to the theta rhythm [“phase precession” (13, 14)], and theta oscillations may play a role in the creation of place (13) and grid (15, 16) firing. How does the temporal organization of the hippocampal formation develop? As the rat pups moved around the environment, theta activity was present in the local field potential at the earliest recording time point of P16. Theta

frequency increased with age and with running speed [as in adults (17, 18)]. Theta amplitude showed a similar profile (Fig. 4) (19). Both the slope and intercept of the frequency-speed relation increased with age ($P < 0.001$) (Fig. 4C). Significant proportions of cells in CA1 and MEC showed theta-modulated firing from the earliest ages. The proportions in each region were approximately equal, started from around 20% at P16, and were not significantly different from adult levels by P22 (Fig. 4D).

Finally, the frequency of modulation (indicated by the power spectrum of the spike-train autocorrelogram) of grid and place cell firing was slightly higher than the simultaneously recorded local field potential theta (Fig. 4, E and F); this finding is consistent with the presence of phase precession. We did not systematically record on the linear track to test for this, but can report one observation of phase precession in five CA1 cells as early as P17 (fig. S11).

Could any of our results reflect changes in behavior, such as speed of movement (17, 18)? Speed of movement initially slows between P16 and P20 and then rises steadily, producing a U-shaped pattern with age (fig. S12A), mirrored by an inverted U-shaped pattern in the number and duration of periods of immobility (fig. S12, B to D). Coverage of the environment and distribution of heading directions did not vary across the recording period (fig. S13). The observed monotonic changes in spatiality seem unlikely to reflect these factors, which we confirmed by filtering the data to equate median speeds across all ages (fig. S12, E to G). Changes in the quality of tetrode recordings with age can also be discounted (fig. S2, F and G), as can

Fig. 4. Movement-related theta rhythmicity of the local field potential (LFP) and cell firing. (A to C) LFP theta oscillations are present at the earliest age recorded, increase in frequency with age (A) and (B), and increase with running speed at every age (C). (A) Samples of LFP from different ages. (B and C) Mean theta frequency for periods of translational motion are shown versus age (B) and running speed (C). Error bars show SEM; (A) and (C) are color coded by age. (D) Theta-modulated firing is present at the earliest ages in CA1 and MEC, and the proportions of theta-modulated cells increase with age in both areas (CA1: $r = 0.34$, $P < 0.01$; MEC: $r = 0.36$, $P < 0.001$) and are not significantly different from adult by P22 ($P = 0.74$, Tukey’s post hoc test). The theta-band modulation of firing in CA1 place cells (E) and entorhinal grid cells (F) is higher in frequency than the



ongoing LFP theta, and the frequency difference does not change significantly with age (place cells: $r = 0.05$, $P = 0.28$; grid cells: $r = 0.08$, $P = 0.32$).

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changes in more general properties, such as firing rates or percentage of complex spikes (fig. S14).

Because early directional firing is stable relative to the environment, it must use environmental cues as well as interoceptive inputs. In addition, directional modulation remains parallel across the whole environment, even during the rat's first-ever exploration of the recording environment (fig. S15A), which indicates that, as in the adult (7), it does not reflect a simple association to a single cue. Furthermore, when tested in two visually different environments, the preferred directions of simultaneously recorded cells rotated together coherently (fig. S15, B and C). These observations suggest the presence of functional sensory input to MEC at P16 and that directional firing could not be produced solely by experience-dependent plasticity driven by movements within the nest before exploration. The timing of development of the different spatial cell types suggests that ontogeny recapitulates phylogeny insofar as the directional signal originates in the brainstem, the place signal originates in archicortex (i.e., hippocampus proper), and the grid cells originate in neo/transcortex.

Stable directional firing, place cell firing, and theta-band temporal organization occur before significant proportions of adultlike grid cells fire. These three factors may combine stable adultlike grid cell firing (15, 16) with further physiological developments [e.g., of MEC stellate cell intrinsic membrane potential oscillations (20)], to create. Once formed, simultaneously recorded grids have similar wavelengths and orientations, as in the adult (6) (fig. S16); these findings are consistent with the presence of coherent ensembles (21). In addition, the appearance of place cell firing with trial-to-trial stability before stable grid cell firing implies that place cell firing can be driven by inputs other than those from grid cells, including environmental inputs, such as boundary vector cells (22–24) or local cues (24), acting together with the (highly stable) directional cells. Our results, together with evidence that place cell firing is not abolished by entorhinal cortex lesions (25), call into question the hypothesis that entorhinal cortex grid cells provide the only spatial input to the place cells. Both place and grid cell firing continues to develop after P20, more rapidly for grid than place cells. Although both systems appear to be interdependent in the adult (26), their differential developmental time courses suggest that interconnectivity develops after pups begin to explore. For example, the presence of theta-modulated firing in both regions at the earliest ages suggests that each area has oscillatory machinery, such as that required for phase precession (16, 27). Controlled rearing studies will be required to further disentangle the dependencies of these different spatial representations on each other and on experiential and innate processes.

Our results put the development of the place and directional systems earlier than previously reported (28) and have general implications for the

interaction of innate and experientially acquired knowledge in spatial cognition. The expression of some types of spatial learning ability continues to improve for a long time after the components of the cognitive map are relatively mature, which suggests that the rate-limiting step may be the use of spatial signals by the rest of the brain. However, some types of spatial behavior in rats, such as spatial orientation based on enclosure geometry (29), are likely directly controlled by head-direction cells, so that our evidence for an early, perhaps preconfigured, directional firing would be consistent with the early appearance of this behavior in humans (30).

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Development of the Spatial Representation System in the Rat

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In the adult brain, space and orientation are represented by an elaborate hippocampal-parahippocampal circuit consisting of head-direction cells, place cells, and grid cells. We report that a rudimentary map of space is already present when 2½-week-old rat pups explore an open environment outside the nest for the first time. Head-direction cells in the pre- and parasubiculum have adultlike properties from the beginning. Place and grid cells are also present but evolve more gradually. Grid cells show the slowest development. The gradual refinement of the spatial representation is accompanied by an increase in network synchrony among entorhinal stellate cells. The presence of adultlike directional signals at the onset of navigation raises the possibility that such signals are instrumental in setting up networks for place and grid representation.

The hippocampus and entorhinal cortex are key components of the brain's network for representing an animal's position in

external space (1, 2). In the hippocampus, place cells fire selectively when the animal visits a specific part of the environment (3). Cortical

Development of the Hippocampal Cognitive Map in Preweanling Rats

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The Space in Your Head

Space, and events associated with places and spaces, are represented in the brain by a circuitry made of place cells, head direction cells, grid cells, and border cells. These cell types form a collective dynamic representation of our position as we move through the environment. How this representation is formed has remained a mystery. Is it acquired, or are we born with the ability to represent external space (see the Perspective by **Palmer and Lynch**)? **Langston et al.** (p. 1576) and **Wills et al.** (p. 1573) investigated the early development of spatial activity in the hippocampal formation and the entorhinal cortex of rat pups when they first began to explore their environment. Rudiments of place cells, head direction cells, and grid cells already existed when the pups made their first movements out of the nest. A neural representation of external space at this early time points to strong innate components for perception of space. These findings provide experimental support for Kant's 200-year-old concept of space as an a priori faculty of the mind.

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